Detection and Prediction of Epileptic Seizures

Duun-Henriksen, Jonas; Sørensen, Helge Bjarup Dissing; Kjær, Troels W.; Thomsen, Carsten E.

Publication date:
2013

Document Version
Publisher's PDF, also known as Version of record

Technical University of Denmark

Jonas Duun-Henriksen

Detection and Prediction of Epileptic Seizures

PhD thesis, October 2012

DTU Electrical Engineering
Department of Electrical Engineering

hypo safe®

Technical University of Denmark
Department of Electical Engineering
DK-2800 Kgs. Lyngby
Denmark

Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Technical University of Denmark.

Preface

During the year 2008, I was writing my Master's thesis on the subject *Seizure Prediction on the Basis of iEEG Recordings* at Ørsted•DTU. Luck would have it, that the newly started company HypoSafe A/S became aware of my project and invited me and my supervisor Helge B.D. Sørensen to a discussion regarding a future collaboration with me as a PhD-student. Our chemistry seemed to match, so in February 2008, the application for an industrial PhD was accepted, and my research project began. Collaborating partners were the Biomedical Engineering section at DTU Electrical Engineering, Department of Clinical Neurophysiology at Copenhagen University Hospital Rigshospitalet and HypoSafe A/S.

As it is an industrial PhD 1/3 is financed by the Danish Agency for Science Technology and Innovation under the Ministry of Science, Innovation and Higher Education. The remaining 2/3 is financed by HypoSafe A/S.

The current PhD dissertation presents the primary research findings during the period from February 2008 to October 2012. It constitutes a partial fulfillment of the requirements for the PhD degree along with other activities such as teaching, following courses, participating in conferences, supervising students through bachelor and master projects, and being incorporated into the standard operating procedures at HypoSafe A/S.

The dissertation consists of a summary report, three original research journal papers, three conference papers, and one abstract.

Jonas Duun-Henriksen

Kgs. Lyngby, October 2012

Acknowledgement

During the employment of my PhD study, I have met a lot of people who deserves an appreciation. First of all, I would like to mention my four supervisors: Principal supervisor, Associate Professor MSK, PhD Helge B.D. Sørensen from the Technical University of Denmark, clinical supervisor Chief Physician, Associate Professor, PhD Troels W. Kjær from Copenhagen University Hospital Rigshospitalet, Associate Professor, PhD Carsten E. Thomsen from Copenhagen University, and industrial supervisor PhD Rasmus E. Madsen from HypoSafe A/S. I appreciate your competent supervision and the stimulating and interesting discussions we have had.

The staff at the Department of clinical neurophysiology at Copenhagen University Hospital Rigshospitalet deserves an appreciation for taking interest in my project and always performing the extra recordings with a smile. A special thanks to the engineers at the department, especially Martin Nøhr, as well as technician Lennart Derm, who were most helpful in collecting and extracting data in the intra-extracranial study.

I am grateful to the entire staff at HypoSafe A/S for including me as a regular staff member from the beginning, as well as providing a joyful and inspiring work environment. Despite various setbacks in the development of our device, the positive spirit at the office has never failed. Especially Line S. Remvig deserves a thanks for great discussion during her time as a graduate student, as well as taking part of supervising meetings after her graduation. Also thank you to CEO Rasmus S. Jensen for always believing in me and my competencies within epilepsy research as well as providing the means for great research.

My colleagues at the Biomedical Engineering section, DTU Electrical Engineering, are highly appreciated including the Biomedical Signal Processing group where valuable discussions have often provided food for thought. In particular my office mate PhD Isa Conradsen has taken part of many a discussion on academic as well as personal level.

Finally, my wife Anne Katrine Duun-Henriksen deserves the dedication of this dissertation. You have encouraged, supported and discussed every single detail of my research with me. The research level would not had been the same without your endorsement.

Abstract

Approximately 50 million people worldwide suffer from epilepsy. Although 70% can control their seizures by anti-epileptic drugs, it is still a cumbersome disease to live with for a large group of patients. The current PhD dissertation investigates how these people can be helped by continous monitoring of their brain waves. More specifically, three issues were investigated: The feasibility of automatic seizure prediction, optimization of automatic seizure detection algorithms, and the link between intra- and extracranial EEG.

Regarding feasibility of automatic seizure prediction, neither the author nor any other in the seizure prediction society have yet obtained clinical applicable prediction results. However, this should not be taken as discouraging for the future. New large public databases have emerged during 2012 which might provide the means to identify patterns leading to reliable seizure prediction algorithms.

More promising results were obtained in the investigating of possible use of an outpatient EEG monitoring device for idiopathic generalized epilepsy patients. Combined with an automatic seizure detection algorithm such a device can give an objective account of the paroxysm frequency, duration, and time of occurrence. Based on standard EEG data from 20 patients recorded in the clinic, the log-sum of wavelet transform coefficients were used as feature input to a classifier consisting of a support vector machine. 97% of paroxysms lasting more than two seconds were correctly detected without any false positive detections. This was obtained using a generic algorithm on the signals from only a single frontal channel. Applying the same algorithm architecture on EEG data from two outpatient children monitored for approximately three entire days each, the sensitivity was 90% and the false detection rate was 0.12/h. When more recordings are collected, the outpatient algorithm can be further optimized and results should improve.

The final investigation examined the relationship between spontaneous, awake intra- and extracranial EEG. Seven patients with electrodes placed subdurally as well as subgaleally were used to estimate the *field of vision* of a single extracranial channel. By computation of the coherence between the channels, the well recognized hypothesis stating that the skull acts as an electroencephalographic averager was proven correct. Although coherence was significant in an accumulation area of 150 cm^2, only channels within a cortical area of approximately 30 cm^2 showed to increase the coherence. The increase seemed to progress linearly with an accumulation area up to 31 cm^2, where 50% of the maximal coherence was accumulated from only 2 cm^2 (corresponding to one channel), and 75% from 16 cm^2. The coherences of different frequency bands below 16 Hz all seem to have similar declines as a function of the Euclidean distance between channels. Frequencies between 16 and 30 Hz have a steeper decline and will only show coherent parts to cortical channels within 60 cm^2. There is no coherence for frequencies above 30 Hz at any distance.

A lot of patients with epilepsy still struggle with a dreadful fear of suddenly having a seizure. The current PhD study identified topics where an EEG monitor could provide improvement in the patient's quality of life. By algorithm development, implementation and testing, a step toward such a device is presented.

Resumé

Cirka 50 millioner lider af epilepsi verden over. På trods af at 70% kan kontrollere deres anfald med antiepileptisk medicin, er det stadig en besværlig sygdom at leve med for en stor gruppe patienter. Dette PhD-projekt omhandler hvorledes disse personer kan hjælpes med kontinuerlig monitorering af deres hjerneaktivitet. Helt specifikt blev tre emner undersøgt: Muligheden for automatisk anfaldsforudsigelse, optimering af en automatisk anfaldsdetektionsalgoritme og sammenhængen mellem intra- og ekstrakranielt EEG.

Angående automatisk epileptisk anfaldsforudsigelse har hverken denne forfatter eller nogen andre forskere været i stand til at opnå klinisk brugbare resultater. Dette skal dog ikke tages som nedslående for fremtiden. Nye meget store offentlige databaser er åbnet op i 2012. De vil forhåbentlig give forskerne mulighed for at identificere mønstre i patienternes EEG, som kan føre til pålidelige anfaldsforudsigelsesalgoritmer.

Derimod blev der opnået mere lovende resultater i en undersøgelse af brugen af et ambulant EEG monitoreringsapparat til brug ved idiopatisk generaliseret epilepsi. Kombineret med en automatisk anfaldsdetektionsalgoritme vil sådan et apparat kunne give en objektiv opgørelse over frekvensen, varigheden og tidspunktet for anfaldsmønstrenes optræden. Baseret på standard-EEG data fra 20 patienter optaget i klinikken, kunne en log-sum af wavelet transformerede koefficienter bruges som input til en support vektor maskine. Dette resulterede i at 97% af anfaldsmønstre med varighed på mindst 2 sekunder blev korrekt detekteret uden nogen falsk positive detektioner. Dette blev opnået med en generisk algoritme på signalet fra kun en enkelt frontal EEG kanal. Ved at benytte samme algoritmestruktur på data fra to ambulante børn, som blev monitoreret i omtrent tre hele dage hver, blev sensitiviteten på 90% og den falske detektionsrate på 0,12/t. Når flere monitoreringer bliver udført, vil algoritmen kunne optimeres yderligere, så bedre resultater opnås.

Den sidste undersøgelse gik på sammenhængen mellem spontan, vågen intra- og ekstrakranielt EEG. Syv patienter med elektroder placeret subduralt og subgalealt blev benyttet til at estimere *synsfeltet* for en enkelt ekstrakraniel kanal. Ved at beregne kohærensen mellem kanalerne, kunne den anerkendte hypotese om at kraniet fungerer som spatial midler eftervises. På trods af at kohærensen var signifikant over et kortikalt område på 150 cm^2, var det kun kanaler inden for et område af cirka 30 cm^2 som bidrog til højere kohærens. Forhøjelsen var lineær, hvor 50% af den maksimale kohærens blev opnået ved 2 cm^2 (svarende til en kanal) og 75% blev opnået ved 16 cm^2. Kohærensen for frekvensbånd under 16 Hz havde ens fald som funktion af den Euklidiske afstand mellem kanalerne. Frekvenser mellem 16 og 30 Hz havde et hurtigere fald og viste kun kohærente værdier for et kortikalt areal på 60 cm^2. Der var ingen kohærens for frekvenser over 30 Hz uanset afstand.

Mange patienter kæmper stadig med en daglig frygt for et pludseligt epileptisk anfald. Denne PhD-afhandling identificerer steder hvor en kontinuer EEG monitor kan give patienter en forbedret livskvalitet, og et skridt mod sådan et apparat er opnået ved at udvikle, implementere og teste algoritmer til automatisk anfaldsdetektion.

Abbreviations

AED	Anti-epileptic drug
CAE	Childhood absence epilepsy
CSWS	Continuous spikes and waves during slow sleep
CT	Computed tomography (scan)
db4	Daubechies 4
ECoG	Electrocorticography
eEEG	Extracranial EEG
e/eEEG	Extracranial extracranial EEG (comparison)
e/iEEG	Extracranial intracranial EEG (comparison)
EEG	Electroencephalography
EMU	Epilepsy monitoring unit
F	Female
FDR	False detection rate
FPR	False prediction rate
FSPEEG	Freiburg seizure prediction EEG (database)
HV	Hyperventilation
iEEG	Intracranial EEG
i/iEEG	Intracranial intracranial EEG (comparison)
IGE	Idiopathic generalized epilepsy
ILAE	International League Against Epilepsy
IWSP4	International Workshop on Seizure Prediction 4
M	Male
MPC	Mean phase coherence
MRI	Magnetic resonance imaging
n.ab.	Nothing abnormal
n.s.	Not specified
NA	Not available
parox.	Paroxystic
PS	Photic stimulation
RHEEG	Rigshospitalet EEG (database)
sEEG	Scalp EEG
SUDEP	Sudden unexpected death in epilepsy
SVM	Support vector machine
TLE	Temporal lobe epilepsy
WT	Wavelet transform

CONTENTS

CHAPTER

ONE

INTRODUCTION

In industrialized countries, the overall prevalence of epilepsy is estimated to be 0.5-0.9% [12]. In Denmark there are approximately 35.000 epilepsy patients of whom almost 10.000 cannot become seizure free on traditional anti-epileptic drugs. It is a disease that has a tremendeous impact on life for those involved. Although most people know someone with epilepsy, they might not be aware of it as it is a disease that is tabooed in the society. This is most likely due to the society's ignorant knowledge on the patients. Many believe that epilepsy patients are disabled and that sufferers are unemployable, unable to drive, play video games, or watch television. While this is true for a small proportion there are also those at the other end of the spectrum; epileptics who live normal lives, controlling their condition with drugs or diets. If those affected by recurring seizures had the possibility of better medication or technological devices providing safety in form of alarms to relatives or instructions to observers how to react when a seizure strikes, they might become more equal to those with well treated epilepsy. The industrial partner of the current PhD-study, HypoSafe A/S, is developing a small subcutaneous EEG monitor for prediction of hypoglycemia in diabetes patients. They are interested in whether their device can help improving the quality of life for the epilepsy patients as well. Those aspects led to the following overall objectives:

Objectives

- To investigate the feasibility of seizure prediction
- To investigate the state-of-the-art in seizure detection and improve the performance
- To identify the area most applicable for a small EEG recording device, and apply automatic seizure detection algorithms to decide the detection performance
- To investigate the link between intra- and extracranial EEG

An account for why these objectives was outlined is given at the end of this chapter. First the background of epilepsy (section 1.3) and the consequences for patients (section 1.4) should be established together with an introduction of HypoSafe A/S and an evaluation of their interest in the project (section 1.5).

1.1 Thesis Outline

During the PhD-project a total of three journal papers, three conference papers, and one abstract were completed (see Appendix A). Those papers are the pivot of the dissertation. Instead of paraphrasing the articles, the main text in the dissertation is focused on why we have made the investigation, a very short summary of obtained results, and a conclusion that reflects upon the findings and their consequences for the epilepsy research as well as patient society. When relevant, a discussion of future interest points are given. Methods, results and discussions dealt with in the papers are not restated in the dissertation unless new unpublished aspects approaches. Papers with a high degree association are treated in the same chapters.

The thesis is structured in the following way:

Chapter 1: The introduction to the thesis including an outline of the structure as well as a short introduction to the physiology behind epilepsy and a discussion of the consequences for the patients and relatives. Finally, the involved industrial partner, HypoSafe A/S, is introduced and their motive of interest in the project is explained.

Chapter 2: A study that first proved seizure prediction to be of high interest, but were later discarded due to a more throughout analysis. The seizure prediction society has changed its belief in the feasibility of forecasting substantially during the time period of the current project. Results from the new analysis will be given together with an elaboration upon pitfalls for many new scientists. The expectations for the future is finally assessed.

Chapter 3: An analysis of how levels in a wavelet transform is dependent on modality (intra- or extracranial EEG), and results from an optimization of the optimal channel selection method that should be used for intracranial automatic seizure detection.

Chapter 4: An investigation of the optimal channel for automatic seizure detection of childhood absence epilepsy, and a parameter optimization to estimate obtainable detection performance. Also, a preliminary outpatient study on patients with idiopathic generalized epilepsy is presented.

Chapter 5: An analysis of and reflections on subdural to subgaleal EEG signal transmission and the affectors that influence the conduction.

Chapter 6: A conclusion to wind up on the overall objectives and evaluate the findings in the PhD-study.

1.2 Scientific Contributions

The scientific contributions of this PhD project are mainly collected in three journal papers, three conference papers, and one abstract. Additional co-authored papers and applications to the Regional Research Ethics Committee are listed at the end of the following publication list. The numbering refers to their placement in the appendix. The author of this dissertation is cited as Jonas Henriksen prior to September 2010, and Jonas Duun-Henriksen thereafter.

Journal papers

A.4 Duun-Henriksen J., Kjaer T.W., Madsen R.E., Remvig L.S., Thomsen C.E., Sorensen H.B.D. Channel selection for automatic seizure detection. Clinical neurophysiology. 2012;123(1):84-92.

A.6 Duun-Henriksen J., Kjaer T.W., Madsen R.E., Jespersen B., Duun-Henriksen A.K., Remvig L.S., Thomsen C.E., Sorensen H.B.D. Subdural to subgaleal EEG signal transmission: the role of distance, leakage and insulating affectors. Submitted to Clinical Neurophysiology.

A.7 Duun-Henriksen J., Madsen R.E., Remvig L.S., Thomsen C.E., Sorensen H.B.D., Kjaer T.W. Automatic detection of childhood absence epilepsy seizures: toward a monitoring device. Pediatric neurology. 2012;46(5):287-92.

Conference papers

A.2 Henriksen J., Kjaer T.W., Madsen R.E., Thomsen C.E., Sorensen H.B.D. Patient-specific rigorously methodological test of the mean phase coherence. IWSP4. 2009. (not published)

A.3 Henriksen J., Remvig L.S., Madsen R.E., Conradsen I., Kjaer T.W., Thomsen C.E., Sorensen H.B.D. Automatic seizure detection: going from sEEG to iEEG. Conference proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. 2010:2431-4.

A.5 Duun-Henriksen J., Kjaer T.W., Madsen R.E., Remvig L.S., Thomsen C.E., Sorensen H.B.D. Correlation Between Intra- and Extracranial Background EEG. Conference proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. 2012:(accepted for publication)

Abstracts

A.1 Henriksen J., Kjaer T., Thomsen C.E., Madsen R.E., Sorensen H.B.D. Proceedings IEC. Feasibility of Seizure Prediction from intracranial EEG Recordings. Epilepsia. 2009;50(Suppl. 1):73.

Co-authored papers

- Sorensen T.L., Olsen U.L., Conradsen I., Henriksen J., Kjaer T.W., Thomsen C.E., Sorensen H.B.D. Automatic epileptic seizure onset detection using matching pursuit: a case study. Conference proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. 2010:3277-80.
- Petersen E.B., Duun-Henriksen J., Mazzaretto A., Kjaer T.W., Thomsen C.E., Sorensen H.B.D. Generic single-channel detection of absence seizures. Conference proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. 2011:4820-3.

Regional Research Ethics Committee applications (only in Danish)

B.1 Continuous Subcutaneous EEG Measurements for Detection and Prediction of Epileptic Seizures. Record no. H-1-2009-140

B.2 Repeated Long-term-EEG Measurements in Child Epilepsies. Record no. H-3-2011-054

1.3 Epilepsy

Epilepsy is not one, but many complex neurological diseases manifesting themselves by abnormal electrical activity in larger or smaller parts of the brain. According to the newest proposal from the International League Against Epilepsy (ILAE), it is defined as [18]:

- a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure.

While an epileptic seizure is defined as:

- a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.

Epilepsy is diagnosed by a combination of anamnesis and tests such as video-EEG, CT, MRI, chromosome and neuro-metabolic examinations. The foundation for the diagnosis is a profound description of the seizure based on interviews with the patient as well as persons having observed an event. EEG alone can never confirm nor reject the diagnosis, although it stands as a strong indicator. The interviews of observers are essential since the cause and the symptoms may vary a lot between the different epilepsies

as well as seizure types. Some seizures, such as in tonic-clonic epilepsy, involves fierce convulsions of arms and legs, while others, such as in childhood absence epilepsy, merely consists of staring episodes. It is therefore of high importance to classify the epilepsy correctly to [24]:

- Give an optimal pharmacological treatment
- Give guidance on prognosis and recurrence risk
- Assess indication for possible further paraclinical diagnosing
- Assess indication for non-pharmacological treatment (such as diet, surgery, etc.)
- Give guidance on indication for genetic diagnosing
- Obtain international understanding of a given classification

A seizure is caused by an abnormal hypersynchronization of the dendritic potentials. This can be due to lack of neural inhibition or an abnormal high number of excitable cells in a neural column in the cortex. Most likely, the hypersynchronization emerges due to changes in the neurotransmitters or membrane properties. The onset of the seizure can either be *focal* or *generalized*. If focal, the seizure begins at a confined area in a neural network, and is always restricted to a single hemisphere, although it may evolve into a bilateral convulsive seizure. The generalized seizures begin somewhere but are rapidly engaging bilaterally distributed networks [6, 7].

As mentioned previously, a common way to examine e.g. whether the seizure is focal or generalized is by EEG - preferably together with simultaneous video recording of the patient. Both the *interictal* (between seizures) and *ictal* (during seizures) EEG offer important prognostic and classification information. Interictal background EEG frequencies that are slower than normal for age can suggest a structural/metabolic epilepsy, while normal background may suggest genetic or unknown epilepsy.
The etiology is defined as [7]:

Genetic: The epilepsy is most likely a direct result of a known or presumed genetic modification where epileptic seizures are the core symptoms.

Structural/metabolic: The epilepsy is a consequence of a distinct structural or metabolic condition or disease, which has been shown to cause a considerable increased risk of developing epilepsy. Those conditions can be both acquired or genetic.

Unknown: The origin of the epilepsy cannot be determined; it can be genetic or structural/metabolic, but has not yet been documented.

It is impossible to give a general description of the EEG appearance of an epileptic seizure, although often it will increase in amplitude, become synchronous across channels and follow a more deterministic pattern than the background EEG. Onset zone and spread pattern is completely dependent on seizure type.

Stimulation such as hyperventilation, stroboscopic light or anti-epileptic drug tampering might induce epileptic seizures. These methods are all used in the clinic to provoke a seizure. If a seizure is persistent or repeats itself without restitution for more than 30 minutes, the patient is in *status epilepticus*. All types of epilepsy can cause status epilepticus, but especially convulsive types are potentially life threatening. Seizures lasting more than 5 minutes should therefore be suspected to enter status epilepticus and treated increasingly aggressive according to an established standard [45].

1.4 Consequences for the Patients

As stated in the previous section, epilepsy patients as a group is very heterogeneous. Some are newly born and some are old. Some have severe convulsions during a seizure while others barely react to it, some will experience loss of conscience while others do not, and some will undergo progressive retardation while some might even be intellectually stimulated by the seizures. The consequences for patients having epilepsy are therefore diverse.

Patients with poorly treated convulsive epilepsy such as *generalized tonic-clonic epilepsy* frequently suffer from injuries related to seizures [48]. This is the most apparent hazard, although more looming risks are hiding behind the syndrome, as summarized in Fig. 1.1. The constant fear of suddenly having a seizure is the single most crippling aspect and the one that most negatively impacts life span and quality of life for the patients [4]. It entails a high level of anxiety that can lead to stigmatization as well as depression. It often makes the patients feel helpless, and they tend to isolate themselves to avoid the embarrassment

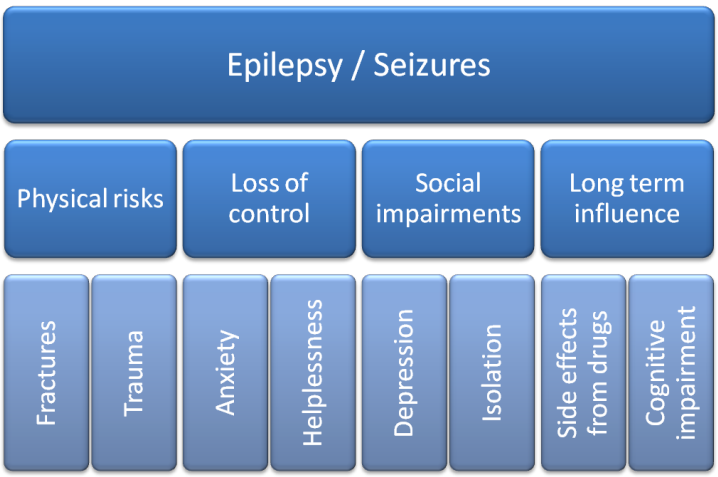


Figure 1.1: Consequences of sudden, unforeseen epileptic seizures.

and danger of having a seizure in public. The depression is associated with a suicidal ideation, and thus a higher suicide rate [22].

Patients having many seizures affecting their conscience (previously denoted complex) such as in *childhood absence epilepsy*, may have learning and attention difficulties. Those problems often result in a poor ability to stay focused on a certain task and patients might be (wrongly) labeled as misbehaving.

Unless the patient has been seizure free for at least one year, he or she is prohibited to drive, and strongly advised against swimming. These are just extra factors that adds to the disability. Approximately 70% of the patients respond to the use of antiepileptic drugs (AEDs), but only 15% of these achieve full control of seizures without side effects [4]. Most disabling side effects are tiredness and memory problems as well as dizziness, mood problems, and concentration issues. The pharmacokinetics and -dynamics of newer drug agents having entered the market during the last two decades have mainly improved the adverse effects, while the number of patients responding has remained the same [9].

Furthermore, it is well known that patients living with medically intractable epilepsy has a risk of *Sudden Unexpected Death in Epilepsy* (SUDEP), defined as *sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy with or without evidence for a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause of death* [32]. Unfortunately, only little is known about how to avoid SUDEP, although factors such as poor seizure control and no nightly supervision are described as risk increasing.

Based on the understanding of the consequences of epilepsy, it stands clear that technological solutions can probably help the various problems. The following section reflects on where an EEG monitor developed by HypoSafe can be of assistance.

1.5 The Role and Interest of HypoSafe A/S

HypoSafe is a relatively new company founded in 2005. They are developing the world's first 24/7 online EEG monitoring device dedicated to diabetes patients unable to feel and respond to a critically low blood glucose level. By warning the carrier before a critically low blood glucose level is reached, the device prevents hypoglycemia with potentially fatal consequences. The device consists of two parts: An inner device with electrode contact points that is implanted in the subcutaneous layer, and an outer device with a processing unit that can be worn behind the ear, see Fig. 1.2. The two devices can communicate through an inductive link, so that no transcutaneous wires are needed. The outer device is able to provide the inner device with power through the inductive link, so that no maintenance is needed for the inner device. It can thus remain implanted for several years.

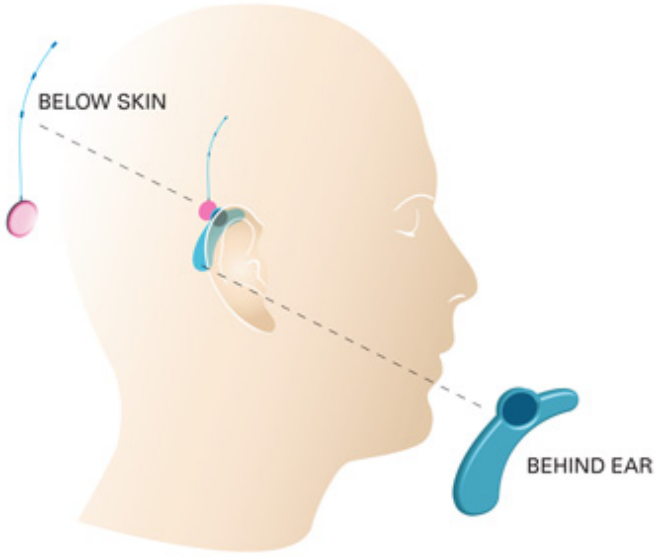


Figure 1.2: A sketch of the intended setup of the HypoSafe device.

Today, EEG is primarily monitored by scalp electrodes attached to the head with a cap or special electrode paste. It is a procedure that takes some minutes, and leaves the patient with wires on the head. HypoSafe has the idea that there is no need for such large uncomfortable systems that are impossible to carry around permanently. By a small procedure, the inner HypoSafe device can be implanted across the temporal lope in just 15 minutes, and after a few days of wound healing it is possible to record EEG instantly simply by attaching the outer device behind the ear.

Although the device is developed for the purpose of diabetes, it is a logical step to investigate the feasibility of using the device for other diseases that are manifested as abnormal cortical behavior and observable by only one or two EEG channels located temporally. The often distinct EEG patterns in epilepsy made it an obvious choice for the next area.

Since the HypoSafe device is able to deliver days and days of continuous EEG data, it is not economically feasible to have a trained expert screening it all for pathological patterns. Instead, an automatic seizure onset detector or predictor should be employed to draw the attention to prominent time periods. Fig. 1.3 describes the possible applications for the HypoSafe device together with an automatic seizure detector or predictor. The value can be seen as three-fold:

1) Monitoring system: By quantification of epileptic events, an objective value for the frequency and duration of the seizures can be computed. These informations together with the time of day the seizures occur can be used by the treating physician to optimize the medication scheme. Instead of the patient and

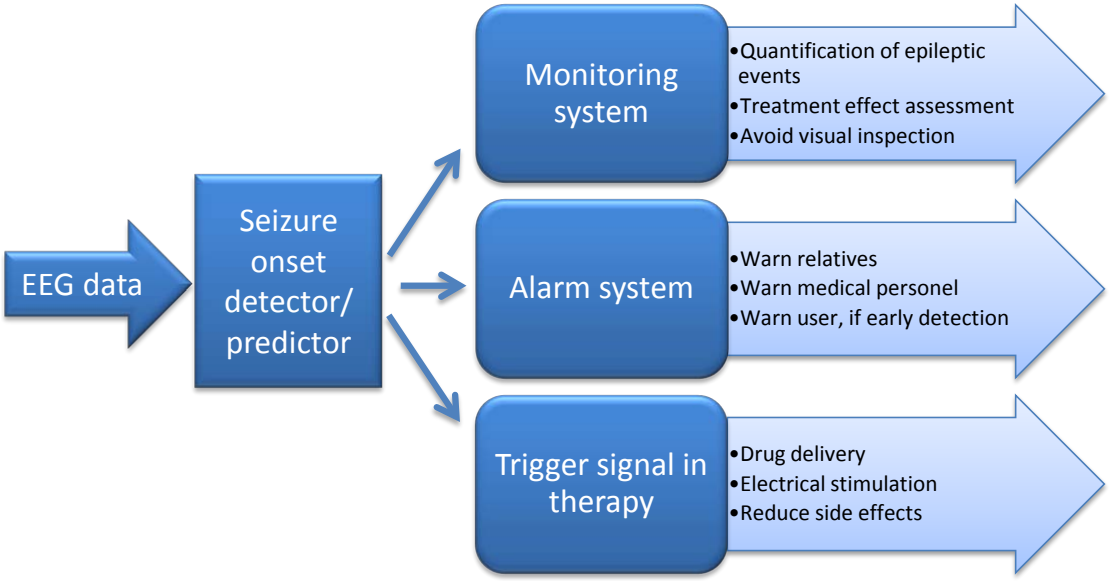


Figure 1.3: Possible applications for an automatic seizure detection/prediction device.

relatives taking a day off at work to go to the hospital, have the EEG electrodes attached and wait for the examination to finish, a measurement with the HypoSafe device can be done at home, as often and as long time as needed without the concern of spending hospital resources. It will cause less inconvenience for the patient, health personal, as well as relatives. The intention is to provide lowered expenses and a better treatment plan.

2) Alarm system: Can be relevant for patients having seizures infrequently, but with a considerable anxiety of ending up in a dangerous or unpleasant situation due to the attack. The alarm could alert a relative or health care personal which could give a reassurance to the patient as well as his or hers family. Especially parents of children with generalized tonic-clonic seizures often report that they cannot sleep if they are not in the same room as the child. An alarm system would allow the child to sleep in his or hers own room, and then the parents could come to assist if the alarm intercepts a nocturnal seizure. Older people can also benefit from an alarm that detects seizures. Imagine an epileptic fit happening at home and the person is physically injured. An alarm could be sent to a responsible person, who could check up on the patient and thus avoid him or her lying paralyzed until a random visit by someone. Finally, if the alarm system was able to predict a seizure, it would render vital importance for a large group of patients with intractable epilepsy as stated in section 1.4.

3) Trigger therapy: A system that delivers a small dose of fast acting anti-epileptic drugs, cools a certain part of the brain, or trigger deep brain stimulation could cease a seizure immediately - hopefully before it really kicks in. The last two methods might help people who do not respond to AEDs, while the first

might help those who are affected by substantial side effects. The drug administration would then only be triggered when actually needed, instead of a continuous dose.

This brings us back to the objectives in the beginning of this chapter:
The feasibility of seizure prediction should be investigated, as it would have the most epoch-making effect on the community. With persuasive seizure prediction, epilepsy patients can be alarmed to prevent dangerous and embarrassing situations and thus hopefully become more confident, extrovert and avoid depression.
For monitoring purposes, a prospective efficient seizure detection algorithm should be identified and implemented, and the algorithm should be optimized to the epilepsy type which is the most prudent for a HypoSafe device.
Finally, as the HypoSafe EEG is based on extracranial EEG, it is of high interest to understand how it relates to the intracranial EEG and how much information is lost due to the transmission through the skull. While this might not result in direct applicable technologies, it provides basic science leading to better understanding of extracranial potentials.

CHAPTER

TWO

PREDICTION OF EPILEPTIC SEIZURES

Most patients with recurring epileptic seizures are affected both physiologically and psychologically. The constant anxiety of suddenly having an epileptic fit can drive the patients into solitude and depression. If it is possible to warn the patient a few minutes or perhaps just seconds before the seizure, he or she would be able to take a whole new set of necessary precautions, and perhaps even do something to prevent the seizure from ever happening.

The current chapter is a supplement to the abstract *Feasibility of Seizure Prediction from Intracranial EEG Recordings* (Appendix A.1) and the conference paper *Patient-Specific Rigorously Methodological Test of the Mean Phase Coherence* (Appendix A.2). The following objectives were defined:

Objectives

- To investigate the feasibility of seizure prediction by relating to the results of other researchers and calculating performance estimations on own data.
- To investigate the performance gain by using a patient-specific approach instead of generic.

After the conference paper was presented at the *International Workshop on Seizure Prediction 4* (IWSP4), a subsequent analysis showed that it was not possible to extrapolate results to continuously recorded data. These results have not been published previously, but will be presented here, together with an analysis of where most researchers make mistakes when they still publish results on seizure prediction and what is needed to correct these mistakes. The chapter will end up with a conclusion on the feasibility of seizure prediction.

2.1 History of Seizure Prediction

The history of automatic seizure prediction dates back to the 1970es although it was not until the 1990es the field gathered wide interest. Measures such as Lyapunov exponents, entropy, or correlation density were justified by their ability to model complicated, apparently irregular behavior of nonlinear complex systems like the human brain. Many of these studies gave enthusiasm toward the ability of predicting seizures minutes to hours before onset [23, 29].

The new millennium was marked by the transition from uni- to bi- or multivariate measures. New research identified the epileptogenic process to be associated with synchronized changes in a network of components spread out over the entire brain [31]. This period was also influenced by the possibility of mass storage of data instead of sample recordings. New assessments of the predictability on long-term datasets challenged the reliability of the optimistic results reported previously [47]. The problem was, that prospective statistical evaluation was often never conducted. Validation of the difference between the preictal and interictal state was not implicit, or an in-sample optimization method lead to heavy overfitting of data [30].

In 2000, the *International Seizure Prediction Group* was formed to address the issue of non-conformity in performance testing. They found that standardization of analysis, data requirements, performance criteria, and nomenclature was needed [29]. Furthermore, it was concluded that large international databases were needed to validate the prediction performance on common datasets.

In recent years, the most innovative step that has emerged, was the idea of probabilistic forecasting [25, 40]. Instead of a deterministic approach, where a predictor decides whether a seizure will occur or not within a given time horizon, a probability for such an event is given. An explicit alarm is thus not raised, instead, the patient is provided with a probability of how likely it is that a seizure strikes within a given interval. The Brier score [8], defined as the average quadratic deviation between predicted probability for an event and its outcome, measures the accuracy of probabilistic forecasting methods. This, together with modifying the classification threshold with circadian changes showed to make seizure prediction significant in 38% of patients with intracranial electrodes [40]. The authors state that there is still a large gap between significant seizure prediction and clinical applicable seizure prediction although they do not elaborate on where this threshold is.

2.2 Results Based on Rigshospitalet Database Summary

In the paper *Patient-specific Rigorously Methodological Test of the Mean Phase Coherence* (see Appendix A.1) we showed that a patient-specific automatic seizure detection algorithm outperformed a generic setup

based on data collected from four patients admitted to the epilepsy monitoring unit at Rigshospitalet (RHEEG database). A significant improvement ($p\text{-}value < 0.05$) of 23% in sensitivity and a decrease of 0.30 false predictions per hour rendered a prediction performance with a sensitivity of 74% and false prediction rate of 0.23/h. For two out of the tested four subjects, the performance was probably clinically applicable.

The results were based on the assumption that the *mean phase coherence*, MPC, between two focal electrocorticographical channels, drops down prior to a seizure as also hypothesized by Mormann et al. 2000, [31]. For details on the implementation and settings see Appendix A.2 or [23]. At the *International Workshop on Seizure Prediction 4* (IWSP4), discussions with some of the leading researchers led to further analysis of data. It was criticized that data were not prospectively collected, and suggested that a surrogate seizure testing approach was used to test for significance [3].

2.2.1 New Assessment of Results

Originally, the RHEEG database for seizure prediction was collected in the same manner as the Freiburg Seizure Prediction EEG (FSPEEG) database. Only seizures where at least 50 min of non-ictal data preceded the onset were included, and at least 24 hours of interictal data that were not within three hours of a seizure were extracted.

At the IWSP4 this sampling method was criticized as discussed later (see section 2.3). Instead data were extracted in full, and reviewed for undetected abnormalities in the EEG. Not less than 12 extra paroxysms (without clinic) were identified in the four patients. Although these paroxysms might not have the same impact on the life of the patient, we do not know how they affect the EEG in the preparoxystic period, and should thus be included for analysis.

Fig. 2.1 shows the periods of recording for each patient, together with the identified paroxysms (with and without clinic) and the calculated *mean phase coherence*, MPC. This is an overview of the entire recordings why the detailed shifts are concealed in the resolution. Thus, we are only able to visually register trends with a duration of at least five minutes. For patient 2 and 3, the MPC seems to be elevated in the beginning of the recording, and for patient 2 and 4 we see an elevation at the end. A large part of the interictal EEG for patient 2 and 3 is extracted from the elevated area which explains why exactly these two patients obtain the best seizure prediction performance. Although one might argue that these two patients are the only two without paroxysms in the beginning of the file, and thus at that time not in a state close to initiate a seizure, it is a too small dataset to base such a hypothesis on. Furthermore, as patient 2 had an elevated MPC level in the end of the recording where multiple paroxysms takes place, the hypothesis of lowered MPC in the preictal period seems weak.

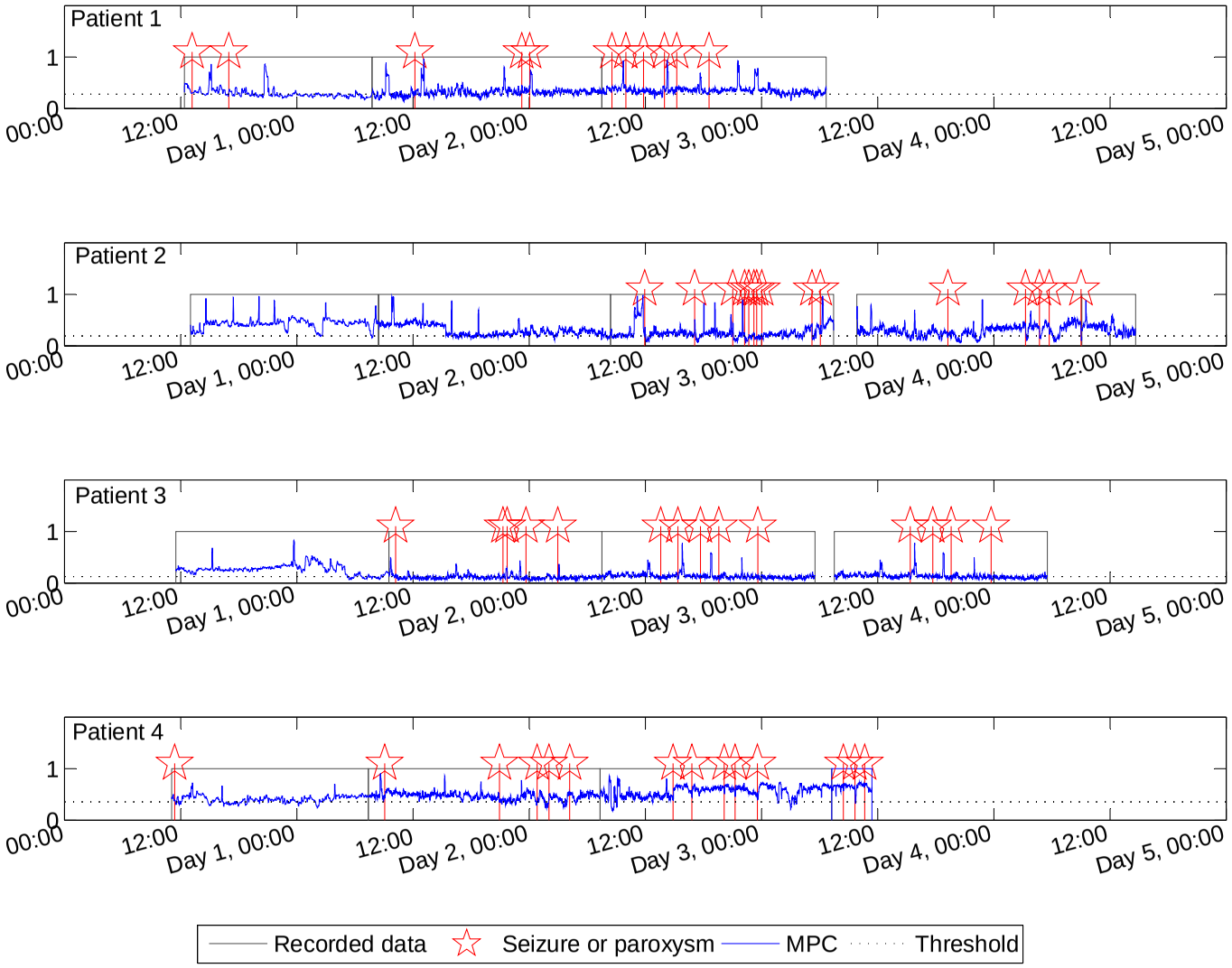


Figure 2.1: Overview of patient recordings in the RHEEG database together with identified seizure or paroxysm onsets and the mean phase coherence for two focal channels.

Besides the visual overview analysis based on Fig. 2.1, a more detail oriented inspection was carried out. For each paroxysm, the preceding 60 minutes of MPC was visually studied. No particular drop in MPC could be identified compared to the interictal period.

Based on the macro as well as micro analysis, it was decided that the data foundation and/or the prediction method was not fit for seizure prediction. Tendencies did point toward some level of predictability for some paroxysms, but a very large database with very long continuous EEG recordings were needed before reliable performance statistics for seizure predictability could be assessed.

2.3 Criticism of the FSPEEG Database

The Freiburg Seizure Prediction EEG database (FSPEEG) is probably the most used database for validation of seizure prediction algorithms. It is still available at http://epilepsy.uni-freiburg.de/freiburg-seizure-prediction-project/eeg-database and at the 2011 and 2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society no less than four and two papers, respectively, based a seizure prediction method and calculations on this database. Unfortunately, multiple issues compromise the quality and credibility of such results:

- Data are not extracted in full. Preictal and ictal periods are cut out and presented individually. 11 out of 87 seizures have a preictal period of less than 60 minutes. Today, it is not agreed upon, whether the preictal period is likely to be 2 minutes or 4 hours [30]. If it is longer than the period given in the recorded files, this cannot be tested. Since the *prediction horizont* can maximally be set to 48 minutes in the FSPEEG database - a potential true preictal event recorded before this period would render a false positive prediction, that cannot be included in tests on the database.
- For 13 out of 21 patients, all seizures are either recorded before or after the interictal data. This means that a potential variation of the EEG due to e.g. state of vigilance or drug withdrawal can confound the results.
- For six of the patients, the interictal period is collected as 24 hours of successive recording. For the remaining patients, periods are removed. This means that the entire circadian rhythm that definitely influence the EEG is not included.
- Sampling frequency is only 256 Hz (512 Hz for one patient). According to the Nyquist frequency, this leaves us with frequencies up to 128 Hz. Recent research have suggested preictal events in the 80-500 Hz range [26] and thus mostly outside the available frequency band. If high frequency oscillations are suitable for predicting seizures, this cannot be tested.

- Data are not continuous. Recordings for 12 of the patients are divided into epochs of 1 hour, each with a gap of 1-4 seconds in between.
- Only a subset of three focal and three extra-focal channels from the recordings are given and those channels were selected retrospectively by neurophysiologists who had knowledge on the entire data file for each patient.
- There is no information on used reference electrode(s). It is therefore not possible to assess the influence by it.
- No postoperative outcome is given (Engel class) which might be related to how predictable the seizures are.

Furthermore, the quality and correctness of the individual seizures might be questioned. In a paper by Aarabi et al., 2009 [1], the FSPEEG database was used to assess the performance of an automatic seizure detection algorithm. They discarded nine seizures and more than 200 hours of interictal data (corresponding to 2/5 of all recordings). In a personal correspondence (see Appendix C) they replied to why the entire database was not used:

"There were a few problems. First of all, the quality of EEG recordings in some patients was not good enough for any analysis. Then, there were some false seizures that were wrongly determined as seizures. After verifying them with our EEG expert, We asked epileptologists in the Epilepsy Center of the University Hospital of Freiburg, Germany, nobody answered, so we had to discard them from our analysis. Regards, Ardalan".

Although the approach of discarding data is highly criticizable, it shows that the group has spend time on evaluating data quality, and found a lot of it unfit for analysis.

2.4 New Large Databases

Section 2.2 and 2.3 showed that seizure prediction research is hindered by limited access to continuous, high quality, well annotated, broad-band recordings from humans. Although a lot of clinical neurology departments worldwide record such data on a weekly basis, previously no joint database has existed. This is probably due to the fact that it is extremely labor intensive to collect, filter and annotate the files.
Recently, two large initiatives have made their data available:

International Epilepsy Electrophysiology Portal (http://www.ieeg.org) funded by the National Institutes of Health, U24 NS063930-01A1 and the National Science Foundation IIS-1050448, centered at the University of Pennsylvania and Mayo Clinic. The portal opened in June 2012. At least 30 complete records

are available currently. Only a limited number of active users have access for now, but soon it will open up for more scientists.

EPILEPSIAE - Evolving Platform for Improving Living Expectation of Patients Suffering from IctAl Events (http://www.epilepsiae.eu/) a EU-founded FP7 eHealth project (Grant 211713). In September 2012 a dataset consisting of 30 surface recordings and 30 intracranial recordings was made available. They have announced that a total of 250 datasets (of which 50 are intracranial) will be made available in 2013. Each dataset provides EEG data for a continuous recording time of about 150 hours (> 5 days) on average at a sampling rate from 250 Hz up to 2500 Hz. Clinical patient information and MR imaging data (most datasets) supplement the EEG data.

2.5 Conclusion

Although seizure prediction seemed very feasible based on the results at the turn of the millennium, more statistical approaches later showed that we are still far from a clinical applicable method. Within the last few months, two large databases with high-quality, long term recordings have surfaced. These will probably boost the prediction society due to two reasons: 1) scientists without a clinical collaborator now have access to data, 2) the individual research groups are able to compare the performance of their prediction algorithms on the same data and thus obtain better estimates of the most promising methods. Unfortunately, at the time being, no papers based on any of the large databases have yet presented results showing clinically applicable seizure prediction results.

The present project stopped focusing on seizure prediction when it became clear that data were too limited to make statistical reliable algorithms. Perhaps when very long-term outpatient data become available, recorded with a device such as the HypoSafe device, we are able to observe true predictors for epileptic seizures.

CHAPTER

THREE

DETECTION OF SEIZURES INTRACRANIALLY

After the automatic seizure prediction project was postponed, automatic seizure detection became the field of interest. Most of the large acquisition systems for routine EEG applications have their own software for automatic detection of seizures. Trying the algorithms in Stellate Harmonie (Stellate Systems Inc., Montreal, Canada) quickly showed some limitations of the system. Most obvious was the lack of an automated approach to select which channels to analyze. If all channels were used, focal seizures without spread might be missed, if a single channel was used, multi-focal epilepsy might miss some seizures and the algorithm would be very sensitive to noise in the signal from that channel.

The current chapter is a supplement to the papers *Automatic seizure detection: going from sEEG to iEEG* (Appendix A.3) and *Channel Selection for Automatic Seizure Detection* (Appendix A.4).
The following were defined as objectives:

Objectives

- To identify the most promising automatic seizure detection algorithm in scalp and intracranial EEG.
- To optimize the algorithm for automatic seizure detection.
- To investigate how channels should be included for optimal automatic seizure detection.

Many of the criticized problems with the FSPEEG database for seizure prediction (see section 2.3), are also true if the database is used for seizure detection evaluation. Still, it was used in our study of algorithm setup differences between scalp and intracranial EEG (sEEG and iEEG) in lack of better. The validity of the core finding: ”which levels in a wavelet transform are optimal to use”, should not be questioned, but the detection performance might be biased.

For the study on channel selection, the Flint Hills Scientific database was acquired [19]. It was, at the time, the most comprehensive publicly available iEEG database.

3.1 Results Summary

In a preliminary literature study, it was found that an approach involving a wavelet transform and log-sum calculation of windowed subbands as features and a support vector machine (SVM) for classification yielded good results for scalp EEG [43]. For details on the implementation and settings see Appendix A.4. When the same algorithm was applied to the focal channels of the intracranial EEG data in the FSPEEG database, the best features included wavelet detail level 1-7 containing frequencies from 1-128 Hz. In the original paper on sEEG, only level 4-7 containing 1-16 Hz were used for detection. Their implementation reached a sensitivity of 91% and a false detection rate (FDR) of 0.22/h [43]. Using the same wavelet detailbands on iEEG resulted in a sensitivity of 86% and an FDR of 0.39/h, but extending the wavelet levels to 1-7 yeilded a considerable improvement to a sensitivity of 96% and an FDR of 0.20/h. The results can be difficult to compare since they are based on two different patient groups, but within the intracranial dataset, an improvement of 10% in sensitivity and 0.19/h in FDR was obtained by inclusion of the wavelet detail bands containing higher frequencies. The performance results were very similar to those reported by others [11, 20].

As mentioned in section 2.3, one of the problems with the FSPEEG database, is that channels are selected and categorized as focal or extra-focal retrospectively. This means that a person with knowledge of the entire dataset has chosen those channels he or she has found most fit for analysis. This is retrospective knowledge that should not be available when optimizing algorithms in a training phase and it preludes the opportunity of online analysis. A prospective way of selecting channels would thus be of high value.

At the IWSP4 the Flint Hill Scientific database with 10 long-term ECoG recordings was released. We acquired this database, and implemented the wavelet transform for feature selection and support vector machine for classification as described in appendix A.4. For optimal selection of channels, several approaches were investigated: 1 and 2) maximum variance during training seizures (*var*) with and without background variance extracted, 3 and 4) maximum entropy during training seizures with and without background extracted, 5) maximum Fisher criterion with seizure data and interictal data constituting the two classes (not shown in paper), 6) maximum components in a principal component analysis (not shown in paper), 7) after choice by a neurophysiologist who only saw the training seizures and interictal EEG, 8) using the retrospectively appointed focal channels by specialists at Flint Hills Scientific, and finally 9) an approach that chooses the channels totally by random.

Best automatic channel selection method was maximum variance during training seizures and the selection made by the neurophysiologist. A sensitivity of 96 % and false detection rate of 0.14/h were obtained for

these two methods. This is an increase of 4% in sensitivity compared to seizure detection using channels recorded directly on the epileptic focus. The optimal number of channels to include in the algorithm is between three and six (see Fig. 6 in Appendix A.4).

3.2 Conclusion

Substantial improvements were obtained when three to six channels were used instead of e.g. one or more than 10. These channels should be chosen by their high variance during seizures instead of the focal onset. Since the mean of an EEG signal is zero, the variance is proportional to the power in the signal. High amplitude, and thus high power during the seizures is expected to provide easier automatic seizure detection. Thus, the finding of high variance as optimal channel selector is not surprising.

Not only have the papers described in this chapter contributed to a more automatized seizure detection approach, it has also contributed with knowledge for the neurophysiologists on how to interpret EEG recordings. It is clear from the findings that the focal channels are not necessarily those with the highest amplitudes and therefore not necessarily most suitable for seizure detection analysis.

CHAPTER

FOUR

AUTOMATIC DETECTION OF CHILDHOOD ABSENCE EPILEPSY SEIZURES

In the previous chapter, efficient methods for feature extraction and classification were identified. Even though a lot of groups around the world are working on optimization of automatic seizure detection, it seems as though only few plan to incorporate their software with own or collaborators hardware. The current PhD project set out to investigate how such an integrated system could work. In this chapter, preliminary steps toward a surface HypoSafe monitoring device and algorithm are explained.

The current chapter is a supplement to the paper *Automatic Detection of Childhood Absence Epilepsy Seizures: Toward a Monitoring Device* (Appendix A.5).
The following were defined as objectives:

Objectives

- To identify a patient group suitable to gain from a HypoSafe monitoring device.
- To identify, extract and anonymize EEG recordings from this patient group available in the database at the Department of clinical neurophysiology, Rigshospitalet.
- To optimize the feature extraction and classification routine for these recordings and investigate which channel that gives the best results if only a single channel is used.
- To evaluate the feasibility of monitoring outpatients with a seizure detection algorithm.

This chapter constitutes the applied science in the dissertation. The objectives originate directly from the interest of HypoSafe A/S. It will therefore follow a form where prospective patient groups are investigated by literature study and interviews. A clinical pilot study then provided the foundation for a final outpatient study. In the end of the chapter, a reflection on how health care personal might employ information given by the HypoSafe device is given.

4.1 Patient Groups with Monitoring Benefits

Like most other published algorithms, the method for automatic seizure detection explained in chapter 3 does not focus on a specific patient group other than it is epilepsy patients monitored intracranially in an epilepsy monitoring unit. This seems to be undesirable as the seizures have very different morphologic appearance in the EEG. For that reason, a primary group suitable to gain from a HypoSafe device should be identified. A literature study together with discussions with, among others, chief physician, PhD, MD Troels W. Kjær from Department of Clinical Neurophysiology, Rigshospitalet, chief physician, PhD, MD Sándor Beniczky from the Danish Epilepsy Center, Dianalund and professor, PhD, MD Peter Uldall from Pediatric Department, Rigshospitalet led to identification of three potential groups of epilepsy patients with a probable need of an unobtrusive monitoring device:

Childhood Absence Epilepsy (AE): Absence epilepsy is a rather common type of epilepsy that occurs in children between the age of 4-10 years. Seizures are characterized by being brief (approximately 4-20 s) but frequent. Some patients experience hundreds a day. The children do not experience the absences themselves as they involve severe impairment of consciousness. This means that the children are often having attention deficits and thereby also learning difficulties. Diagnosis is made upon history of absence seizures and the observation of approximately 3 Hz spike-and-wave discharges in a standard EEG. Those discharges occur simultaneously all over the brain, although the amplitude is known to be higher in the frontal region [39]. Parents and other observes are often extremely underestimating the true number of seizures [27].

Prognosis is excellent in well-defined cases with most patients growing out of their epilepsy after a few years. The purpose of medication is to eliminate or reduce the frequency of the absence seizures, without causing side-effects more serious than the epilepsy itself. There is often a correlation between the number of discharges and size of medication dose. It is debated how long a medication scheme must be continued before an off-medication trial period should be conducted [36]. Phasing-out of the anti-epileptic drugs is often initiated after two years of seizure freedom. EEG confirmation of no seizure recurrence is recommended.

Currently there are about 5000 children with absence epilepsy in Denmark with approximately 1500 new cases every year. Each child is followed by specialized clinics to assess the state of their epilepsy. A monitoring device will give an objective account of the frequency, duration, and time of day the paroxysms occur, leading to a hopefully better medication scheme.

Continuous Spikes and Waves during slow Sleep (CSWS): An epilepsy type often with a partial-onset. Occurs in children between 4 and 12 years of age. It is characterized by abnormal nocturnal EEG patterns without clinic. The patients outgrow the abnormal patterns, but have undergone a severe retardation while it lasted. Parents are thus often willing to undergo inconvenient examinations to ensure optimal treatment.

Early medication is recommended to prevent cognitive deceleration.

Today, patients are monitored twice a year. A more frequent monitoring will probably be of high value for more optimal anti-epileptic drug dosing. There are perhaps only 50 CSWS patients in Denmark.

Temporal Lobe Epilepsy (TLE): A partial-onset epilepsy that can show secondary generalization. Partial-onset epilepsies account for about 60% of all adult epilepsy cases, and TLE is the most common single form causing refractory epilepsy. Patients can be of any age, although children and elderly have much higher prevalence. In order to assure correct diagnostics and choose the right treatment regimen the most complex patient cases requires hospitalization for 14-30 days. It will have a huge impact for the treatment resistant patients if they have an alarming device that can inform a relative or health care professional when a seizure is detected. Most drug resistant TLE patients would probably be interested in such a device.

Furthermore, the device is of high interest for monitoring purposes. Since many TLE patients do not experience the seizures themselves, an objective account of the frequency, duration and typical time of day of seizure occurrence, could provide a better consultation and perhaps optimization of medication scheme. At the Danish Epilepsy Center they have approximately one TLE patient in their epilepsy monitoring unit every week.

4.1.1 Evaluation of Primary Patient Group

It is believed that a single channel device is sufficient to monitor all of the above diseases, although CSWS and TLE have a partial onset where the electrode should be placed above that part of the brain. For CAE and CSWS the device should only be used for offline assessment of seizure activity. The heterogeneity between EEG appearances is probably higher in the TLE group, making it harder to develop a generic algorithm for all patients. There are only very few patients with CSWS. Absence seizures are those with the most distinct onset and termination.

With all of the above facts considered, the focus was chosen to be on CAE. Since the type of epilepsy is in the softer end of the scale, and the patients are children, it was considered to much of an procedure to implant the subcutaneous electrodes. A surface device with electrodes placed on the scalp was instead rendered feasible.

Based on recordings extracted from the database at Department of clinical neurophysiology, Rigshospitalet, an assessment of where surface electrodes should be placed and how well paroxysms can be detected was undertaken. This is the study described in the paper: *Automatic Detection of Childhood Absence Epilepsy Seizures: Toward a Monitoring Device* (Appendix A.5).

4.2 Clinical Performance Summary

The algorithm architecture with a log-sum of the wavelet coefficients in different detail bands and a non-linear support vector machine for classification, as found effective for seizure detection in the previous chapter, were implemented (see Appendix A.4 and A.5). In the database at the Department of clinical neurophysiology, Rigshospitalet, 20 patients with CAE were identified. A total of 11 hours and 23 minutes of EEG data were extracted containing 125 paroxysms lasting more than 2 seconds. Using only the F7-Fp1 channel 97.2% of paroxysms could be detected without any false detections. Fig. 4.1 shows a paroxysm together with the gold standard registration by a neurophysiologist, and the automatic detection by the algorithm. By comparison of the results, the latency and difference in length between the two can be determined, see Fig. 4.2. The algorithm was able to detect paroxysms only 0.74 ± 0.87 s after the gold standard onset, and it estimated the mean length to be only 1.4 ± 2.1 s different from what the neurophysiologist found.

The high performance results are based on two important findings: 1) The homogeneous group of childhood absence epilepsy patients are exceptionally well suited for automatic seizure detection due to a very well defined high amplitude spike-wave pattern containing both low and high frequencies distinguishing it from most artifacts. 2) Inclusion of high frequency detail bands in the wavelet transform. Despite the fact that only little high frequency content is transmitted through the skull, it still stood out from the background EEG during paroxysms. Those high frequency detail bands have usually not been included by others working with similar algorithm architectures for scalp EEG [43, 44].

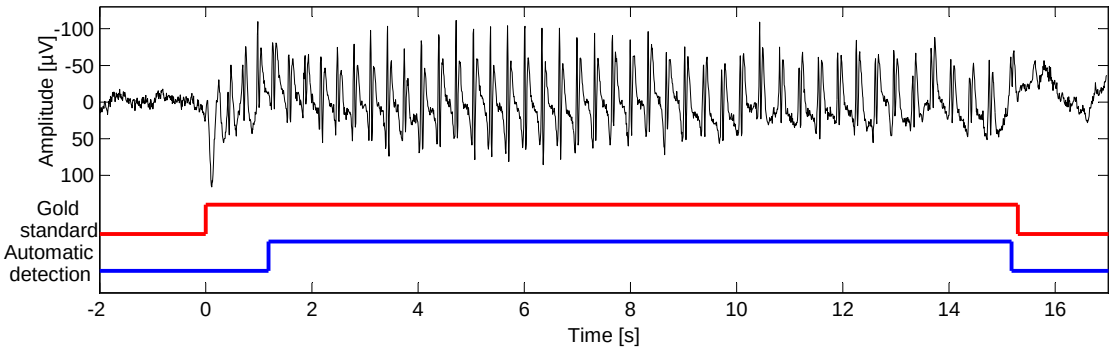


Figure 4.1: A paroxysm from channel F7-Fp1 obtained in the ambulatory study on patient 6. When the red line is elevated the neurophysiologist has registered a paroxysm. An elevated blue line indicates the automatic detection by the algorithm.

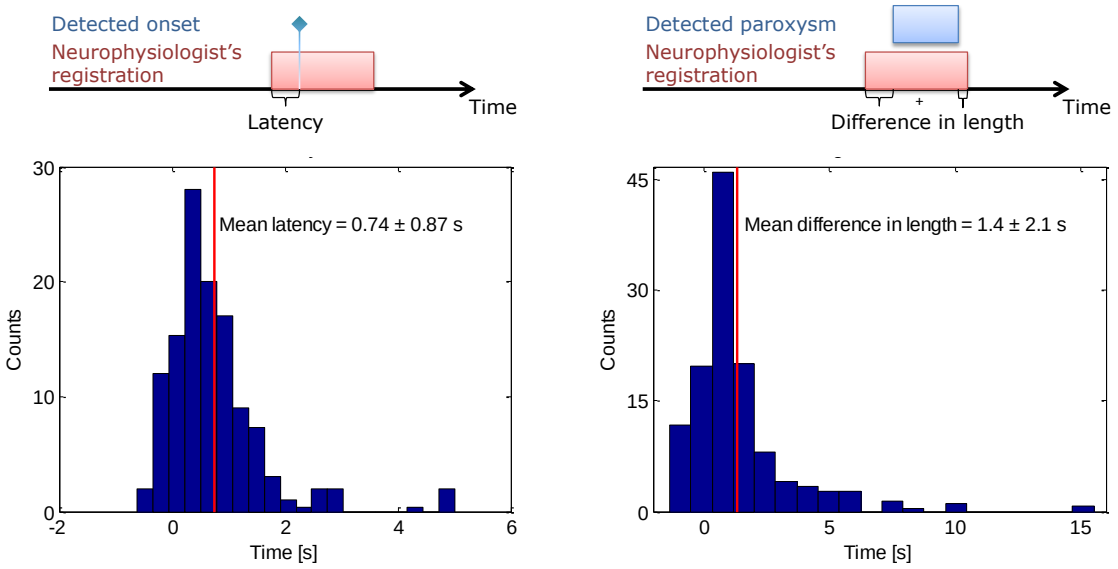


Figure 4.2: A comparison between the algorithm detection and the gold standard registration by a neurophysiologist.

4.3 Feasibility of Outpatient Monitoring

The results given in the previous section are obtained on clinical data with only few artifacts. Resources are not available at the hospitals to have the patients admitted often for monitoring, neither is it feasible to have the patient monitored for more than the duration of a standard EEG recording of 30 minutes. In the cases where more frequent monitoring would benefit the treatment of the patient, a device that is worn on an outpatient basis an entire day would provide better insight on frequency, duration and time of day the epileptic paroxysms occur. Since there are no resources to screen such long-term monitoring recordings, an automatic seizure detector with high performance and robustness against noise should be applied.

This section describes how preliminary outpatient measurements were performed and presents an assessment of obtainable sensitivity and false detection rate. Since it was difficult to find enough childhood absence epilepsy patients to include in the study, we chose to include all children admitted with or for investigation of idiopathic generalized epilepsy. Everyone in this group of patients exhibits absence seizures although these seizures might be atypical or develop into generalized tonic-clonic seizures.

Table 4.1: Results of previously published studies on ambulatory automatic absence detection. n.s. is not specified.

Study	# of patients	Time recorded	# of channels	Minimum parox length	Sensitivity [%]	FDR [/h]
Carrie & Frost [10]	5	10-12 h	1	3 s	94.8	0.16
Ehrenberg & Penry [17]	7	12 h	4	n.s.	85	0.10
Koffler & Gotman [28]	8	20 h	3	n.s.	70	2.4-10
Principe & Smith [37]	6	6 h	1-4	3 s	91	0.24
Quy et al. [38]	n.s.	24 h	4	1 s	91.5	n.s. (6%)
Xanthopoulos et al. [49]	6	2-24 h	16	2.1 s	94.6	1.07

4.3.1 History of Ambulatory Automatic Absence Detection

Six studies investigating the feasibility of ambulatory monitoring of absence epilepsy patients were identified [10, 17, 28, 37, 38]. Their results are summarized in Table 4.1. It is remarkable that the first five dates back to the seventies or eighties, while only the last one is within recent years. Other newer studies such as [2, 44] have only tested their algorithms on clinical standard EEG data. As mentioned earlier, those data are almost free of artifacts such as from movement and chewing. Neither do they represent an EEG originating from the natural impressions in the patients everyday life. A present-day study with an improved data acquisition systems available is therefore of high relevance.

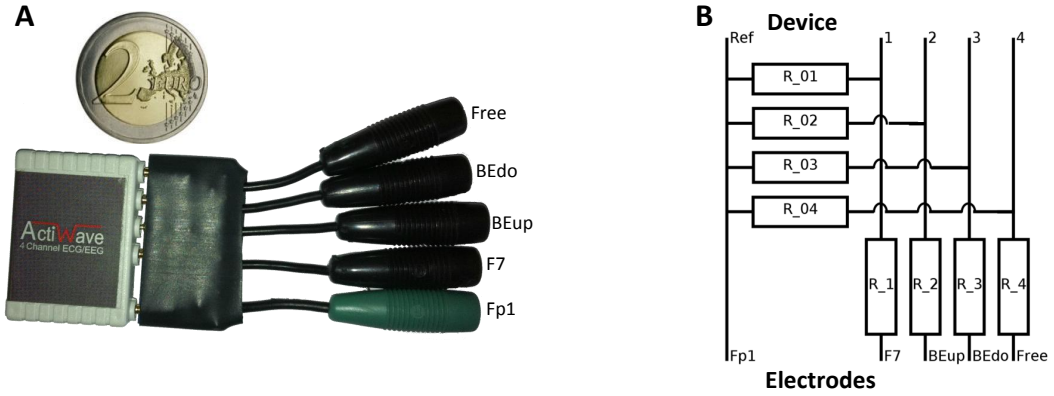


Figure 4.3: A) The ActiWave device including a transformer to reduce voltage by half. The green connector is the reference to the rest of the connectors. B) The electrical circuit in the transformer. The fourth channel was not used in the experimental setup. BEup and BEdo refers to electrode positions Behind the Ear, up and down.

4.3.2 The ActiWave Device

The ActiWave device (CamNtech, Cambridge, UK) was found suitable for outpatient monitoring due to its small size, see Fig. 4.3A. It is possible to record four channels, all referenced to the same electrode. The frequency band spans from 0.3 to 50 Hz and the dynamic range is 400 μV peak to peak. A preliminary recording on an absence epilepsy patient showed cutting in the signal due to very high amplitude signals during paroxysms. Therefore, a transformer (based on resistors, not coils) was designed to reduce the voltage by a factor two, see Fig. 4.3A and B. When all resistors have the same resistance, halving of the voltage, U, can be shown by Ohm's law, see Fig. 4.3B:

$$\begin{aligned} I_{Fp1-F7} &= I_{Ref-1} \Leftrightarrow \\ \frac{U_{Fp1-F7}}{R_1 + R_{01}} &= \frac{U_{Ref-1}}{R_{01}} \Rightarrow \\ U_{Ref-1} &= \frac{R_{01}}{R_1 + R_{01}} U_{Fp1-F7} \\ &= \frac{1}{2} U_{Fp1-F7} \end{aligned} \tag{4.1}$$

The resistance was chosen to be 220 kΩ. This is much lower than the device input impedance of 10 MΩ and much higher than usual skin impedance of approximately 5 kΩ. The voltage devision will thus only occur over the resistors. It is important to investigate whether the resistors cause too much noise in the recording. The noise power from the resistors, R, is equal to the noise power from the parallel connection of the two. So $R = R_1||R_{01} = 220\text{k}\Omega||220\text{k}\Omega = 110\text{k}\Omega$. The voltage variance, $\bar{v_n^2}$, is then found to:

$$\begin{aligned} \bar{v_n^2} &= 4k_B T R \\ &= 4 * 1.3807 * 10^{-23}\text{J/K} * 293.15\text{K} * 110\text{k}\Omega \\ &= 1.82 * 10^{-15}\text{V}_{\text{rms}}^2/\text{Hz} \end{aligned} \tag{4.2}$$

where k_B is Boltzmann constant and T is the ambient temperature in Kelvin set to 20°C. More interesting is the noise voltage, v_n, in a given band width, BW. For the ActiWave device this is in the 0.3 - 50 Hz band due to analogue filters:

$$\begin{aligned} v_n &= \sqrt{\bar{v_n^2} * BW} \\ &= \sqrt{1.82 * 10^{-15}\text{V}_{\text{rms}}^2/\text{Hz} * (50 - 0.3)\text{Hz}} \\ &= 301\text{nV}_{\text{rms}} \end{aligned} \tag{4.3}$$

With the transformer attached, the dynamic range is 800μV. When measuring with 10 bits precision, the discrete voltage resolution is $800\mu\text{V}/2^{10} = 0.78\mu$V. As the thermal noise in the resistors is assumed

white, the resistor noise contribution is small compared to e.g. the discretization noise. When specific frequency bands are used, BW in equation (4.3) becomes smaller so the resistor noise will have even less impact.
Furthermore, the transformer has the property that it converts the 1mm connector pins on the device into 1.5mm connector pins as used as standard for electrodes delivered from Ambu (Ballerup, Denmark).

The ActiWave device has only 24 Mbytes of memory available. If sampling frequency is set to 128 Hz and resolution to 10 bit, the memory restriction only allows 14 hours and 33 minutes of recording on three channels. If 24 hours of EEG is needed, the device must be switched to a new one during the recording.

4.3.3 Experimental Setup

An application to the Regional Research Ethics Committee regarding repeated long-term EEG monitoring of idiopathic generalized epilepsy patients was accepted (Danish application in Appendix B.1). In the protocol, it is described that children with absence epilepsy are asked to participate. They must wear the ActiWave device for 24 hours during four independent days within approximately one month, see Fig. 4.4.

Two Ambu Neuroline 700 electrodes are attached to the patients forehead (approximately at position Fp1 and F7 according to the international 10/20 system), and two behind the left ear, see Fig. 4.5. The Ambu Neuroline 700 electrodes were chosen due to their small attachment area but still good contact to the skin. The positions of the electrodes were based on the result of the clinical as study, as well as the interest of HypoSafe to investigate if a conceal device behind the ear could be sufficient. Although the electrode placed at Fp1 was used as reference to all orther electrodes, the deviation behind the ear can be obtained

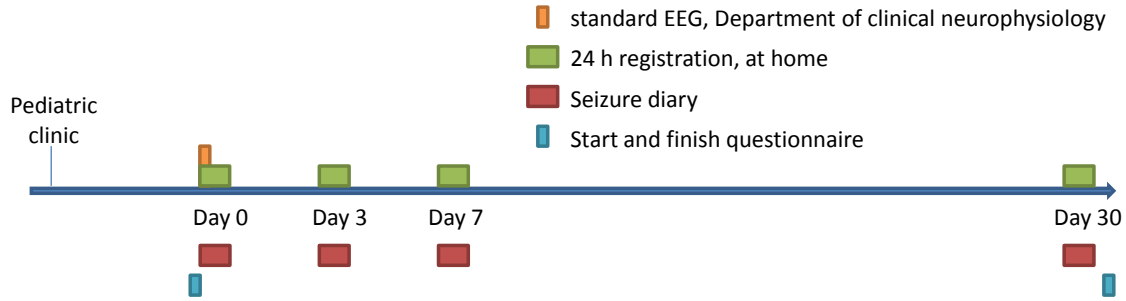


Figure 4.4: Sequence of events in the outpatient study. The patient is referred by the pediatric clinic at Rigshospitalet. At the first day of the study, he or she appears at the Department of Clinical Neurophysiology for a standard EEG. The ActiWave device is attached and records simultaneously. The ActiWave device remain attached after the standard EEG recording and keeps recordings until the following morning. Another three days of recording with the ActiWave device should be performed within approximately one month. Study days given in the figure are only indicative.

mathematically. Electrodes are mounted by a specialist in the morning and removed the following morning by the patient him- or herself. The only restriction the patients is asked to follow is not to expose the device to water, otherwise they should retain a normal day.
Data are sampled at 128 Hz with 10 bit precision. Although the results from the clinical evaluation showed that frequencies in the 50-100 Hz could contribute to improved detection performance it was not possible to increase the sampling rate due to memory shortage. The device furthermore had a nonadjustable analogue low-pass filter at 50 Hz, so the gain of a higher sampling frequency would be limited.

The algorithm architecture described in *Automatic Detection of Childhood Absence Epilepsy Seizures: Toward a Monitoring Device* (Appendix A.5) was used for training and testing on each patient separately. Although a generic algorithm should be sufficient [16, 35], data were too scarce to train and test such a model. Paroxysms registered during the first day of recording were used for training of the model together with 10 times as many interictal epochs. Afterwards, the same recording was used for classification. All false positive epochs were included in an updated model. This model was then applied to the remaining unknown data (the test set). Performance results are only based on the latter test.
Only the channel corresponding to Fp1-F7 was used for analysis as it was found best for automatic detection in the clinical study [16].

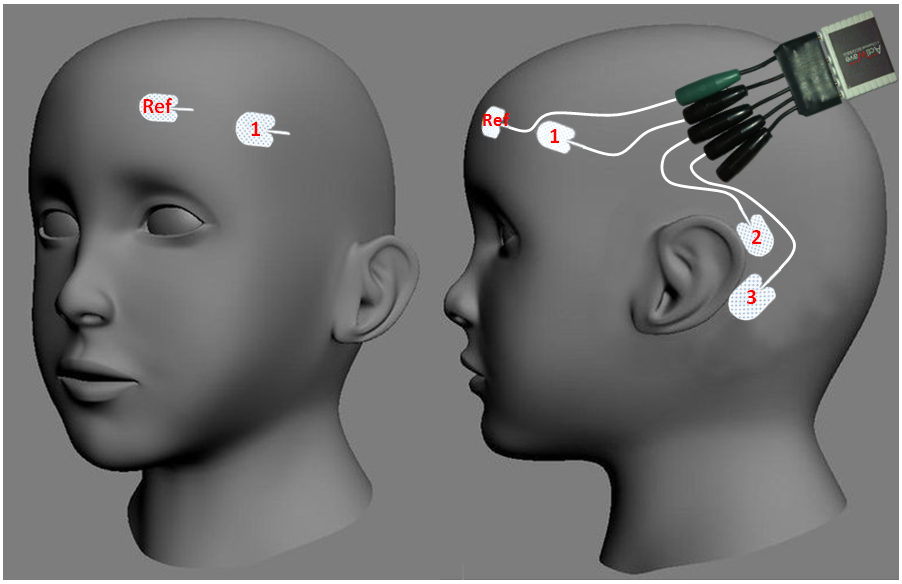


Figure 4.5: Illustration of electrode placement on head. Ambu Neuroline 700 electrodes were used. Ref-electrode is approximately placed at Fp1 and 1-electrode at F7. Electrodes 2 and 3 are placed behind the upper part of the ear (BEup) and behind the lower part of the ear (BEdo). Head model made by Ben Cole.

Table 4.2: Patient specifications in the study with repeated long-term EEG monitoring. HV is during or up to three minutes after *hyperventilation* and PS is during *photic stimulation*. parox. is *paroxystic activity* and n.ab. is *nothing abnormal*.

Patient	Age	Gender	HV	PS	Time Recorded	Note
1	11	M	parox.	n.ab.	3 days 2 h	
2	15	F	parox.	n.ab.	3 days 5 h	Atypical absences
3	5	F	n.ab.	n.ab.	20 h	Epilepsy but no absences
4	14	F	n.ab.	n.ab.	3 days 23 h	No paroxysms detected
5	8	M	n.ab.	n.ab.	23 h	No epilepsy
6	11	F	parox.	n.ab.	2 days 17 h	
7	16	M	n.ab.	n.ab.	3 days	No paroxysms detected

During the monitoring, parents were asked to be extra aware of absence seizures and note in a seizure diary if they observe any. They were also asked prior to the beginning of the study what they expect to gain from the study, how bothered the child is of the seizures, and how bothered the parents are. After the fourth and final recording parents are asked how they think the study went, if they have gained what they had hoped for, and how bothered the child was by the device due to psychological and physiological issues (annoyed by wires, itching at electrodes etc.).

4.3.4 Results

A total of seven patients (three male) were included in the investigation before the deadline of this dissertation, see Table 4.2: one did not have epilepsy, one was diagnosed with an epilepsy type not containing absence seizures, two were well medicated and showed no absences during the recordings, and one showed atypical absences during the recording. This left us with two patients to test the automatic seizure detection algorithm on. As this population is very small, the results are reported as two case studies.

Patient 1 is an 11-year-old male with newly diagnosed absence epilepsy. For the first recording he had still not begun medication. Parents reported that he had a few absences a day but not everyday. Results from this patient are also reported in [16], see Appendix A.5. Patient 6 is an 11-year-old female with medication resistant CAE. Parents reported that she had one absence a week.

Table 4.3 summarizes the results for each of the two patients. If the test results are pooled, a sensitivity of 90% and a false detection rate of 0.12/h is obtained. This results in a positive predictive value of 81%. For the clinical data the sensitivity was 97.2% without any false detection. The positive predictive value was thus 100%.

Table 4.3: Algorithm performance after monitoring on two patients in their every day living. Results are given as patient 1/patient 6. The fourth day is not available (NA) for patient 6. Supervision time is the time spend for one or two parents together with the child during the recording.

Day	Gold-Standard Detections	Parents' Detections	Supervision Time [h]	True Positives	False Negatives	False Positives
1	9/22	0/1	8.6/3	*All paroxysms used for training*		
2	18/14	0/0	9.2/3.3	17/14	1/0	1/3
3	2/16	0/1	5.8/9.8	2/13	0/3	1/7
4	0/NA	0/NA	11.6/NA	0/NA	0/NA	0/NA
Total	29/52	0/2	35.2/16.2	19/27	1/3	2/10

For the two patients, a total of 139 hours and 10 minutes of EEG was recorded. The time recorded was less than (4 days + 3 days)·24h = 168h due to involuntary detachment of electrodes during night and voluntary early detachment of electrodes in the morning prior to recording of an entire 24 hours.

In the recording period 81 paroxysms lasting longer than two seconds were identified by visual inspection of the EEG corresponding to 0.58 paroxysms/h. The parents' supervision time amounted to 51.4 h in which only two paroxysms were observed. This corresponds to a rate of 0.04 paroxysms/h. Assuming that the paroxysms occur uniformly distributed over the entire day, the parents only detected $\frac{0.04\frac{parox.}{h}}{0.58\frac{parox.}{h}} \cdot 100\% = 6.7\%$ of the paroxysms occuring under supervision, and only $\frac{2parox.}{81parox.\cdot\frac{(4days+3days)\cdot 24h/day}{139.2h}} \cdot 100\% = 2.1\%$ of the total number of paroxysms, when correcting for the missing periods without measurements. The 6.7% detection rate is comparable to an earlier study by Keilson et al. [27] who found that only 6% of daytime paroxysms lasting longer than three seconds were detected by the parents.

According to the questionnaire, three out of seven patients were displeased by wearing the electrodes and ActiWave device. The parents reported though, that often it was only for the first 15 minutes after it was mounted. After that, the child almost forgot about it for the rest of the day. For those children with a positive attitude towards the device, one 11-year-old boy said he looked forward to show it to his friends in school, and a 14-year-old girl would use it to tell about her disease at her new school.

All of the parents reported that they were pleased with participating in the study. For the parents of the children where no paroxysms were found, they were pleased to be assured that their child was well medicated. For the others, one parent was surprised that the child was also having paroxysms at night. And one family, who only thought their daughter had one seizure a week, was pleased that further tests for a metabolism disorder were initiated when it was found that she actually had up to 20 paroxysms a day. Finally, one parent reported that she found her daughter to be more present after paroxysms detected in the EEG led to an increase in medication dose.

4.3.5 Discussion

The performance of outpatient monitoring was much better than previous studies, but somewhat worse than expected. Several issues should be considered though before accepting the results. First of all, it should be acknowledged that this investigation was only preliminary. No effort has yet been put into investigating optimization issues when applying an algorithm developed on clinical data onto ambulatory data. There were obvious artifact issues that should probably be taken care of before feature extraction. Furthermore, the results are based only on two persons. Even though a patient-specific approach was used, data included for training of the models was probably too sparse. When more patients are included in the study, better models can be obtained.

The third study day for patient 6 was contaminated by a lot of white noise probably due to a bad electrode contact. This day was responsible for the majority of false registrations, i.e. three false negative and seven false positive registrations. This observation has led to more rigid investigations of electrode contact quality after attachment to the patient. It has also led to design changes in the device developed by HypoSafe A/S. The specific changes are confidential but relies among other things to electrode attachment and standardization of electrode distance.

Patient 1 started medication after the first examination day. On day two he had just started medication two days previously, so no effect was seen. On day tree (13 days after drug initiation) a drop in number of paroxysms was identified, and on the final recording day (32 days after drug initiation) no paroxysms were recorded. This is the text book example of how a well treated patient should react. Although the extra long-term investigation did not lead to any change in medication, it assured the patient, parents and physicians that the treatment was effective.

According to the questionnaire answered by the parents, it does seem as though the ambulatory recordings are equally benefiting the patient as well as the parents. The children do not acknowledge the absences themselves, so most often they are uncomprehending to what happens to them. They feel intimidated by a diagnosis affecting their mind, and especially during the pre-teen and teenage years, a self awareness oppose the enthusiasm towards wearing a device that might contribute to a sickening [5]. Even though the children do understand that a quantification of paroxystic events might help them, many will rather ignore the disease. Therefore, a lot of the pressure lies on the parents, who naturally are very interested in how the status of the epilepsy is for their child.

Further studies are needed before optimal models can be developed and we can reliable assess the performance of an automatic seizure detection algorithm on ambulatory data. The higher quality of the measurements, the more likely it is to obtain performances close to those obtained in the clinic.

4.3.6 Decision Support System

Although it is believed that the overall performance can approach the clinical performance when more and better data are obtained, it is not the idea that the treating physician should never see the paroxysms. First of all; the physician should validate the detected paroxysms as long as the performance has not been shown to be perfect. Secondly; information about time-related development of a paroxysm can provide knowledge to the physician about the state of the epilepsy. For this purpose, a graphical user interface was developed as seen in Fig. 4.6. In the upper part of the figure, it is possible to evaluate the paroxysm activity based on the number of paroxysms per hour. The blue accumulation area is found by cross correlation between a Hanning window with a width of one hour and the detected paroxysms. If the red stars representing detected paroxysms are pressed, the corresponding EEG trace is plotted in the window below. In the lower part of the figure, it is possible to follow the trend in the number of detected paroxysms over time. In untreated cases, the number of paroxysms a day can easily be above 100. The goal is to archive seizure freedom if it is possible without the side effects causing more harm than the paroxysms.

4.4 Conclusion

An analysis of patient groups likely to benefits from a HypoSafe device showed that there is a solid potential for continuous monitoring. In particular the group of patients suffering from idiopathic generalized epilepsy would probably obtain a more optimal treatment by a higher degree of supervision of their EEG.

In a clinical study, the optimal placement of electrodes on the scalp was investigated, and the performance estimated. 97.2% of the 125 paroxysms lasting more than two seconds were detected correctly without any false detections when analyzing channel F7-Fp1. The missed paroxysms all happened during dozing and had an irregular pattern compared to the rest of the paroxysms. This study had the advantage of very few artifacts in the recordings.

A preliminary analysis of an ongoing study on outpatients was not able to obtain the same results. More data are needed before a final conclusion on the performance can be obtained. With a large database of paroxysms with and without polyspikes as well as spike-wave frequencies between 2.5 to 6 Hz would render a better model. Preprocessing algorithms to recognize artifacts could probably also improve the performance.

Compared to the previous chapter, better performance of seizure detectability was archived on childhood absence epilepsy patients with only a single channel than on the various epilepsy types used previously. The fact that a one-channel, generic algorithm on sEEG in this chapter can outperform a three-channel, patient-specific algorithm on iEEG in chapter 3 shows how heterogeneous the different epilepsy types are.

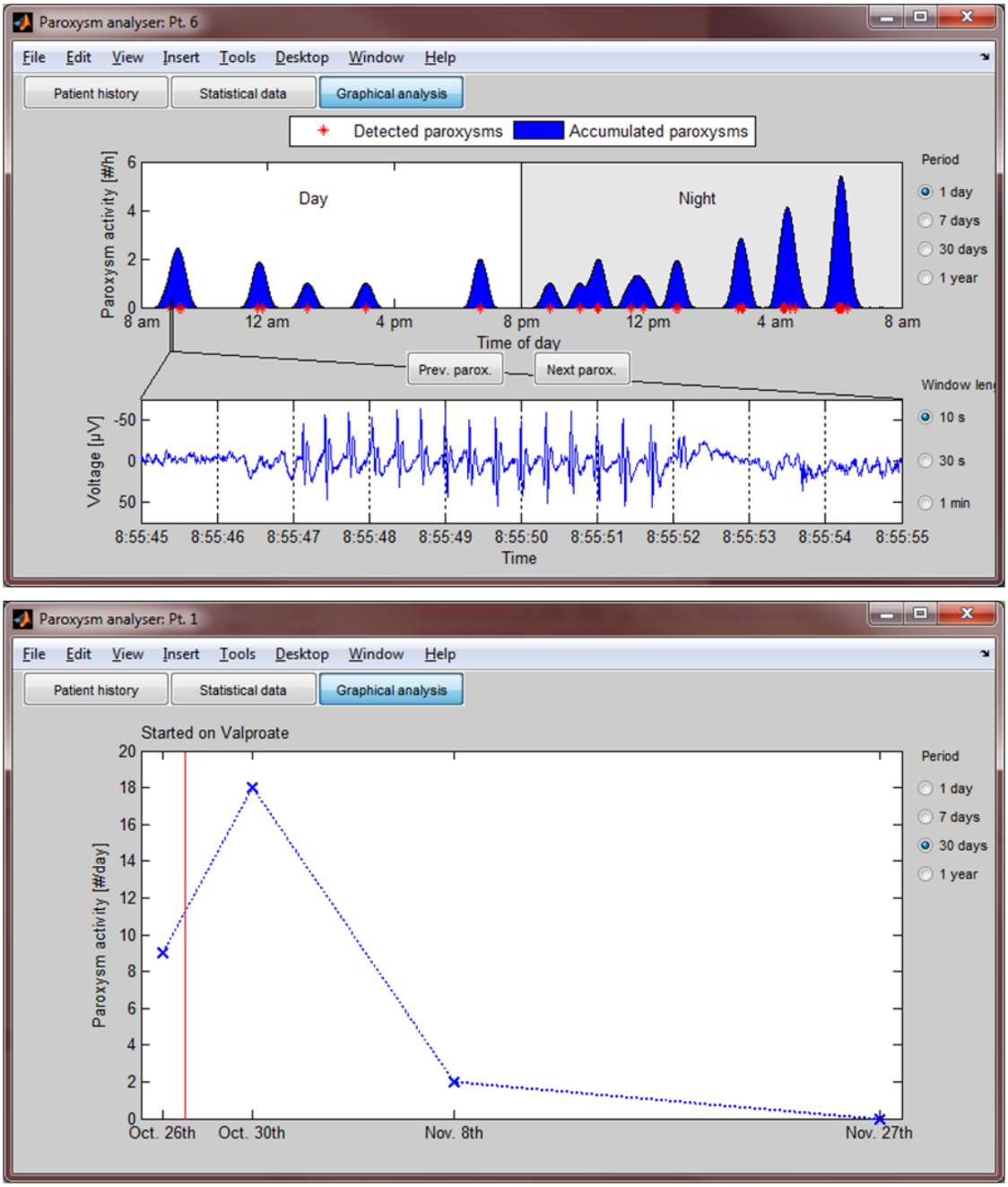


Figure 4.6: A graphical user interface to analyze detected paroxysms. In the top figure (based on the first study day on patient 6), the physician can press the paroxysms marked as red stars in the upper window and validate the detection, as well as understand the time-related development of the paroxysms. In the bottom figure (based on all recordings of patient 1), the number of daily detected paroxysms are presented as a function of time. These figures are for the time being based on the detections made by the expert reviewer.

This should therefore always be taken into account when comparing different automatic seizure detection algorithms.

CHAPTER

FIVE

LINK BETWEEN INTRACRANIAL AND EXTRACRANIAL EEG

Anyone who has seen EEG recorded intra- and extracranially knows that there is a difference between the two. The surface EEG has empirically revealed itself as an efficient diagnostic tool for neurological diseases, despite the fact that the underlying cerebral substrates of the recorded signal are mostly speculative. As the HypoSafe device is recording subcutaneously, it is of great interest to investigate whether it is possible to describe the difference between the EEG recorded under and above the skull.

The current chapter is a supplement to the papers *Correlation Between Intra- and Extracranial Background EEG* (Appendix A.6) and *Subdural to subgaleal EEG signal transmission: the role of distance, leakage and insulating affectors* (Appendix A.7).
The following were defined as objectives:

Objectives
- To estimate how far from an extracranial EEG channel intracranial EEG is coherent.
- To estimate the cortical accumulation area of an extracranial EEG channel.
- To investigate the influence of frequency dependent attenuation over distance.
- To estimate the influence of electric leakage through the craniotomy and insulating effect of subdural grids.

Investigational issues that did not fit into the papers will be given in details and results will be summarized. Finally, a reflection on possible investigations that can extract further information based on the available dataset (described in Appendix A.6) is given.

5.1 Investigational Issues

The propagation of electric activity between the cerebral cortex and the scalp has previously been modeled [21, 33, 34]. Given one potential distribution on the cortex, and one on the scalp, it is possible to establish a system of relations that permits the passage from one to the other. If the cortically measured potentials are assumed to represent the electrical sources in the brain, this propagation model is equal to the *forward problem*. Although this was modeled for the first time many years ago, no empirically measured data have ever been published on the propagation of normal human EEG. Fig. 5.1 illustrates how a single extracranial EEG electrode probably has a *field of vision* that expands over an area of the cortex.

An application regarding a study with electrodes placed intra- and extracranially was accepted by the Regional Research Ethics Committee (research protocol in Danish can be found in Appendix B.2). A total of 11 patients were included, but only seven of them had electrodes aligned intra- and extracranially applicable for the analysis. The database is described in [15] (Appendix A.7).

5.2 Results Summary

Using simultaneously recorded intra- and extracranial EEG channels, we assessed the size of the cortical area contributing to the extracranial EEG, and investigated the influence of the craniotomy and the silastic membrane of intracranial grids on the signal conduction. We estimated the intracranial to extracranial mapping by analyzing at least 10 minutes of spontaneous, resting, awake EEG and ECoG signals from seven patients. Extracranial channels showed significant coherence up to 70 mm from the source, cor-

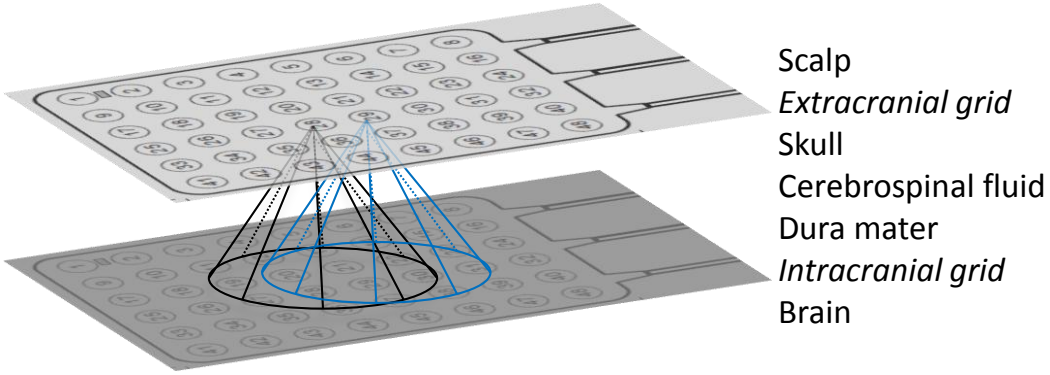


Figure 5.1: The *field of vision* of a single extracranial electrode is believed to be circular on the cortical surface. Two adjacent electrodes have a large accumulation area in common.

responding to an area of approximately 150 cm^2. Based on spatial averaging of intracranial channels, it was found that only channels within an accumulation area of 31 cm^2 contributed positively to a higher coherence. It was possible to double the coherence values when a mean of 8.8 intracranial channels were averaged compared to the single intracranial channel with highest coherence. This is a confirmation of the hypothesis that the skull acts as a spatial averager. The coherence seemed to increase linearly with an accumulation area up to 31 cm^2, where 50% of the maximal coherence was obtained accumulating from only 2 cm^2 (corresponding to one channel), and 75% when accumulating from 16 cm^2.

When the contributions from the different affectors were analyzed, the Euclidean distance between intra- and extracranial channels was found to be accountable for 75% of the coherence in the 4-15 Hz frequency band. The current leakage through the craniotomy and the insulation capacity of the silastic membrane of intracranial grids were accountable for 12% and 13%, respectively.

The coherences of frequency bands below 16 Hz all seem to have similar declines as a function of the Euclidean distance between channels. Frequencies between 16 and 30 Hz have a steeper decline and are only coherent with channels located less than 45 mm apart. There is no coherence between frequencies above 30 Hz at any distance.

5.2.1 Edge Effect in Coherence as Function of Distance

After submission of the paper in Appendix A.7 a new hypothesis was developed. The model fitted to the coherence as a function of distance between channels in Figure 4 in the paper showed an initial increase in coherence for distances between 10-20 mm followed by a steep decline. As the radial distance between intra- and extracranial electrodes was found to be 12 mm in mean, the values in question are those lying directly below the extracranial channels. This increase was therefore described as an edge effect due to physiological differences between patients, as one would think that the channels directly on opposite sites of the skull would have the highest coherence. Although this might bear a part of the reason, another hypothesis might explain the lower coherence for very short distances. Fig. 5.1 shows how two extracranial electrodes next to each other accumulate EEG from the same cortical area. Even though anisotropy of especially the skull will transmit the signals differently to the two electrodes, the electric fields from the common area will be very similar. Due to the bipolar setup, most of the signal from the area directly below the extracranial channel is canceled out.

To test this hypothesis, the extracranial electrode center to center distance was increased from 10 to 30 mm. This should produce a smaller cancellation area, although it will also move the extracranial electrodes away from the electric signals in between them and thus it might not be included in any of the electrodes accumulation areas. As with the 10 mm distance setup, the best model was found in R (vers. R 2.15.1). The coherence was again found to be gamma distributed. A generalized linear model based on a gamma

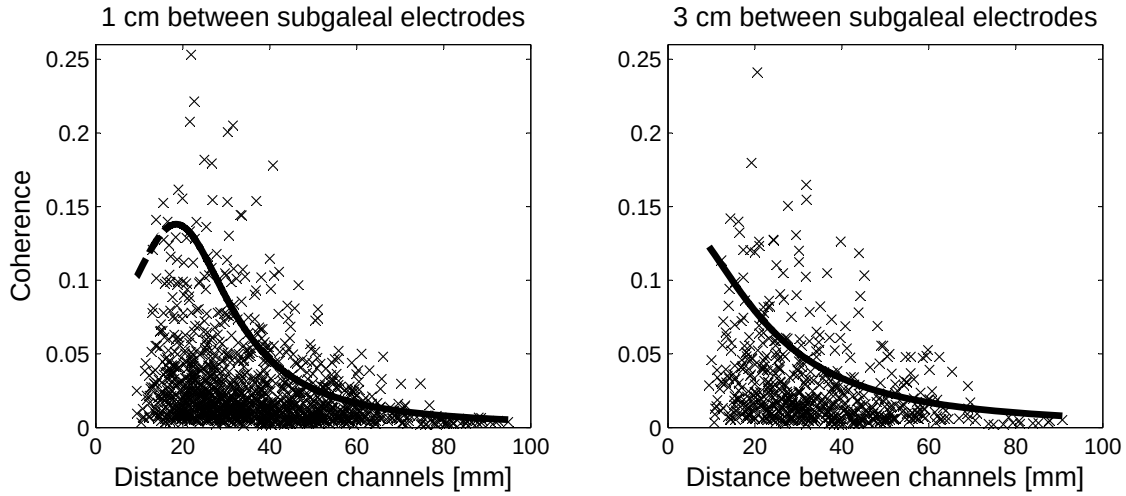


Figure 5.2: Coherence as a function of Euclidean distance between channels. In the left figure, the distance between extracranial channels were 1 cm, in the right figure the distance was 3 cm. Only the model based on 1 cm interelectrode distance showed an initial increase. This might be due to cancellation of the electrical signals directly below the extracranial electrodes.

distribution and patients as blocking factor produced the following model:

$$C_{\varphi}(d_{Eu}, d_{Edge}) = \frac{1}{0.0144 \cdot d_{Eu}^2 + 1.92 \cdot d_{Edge} + 6.853239} \tag{5.1}$$

Only the squared Euclidean distance between signals, d_{Eu}^2, and the intracranial distance to edge of silastic membrane, d_{Edge}, was found significant on a significance level of $\alpha = 0.05$. The Euclidean distance between signals, d_{Eu}, and the extracranial distance to the craniotomy, d_{Cran}, was no longer significant. It should be noted though, as the distance between electrodes increases, it is more likely that the electrodes are placed on either side of the craniotomy. In the case where each electrode is 1.5 cm from the craniotomy, the calculated distance is 0 cm. d_{Cran} can therefore be difficult to interpret for the 3 cm distance.

Fig. 5.2 shows the models for the coherence as a function of the Euclidean distance between channels when the other affectors are set to zero. It is difficult to say whether this peculiarity is an actual effect in the recording, or whether it is purely by coincidence.

5.3 Future Work

The investigations presented in the papers represent a comprehensive although not all-embracing analysis. There is still need for a deeper understanding of which intracranial channels that contribute with high coherence, and how amplitude differences might come into play. The following issues were identified as reasonable next steps for analysis:

- A high correlation between multiple intracranial channels might be due to synchronization of cortical generators, and thus higher probability for the electric currents to reach the scalp. Whether high intra- to intracranial coherence also induce high intra- to extracranial coherence should be investigated.
- Instead of averaging over at least 10 minutes of data and comparing inter-patiently, an analysis showing intra-patient variability would be of high interest. If we are able to obtain a coherence for a certain channel configuration of e.g. 0.25 for five minutes, what would the coherence be for the following five minutes? This would reveal the variability of the cortical generators over time.
- Is there a time delay between intra- and extracranial channels that depends on the distance between channels, craniotomy and silastic membrane properties? This has previously been reported [14, 42] although the assumed delays are probably very small (in the μs range). This could be investigated as a phase spectrum analysis which is complimentary to coherence analysis.
- It would have a huge impact if we were able to flip the problem addressed in this chapter, and calculate the *inverse problem*, and use the extracranial channels in combination to provide a higher coherence to an intracranial channel. Unfortunately, this would probably require extracranial grids instead of strips to archive the needed spatial resolution, and thus a new dataset.

5.4 Conclusion

The area of cortical synchronization necessary to generate a detectable extracranial EEG event has for decades been thought to be 6 cm^2 [13]. Recent studies have challenged this figure and state that the area is more likely to be 10-20 cm^2 based on visual analysis of epileptic spikes [46]. In the current study, the focus was on determining the size of the cortical area correlated with the extracranial spontaneous awake EEG, and what size of area actually contributed positively. A large difference between those two areas were found. The latter termed the *field of vision* was found to be approximately 30 cm^2. The spontaneous awake EEG is thus in mean accumulated from a larger area than necessary to produce a recordable extracranial potential based on spike analysis.

This study was conducted as basic science although it showed to include a large amount of applied science in it. The findings can help electroencephalographers on how they should interpret extracranial EEG records when assessing the cortical substrates.

CHAPTER

SIX

CONCLUSION

Approximately 50 million people worldwide suffer from epilepsy. Even though most people know someone with epilepsy, the disease is tabooed in the society. This is most likely due to an ignorant knowledge about the patients. Several factors entail a high degree of depression among the patients, and a general lowered quality of life is expected after being diagnosed with epilepsy [41]. Providing technological solutions to challenges in the everyday life of an epilepsy patient would improve his or hers quality of life. The work leading up to this dissertation has included making acquaintance of the consequences and problems of different types of epilepsy. The conclusion is that we are dealing with a group of patients where many of them would benefit from a HypoSafe device either for monitoring purposes to provide objective accounts of seizure frequency, duration and time of occurrence, or as an alarm to health care professionals or relatives who could provide help for the distressed during or after a seizure.

The title of the dissertation reads *Detection and Prediction of Epileptic Seizures*. It is a wide formulation that made it possible to examine various issues with the common theme: Using signal processing of EEG data to help epilepsy patients. The different subjects focused on automatic seizure prediction (chapter 2), automatic seizure detection (chapter 3 and 4), and the link between intra- and extracranial EEG (chapter 5).

For most patients, the most disabling aspect of epilepsy is the unforeseen nature of the seizures. They can attack anytime and everywhere. A device capable of predicting seizures and warn the patient would thus provide tremendous benefits. Although the investigations on seizure predictability in chapter 2 ended up showing that it is still not possible to obtain clinically applicable performance results, it should not be taken as discouraging for the future. The new large databases that have emerged during 2012 might provide the means to identify patterns leading to reliable seizure prediction algorithms. We will probably see the results of such investigations during the following year or two.

More promising results were obtained in the work described in chapter 4. A continuous monitoring device

for idiopathic generalized epilepsy patients with an automatic seizure detection algorithm is definitely plausible when it comes to detection performance. In a clinical study 97.2% of paroxysms lasting more than two seconds were detected without any false positive detections. This initiated a study based on outpatients to assess the detection performance when ambulatory artifacts were present. Based on a limited dataset of only seven whole-day recordings on two outpatients, a sensitivity of 90% and a false detection rate of 0.12 per hour were obtained. This results in a positive predictive value of 81% but a fair guess is that better results are obtainable when the quality of the recorded measurements improves and the algorithm is optimized for outpatient data and the artifacts that follow.

While the EEG of the children was monitored, the parents simultaneously kept a diary where they wrote down every time they noticed a seizure. Based on these, it was estimated that the parents only detected 6.7% of the paroxysms while supervising their child, and only 2.1% of the total number of daily paroxysms. Although the dataset was limited, the results correspond to what was found by others [27]. This clearly shows that many children with IGE are probably not receiving the optimal treatment due to the insufficient reporting rate by the parents. This is a clear indication of the need of an objective monitoring device.

The final investigation treated in chapter 5 examined the relationship between intra- and extracranial EEG. The anisotropic nature of the brain and skull induce a high variance in the coherence. Results were thus based on moving average and a gamma-fitted generalized linear model. Although seven patients might be on the lower limit of needed test subjects, it must be acknowledged that the experimental setup is difficult, and that pathological issues dictates the placement of electrodes instead of the study design. The well recognized hypothesis stating that the skull acts as an electroencephalographic averager is correct. Although the coherence was significant in an accumulation area of 150 cm^2, only channels within a cortical area of approximately 30 cm^2 increased the coherence. Channels outside this area contributed with more noise than coherent signal. There is still a lot of work in understanding which cortical areas that contribute to the extracranial EEG, as well as describing the transfer function across the skull.

Several issues were addressed in the current PhD project and they all yielded interesting results that are worth continuing to work on and improve. The Biomedical Signal Processing group at DTU Electrical Engineering led by associate professor, PhD Helge BD Sørensen will try to obtain the EPILEPSIAE database mentioned in section 2.4, and probably start up projects addressing the feasibility of seizure prediction again. HypoSafe A/S has shown high interest in the results of automatic seizure detection on idiopathic generalized epilepsy patients and will continue the project with outpatient monitoring in collaboration with the Biomedical Signal Processing group and the Department of clinical neurophysiology. And finally, chief physician, associate professor, PhD Troels W Kjær from Department of clinical neurophysiology, Copenhagen University Hospital Rigshospitalet, found the results on the link between intra- and extracranial channels extremely interesting and will hopefully be able to run projects investigating the unique dataset of intra- and extracranial EEG further.

BIBLIOGRAPHY

[1] A. Aarabi, R. Fazel-Rezai, and Y. Aghakhani. A fuzzy rule-based system for epileptic seizure detection in intracranial eeg. *Clinical Neurophysiology*, 120(9):1648–1657, 2009.

[2] H. Adeli, Z. Zhou, and N. Dadmehr. Analysis of eeg records in an epileptic patient using wavelet transform. *Journal of neuroscience methods*, 123(1):69, 2003.

[3] R.G. Andrzejak, K. Lehnertz, F. Mormann, C. Rieke, P. David, and C.E. Elger. Indications of nonlinear deterministic and finite-dimensional structures in time series of brain electrical activity: Dependence on recording region and brain state. *Physical Review E*, 64(6):61907, 2001.

[4] S. Arthurs, H.P. Zaveri, M.G. Frei, and I. Osorio. Patient and caregiver perspectives on seizure prediction. *Epilepsy & behavior*, 19(3):474–7, 2010.

[5] T.L. Bennett and M.R. Ho. The neuropsychology of pediatric epilepsy and antiepileptic drugs. In Reynolds C.R. and Fletcher-Janzen E., editors, *Handbook of clinical child neuropsychology*, pages 505–528. Springer, New York, 2009.

[6] A.T. Berg, S.F. Berkovic, M.J. Brodie, J. Buchhalter, J.H. Cross, W. Van Emde Boas, J. Engel, J. French, T.A. Glauser, G.W. Mathern, et al. 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, 2010.

[7] A.T. Berg and I.E. Scheffer. New concepts in classification of the epilepsies: Entering the 21st century. *Epilepsia*, 52(6):1058–1062, 2011.

[8] G.W. Brier. Verification of forecasts expressed in terms of probability. *Monthly weather review*, 78(1):1–3, 1950.

[9] L. Brunbech and A. Sabers. Effect of antiepileptic drugs on cognitive function in individuals with epilepsy: a comparative review of newer versus older agents. *Drugs*, 62(4):593–604, 2002.

[10] J.R. Carrie and J.D. Frost. Clinical evaluation of a method of quantification of generalized spike-wave EEG patterns by computer during prolonged recordings. *Computers and biomedical research, an international journal*, 10(5):449–57, 1977.

[11] A.M. Chan, F.T. Sun, E.H. Boto, and B.M. Wingeier. Automated seizure onset detection for accurate onset time determination in intracranial EEG. *Clinical Neurophysiology*, 119:2687–2696, 2008.

[12] J. Christensen, M. Vestergaard, M.G. Pedersen, C.B. Pedersen, J. Olsen, and P. Sidenius. Incidence and prevalence of epilepsy in denmark. *Epilepsy research*, 76(1):60–65, 2007.

[13] R. Cooper, A.L. Winter, H.J. Crow, and W.G. Walter. Comparison of Subcortical, Cortical and Scalp Activity Using Chronically Indwelling Electrodes in Man. *Electroencephalography and clinical neurophysiology*, 18:217–28, February 1965.

[14] M. Delucchi, B. Garoutte, and R. Aird. The scalp as an electroencephalographic averager? *Electroencephalography and Clinical Neurophysiology*, 14(2):191–196, April 1962.

[15] J. Duun-Henriksen, T.W. Kjaer, R.E. Madsen, B. Jespersen, A.K. Duun-Henriksen, L.S. Remvig, C.E. Thomsen, and H.B.D. Sorensen. Subdural to subgaleal EEG signal transmission : the role of distance , leakage and insulating affectors. *Submitted to Clinical Neurophysiology*, Oct. 8th, 2012.

[16] J. Duun-Henriksen, R.E. Madsen, L.S. Remvig, C.E. Thomsen, H.B.D. Sorensen, and T.W. Kjaer. Automatic detection of childhood absence epilepsy seizures: Toward a monitoring device. *Pediatric neurology*, 46(5):287–292, 2012.

[17] B.L. Ehrenberg and J. Kiffin Penry. Computer recognition of generalized spike-wave discharges. *Electroencephalography and clinical neurophysiology*, 41(1):25–36, 1976.

[18] R.S. Fisher, W.E. Boas, W. Blume, C. Elger, P. Genton, P. Lee, and J. Engel Jr. 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, 2005.

[19] M.G. Frei and Osorio I. The FHS publicly available epilepsy ECoG database. Poster presentation 62nd annual meeting of the American Epilepsy Society, 2008.

[20] A.B. Gardner, A.M. Krieger, and G. Vachtsevanos. One-class novelty detection for seizure analysis from intracranial EEG. *Journal of Machine Learning Research*, 7(6):1025, 2006.

[21] H. Hallez, B. Vanrumste, R. Grech, J. Muscat, W. De Clercq, A. Vergult, Y. D'Asseler, K.P. Camilleri, S.G. Fabri, S. Van Huffel, and I. Lemahieu. Review on solving the forward problem in EEG source analysis. *Journal of neuroengineering and rehabilitation*, 4:46, 2007.

[22] H. Hecimovic, JM Santos, J. Carter, HP Attarian, AJ Fessler, V. Vahle, and F. Gilliam. Depression but not seizure factors or quality of life predicts suicidality in epilepsy. *Epilepsy & Behavior*, 24(4):426–429, 2012.

[23] J. Henriksen. Seizure prediction on the basis of iEEG recordings. Master's thesis, Technical University of Denmark, Ørsted•DTU, 2008.

[24] H. Hjalgrim. Klassifikation af epilepsier - nyt system og ny terminologi. *BestPractice - Psykiatri/Neurologi*, 7:14–15, 2012.

[25] M. Jachan, H. Feldwisch-Drentrup, F. Posdziech, A. Brandt, D.M. Altenmüller, A. Schulze-Bonhage, J. Timmer, and B. Schelter. Probabilistic forecasts of epileptic seizures and evaluation by the brier score. In *4th European Conference of the International Federation for Medical and Biological Engineering*, pages 1701–1705. Springer, 2009.

[26] J. Jacobs, R. Zelmann, J. Jirsch, R. Chander, and J. Gotman. High frequency oscillations (80-500 Hz) in the preictal period in patients with focal seizures. *Methods*, 50(7):1780–1792, 2009.

[27] M.J. Keilson, W.A. Hauser, J.P. Magrill, and J. Tepperberg. Ambulatory cassette EEG in absence epilepsy. *Pediatric neurology*, 3(5):273–6, 1987.

[28] D.J. Koffler and J. Gotman. Automatic detection of spike-and-wave bursts in ambulatory EEG recordings. *Electroencephalography and clinical neurophysiology*, 61(2):165–80, 1985.

[29] K. Lehnertz, F. Mormann, H. Osterhage, A. Muller, J. Prusseit, A. Chernihovskyi, M. Staniek, D. Krug, S. Bialonski, and C.E. Elger. State-of-the-art of seizure prediction. *Journal of Clinical Neurophysiology*, 24(2):147–153, 2007.

[30] F. Mormann, R.G. Andrzejak, C.E. Elger, and K. Lehnertz. Seizure prediction: the long and winding road. *Brain*, 130(2):314–333, 2007.

[31] F. Mormann, K. Lehnertz, P. David, and C. E. Elger. Mean phase coherence as a measure for phase synchronization and its application to the EEG of epilepsy patients. *Physica D*, 144(3-4):358–369, 2000.

[32] L. Nashef. Sudden unexpected death in epilepsy: terminology and definitions. *Epilepsia*, 38(s11):S6–S8, 2007.

[33] P. Nicolas and G. Deloche. Convolution computer processing of the brain electrical image transmission. *International journal of bio-medical computing*, 7(2):143–59, 1976.

[34] P.L. Nunez and R. Srinivasan. *Electric fields of the brain: the neurophysics of EEG*. Oxford University Press, USA, New York, 2nd edition, 2006.

[35] E.B. Petersen, J. Duun-Henriksen, A. Mazzaretto, T.W. Kjaer, C.E. Thomsen, and H.B.D. Sorensen. Generic single-channel detection of absence seizures. In *Engineering in Medicine and Biology Society, EMBC, 2011 Annual International Conference of the IEEE*, pages 4820–4823. IEEE, 2011.

[36] E.B. Posner, K. Mohamed, and A.G. Marson. Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents (review). *The Cochrane Library*, 3, 2010.

[37] J.C. Principe and J.R. Smith. Microcomputer-based system for the detection and quantification of petit mal epilepsy. *Computers in biology and medicine*, 12(2):87–95, 1982.

[38] R.J. Quy, P. Fitch, and R.G. Willison. High-speed automatic analysis of eeg spike and wave activity using an analogue detection and microcomputer plotting system. *Electroencephalography and Clinical Neurophysiology*, 49(1):187–189, 1980.

[39] E. Rodin and O. Ancheta. Cerebral electrical fields during petit mal absences. *Electroencephalography and clinical neurophysiology*, 66(6):457–66, 1987.

[40] B. Schelter, H. Feldwisch-Drentrup, M. Ihle, A. Schulze-Bonhage, and J. Timmer. Seizure prediction in epilepsy: From circadian concepts via probabilistic forecasting to statistical evaluation. In *Engineering in Medicine and Biology Society, EMBC, 2011 Annual International Conference of the IEEE*, pages 1624–1627. IEEE, 2011.

[41] B. Schelter, J. Timmer, and A. Schulze-Bonhage. *Seizure prediction in epilepsy: from basic mechanisms to clinical applications*. Wiley-VCH, 2008.

[42] J.C. Shaw. Correlation and coherence analysis of the EEG: a selective tutorial review. *International journal of psychophysiology*, 1(3):255–66, 1984.

[43] A. Shoeb, H. Edwards, J. Connolly, B. Bourgeois, S. Ted Treves, and J. Guttag. Patient-specific seizure onset detection. *Epilepsy and Behavior*, 5(4):483–498, 2004.

[44] A. Subasi. Application of adaptive neuro-fuzzy inference system for epileptic seizure detection using wavelet feature extraction. *Computers in Biology and Medicine*, 37(2):227–244, 2007.

[45] Sundhedsstyrelsen. *Center for Evaluering og Medicinsk Teknologivurdering, Referenceprogram for epilepsi*, 2005.

[46] J.X. Tao, M. Baldwin, A. Ray, S. Hawes-Ebersole, and J.S. Ebersole. The impact of cerebral source area and synchrony on recording scalp electroencephalography ictal patterns. *Epilepsia*, 48(11):2167–76, 2007.

[47] M. Winterhalder, T. Maiwald, H.U. Voss, R. Aschenbrenner-Scheibe, J. Timmer, and A. Schulze-Bonhage. The seizure prediction characteristic: a general framework to assess and compare seizure prediction methods. *Epilepsy & Behavior*, 4(3):318–325, 2003.

[48] E.C. Wirrell. Epilepsy-related injuries. *Epilepsia*, 47:79–86, 2006.

[49] P. Xanthopoulos, S. Rebennack, C.C. Liu, J. Zhang, G.L. Holmes, B.M. Uthman, and P.M. Pardalos. A novel wavelet based algorithm for spike and wave detection in absence epilepsy. In *BioInformatics and BioEngineering (BIBE), 2010 IEEE International Conference on*, pages 14–19. IEEE, 2010.

APPENDIX

A

PAPERS

A.1
FEASIBILITY OF SEIZURE PREDICTION FROM INTRACRANIAL EEG RECORDINGS

AUTHORS: Jonas Henriksen, Troels W. Kjaer, Carsten E. Thomsen, Rasmus E. Madsen, and Helge B.D. Sorensen

JOURNAL: Epilepsia

YEAR: 2009

VOLUME: 50

ISSUE: Supplement s10

PAGE: 73

DOI: 10.1111/j.1528-1167.2009.02320.x

PUBLICATION HISTORY: Accepted as poster presentation at the 28th International Epilespy Congress Budapest, Hungary, 2009
Published online, October 2nd, 2009

4-DCPG had partial antiepileptogenic effect, evident as a lower number and shorter duration of spontaneous seizures. In addition,(S)-3,4-DCPG prevented impairment of spatial memory observed in adult rats that experienced SE in early life.

Conclusions: The present findings suggest that group III mGluR may be considered a promising target for drug therapy in epilepsy. Activation of these receptors may have not only a short-term, but also long-term beneficial effect.

Supported by Grant Agency of the Czech Republic, grants No. 309/05/2015 and No. 309/08/0292.

p336
FEASIBILITY OF SEIZURE PREDICTION FROM INTRACRANIAL EEG RECORDINGS

J Henriksen[1], T Kjaer[2], C Thomsen[3], R Madsen[4], H Sørensen[1]
[1]Technical University of Denmark, Kgs. Lyngby, Denmark, [2]Rigshospitalet University Hospital, Copenhagen, Denmark, [3]Clinical Oral Physiology, Oral Pathology and Anatomy, Copenhagen University, Copenhagen, Denmark, [4]Hypo-Safe A/S, Kgs. Lyngby, Denmark

Purpose: The current project evaluated the feasibility of providing an algorithm that could warn a patient of a forthcoming seizure based on iEEG recordings.

Method: The mean phase coherence (MPC) feature (Mormann F et al. Phys Nonlinear Phenom 2000;3–4:358–369.) was implemented and tested in a rigorously, out-of-sample manner. The MPC-feature is based on the synchronization measure, explained through the analytic signal approach where the Hilbert transform is used to find the instantaneous phase of an arbitrary signal. By a relative comparison between two different iEEG channels the phase synchronization was calculated. The feature was employed on the FSPEEG database containing 21 patients with 4.1 seizures in average (Winterhalder M et al. Epilepsy Behav. 2003;4(3):318–325.) to assess its predictive performance.

Results: A sensitivity of 55% and a specificity of 62% were obtained after a unified optimization of threshold value and localization of electrodes for all patients. These results are just better than a random predictor. To improve the results the parameters need to be optimized for each patient individually. Before this can be done, a larger database with more seizures recorded per patient is needed.

Conclusion: It was shown that it is possible to anticipate an epileptic seizure to some degree. While the obtained results are still far from clinically applicable, they suggest that by optimization of personal parameters, at least some patients will be able to gain advantage of seizure prediction. The field still needs further investigation though.

p338
ANTIEPILEPTOGENIC EFFECT OF OREXIN B IN THE KINDLING MODEL OF EPILEPSY IN RATS

A Morales[1,2,3], S Bouvard[1,2], M Le Cavorsin[1,2,3], C Bonnet[1,2,3], B Georges[1,2,3], C Moulin[1,2,3], H Kouchi[1,2,3], A Belmeguenai[1,2,3], P Ryvlin[1,2], L Bezin[1,2,3]
[1]Institute for Child and Adolescent Epilepsy IDEE, Lyon, France, [2]University of Lyon, Lyon, France, [3]CNRS UMR5123, Villerubanne, France

Orexin-B (OX-B) is a hypothalamic peptide likely involved in the regulation of sleep, depression and various behavioral activities including feeding. OX-B may also play a crucial role in modulating hippocampal excitability during epileptogenesis, since we have previously demonstrated after pilocarpine-induced status epilepticus that the density of OX-B-positive fibers arising from hypothalamic neurons was profoundly reduced in the dorsal thalamus and hippocampus. Here we tested the hypothesis that OX-B innervation is similarly dysregulated in the amygdala-kindling model of epilepsy, and that the kindling process is delayed by OX-B intracerebroventricular (i.c.v.) injection. We found that fully-kindled adult rats had a reduced density of OX-B innervation in the dorsal thalamus (-25 ± 9 %, $p<0.05$) and the dorsal hippocampus (-48 ± 7 %, $p<0.01$), 2 days after the last stage-5 seizure. This reduction was accompanied by an increase: 1) in the number of OX-B-expressing cells in the lateral hypothalamus, and 2) in prepro-orexin transcript level in the hypothalamus. No variation in orexin-receptors 1 and 2 was found at the transcript level in the hypothalamus and the hippocampus. When OX-B was injected (0.7 nmole in 6 μL, at 1 μL/min) 30 min prior to each amygdala stimulation, we noted that OX-B did alter neither the stimulation threshold, nor the after-discharge duration at all behavioral seizure stages. However, OX-B significantly increased the number of stimulations necessary to reach stages 3–5 seizures ($p<0.001$). Altogether, our results suggest that decreased OX-B innervation may play a role in epileptogenesis, and demonstrate that OX-B administration is antiepileptogenic.

p339
EFFECTS OF AMN082 ADMINISTRATION ON CORTICAL AFTERDISCHARGES DURING RAT BRAIN DEVELOPMENT

E Szczurowska, P Mares
Institute of Physioogy Academy of Sciences, Czech Republic

Metabotropic glutamate receptors (mGluRs) are involved in modulation of glutamatergic neurotransmission and they play a role in many CNS disorders, including epilepsy. Activation of the group III mGluRs (mGLUR4, mGluR6, mGluR7, mGluR8) can represent a therapeutic target for anticonvulsant drugs. We studied effects of AMN082 (N,N Œ-dibenzhydrylethane-1,2-diamine dihydrochloride), an allosteric agonist of mGluR7, i.e. a subtype widely distributed throughout the rat brain, in a model of cortically induced epileptic afterdischarges (ADs). Experiments were performed in rat pups 12, 18 and 25 days old. ADs were elicited by six subsequent rhythmic electrical stimulations of sensorimotor cortex with 20 minutes intervals; after the first AD AMN082 was injected intraperitoneally in a dose of 1 or 5mg/kg. Duration of ADs and their transition into the limbic type of ADs were evaluated. A proconvulsant effect of AMN082 was observed in 12- and 18-day-old rats, where 5mg/kg dose increased duration of spike-and-wave type of ADs. No significant changes were found in 25-day-old animals. A limbic type of ADs was studied only in 25-day-old rats where this type of ADs is more common. AMN082 (especially the 1mg/kg dose) shortened its duration. Opposite effects of AMN082 were found in the two types of cortical afterdischarges. In addition effects vary during development. This may be due to developmental of mGluR7 in brain structures involved in of these types epileptic seizures.

This study was supported by a grant No.305/06/1188 of the Grant Agency of the Czech Republic.

p340
EFFECTS OF EARLY POSTNATAL CAFFEINE EXPOSURE ON SEIZURE SUSCEPTIBILITY OF RATS ARE AGE- AND MODEL-DEPENDENT

J Tchekalarova[1,2], H Kubová[1], P Mareš[1]
[1]Institute of Physiology, Czech Academy of Sciences, Prague, Czech Republic, [2]Institute of Physiology, Bulgarian Academy of Sciences, Sofia, Bulgaria

Repeated postnatal caffeine injections led to decreased seizure susceptibility if tested with aminophylline or convulsants influencing GABAergic inhibition. To study if this effect is general we tested convulsant action of two prototypic agonists of glutamate receptors - N-methyl-D-aspartate (NMDA) and kainic acid (KA) in immature rats with a history of five caffeine injections at postnatal days (PD) 7–11 or 13–17. Caffeine was injected in doses of 10 or 20 mg/kg s.c., control rats received saline. Convulsants were tested 24 h after the last caffeine injection (i.e. at PD 12 and/or 18) or at the age of 25 days in both exposure groups. Two doses of convulsants were used in each group; these doses were chosen according to our previous description of these two models. Generally, doses had

A.2
PATIENT-SPECIFIC RIGOROUSLY METHODOLOGICAL TEST OF THE MEAN PHASE COHERENCE

AUTHORS: Jonas Henriksen, Troels W. Kjaer, Rasmus E. Madsen, Carsten E. Thomsen, and Helge B.D. Sorensen

JOURNAL: Accepted as poster presentation at the 4th International Workshop on Seizure Prediction, 2009, http://www.iwsp4.org (peer-reviewed but not published)

YEAR: 2009

Patient-specific Rigorously Methodological Test of the Mean Phase Coherence

Jonas Henriksen, Troels W. Kjaer, Rasmus E. Madsen, Carsten E. Thomsen, and Helge B.D. Sorensen

Abstract— **Because of the limited number of recordings in existing EEG databases, very few papers have described a patient-specific methodologically rigorous test of features for seizure prediction. In this study, we conducted such a test extracting intracranial EEG from epilepsy patients with at least 6 seizures and using the mean phase coherence (MPC) feature.**

Methods: The MPC was implemented as described by Mormann et al., 2000. It was tested in a generic methodologically rigorous way on the FSPEEG database, Winterhalder et al., 2003. 10 patients were used for training of the algorithm's optimal settings, while the remaining 11 patients were used for testing. With new iEEG extractions from Copenhagen University Hospital, it was possible to obtain training and test sets with adequate numbers of seizures from individual patients. Preictal data from 4 patients was extracted from 11, 7, 7, and 6 seizures respectively together with at least 24 h of interictal data from each individual. We determined the optimal number of training seizures using a variant of the leave-one-out training and test method.

Results: The generic test on the FSPEEG database resulted in a {sensitivity, false prediction ratio} of {0.51, 0.53/h}. For the 4 new patients, the generic results were comparable to the FSPEEG database. The patient-specific approach yielded a mean improvement of {0.23, 0.30/h}. It was found that 5 seizures were optimal for training.

Conclusions: By making the seizure prediction algorithm patient-specific, we achieved considerable improvements in this preliminary study. Clinically applicable results were obtained from3 out of 4 patients. So, although there is still room for further improvements, it can be expected that many epilepsy patients will benefit from patient-specific seizure prediction.

Index Terms—**Epilepsy seizure prediction, mean phase coherence.**

Manuscript received April 4, 2009. The Danish Agency for Science, Technology and Innovation has supported the work of J. Henriksen by granting one third of an industrial PhD scholarship. The rest was granted by the company Hypo-Safe A/S. R. E. Madsen and L. S. Remvig are both employed full-time at Hypo-Safe A/S. Drs. Kjaer, Thomsen, and Sorensen do not have any financial interest in Hypo-Safe A/S. *Asterisk indicates corresponding author*.

*J. Henriksen and H. B. D. Sorensen are with the Biomedical Department of Electrical Engineering, Technical University of Denmark, 2800 Kgs. Lyngby, Denmark (e-mail: [jhe] or [hbs]@elektro.dtu.dk).

T. W. Kjaer is with the Department of Clinical Neurophysiology, Copenhagen University Hospital Rigshospitalet, 2100 Copenhagen, Denmark, (e-mail: neurology@dadlnet.dk).

R. E. Madsen is with HypoSafe A/S, 2800 Kgs. Lyngby, Denmark (e-mail: [rem] or [lsr]@hyposafe.com).

C. E. Thomsen is with the Department of Odontology, University of Copenhagen, 2200 Copenhagen, Denmark (e-mail: cet@odont.ku.dk).

I. Introduction

SINCE the time of Hippocrates, epilepsy has been the subject of interest for many people. Unfortunately, it is still far from thoroughly understood. Next to headache and stroke it is the most common brain disorder. About 1% of the world's population suffers from epilepsy, corresponding to approximately 50 millions. Of these, 25% suffers from seizures which cannot be treated satisfactory with medication or epilepsy surgery [1]. This group of patients often mentions that the most disabling aspect is the sudden, unforeseen way in which the epileptic seizure strikes "like a bolt from the blue" as they put it. The unforeseen seizures create a risk of serious injury, but also, the patient gets a severe feeling of helplessness that has a strong impact on his or hers everyday life. This creates a social stigma causing considerable demoralization, frustration and anxiety for the patient as well as family and friends. ditto

To cope with the unpredictability, some of the patients with intractable epilepsy have resorted to an alternative way of securing themselves. They use dogs, which are trained to anticipate a seizure. "Seizure-alert dogs" are reported to be able to warn the owner of a forthcoming seizure within time periods varying from 15 to 45 min prior to the onset [2]. It is suggested that the dogs detect subtle changes in the behavior of the patient that characteristically precede the seizure even when the patient or relatives close to have no premonition what so ever.

Since dogs are able to anticipate an epileptic seizure on the basis of behavioral changes, one would think that these changes are possible to detect electrically or mechanically as well. If a method to warn a patient of a forthcoming attack can be developed, the unpredictability will disappear and thereby greatly improve his or her quality of life. The feasibility of developing a prediction algorithm is supported by work done at research centers around the world. They have found that a coherence between different mathematical measures applied on the electrical signals from the brain and the time to seizure onset exist [1], [3], [4]. Even though, no one has been able to make the algorithm robust enough to use it in a clinical setting.

Computerized prediction of seizure onset has shown promising results in recent years. The goal is to make an

attention-device that gives an alert to the patient when a seizure is approaching. The primary obstacle is the lack of sufficient large databases to make statistical validation of a patient-specific algorithm rather than a generic "one-size-fits-all" approach [1]. This is also the reason that only few papers have described a patient-specific rigorously methodological test of features for seizure prediction. By extraction of intracranial EEG from epilepsy patients admitted for epilepsy surgery with at least six seizures recorded, we have conducted such a test using the mean phase coherence (MPC) feature.

II. Materials

A. FSPEEG Clinical Data

The Freiburg Seizure Prediction EEG (FSPEEG) database consists of intracranial EEG recordings from 21 patients obtained during invasive pre-surgical epilepsy monitoring in the clinic. These recordings only contain up to five seizures per patient. See [5] for further information.

B. RHEEG Clinical Data

The Rigshospitalet EEG (RHEEG) database was created for the current project. Intracranial EEG data from four patients undergoing pre-surgical epilepsy monitoring with at least 6 seizures were identified and extracted for further analysis. The Schwarzer EEG amplifier with 128 channels and a high pass RC filter of first order with a cut-off at 0.0016 Hz attenuating 6 dB/octave and a low pass Butterworth filter of fifth order with a cut-off at 70 Hz attenuating 12 dB/octave is used. Data are stored in 16 bit and digitized at 200 Hz. See Table I and [6] for further information.

III. Methods

A wide variety of different algorithms with potential for prediction of seizures have been proposed by different scientists [4]. One of the best described methods with the seemingly highest potential for seizure prediction is the *mean phase coherence* (MPC) proposed for seizure prediction by Mormann et al. in 2000 [1]. It is a statistical measure for phase synchronization based on the most common accepted theories on epileptogenesis saying that the pathological neuronal synchronization is playing a crucial role for the development of a seizure. This is supported by observations that non-identical, self-sustained, chaotic oscillators synchronize their phases if the oscillators are weakly coupled (meanwhile, the amplitudes stay uncorrelated) [7]. The MPC-feature is based on the synchronization measure, explained through the *analytic signal approach*: Through the *Hilbert transform*, the *instantaneous phase* of an arbitrary signal can be found. By a relative comparison between two different channels, the phase synchronization is calculated. The MPC was implemented as described by Mormann et al., 2000 [1]:

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

where R is the mean phase coherence, and $\varphi_{1,1}$ is the relative phase between two signals, s_a and s_b, with a ratio of 1:1, defined from the Hilbert transform, $\tilde{s}$:

$$\left|\varphi_{1,1}\right| = \arctan\frac{\tilde{s}_a(t)s_b(t) - s_a(t)\tilde{s}_b(t)}{s_a(t)s_b(t) + \tilde{s}_a(t)\tilde{s}_b(t)}$$

A seizure is predicted when R drops below a certain threshold set to:

$$Threshold = \mu_R - c \cdot \sigma_R$$

where μ_R and σ_R are the mean and standard deviation of R, and c is an arbitrary factor. For the generic test, c was found to be optimal at 1.2 when maximizing the performance function $P = \sqrt{Se \cdot Sp}$ (choice of performance function based on [6]). The best results were achieved when both signals came from focal channels. Even though three focal channels were available, giving three different setup combinations, we only tested one setup to avoid overfitting.

The MPC was tested in a generic methodologically rigorous way on the FSPEEG database which contains 21 patients with 2-5 seizures each [5]. 10 patients were used for training of the algorithm's optimal settings, while the remaining 11 patients were used for testing. The seizure prediction horizon was set to 60 min, while the intervention time was 30 s.

With the new iEEG extractions from RHEEG, it was possible to obtain training and test sets with an adequate number of seizures from individual patients. Preictal data from four patients were extracted from 11, 7, 7, and 6 seizures respectively together with at least 24 h of interictal data from each individual. With a variant of the leave-one-out training and test method, the optimal number of training seizures was determined. Every possible setup for the given number of training seizures was used, so a mean and standard deviation could be estimated.

TABLE I
CLINICAL DATA TOGETHER WITH GENERIC AND PATIENT-SPECIFIC RESULTS FROM THE RHEEG DATABASE

	Patient	***1***	***2***	***3***	***4***	***Mean±Std***
	Seizures	11	7	7	6	7.8±2.2
	Interictal recordings	27 h	28 h	24 h	28 h	26.8±1.9 h
Generic	***Sensitivity* [%]**	91	85	29	0	51±44
Generic	***False prediction ratio* [h]**	0.55	0.71	0.49	0.36	0.53±0.15
Patient-specific	***Sensitivity* [%]**	87	57	86	67	74±32
Patient-specific	***False prediction ratio* [h]**	0.17	0.06	0.15	0.51	0.23±0.03

IV. Results

A. Generic Approach

The generic results in Table I are found by using the optimised parameter values from the FSPEEG database and apply them on the four new recordings from the RHEEG database. A mean of 51% of the seizures were predicted with 0.53 false predictions per hour. The results contain large variance, since patient 1 and 2 actually had sensitivities above 80 %, while patient 3 and 4 only had sensitivities at 29 and 0%.

B. Patient-Specific Approach

We wanted to test how many seizures should be used to train the parameters for the patient-specific approach. Fig. 1 shows the results when the number of training seizures is increased from one to five, which was possible for all patients in the RHEEG database. In this interval it is obvious that the sensitivity rises, without the FPR becoming much larger.

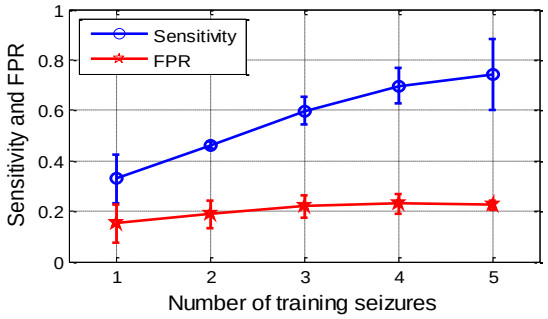


Fig. 1. Mean and standard deviation of sensitivity and false prediction ratio [/h] as function of the number of training seizures for the patient-specific method.

One patient had 11 seizures recorded, so to get a feeling on the development of the curve if more than 5 seizures were used for training, this patient was trained using up to 10 seizures. Fig 2. shows the result. Naturally, it should be noted that this result is only based on one patient, and thus very approximate.

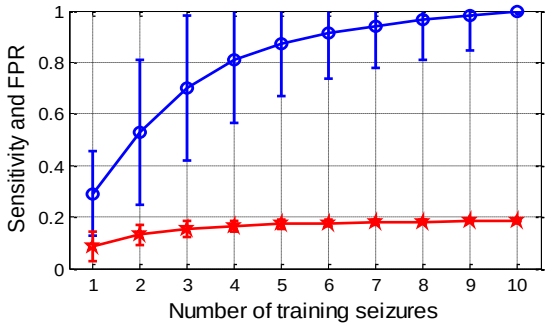


Fig. 2. Mean and standard deviation of sensitivity and false prediction ratio [/h] as function of the number of training seizures for patient 1. The sensitivity increases to 1, while FPR does not get much higher. Since this study is done on only one patient, we can only assume that an increasing number of training seizures will render better results.

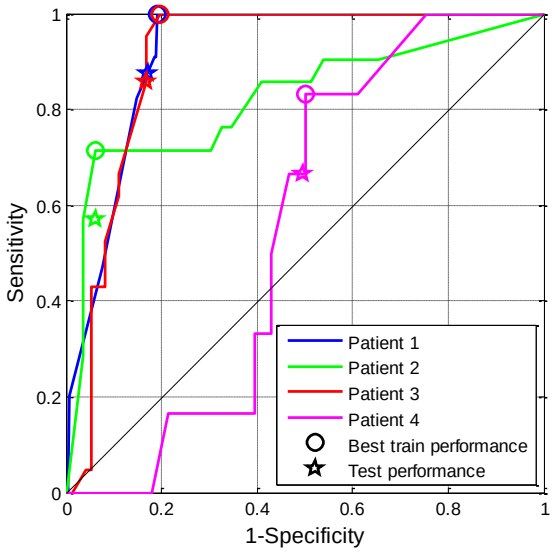


Fig. 3. ROC-curves for training of the patient-specific parameters. The rings mark the best training performance evaluated by determining the max of $P = \sqrt{Se \cdot Sp}$. Parameter values were extracted and evaluated on the test data. These results are shown by stars.

If we choose the number of training seizures to be five in the patient-specific approach, we see in Fig. 3 how the ROC-curve develops when the constant c is varied to choose the threshold mentioned in the method section. The best value is chosen by maximization of the performance function $P = \sqrt{Se \cdot Sp}$. It is shown as the round circle for each patient, and the star indicates the corresponding test performance. The sensitivity and FPR on the test data are also given in Table I. It is seen that patient 1 and 3 did best with sensitivities above 80%, while patient 2 and 4 showed sensitivities at 57 and 67%. The first three patients had low FPR while the last was at 0.51/h.

If we compare the generic results between the two different databases, as shown in Table II, we see consistency. To test for statistical significance between generic and patient-specific results, all generic results are pooled. The mean improvement between a generic and a patient-specific approach is for the sensitivity 20% (*p-value* < 0.04), and for the FPR 0.19/h (*p-value* < 0.01).

TABLE II
A COMPARISON BETWEEN GENERIC RESULTS OF THE FSPEEG AND RHEEG DATABASES

	FSPEEG		**RHEEG**		**Pooled**	
Test patients	11		4		15	
	mean	*std*	*mean*	*std*	*mean*	*std*
Sensitivity	55	39	51	44	54	39
FPR	0.38	0.16	0.53	0.15	0.42	0.17

V. Conclusion

The generic test on the FSPEEG database resulted in a {sensitivity, false prediction ratio} of {55%±39%, 0.38/h±0.16/h}, which is in the range reported by others [8]. The results from the test on the RHEEG database can be found in Table I. The generic seizure prediction results from these patients are comparable to those obtained with the patients in the FSPEEG database. When those patients uses a patient-specific approach, a mean improvement of {23%, 0.30/h} can be found. This is a statistical significant improvement.

We have shown that by making the seizure prediction algorithm patient-specific, considerable improvements were obtained in this preliminary study. Clinically applicable results were achieved from two out of four patients. So, although there is still room for further improvements, it can be expected that many epilepsy patients will benefit from patient-specific seizure prediction.

References

[1] F. Mormann, K. Lehnertz, P. David, and C. E. Elger, "Mean phase coherence as a measure for phase synchronization and its application to the {EEG} of epilepsy patients," *Physica D*, vol. 144, no. 3–4, pp. 358-369, 2000.

[2] V. Strong, S. W. Brown, and R. Walker, "Seizure-alert dogs ﬁfact or fiction?," *Seizure: European Journal of Epilepsy*, vol. 8, no. 1, pp. 62-65, 1999.

[3] K. Lehnertz et al., "State-of-the-art of seizure prediction," *J Clin Neurophysiol*, vol. 24, no. 2, pp. 147-153, 2007.

[4] F. Mormann, R. G. Andrzejak, C. E. Elger, and K. Lehnertz, "Seizure prediction: the long and winding road," *Brain*, vol. 130, no. 2, pp. 314-333, 2007.

[5] M. Winterhalder, T. Maiwald, H. U. Voss, R. Aschenbrenner-Scheibe, J. Timmer, and A. Schulze-Bonhage, "The seizure prediction characteristic: a general framework to assess and compare seizure prediction methods," *Epilepsy & Behavior*, vol. 4, no. 3, pp. 318-325, 2003.

[6] J. Henriksen, "Seizure Prediction on the Basis of iEEG Recordings," Technical University of Denmark, Master's thesis, 2008.

[7] M. G. Rosenblum, A. S. Pikovsky, and J. Kurths, "Phase Synchronization of Chaotic Oscillators," *Physical Review Letters*, vol. 76, no. 11, p. 1804, 1996.

[8] B. Schelter et al., "Testing statistical significance of multivariate time series analysis techniques for epileptic seizure prediction," *Chaos: An Interdisciplinary Journal of Nonlinear Science*, vol. 16, p. 13108, 2006.

A.3
AUTOMATIC SEIZURE DETECTION: GOING FROM SEEG TO IEEG

AUTHORS: Jonas Henriksen, Line S Remvig, Rasmus E Madsen, Isa Conradsen, Troels W Kjaer, Carsten E Thomsen, Helge B D Sorensen

JOURNAL: Conf Proc IEEE Eng Med Biol Soc. 2010

YEAR: 2010

PAGES: 2431-2434

DOI: 10.1109/IEMBS.2010.5626305

PUBLICATION HISTORY: Accepted as poster presentation at the 32nd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), Buenos Aires, Argentina
Published online, November 11th, 2010

32nd Annual International Conference of the IEEE EMBS
Buenos Aires, Argentina, August 31 - September 4, 2010

Automatic seizure detection: going from sEEG to iEEG

Jonas Henriksen[a,b,c], Line S. Remvig[c], Rasmus E. Madsen[c], Isa Conradsen[a], Troels W. Kjaer[b], Carsten E. Thomsen[d] and Helge B.D. Sorensen[a]

***Abstract*— Several different algorithms have been proposed for automatic detection of epileptic seizure based on both scalp and intracranial electroencephalography (sEEG and iEEG). Which modality that renders the best result is hard to assess though. From 16 patients with focal epilepsy, at least 24 hours of ictal and non-ictal iEEG were obtained. Characteristics of the seizures are represented by use of wavelet transformation (WT) features and classified by a support vector machine. When implementing a method used for sEEG on iEEG data, a great improvement in performance was obtained when the high frequency containing lower levels in the WT were included in the analysis. We were able to obtain a sensitivity of 96.4% and a false detection rate (FDR) of 0.20/h. In general, when implementing an automatic seizure detection algorithm made for sEEG on iEEG, great improvement can be obtained if a frequency band widening of the feature extraction is performed. This means that algorithms for sEEG should not be discarded for use on iEEG - they should be properly adjusted as exemplified in this paper.**

I. INTRODUCTION

Next to headache and stroke, epilepsy is the most common brain disorder. Of the world's population, 1% suffers from epilepsy. Most of these patients can be treated out of their recurring seizures with existing medication, behavioral changes or epilepsy surgery, but approximately 25% will continue to experience epileptic seizures [1]. These unforeseen events are a cause of social stigma for the patients, and cause considerable frustration and anxiety for themselves as well as family and friends.

A good seizure detection algorithm could provide a significant improvement of life for many patients and their relatives, if patients are properly warned or the seizures are treated. Both scalp electroencephalography (sEEG) and intracranial EEG (iEEG) can be used as modalities for automatic detection. Scientists using sEEG argue that they are able to make better detection due to the attenuation of interictal spikes and the large variety of different patterns which are not relevant for a simple classification of epileptic and non-epileptic EEG. The iEEG scientists, on the other hand, argues that they have a much better signal-to-noise ratio because their signal is not attenuated by the scalp. That is why they say they are able to see a clearer picture of what is going on in the brain especially at high frequencies.

Corresponding authors: Jonas Henriksen, medicoing@gmail.com, Helge BD Sorensen, hbs@elektro.dtu.dk
[a]DTU Electrical Engineering, Ørsteds Plads, building 349, DK-2800 Kgs. Lyngby
[b]Department of clinical neurophysiology NF-3063, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen
[c]Hypo-Safe A/S, Diplomvej 381, DK-2800 Kgs. Lyngby
[d]Dentist school, Nørre Allé 20, DK-2200 Copenhagen

A direct comparison of automatic seizure detection algorithms between the different modalities, sEEG and iEEG, is not according to our knowledge done before. The approach from [2], based on wavelet analysis and classification of seizures from sEEG has been used as a starting point and adapted to automatic classification of seizures from iEEG. An optimization of the feature extraction has been performed, and improvements will be presented.

II. MATERIALS AND METHODS

A. Clinical Data

The FSPEEG database of the Epilepsy Center of the University Hospital of Freiburg, Germany consists of iEEG recordings from 21 patients [3]. All patients suffered from medically intractable focal epilepsy and were scheduled for epilepsy surgery. Data were recorded directly from focal areas during invasive pre-surgical epilepsy monitoring in the clinic. Data were acquired using a Neurofile NT digital video EEG system with 128 channels, a sampling rate of 256 Hz, and a 16 bit analogue-to-digital converter. No filters were applied to the stored data. Out of the 128 recorded channels, six were extracted for the database by visual analysis by certified epileptologists from the Epilepsy Center. Three of these channels were labeled focal and three extra-focal. For each patient, pre- and interictal data were recorded. There were between two and five extracted intervals of 50 to 112 min of preictal activity for each patient. To be able to make a patient-specific rigorously methodological training and testing, only patients with 4 or more recorded seizures were selected. This amounted to 16 patients with a total of 74 seizures. The interictal data contained approximately 24 hours of iEEG without seizure activity. Access to the FSPEEG database is possible through https://epilepsy.uni-freiburg.de/freiburg-seizure-predictionproject/eeg-database where additional information about the dataset is also available. The flow diagram for data handling can be seen on Fig. 1.

1) Division of data: Data were divided into a patient-specific training and test set. The ictal training set consisted of all but one of the patient's ictal EEG-periods; the remaining being used as test. Performance was then evaluated using a leave-one-out cross validation scheme. For the non-ictal training set, random epochs from the first 15 min of each whole hour of recording were used. This was chosen so that we had EEG training epochs distributed over the entire day, which is important since EEG changes due to vigilance varies during the day. The number of non-ictal training epochs were optimized as a ratio of the available number of ictal epochs (Fig. 3 shows the optimization). The test was conducted on

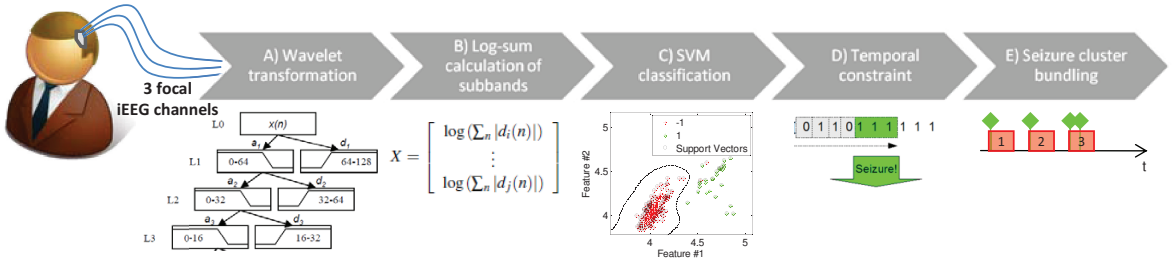


Fig. 1. Flow diagram of data handling.

the last half hour from each whole-hour recording, plus the last half hour in the preictal recording. Non-ictal testing time for each patient was then 12.5 hours.

B. Pre-processing

Epochs of 2 seconds (equaling 512 samples) were extracted and features were calculated and then classified. Each epoch overlapped the previous with 1 s. Since data were of varying quality, an artifact removal constraint was applied; if 10 or more following samples had the same value, a hardware error was anticipated and that epoch could not be classified as belonging to a seizure. For the signal $x(n)$ this can be expressed as:

$$\sum_{k=0}^{9} |x(n-k-1)-x(n-k)| = 0 \Rightarrow \\ epoch\ class = 0, \tag{1}$$

where $|\cdot|$ denotes the absolute value and $epoch\ class = 0$ means that it does not belong to a seizure. This is similar to the approach by Gotman et al.[4].

C. Feature extraction

Many features have been proposed for epileptic EEG analysis. We have chosen to focus on the wavelet analysis which is reported to be one of the best performing features for seizure detection [2].

1) Choosing the right feature: The morphology of EEG waveforms can be represented by their allocation of energy within different frequency bands. Normally, this energy is extracted by use of a short time Fourier Transform (FT). This represents the evolution of the signal spectrum over time, but it only reflects fixed frequencies during the entire time-frequency picture. The introduction of short time windows to obtain time localization information has a detrimental effect upon frequency resolution because of a reduced number of samples used in the FT calculation.

One way to avoid this detrimental effect is by applying the wavelet transform (WT) instead. It provides a much more flexible way of representing a signal because of the possibility of variable sized windows, and hence variable frequency resolutions. Thus, the WT provides accurate frequency information but poor time resolution at low frequencies and accurate time resolution but poor frequency resolution at high frequencies.

2) Multi level wavelet decomposition: While a Fourier analysis of a signal consists of sinusoid decomposition, a wavelet analysis shift and scale a mother wavelet to decompose the signal into subbands. Fig. 2 shows how the discrete wavelet transform is calculated by applying a lowpass and a highpass filter splitting the signal equally into its low and high frequency components. The resulting low frequency subband signal is called approximations, a_L, and the high frequency subband signal is called details, d_L. For each level, L, in the wavelet transform, the approximation can be divided into a new approximation and detail subband. In each iteration, the highest frequency in the detail band will be reduced by half. It is therefore possible to downsample the signal by the same amount, and thus leaving only half the data points.

The low- and highpass filters used to calculate the approximations and details were found on basis of a mother wavelet. We used the fourth member of the Daubechies

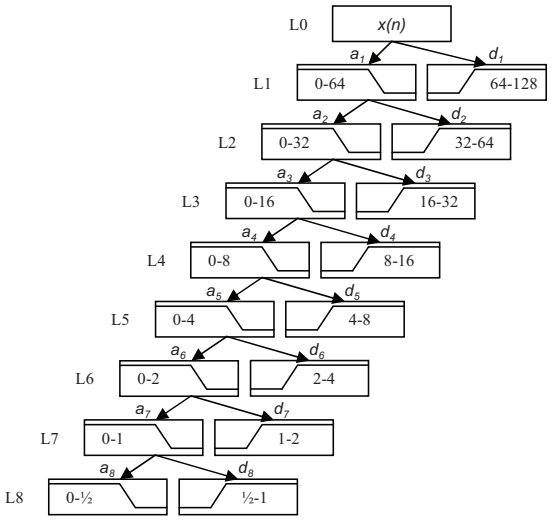


Fig. 2. 8 levels of wavelet decomposition for a signal $x(n)$ sampled at 256 Hz. a_L is the L'th approximation band, and d_L is the corresponding detail subband. The numbers in the boxes are the frequencies represented in the present box.

wavelet family. It presents a maximally flat response in its passband as well as minimal leakage in its stopband [2].

3) Log-sum transform: The subband signals $\{d_1, \ldots, d_j\}$ are not suitable to be used as input to a classifier due to high sensitivity to noise. Instead a nonlinear log operator was applied to the summed absolute signal to amplify small differences [2]:

$$F(epoch) = \begin{bmatrix} \log\left(\sum_k |d_i(k)|\right) \\ \vdots \\ \log\left(\sum_k |d_j(k)|\right) \end{bmatrix}, \qquad (2)$$

where k is running over the WT coefficients, d_i is the lowest detail band level included in the feature extraction, and d_j is the highest.

Shoeb et al. [2] reported that it was best to use the 4th to 7th decomposition level to extract features from scalp EEG when using a sampling frequency of 256 Hz. They argued that these were the time-scales corresponding to frequencies between 0.5-25 Hz where also Gotman et al. [5] had shown the characteristics of the seizure onset to be present. All lower decomposition levels did not contain any extra information. Intracranial EEG has a wider frequency band because of the high frequency attenuation by the scalp. It is therefore investigated whether an inclusion of high frequency containing decomposition levels are beneficial when using iEEG.

D. Classification

1) Support vector machine: The support vector machine (SVM) belongs to the class of machine learning classifiers, which refers to classifiers applying algorithms capable of learning from data. They work in two steps; the learning (or training) step, where the algorithm learns an optimal decision function from a set of input variables (training data), and the classification step, where it classifies new input data according to the previously learned decision function.

The SVM is a popular binary supervised learning classifier, which possesses the important property that the determination of the model parameters corresponds to a convex optimization problem, so that it will never converge to a local optimum. A general linear model serves the basis of the classifier, so it is applied in combination with a kernel method to formulate nonlinear extensions of the linear algorithm, whenever nonlinear trends in the data are present [6]. This is accomplished through proper mapping of the data to a high-dimensional kernel induced feature space.

The decision boundary is generated by maximization of the distance margin between chosen support vectors from the two classes in the training data. The support vectors are extracted from the training data by choosing those points which are most similar to the points in the opposite class. We use the SMV^{light} package specified in [7], with a nonlinear radial basis kernel which previously was shown to give the best distinction between seizure and non-seizure data [2].

2) Temporal constraints: To avoid false detections due to short-time, seizure-like activity, a temporal constrain, requires at least T consecutive 2-second iEEG epochs to be declared as belonging to the seizure class [2]. The choice of T is a trade-off between avoiding a great number of false detections between actual seizures, and maintaining the potential for short detection latencies, as well as allowing for detection of seizures of short duration. $T = 3$epochs was found to be optimal. When using 50% overlap between epochs, the shortest duration of a detectable seizure is 4 s.

E. Post-processing

When the temporal constraint is fulfilled and a seizure determined, a post-processor unifies seizure segments that are in close temporal proximity [8]. In this refractory period, new seizures cannot be classified which means that false detections that occur close to each other will only be counted as one seizure. If a seizure has multiple detections, these will also only be counted as one and thereby limit the number of false positives. The refractory period cannot be too large, since a false detection shortly before onset can make the detector miss the true onset, and thus prolong the latency. The refractory period was set to 30 s.

III. RESULTS

After an optimization which can be seen in Fig. 3 (here on the $d_1 - d_7$ wavelet transform), we found that the best performance was obtained with a ratio between ictal and non-ictal epochs of 8 and a cost-factor, J, of 0.4. This means, that in the training model, errors on the ictal examples outweigh errors on the non-ictal examples. If we let the cost-factor vary and keep all other variables constant, we get the ROC curve shown in Fig. 4. It is evident that by inclusion of the lower levels of the WT subband signals, a better performance can be obtained. There does not, however, seem to be a significant difference between inclusion of the 8th level or not. If the performance is optimized by minimization of

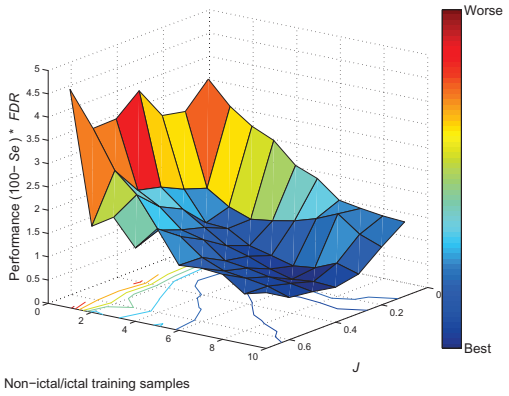


Fig. 3. Optimization of the cost-factor J and ratio between non-ictal and ictal training samples. The performance defined as $(100 - Se) * FDR$ should be as low as possible. The best result is for a $J = 0.4$ and a ratio of 8.

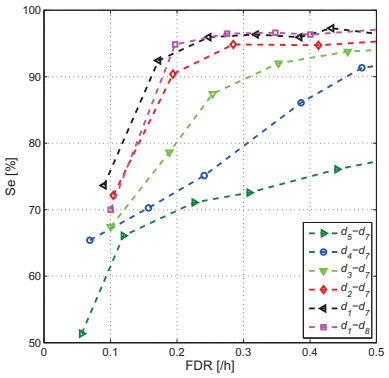


Fig. 4. ROC of results when making a feature extraction based on different levels in the WT. The blue line ($d_4 - d_7$) corresponds to our implementation of the method by Shoeb et al. [2]. It is easily observable that better performance can be obtained when expanding the levels to $d_1 - d_7$ or $d_1 - d_8$.

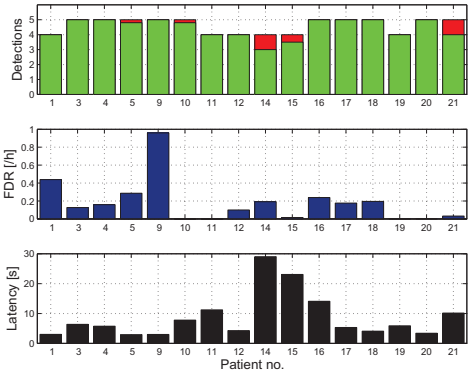


Fig. 5. Patient-specific results. In the top panel, the bars indicate the number of true positives (green) and false negatives (red). Results are based on the mean of 10 test runs.

$(100 - Se) * FDR$ the best result is a sensitivity of 96.4% and an FDR of 0.20/h corresponding to 4.8 false detections a day. The average latency of detection after seizure onset for this performance is 8.7 s.

IV. CONCLUSIONS AND FUTURE WORKS

A. Conclusions

We have shown that a feature extraction and classifier optimized for scalp EEG can be used for intracranial EEG after being properly modified. A method implemented for sEEG [2] was reported to reach a sensitivity of 91% and an FDR of 0.22/h. We showed on Fig. 4 that when implemented on iEEG it could only perform with a sensitivity of 86% and an FDR of 0.39/h when settings where similar. If the method was optimized for iEEG, i.e. inclusion of low level WT subband signals, it was possible to perform even better than the original implementation with a sensitivity of 96.4% and an FDR of 0.20/h. Atlhough the patients belonged to a quite inhomogenious group [3], it can be seen on Fig. 5 that the algorithm performed very similar across patients.

B. Future Works

In Fig. 5 it should be noted that the reason that patient 14 and 21 always have one seizure that cannot be detected, is that they suffer from two different kinds of seizures that are manifested differently in the EEG. When we train on one of the types, it was not possible to register the other type. This could had been counteracted by use of a generic training database containing EEG manifestations of different seizure types. A generic training database could also contain different artifacts which would induce a lower FDR. We will therefore look into generation of such a database.

In general could we conclude that our findings provided room for a closer collaboration in algorithm development between scientist primarily using sEEG or iEEG. We will look into improvement of existing automatic seizure detection algorithms by use of simultaneous scalp and intracranial EEG. We believe that a more robust algorithm with even better performance can be obtained when using both modalities simultaneously.

V. ACKNOWLEDGMENTS

We would like to thank the Danish Agency for Science Technology and Innovation for supporting the work by Jonas Henriksen with an industrial PhD-scholarship.

REFERENCES

[1] J. Annegers, "The epidemiology of epilepsy," *The treatment of epilepsy: principles and practice. 2nd ed. Baltimore: Williams & Wilkins*, pp. 165–72, 1997.

[2] A. Shoeb, H. Edwards, J. Connolly, B. Bourgeois, S. Ted Treves, and J. Guttag, "Patient-specific seizure onset detection," *Epilepsy and Behavior*, vol. 5, no. 4, pp. 483–498, 2004.

[3] R. Aschenbrenner-Scheibe, T. Maiwald, M. Winterhalder, H. Voss, J. Timmer, and A. Schulze-Bonhage, "How well can epileptic seizures be predicted? An evaluation of a nonlinear method," *Brain*, vol. 126, no. 12, p. 2616, 2003.

[4] J. Gotman, "Automatic recognition of epileptic seizures in the EEG.," *Electroencephalography and Clinical Neurophysiology*, vol. 54, no. 5, p. 530, 1982.

[5] J. Gotman, J. Ives, and P. Gloor, "Frequency content of EEG and EMG at seizure onset: possibility of removal of EMG artefact by digital filtering.," *Electroencephalography and clinical neurophysiology*, vol. 52, no. 6, p. 626, 1981.

[6] V. N. Vapnik, *The Nature of Statistical Learning Theory*. Springer, 1995.

[7] T. Joachims, "Learning to classify text using support vector machines: Methods, theory, and algorithms," *Computational Linguistics*, vol. 29, no. 4, 2002.

[8] A. Gardner, A. Krieger, and G. Vachtsevanos, "One-class novelty detection for seizure analysis from intracranial EEG.," *Journal of Machine Learning Research*, vol. 7, no. 6, p. 1025, 2006.

A.4
CHANNEL SELECTION FOR AUTOMATIC SEIZURE DETECTION

AUTHORS: Jonas Duun-Henriksen, Troels W Kjaer, Rasmus E Madsen, Line S Remvig, Carsten E Thomsen, Helge B D Sorensen

JOURNAL: Clinical Neurophysiology

YEAR: 2011

VOLUME: 123

ISSUE: 1

PAGES: 84-93

DOI: 10.1016/j.clinph.2011.06.001

PUBLICATION HISTORY: Published online, Juli 13th, 2011

Clinical Neurophysiology 123 (2012) 84–92

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Channel selection for automatic seizure detection

Jonas Duun-Henriksen [a,b,c,*], Troels Wesenberg Kjaer [b], Rasmus Elsborg Madsen [c], Line Sofie Remvig [c], Carsten Eckhart Thomsen [d], Helge Bjarup Dissing Sorensen [a,*]

[a] Technical University of Denmark, Department of Electrical Engineering, Building 349, Oersteds Plads, 2800 Kgs. Lyngby, Denmark
[b] Department of Clinical Neurophysiology, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen, Denmark
[c] Hypo-Safe A/S, Diplomvej 381, 2800 Kgs. Lyngby, Denmark
[d] Department of Odontology, Copenhagen University, Noerre Allé 20, 2200 Copenhagen, Denmark

ARTICLE INFO

Article history:
Accepted 2 June 2011
Available online 12 July 2011

Keywords:
Epilepsy
EEG
Automatic seizure detection
Channel selection

HIGHLIGHTS

- The current study is an evaluation of different methods for channel selection preceding automatic seizure detection.
- When choosing channels for an automatic seizure detection algorithm, best choice is the three channels with the highest variance during training seizures.
- Using the highest variance selection method, the seizure detection performance is similar to when a neurophysiologist chooses the channels he finds best suited.

ABSTRACT

Objective: To investigate the performance of epileptic seizure detection using only a few of the recorded EEG channels and the ability of software to select these channels compared with a neurophysiologist.
Methods: Fifty-nine seizures and 1419 h of interictal EEG are used for training and testing of an automatic channel selection method. The characteristics of the seizures are extracted by the use of a wavelet analysis and classified by a support vector machine. The best channel selection method is based upon maximum variance during the seizure.
Results: Using only three channels, a seizure detection sensitivity of 96% and a false detection rate of 0.14/h were obtained. This corresponds to the performance obtained when channels are selected through visual inspection by a clinical neurophysiologist, and constitutes a 4% improvement in sensitivity compared to seizure detection using channels recorded directly on the epileptic focus.
Conclusions: Based on our dataset, automatic seizure detection can be done using only three EEG channels without loss of performance. These channels should be selected based on maximum variance and not, as often done, using the focal channels.
Significance: With this simple automatic channel selection method, we have shown a computational efficient way of making automatic seizure detection.

1. Introduction

The everyday life of a person with treatment resistant epilepsy can be very frustrating. The unforeseen nature of seizures has a tremendous psycho-social effect (Gilliam et al., 1997). Though many new anti-epileptic drugs have been introduced in the last two decades, the primary outcomes have been towards avoidance of physical and psychiatric adverse effects and prevention of cognitive decline in individual patients (Lundbech and Sabers, 2002). Thus, the percentage of patients with untreatable epilepsy is still approximately 25% as it was 10 years ago (Mormann et al., 2007).

To help this group of patients in whom seizures cannot be prevented, a large group of scientists are investigating the feasibility of predicting epileptic seizures. If epileptic seizures can be predicted successfully, it will make the patient able to prepare and lie down to prevent injury from a fall or by taking a fast acting anti-convulsive drug that will prevent the seizure. Another potential of reliable seizure prediction is the automated electrical stimulation or drug intervention. In this way, a forthcoming seizure

* Corresponding authors. Addresses: Technical University of Denmark, Oersteds Plads, Building 349, Room 109, 2800 Kgs. Lyngby, Denmark. Tel.: +45 6178 9966; fax: +45 4588 0117 (J. Duun-Henriksen), Technical University of Denmark, Oersteds Plads, Building 349, Room 112, 2800 Kgs. Lyngby, Denmark. Tel.: +45 2382 3384; fax: +45 4588 0117 (H.B.D. Sorensen).
E-mail addresses: jhe@elektro.dtu.dk (J. Duun-Henriksen), hbs@elektro.dtu.dk (H.B.D. Sorensen).

1388-2457/$36.00 © 2011 Published by Elsevier Ireland Ltd. on behalf of International Federation of Clinical Neurophysiology.
doi:10.1016/j.clinph.2011.06.001

could be avoided completely. Unfortunately, it seems that all currently available methods are still not fully developed (Mormann et al., 2007). Either the prediction performance is not yet satisfactory or the results have been obtained retrospectively, and true performance in an online setting therefore not validated.

As an alternative or addition to anti-epileptic drugs, some patients could benefit from a *seizure alarm*. Warning care takers of an ongoing seizure may lead to closer observation or perhaps relevant intervention (Nicolelis, 2001). Such seizure detection system could provide a significant improvement in quality of life for many patients and their relatives.

The automatic seizure detection can also be used for daily monitoring of a patient to provide an objective, quantitative measure of seizure activity. This may enable physicians to test different medications and assess whether a change in therapy would be beneficial without repeatedly having to admit the patient for EEG monitoring.

Because the characteristics of the electrical activity of the brain change when a seizure strikes, it is reasonable to base an automatic seizure detector on EEG-recordings. One of the first widely applicable automatic seizure detection algorithms was that of Gotman (1982). He used a coefficient of variation as a measure of the duration of half-waves. Multiple studies have applied this method and shown sensitivities of 70–95% and false detection rates (FDR) of 1–3/h (Qu and Gotman, 1993). With increasing computer power more advanced algorithms have been developed and better performances obtained. Osorio et al. (2002) presented a wavelet based seizure detection algorithm that showed perfect sensitivity and only 0.1 false detections per hour. However, in their analysis, they chose to count detections of subclinical seizures as true. Khan and Gotman (2003) improved Gotman's original 1982 detection algorithm to be able to detect 90% of the seizures correctly with an FDR of only 0.3/h.

Based on these reports and other existing automatic seizure detection algorithms, several systems for epilepsy monitoring are on the market (e.g. from Zhongdazhong Medical Equipment, Shenyang City, China, Cadwell Laboratories, Kennewick, USA, Nihon Kohden Corporation, Tokyo, Japan or Natus Medical Inc. (former Stellate Systems Inc.), San Carlos, USA). In general, the automatic seizure detection algorithms function by use of one or several training seizures identified by a neurophysiologist. You can then choose either an automatic or manual channel selection, followed by a seizure classification with the systems algorithm. As mentioned, several researchers have demonstrated strong seizure detection algorithms, but the attention towards the channel selection has been limited. The importance of this can be understood by looking at 50 EEG traces in Fig. 1. Though the patient is affected by the seizures on most of the channels, it is not trivial to assess which channels are optimal for automatic seizure detection. Furthermore, if the selection is based on the assessment by a trained neurophysiologist, it is a subjective and time consuming process.

Some studies describe different ways to select the best features calculated for all channels (Minasyan et al., 2010; Shih et al., 2009). If only a limited number of features are selected, this also means that a reduced number of channels will be used. Unfortunately, it is a computationally very heavy method necessitating feature calculation for all channels during the training period followed by an optimization of feature selection. Shih et al. (2009) found the

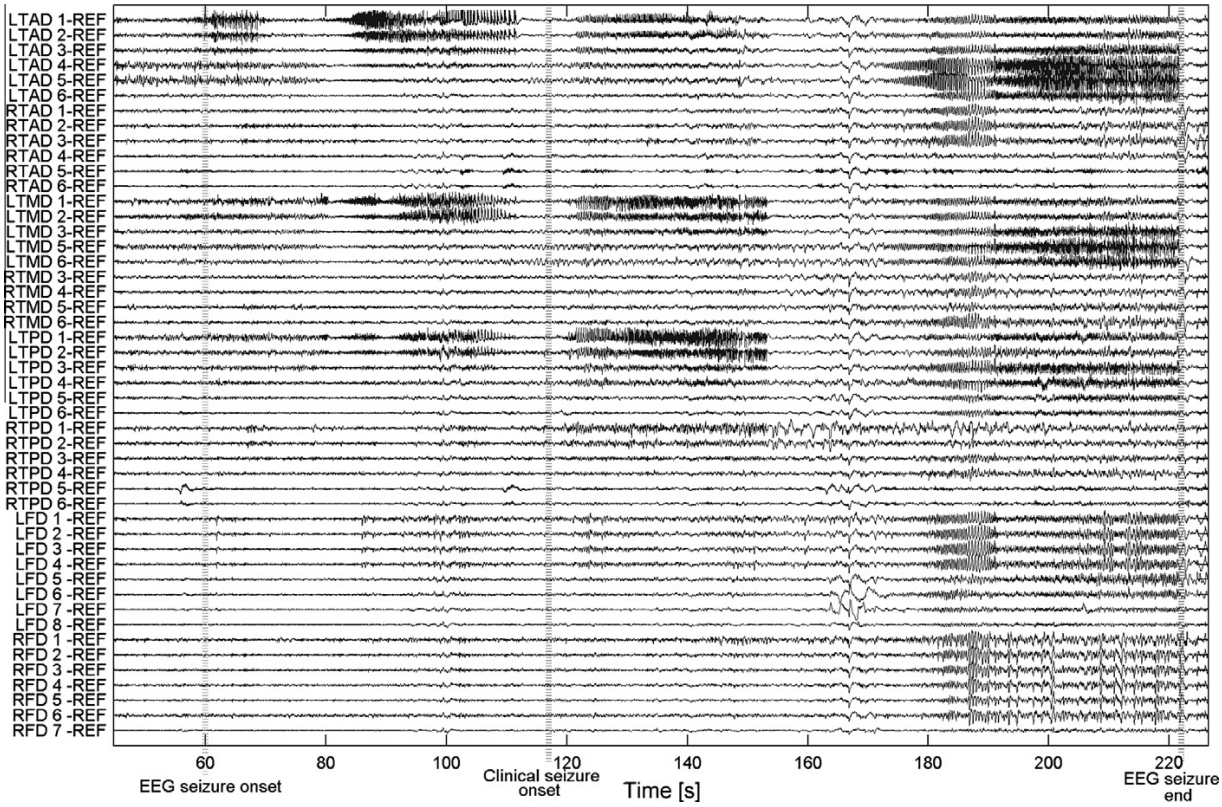


Fig. 1. Fifty intracranial EEG traces during a seizure from the recording of patient 2. Assessing which channels to use for automatic seizure detection is not always trivial. Using all the seizures from the same data set as seen above, a neurophysiologist found the focal channels to be LTAD 1 and 2 and LTMD 1. It is not obvious though, that these channels are also the best for an automatic seizure detection algorithm.

optimal number of channels to be in average 4.6 when using a feature selection approach.

In the present paper we evaluate the performance of an automatic seizure detection algorithm based on different methods for automatic selection of channels on which the detection is based. The method thus operates in two stages: first it selects the channels used for further analysis based on a simple feature, and then it performs a more comprehensive analysis by a wavelet feature extraction and support vector machine classification. In a clinical application, the number of channels recorded intracranially would not change, but the time spent by the neurophysiologist selecting the channels for automatic seizure detection analysis is eliminated. Previous papers have addressed similar multistage approaches (Glover et al., 2002; Klatchko et al., 1998). They both identify candidate segments, and then decide whether they stem from seizure activity or not. Our approach is somewhat different as it identifies the best channels for seizure detection, and then focuses the computational power on these channels.

The results are compared with detection performances from three channels recorded at the epileptogenic focus, and three channels selected by a neurophysiologist. Furthermore, we have looked at the detection performance as a function of the number of channels used as input to the algorithm for automatic seizure detection.

2. Methods

2.1. Clinical data

The Flint Hills Scientific (FHS) publicly available ECoG database consists of iEEG recordings from 10 patients undergoing inpatient intracranial monitoring for epilepsy surgery evaluation at the University of Kansas' Comprehensive Epilepsy Center, Kansas City, USA (Frei et al., 2008). Data were recorded directly from focal areas during invasive pre-surgical epilepsy monitoring in the clinic. Acquisition of data were done using conventional monitoring equipment (BMSI; Los Gatos, CA, USA) with 48–64 channels, a sampling rate of 239.75 Hz, and a 10 bit analog-to-digital converter.

The database contains a total of 59 clinical seizures in 1419 h of recorded data. *Electrode locations* are, together with *clinical seizure onset*, *EEG seizure onset* and *EEG seizure end*, given by expert visual review. Access to the FHS database is possible through http://www.fhs.lawrence.ks.us/PublicECoG.htm.

2.1.1. Division of data into training and test set

Data were divided into a patient-specific training and test set. To maintain causality in testing, training seizures were always taken from the beginning of the file, and only data after the last training seizure would be used for testing. The amount of non-ictal training epochs as a ratio of the available amount of ictal epochs was set to a ratio of 10 (Henriksen et al., 2010). All non-ictal training epochs were chosen randomly from the training set. Table 1 states the number of test seizures and hours of non-ictal test data when the first three seizures are used as training seizures.

Table 1
Overview of the 10 patients in the Flint Hills Scientific database. Test seizures and test non-ictal data are based on the use of three training seizures.

Patient no.	# of available seizures	Total amount of non-ictal data (h)	# of test seizures	Duration of test non-ictal data (h)	Duration of training seizures
1	6	85.4	3	43.1	5 min 32 s
2	4	128.4	1	83.5	4 min 34 s
3	4	98.3	1	34.0	6 min 38 s
4	7	167.2	4	78.1	6 min 0 s
5	4	92.3	1	70.1	5 min 30 s
6	8	213.9	5	83.3	5 min 31 s
7	6	234.7	3	104.8	5 min 12 s
8	3	117.6	0	40.8	3 min 40 s
9	11	138.3	8	35.6	7 min 29 s
10	6	142.1	3	66.1	4 min 27 s
Total	59	1419	29	639	54 min 33 s

2.2. Channel selection

Multiple problems of channel selection can be addressed: (1) computational load of the seizure detection algorithm increases as a function of increasing the number of channels. (2) Computational load of reducing the number of channels if doing it based on studying relevant features. (3) Robustness and reliability if using only a single channel. (4) Potential over-fitting if using many channels.

While the first two issues are merely a matter of sufficient computer power and time, these are still important to address if faster and easier algorithms can solve the same task. Issue three concerns single channel detection which has been shown to suffice for some patients (Shih et al., 2009), but lack robustness for others. The problem with the last issue is that the more channels available for feature extraction, the more features available for the classifier to discriminate complex patterns. If the seizure patterns have not spread to more than the channels above the focus, features calculated on extra-focal channels during this period will have values equivalent to features calculated on background EEG (or perhaps pre-ictal EEG). The classifier will therefore have a larger overlap between the ictal and non-ictal training data. Trying to model this overlap is over-fitting of data. Later, we will address for how many channels the over-fitting begins.

Previously, when scientists reported on automatic seizure detection algorithms, the channel selection was either based on neurophysiologists' judgement (Aschenbrenner-Scheibe et al., 2003; Osorio et al., 2002) or on the features rather than the raw data from the channels (Minasyan et al., 2010; Shih et al., 2009). When based on the neurophysiologists' judgement, it depends very much on the capabilities of the evaluator. The results of this subjective approach can vary a lot between persons, but also within one person. It depends on the person's watchfulness and experience at the given time he or she selects the channels.

Normally it is the data recorded from channels lying at the epileptic focus, and perhaps those lying in the vicinity, that constitutes the selected channels. However, those channels are chosen based on the entire recording, including the part that is later used for testing the performance of the automatic seizure detector. This retrospective use of knowledge can lead to a result that is not representative of the actual performance – especially if knowledge of the epileptic focus is based primarily on a seizure that comes from the test part of the data.

Minasyan et al. (2010) used the mutual information concept as the feature selection criterion. They report that it is a measure of general interdependence between features within each channel. This means that it is used for minimization of the number for features, but not necessarily for reduction in the number of channels. Shih et al. (2009) on the other hand, are interested in reducing the number of channels for lowering energy consumption when the EEG is used in an ambulatory setting for continuous monitoring. They use the wrapper approach (Kohavi and John, 1997) for a backward elimination feature selection. The algorithm is trained and tested with all but the features from a single channel. This is done for all the channels where upon the least influential channel is removed. The reduction of channels continues until a suitable amount is reached. With this comprehensive method, Shih et al. showed that it was possible to reduce the number of channels from

18 to a mean of 4.6 without loss in performance of automatic seizure detection on scalp EEG.

Our channel selection algorithm is designed to select the best channels as simple and fast as possible without having to make a feature extraction for all the channels. We will compare our seizure detection performance, where the channels are chosen automatically, with the results where the channels are chosen by a neurophysiologist who has only been introduced to the training data. Finally, we will see whether the algorithm actually performs better when the true focal channels are used as input channels for the classifier. Following is the description of the methods for channel selection:

2.2.1. Based on variance

A simple measure of variance of EEG signal amplitude was used to select the channels for feature extraction and classification.

$$V_{ict}(c) = \frac{1}{k}\sum_{i=1}^{k}(x_c(i) - \mu_c)^2$$

where x_c is training seizure data for channel c, μ_c is the mean of training seizure data for channel c, and k is the number of samples of training seizure data. k is thereby equal to the sampling frequency multiplied with the total length of the training seizures for each patient. The N channels used as input to the classifier were chosen as the N channels with the highest values of $V_{ict}(c)$.

$$\text{chosen channels} = \max_{1:N}\{V_{ict}(c)\}$$

This way of selecting the channels will be called '*var*' in the following.

2.2.2. Based on difference in variance

The same measure of variance was used as above, but with the extension that it was also calculated for the non-ictal training data, $V_{non\text{-}ict}(c)$. The reasoning was that $V_{non\text{-}ict}$ represents the background variance which would then be deducted.

$$V_{diff}(c) = V_{ict}(c) - V_{non-ict}(c)$$

The N input channels are selected in the same way as in the '*var*' method. We call this way of selecting the channels for '*dvar*'.

2.2.3. Based on entropy

When the EEG is seen as a random variable, the entropy is a measure of the uncertainty. The information contained in the time series is given in bits from the following equation:

$$H(c) = -\Sigma^n p(x_i)\log_2 p(x_i)$$

where $H(c)$ is the entropy for each channel c and $p(x_i)$ is the probability mass function. The N channels with highest entropy were chosen as input to the automatic seizure detector. This selection method will be called '*ent*'.

2.2.4. Based on random selection and extra focal channels

The previously described methods all choose the channels by calculation of a descriptive measure of the EEG. To show that an intelligent way of channel selection is important, two naïve methods of channels selection were employed. (1) N channels were chosen randomly without any prior knowledge. (2) The N channels were chosen as data recorded away from the epileptogenic focus. While the first method will choose channels that contain epileptic patterns from time to time, the latter method will always miss the onset.

2.2.5. Based on doctor's choice

A board certified clinical neurophysiologist was given the part of data that was preceding and including the patient's third seizure. This was the training part of the data. He was asked to choose the three channels (corresponding to $N = 3$ in the previous algorithms) best suited for distinguishing seizures. Three channels were used for the selection method called '*doctor's choice*' because this often corresponds to the number of channels located above the epileptic focus. When the different methods are compared with '*doctor's choice*' N will always be fixed to three. The neurophysiologist performing this part of the test had never seen this dataset before.

2.2.6. Based on retrospective focus knowledge

Based on all data available, a trained neurophysiologist from FHS has identified the electrodes placed above the focus of the seizures for each patient. Though this is a retrospective analysis, and thus offline, we have included the analysis of focal channels to evaluate the performance.

If only two channels were identified as focal (three cases), the nearest electrode was included as well to make the number of channels equal to those in the other tests. If more than three focal channels were identified (one case), those furthest apart were selected. Since channels recorded in the vicinity of each other have a high correlation, we chose those furthest apart to ensure most diversity in the training data. This will furthermore minimize the possibility of false positive detections due to non-seizure artifacts with a small spatial distribution.

2.3. Feature extractions

The algorithm must work online to be applicable in a continuous monitoring device. Epochs of approximately 2 s (480 samples) were extracted and features calculated. Each epoch overlapped the previous with 1 s.

Many features have been proposed for epileptic EEG seizure detection. We have decided to focus on the wavelet analysis which is reported to be one of the best performing features for seizure detection (Osorio et al., 1998; Shoeb et al., 2004).

2.3.1. Choosing the right feature

The morphology of EEG waveforms can be represented by their allocation of energy within different frequency bands. Normally, this energy is extracted using a short time Fourier Transform (FT), which in turn represents the evolution of the signal spectrum over time. The introduction of short time windows to obtain better time localization has a negative effect upon frequency resolution because of the reduced number of samples used in the FT calculation.

One way to avoid this detrimental effect is by applying the wavelet transform (WT) instead. It provides a much more flexible way of representing a signal because of the possibility of variable sized windows, and hence variable time and frequency resolutions. The WT provides accurate frequency information but poor time resolution at low frequencies and accurate time resolution but poor frequency resolution at high frequencies.

2.3.2. Multi level wavelet decomposition

While a Fourier analysis of a signal consists of sinusoid decomposition, a wavelet analysis shifts and scales a *mother wavelet* to decompose the signal into subbands. Fig. 2 shows how a discrete wavelet transform is calculated by applying a lowpass and a highpass filter splitting the signal equally into its low and high frequency components. The resulting low frequency subband signals are called approximations, a_L, and the high frequency subband signals are called details, d_L. For each level, L, in the wavelet transform, the approximations can be divided into a new approximation and detail subband signal. In each iteration, the highest frequency in the detail band will be reduced by half. It is therefore

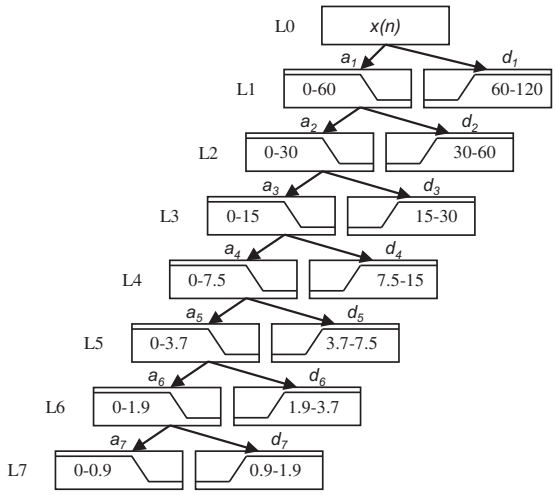


Fig. 2. Seven levels of wavelet decomposition for a signal $x(n)$ sampled at 239.75 Hz. a_L is the L'th approximation band, and d_L is the corresponding detail subband. The numbers in the boxes are the frequencies represented in the present box.

possible to downsample the signal by the same amount, and thus leaving only half the data points.

The low- and high-pass filters used to calculate the approximations and details were found on basis of a mother wavelet. A mother wavelet is a basis function used to calculate the filter characteristics. By use of the fourth member of the Daubechies wavelet family, we obtained filters presenting a maximally flat response in their passbands as well as minimal leakage in their stopbands (Shoeb et al., 2004).

The subband signals $\{d_0, \ldots, d_j\}$ are not suitable as input to a classifier due to a high sensitivity to noise. Instead, to amplify small differences, a nonlinear log operator was applied to the summed absolute signal:

$$F(epoch) = \begin{bmatrix} \log\left(\Sigma_k |d_i(k)|\right) \\ \vdots \\ \log\left(\Sigma_k |d_i(k)|\right) \end{bmatrix},$$

where k is running over the WT coefficients, d_i is the lowest detail band level included in the feature extraction, and d_j is the highest.

Shoeb et al. (2004) reported that the 4th–7th decomposition level was optimal to extract features from scalp EEG recorded with a sampling frequency of 256 Hz. They argued that these levels were the time-scales corresponding to frequencies between 0.5 and 25 Hz where also Gotman et al. (1981), have shown the characteristics of the seizure onset to be present. All lower decomposition levels, containing the high frequency components, did not contain any extra information when using sEEG. In Henriksen et al. (2010), it was shown that using intracranial EEG (iEEG) the lower decomposition levels could profitably be used. Thus, we have used $i = 1$ and $j = 7$.

2.4. Classification

2.4.1. Support vector machine

The support vector machine (SVM) belongs to the class of machine learning classifiers referring to algorithms capable of learning from data. These work in two steps; the learning (or training) step; in which the algorithm determines an optimal decision function from a set of input variables (training data), and the classification step; where it classifies new input data according to the previously learned decision function.

The SVM is a popular binary supervised learning classifier, which possesses the important property that the determination of the model parameters corresponds to a convex optimization problem, so it will never converge to a local optimum. A general linear model serves as the basis of the classifier. It is applied in combination with a kernel method to formulate nonlinear extensions of the linear algorithm, whenever nonlinear trends are present in the data (Vapnik, 1995). This is accomplished through mapping of the data to a high-dimensional kernel induced feature space.

The decision boundary is generated by maximization of the distance between chosen support vectors from the two classes in the training data. The support vectors are extracted from the training data by choosing those points which are most similar to the points in the opposite class. We use the SMV^{light} package specified in (Joachims, 1999). The kernel was chosen to be a nonlinear radial-basis kernel with a γ of 0.5 and a cost-factor J varied between 0.05 and 0.5. This cost-factor explains how the errors from the ictal epochs in the training data outweigh the errors from the non-ictal epochs. It is given as a relative measure so that a value of J between 0 and 1 means that the wrongly classified epochs from the non-ictal training set pull more in the decision boundary than the wrongly classified epochs from the ictal training set. The opposite is seen if J is larger than 1.

2.4.2. Temporal constraints

To avoid false detections due to short-time interictal discharges or other transient artifacts, a temporal constrain, T, requires at least four consecutive 2-s iEEG epochs to be declared as belonging to the seizure class by the SVM classifier (Henriksen et al., 2010). The choice of T is a trade-off between avoiding a great number of false detections between actual seizures, and maintaining the potential of short detection latencies, as well as allowing detection of short duration seizures. Using 50% overlap between epochs, the shortest duration of a detectable seizure is 5 s.

2.5. Refractory period

When the temporal constraint is fulfilled and a seizure thereby detected, a refractory time variable is initiated making it impossible to detect a new seizure (Aarabi et al., 2009; Gardner et al., 2006; Qu and Gotman, 1993). The reasoning for this process is that seizure registrations detected in close relation should be counted as only one. Thus, in the refractory period new seizures cannot be classified. False detections occurring close to each other will also be counted as only one false positive. When using a refractory period, we introduce some limitations. One disadvantage is the registration of multiple seizures closely following each other. They will be counted as only one seizure. While known that seizures often occur in "trains", we seldom see them within just 1 min of one another. By selecting a refractory period of only 30 s, as in Aarabi et al. (2009), the fusion of seizures should be avoided. Another limitation of the refractory period is that a false detection shortly before onset can make the detector miss the true onset. In our study we found that these limitations were outweighed by the advantages.

3. Results

It was our primary goals to evaluate the influence of different methods for choosing channels for automatic seizure detection, and investigate how the number of channels affected the performance. To make those assessments we computed pseudo-ROC

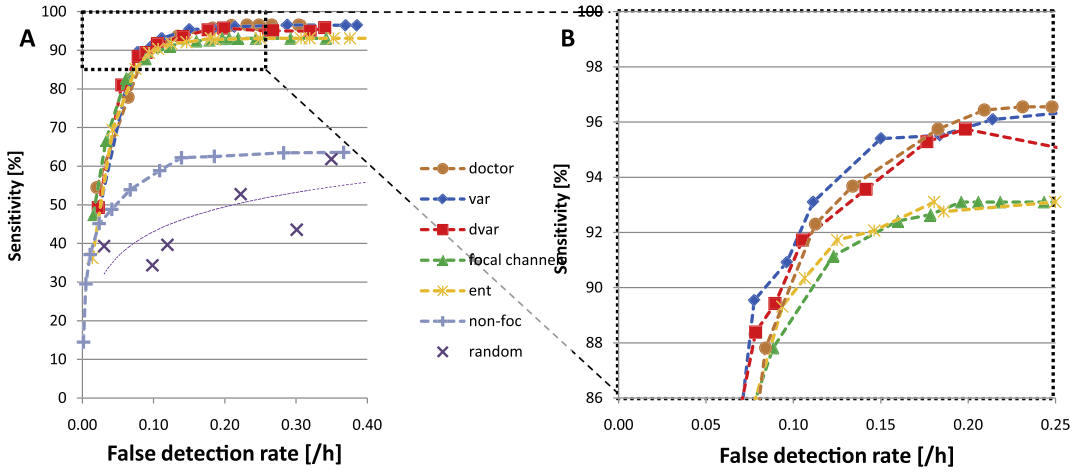


Fig. 3. ROC curves of automatic seizure detection performance dependent on different methods of selecting three channels to calculate the features upon. In (A) it is seen that the different intelligent ways of selecting the channels all perform much better than randomly selection of channels. In (B) it can be seen that the *var*, *dvar* and *doctor's choice* all perform similarly.

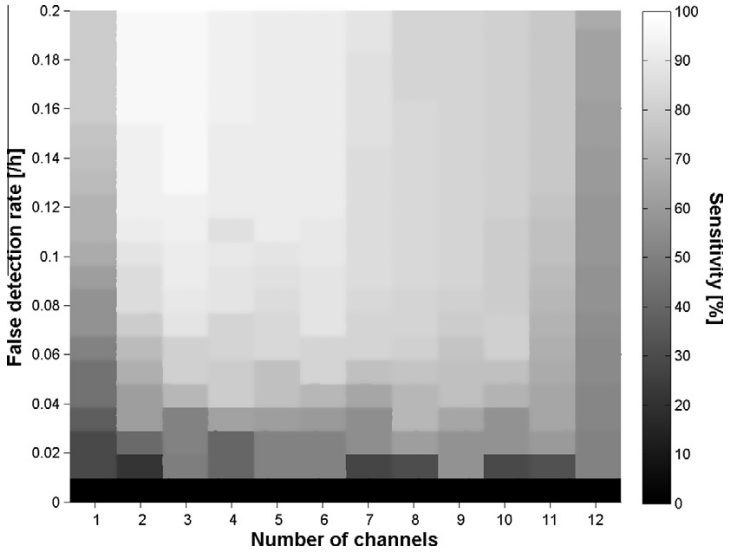


Fig. 4. Performance as a function of the used number of channels in the *var* selection method.

curves as seen in Figs. 3 and 4. They are based on sensitivity, defined as true seizure detections of all test seizures, in the ordinate axis and false detection rate, defined as false seizure detections per hour, on the abscissa. In our case, the ROC curves appear by changing the cost-factor *J* in the SVM classifier.

Fig. 3 shows the results of the different methods to choose the three optimal channels for automatic seizure detection. From (A) it is clear that if the channels are chosen randomly, it is not possible to make a satisfactory classification. If channels are instead chosen more intelligently, we are able to obtain a much better performance. (B) shows a magnification of the top left corner of the ROC curve. It is shown that the methods '*var*' and '*dvar*' perform similarly to the method '*doctor*' where a neurophysiologist has chosen the channels. If the focal channels are used instead, it is clear that sensitivity is lower for the same FDR. Table 2 compares the results for each method.

To test whether the difference between the ROC curves were statistically significant, paired *t*-tests were conducted on read-off sensitivities at fixed FDRs {0.1, 0.15, 0.2, 0.25, 0.3} for the different channel selection methods. These FDR values were chosen since they represent the clinically interesting part of the ROC curves. The *t*-tests showed that the methods '*var*', '*dvar*' and '*doctors choice*' were all statistically significant better (p-value <0.01) than the other methods. A significant difference could not be shown between these three best methods.

Naturally, the described differences in performance occur due to different channel selections. The channels selected for different cases were therefore analyzed. Table 3 states the selected channels when $N = 3$. If we look at the selected channels for patient 1, it can be seen that all the methods use channel number 18, while *doctor's choice* and *var* selection also have channel 34 in common. This means that the focal channels and *doctor's choice* have a *uniformity*

Table 2
Comparison of best performance for the different methods of selecting the three optimal channels for automatic seizure detection. Results are obtained after simulation of 30 different training models and given as mean ± standard deviation.

Method	*Focal channels*	*doctor*	*var*	*dvar*	*ent*	*non-foc*	*Randomly*
Sensitivity (%)	92.4 ± 8.8	95.7 ± 9.0	95.4 ± 11.2	95.3 ± 14.9	91.7 ± 16.6	62.2 ± 5.7	61.8 ± 24.1
FDR (/h)	0.16 ± 0.005	0.18 ± 0.006	0.15 ± 0.005	0.18 ± 0.051	0.12 ± 0.003	0.139 ± 0.006	0.35 ± 2.48

Table 3
The selected channels for each patient dependent on selection method.

Patient	Focal channels	*doctor's* choice	*var* selection
1	[18 17 19]	[18 34 35]	[18 34 3]
2	[1 2 17]	[1 2 17]	[4 1 5]
3	[9 10 11]	[9 1 18]	[9 41 27]
4	[5 17 34]	[18 34 33]	[30 25 3]
5	[17 18 1]	[1 17 3]	[1 17 2]
6	[1 3 2]	[10 11 1]	[11 10 12]
7	[61 26 27]	[10 11 57]	[18 61 10]
8	[17 18 9]	[26 33 34]	[33 1 26]
9	[17 18 19]	[18 19 26]	[26 63 41]
10	[17 18 33]	[33 17 57]	[57 33 17]

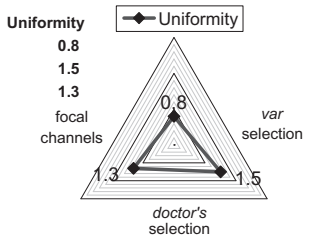


Fig. 5. The uniformity between the selected channels dependent on the selection method. The above uniformity measure is based on selection of the optimal three channels. It is a measure of how many channels the different selection methods have in common in mean.

of one, while *doctor's choice* and *var* selection have a uniformity of two for this patient. As seen on Fig. 5, the focal channels and the *var* selection method had a mean of only 0.8 channels in common per patient. The focal channels versus *doctor's choice* for automatic seizure detection algorithm had a uniformity of 1.3, while the *var* selection method and *doctor's choice* had the highest uniformity of 1.5. This means that the latter comparison showed to have half of the channels in common.

Based on the ROC curve in Fig. 3, the *var* method showed to be at least as good at selecting optimal channels as a neurophysiologist. It was therefore investigated how many channels were optimal for best automatic seizure detection. Figs. 4 and 6 show the FDR and sensitivity as a function of the number of channels. To ease the interpretation, the FDR is fixed at 0.1/h to be able to compare the sensitivities in Fig. 6B. As seen, it does not render any significant change in performance using from 2 to 6 channels. Using only one or more than six channels results in a lower sensitivity.

Fig. 4 shows that with a FDR selection higher than 0.1/h, two or three channels render the highest sensitivities, while selection of five or more channels seems to have reached the highest sensitivity at an FDR of approximately 0.12/h.

Since the performance was the same when using 2–6 channels, we might as well choose the lower number for faster computation and less power consumption. It was chosen though to continue the investigation with the use of three channels, since this often covers the area of the epileptogenic focus. With this setting, the performance for the individual patient can be investigated. Fig. 7 shows this relationship. Patient 1 has the lowest sensitivity, since one seizure is never detected independent of method for channel selection. When inspecting data, it was found that this seizure is from a different focus than those seen among the training seizures. The chosen channels are therefore never affected by that seizure. This is also the reason that the ROC curves seen in Fig. 3 never reach sensitivities higher than 96% within the given FDR limits.

4. Discussion

We have shown that with a simple selection method for finding the optimal channels for automatic seizure detection, a sensitivity of 96% and an FDR of 0.14/h can be obtained. This is comparable to a similar study by Shih et al. (2009), who reported a sensitivity of 97% and an FDR of 0.19/h. Which result is better depends on how you weigh sensitivity against FDR. A high sensitivity is important to detect as many seizures as possible, but a low FDR is also central when it is to be used by clinicians.

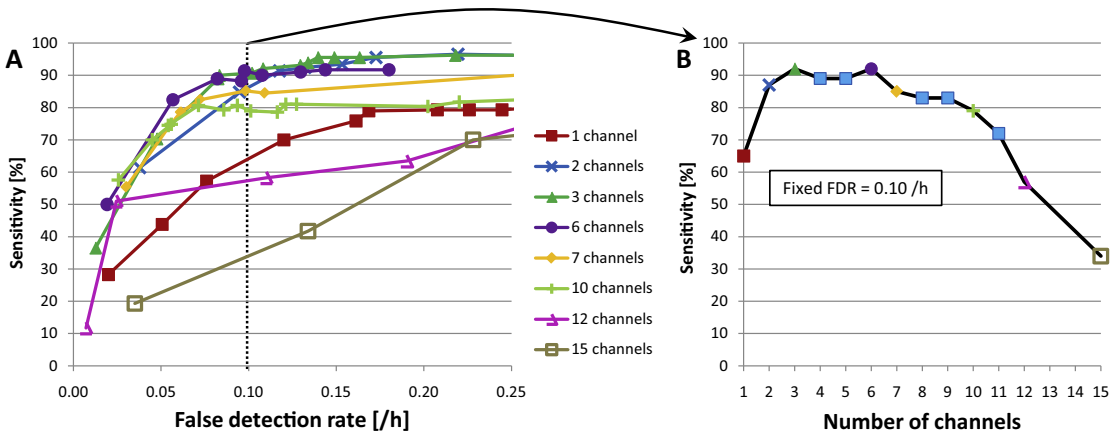


Fig. 6. (A) ROC curves for different number of channels. In (B) FDR is fixed to 0.10/h. The highest sensitivity is obtained using 3–6 channels as input.

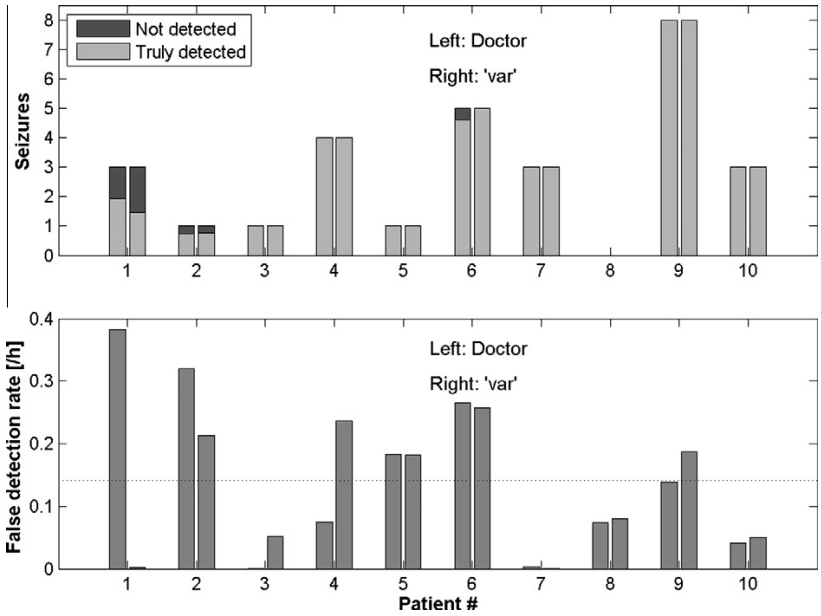


Fig. 7. Patient individual performance using the three channels selected by the neurophysiologist compared to the *var* method.

While Shih et al. used a more advanced selection method to select 4.6 channels in average we found a very simple method to extract only 2–3 channels. It should be noted though, that they use scalp EEG rather than intracranial EEG as in our case. By using intracranial EEG we have the advantage of a wider power spectrum. With a sampling frequency of 240 Hz we are able to look at frequencies up to 120 Hz according to the Nyquist criterion, although an anti-aliasing low pass filter was applied with a cut-off at 70 Hz. Still, Fisher et al. (1992), found an increase in power for frequencies above 35 Hz when an electrodecremental pattern was seen at seizure start.

4.1. The use of three channels

Regarding channel selection we argued that the neurophysiologist should select three channels since this is often the number covering the epileptic focus. Based on the optimal channel selection method '*var*', the best performance was achieved using 2–6 channels. This is not surprising considering that some partial seizures never spread to more than six channels. Selecting more means that channels without seizure EEG manifestations will be used in the automatic seizure detection algorithm. This corresponds to pure noise for the algorithm. Furthermore, in Fig. 4 it is shown that by using only two or three channels, the highest sensitivities could be obtained. Selection from three channels is thus considered a reasonable choice. Analyzing Fig. 4 also showed us, that the increasing rate of sensitivity as a function of the FDRs was similar regardless of the number of channels used.

4.2. Performance better than focal channels

That a simple channel selection method as *var* was shown to be better than the selection of channels recorded over the epileptic focus can seem odd. We believe though, that there is a logical explanation. Neurophysiologists identify focal channels on the basis of the earliest EEG changes. Though these channels contain the earliest changes it is not evident that they also have the most pronounced effect of the seizure later in the course. The *var* method selects the channels with the most pronounced effect of the seizure independent of early EEG changes. The drawback is long detection latency. However, the scope of this study was a high sensitivity and a low FDR, the detection latency was secondary. The reason for choosing this approach was based on the premise that the automatic seizure detection is used as a tool for the neurophysiologist to be guided towards the interesting parts of data. He or she should then recognize the true onset and diagnose based on this. The mean detection latency was 25.5, 17.8 and 20.9 s for the *focal channels*, *doctor's choice*, and *var* method, respectively. This is somewhat higher than what is reachable if the goal is early onset detection.

4.3. Performance similar to 'doctor's choice'

When a neurophysiologist was asked to select the optimal channels for an automatic seizure detection algorithm, we saw that the performance was similar to that of the *var* selection method. Though the ROC-curves of Fig. 3 differ a little, the difference was within normal variation. Furthermore, from Fig. 7 we obtain that the patient individual performance is similar for the *doctor's choice* and *var* method.

We also saw that the uniformity in channel selection was highest at a degree of 1.5 between *doctor's selection* and *var* selection. If the neurophysiologist's choice is defined as the golden standard, this will to some extent confirm that the channels chosen by the *var* method are reasonable.

With a simple automatic channel selection the goal of fully automatic seizure detection is closer. With the *var* selection method implemented in detection software, it is no longer necessary for the neurophysiologist to do the tedious and time consuming task of visually inspecting multiple channels of EEG data to select a proper number of EEG channels.

A sensitivity lower than 100% keeps many professionals from using automatic seizure detection software. They argue that especially the missed seizures are interesting because they often originate from a different focus and will have an influence on the diagnosis due to the potential of multiple foci. Still, a lot of time is spent in the epilepsy monitoring unit looking for alike seizures

to establish how affected the patient is. Until 100% sensitivity can be obtained, an automatic seizure detector will therefore be best fit for giving a fair guess at how many seizures a patient has. After analyzing which seizures the automatic seizure detector missed, it seems possible to obtain 100% sensitivity as long as all seizures are generalized or secondary generalized and thus evident on all channels. Twenty-four of the analyzed seizures were of this type.

Our channel selection approach can be improved by continuous evaluation of the selected channels. This would enable the program to change its focus by reselecting the channels with the highest variance. The program is not only based on the temporal evolution then, but also the spatial much as the method by Klatchko et al. (1998). An analysis of the missed seizures showed that continuous reselection of the channels would rectify all of the false negatives, but also increase the FDR. We do believe though, that tests on a larger database with more multi-focal partial seizures are necessary before we can report on total success with this approach.

The findings in the current study clearly showed that channels for automatic seizure detection should not be chosen from the focus, but rather based on the channels with the highest variance during seizures or by a neurophysiologist. Since the latter is time consuming and somewhat defeats the object of an automatic seizure detector as it requires the neurophysiologist to spend time on reading the data and getting an overall impression, our suggestion for a channel selection method provides a more automated method for seizure detection.

Financial support

The Danish Agency for Science, Technology and Innovation has paid one third of an industrial PhD scholarship supporting the work by Jonas Duun–Henriksen.

Acknowledgments

The authors would like to thank Flint Hills Scientific, L.L.C. and NIH/NINDS Grant No. 3R01NS046602-03S1 for development of the freely accessible database. Open databases are the source of better and easier comparison between scientific works. We would also like to thank Isa Conradsen and Anne Katrine Duun–Henriksen for proof reading and rewarding discussion of the results.

References

Aarabi A, Fazel-rezai R, Aghakhani Y. A fuzzy rule-based system for epileptic seizure detection in intracranial EEG. Clin Neurophysiol 2009;120(9):1648–57.

Aschenbrenner-Scheibe R, Maiwald T, Winterhalder M, Voss HU, Timmer J, Schulze-Bonhage A. How well can epileptic seizures be predicted? An evaluation of a nonlinear method. Brain 2003;126(Pt 12):2616–26.

Fisher RS, Webber WR, Lesser RP, Arroyo S, Uematsu S. High-frequency EEG activity at the start of seizures. J Clin Neurophysiol 1992;9(3):441–8.

Frei MG, Osorio I, Frei AW. The FHS publicly available ECoG database. In: Poster presentation, 62nd annual meeting of the American Epilepsy Society; 2008.

Gardner AB, Krieger AM, Vachtsevanos G, Litt B. One-class novelty detection for seizure analysis from intracranial EEG. J Mach Learn Res 2006:71025–44.

Gilliam F, Kuzniecky R, Faught E, Black L, Carpenter G, Schrodt R. Patient-validated content of epilepsy-specific quality-of-life measurement. Epilepsia 1997;38(2):233–6.

Glover JR, Ktonas PY, Shastry M, Kumar AT, Muktevi V. Methodology and system architecture for automated detection of epileptic seizures in the neonatal EEG. Annu Int Conf IEEE Eng Med Biol Proc 2002;1:70–1.

Gotman J, Ives J, Gloor P. Frequency content of EEG and EMG at seizure onset: possibility of removal of EMG artefact by digital filtering. Electroencephalogr Clin Neurophysiol 1981;52(6):626–39.

Gotman J. Automatic recognition of epileptic seizures in the EEG. Electroencephalogr Clin Neurophysiol 1982;54(5):530–40.

Henriksen J, Remvig LS, Madsen RE, Kjaer TW, Thomsen CE, Conradsen I, et al. Automatic seizure detection: going from sEEG to iEEG. Conf Proc IEEE Eng Med Biol Soc 2010;1:2431–4.

Joachims T. Making large-scale support vector machine learning practical. In: Schölkopf B, Burges CJC, Smola AJ, editors. Advances in kernel methods: support vector learning. MIT Press; 1999. p. 169–84.

Khan Y, Gotman J. Wavelet based automatic seizure detection in intracerebral electroencephalogram. Clin Neurophysiol 2003;114:898–908.

Klatchko A, Raviv G, Webber WR, Lesser RP. Enhancing the detection of seizures with a clustering algorithm. Electroencephalogr Clin Neurophysiol 1998;106(1):52–63.

Kohavi R, John GH. Wrappers for feature subset selection. Artif Intell 1997;97(1–2):273–324.

Lundbech L, Sabers A. Effect of antiepileptic drugs on cognitive function in individuals with epilepsy: a comparative review of newer versus older agents. Drugs 2002;62(4):593–604.

Minasyan GR, Chatten JB, Chatten MJ, Harner RN. Patient-specific early seizure detection from scalp electroencephalogram. J Clin Neurophysiol 2010;27(3):163–78.

Mormann F, Andrzejak RG, Elger CE, Lehnertz K. Seizure prediction: the long and winding road. Brain 2007;130(2):314–33.

Nicolelis MAL. Actions from thoughts. Nature 2001;409:403–7 [January].

Osorio I, Frei MG, Wilkinson SB. Real-time automated detection and quantitative analysis of seizures and short-term prediction of clinical onset. Epilepsia 1998;39(6):615–27.

Osorio I, Frei M, Giftakis J, Peters T, Ingram JM. Performance reassessment of a real-time seizure-detection algorithm on long ECoG series. Epilepsia 2002;43(12):1522–35.

Qu H, Gotman J. Improvement in seizure detection performance by automatic adaptation to the EEG of each patient. Electroencephalogr Clin Neurophysiol 1993;86(2):79–87.

Shih EI, Shoeb AH, Guttag JV. Sensor selection for energy-efficient ambulatory medical monitoring. Mobisys 2009:347–58.

Shoeb A, Edwards H, Connolly J, Bourgeois B, Treves ST, Guttag J. Patient-specific seizure onset detection. Epilepsy Behav 2004;5(4):483–98.

Vapnik VN. The nature of statistical learning theory. 2nd ed. New York: Springer; 1995.

A.5
AUTOMATIC DETECTION OF CHILDHOOD ABSENCE EPILEPSY SEIZURES: TOWARD A MONITORING DEVICE

AUTHORS: Jonas Duun-Henriksen, Rasmus E Madsen, Line S Remvig, Carsten E Thomsen, Helge B D Sorensen, Troels W Kjaer

JOURNAL: Pediatric Neurology

YEAR: 2012

VOLUME: 46

ISSUE: 5

PAGES: 287-292

DOI: 10.1016/j.pediatrneurol.2012.02.018

PUBLICATION HISTORY: Published online, February 14th, 2012

Pediatric Neurology 46 (2012) 287–292

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Automatic Detection of Childhood Absence Epilepsy Seizures: Toward a Monitoring Device

Jonas Duun-Henriksen MSc[a,b,c], Rasmus E. Madsen PhD[c], Line S. Remvig MSc[c], Carsten E. Thomsen PhD[d], Helge B.D. Sorensen PhD[a], Troels W. Kjaer MD, PhD[b,*]

[a] Department of Electrical Engineering, Technical University of Denmark, Lyngby, Denmark
[b] Department of Clinical Neurophysiology, Copenhagen University Rigshospitalet, Copenhagen, Denmark
[c] Hypo-Safe A/S, Lyngby, Denmark
[d] Department of Odontology, University of Copenhagen, Copenhagen, Denmark

ARTICLE INFORMATION

Article history:
Received 19 October 2011
Accepted 14 February 2012

ABSTRACT

Automatic detections of paroxysms in patients with childhood absence epilepsy have been neglected for several years. We acquire reliable detections using only a single-channel brainwave monitor, allowing for unobtrusive monitoring of antiepileptic drug effects. Ultimately we seek to obtain optimal long-term prognoses, balancing antiepileptic effects and side effects. The electroencephalographic appearance of paroxysms in childhood absence epilepsy is fairly homogeneous, making it feasible to develop patient-independent automatic detection. We implemented a state-of-the-art algorithm to investigate the performance of paroxysm detection. Using only a single scalp electroencephalogram channel from 20 patients with a total of 125 paroxysms >2 seconds, 97.2% of paroxysms could be detected with no false detections. This result leads us to recommend further investigations of tiny, one-channel electroencephalogram systems in an ambulatory setting.

Introduction

Childhood absence epilepsy is a common idiopathic generalized epilepsy syndrome [1]. It is manifested in the electroencephalogram as paroxysms of high-amplitude, bilateral synchronous, symmetric, approximately 3 Hz spike-wave patterns on an otherwise normal background. A very close correlation generally exists between paroxysms of more than 2 seconds in duration and the clinical appearance of absences characterized by interruptions of intentional behavior, impaired consciousness, and for some, a blank stare accompanied by lip smacking, upward gaze, or eye blinking. Childhood absence epilepsy presents in children between ages 4 and 10 years, peaking at ages 6-7 years. A strong genetic predisposition is evident, with occurrence more often in girls than in boys. The very frequent absences (several to hundreds a day) exert a negative impact on an otherwise normal child. Untreated children often exhibit learning and attention difficulties because of their alterations of consciousness [2].

Children diagnosed with childhood absence epilepsy usually demonstrate favorable long-term outcomes. Approximately 90% of patients become seizure-free on antiepileptic drugs [3,4], and for 65%, a total remission after 1-2 years of seizure freedom is achieved [5].

The pediatric neurologist's main objective is to neutralize all absences as long as the side effects do not exert too detrimental an effect. The goal of zero absences is motivated by cognitive issues and physical safety [3,6]. Moreover, for those reasons, scientists have studied the advantages of ambulatory electroencephalogram monitoring for better drug dosages [7-9]. Ambulatory electroencephalogram monitoring has not proved unequivocally better than routine electroencephalograms at establishing control of absences. However, ambulatory electroencephalogram monitoring does offer a broader, better understanding of the frequency and duration of paroxystic electroencephalogram activity, compared with results in the clinical setting or according to parental report. Comparisons of a parent's history of a patient's seizures, observations by nurses, intensive observations by a trained observer, routine electroencephalogram results with hyperventilation and photic stimulation, and 12-hour telemetered electroencephalography indicated that 12-hour telemetered electroencephalography was the most reliable [10]. Reportedly, parents acknowledge only 6% of daytime paroxysms lasting longer than 3 seconds [11].

* Communications should be addressed to: Dr. Kjaer; Department of Clinical Neurophysiology; Copenhagen University Rigshospitalet; Blegdamsvej 9, NF 3063; 2100 Copenhagen, Denmark.
E-mail address: neurology@dadlnet.dk

0887-8994/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.pediatrneurol.2012.02.018

In the protocol for diagnosing childhood absence epilepsy and deciding on relevant drugs and doses, a patient's history is considered together with an approximately 30-minute standard scalp electroencephalogram. To provoke an absence seizure, the child is usually asked to hyperventilate or is exposed to intermittent photic stimulation. This examination involves two shortcomings: it does not cover circadian variation, and it fails to investigate how profuse the seizures are in a normal daytime setting. On the other hand, a clinical evaluation provides the means to obtain high-quality electroencephalogram data, with few artifacts and the possibility of performing a video electroencephalogram. To cover circadian variations, patients could be admitted to an *epilepsy monitoring unit*, but this approach is considered too expensive and cumbersome in light of the limited benefits.

An ambulatory long-term electroencephalogram involves the disadvantage of creating a huge amount of data, requiring extensive resources for examination. In the 1970s and 1980s, multiple research groups sought to create an algorithm that would automatically recognize paroxystic activity in electroencephalogram recordings of children with absence seizures [12-15]. With the methods available, they did not reach sensitivities higher than 80% and false detection rates below 2/hour. These results were deemed too faulty for use in a clinical setting.

However, the automatic detection of seizures has remained a popular subject in the literature, and many authors appear unwilling to acknowledge the very different electroencephalographic morphologies dependent on type of epilepsy and seizures. Often a certain method of detecting seizures is reported to perform with a given sensitivity and specificity for epilepsy in general, although the performance is most likely accurate only for the seizures under investigation.

We investigate how well an algorithm for automatic seizure detection can perform if we limit the target group to patients with childhood absence epilepsy. The paroxystic electroencephalogram patterns of these patients are very distinct, and little intrapatient and interpatient variability is evident [16].

If patients, and especially children, are to wear an ambulatory electroencephalogram monitoring device, it should be comfortable, discreet, robust, and safe to use. The optimal solution would involve a device ready to use in any patient without need to tweak different parameters or train the algorithm in seizure patterns before putting it into operation. To meet these requirements, we chose to focus on the design of a biomedical signal-processing algorithm that is generic (i.e., works on all patients without patient-specific optimization) and able to detect paroxystic activity from only a single electroencephalogram channel. The generic nature of the device makes it much easier for the physician to apply, and the use of only a single electroencephalogram channel reduces the need for numerous annoying electrodes, wires, and demands for large recording devices.

Materials and Methods

Clinical data

Standard electroencephalogram recordings from 20 patients (13 female), diagnosed with childhood absence epilepsy, were used for training and testing an algorithm for the automatic detection of seizures. The children's mean age was 7.5 years, with a standard deviation of 1.8 years. Nineteen electroencephalogram channels were acquired according to the international 10/20 system with Cadwell Easy II (Cadwell Laboratories, Inc., Kennewick, WA) (18 patients) or Stellate Harmonie (Stellate Systems, Inc., Montreal, Quebec, Canada) (two patients). All channels were filtered with a pass band of 0.53-70 Hz, and digitized at a rate of 200 Hz. In total, 125 paroxysms longer than 2 seconds were identified (47% of all paroxysms) by a board-certified clinical neurophysiologist. In total, 11 hours and 23 minutes of electroencephalogram data were available. All data analysis was performed using MATLAB (The MathWorks, Inc., Natick, MA). Single-channel analysis was performed on channels from a transversal montage and a longitudinal montage. Data were divided into 2-second epochs, with 50% overlap between each.

To perform a proof-of-concept evaluation on a real-world ambulatory measurement, we applied our algorithms to 4 nonconsecutive days of measurement on an 11-year-old boy with newly detected spike-wave paroxysms. The patient began to receive valproate after the first recording day. Data were recorded with a four-channel ActiWave device (CamNtech, Ltd., Cambridge, United Kingdom), with a 128 Hz sampling rate and a pass band of 0.3-50 Hz. Analyzed electrodes were positioned corresponding to the frontal channel: F7-Fp1.

Feature extraction

The well explored *wavelet transform* has proved a strong method to characterize electroencephalogram signals [17-19]. Regarding the description of absence paroxysms, the Daubechies 4 *mother wavelet* has proved especially efficient [20,21]. Despite multiple reports on the irrelevance of detailed decompositions containing frequencies above 30 Hz in scalp electroencephalograms [17,22], we chose to explore the relevance of the first detail levels, down to level 6 (annotated as d6). With a sampling frequency of 200 Hz, the multilevel wavelet detail decomposition contains several frequencies: d1, 50-100 Hz; d2, 25-50 Hz; d3, 12.5-25 Hz; d4, 6.25-12.5 Hz; d5, 3.13-6.25 Hz; and d6, 1.56-3.13 Hz. To capture the information of waveform components within each of the sub-band signals, the absolute log-sums of each of the decomposed 2-second epochs were computed, as in our previous work [19].

To improve the robustness of the algorithm further, the number of zero crossings and a maximum threshold for absolute amplitude were applied to recognize artifacts. If more than 20 positive zero crossings were registered during a 2-second epoch, the signal most likely originated from a muscle artifact, and was therefore not considered an epileptic paroxysm. Likewise, a maximum threshold of ± 800 μV signal amplitude from baseline was set to recognize distortion or other high-amplitude artifacts.

Classification

The challenge of detecting seizures was treated as a binary classification problem. We used the SVM^{light} implementation of a support vector machine classifier for MATLAB [23]. Given a set of training examples, each marked as containing a paroxystic electroencephalogram or not, the support vector machine training algorithm builds a model for classification. This model uses only the training examples best suited for obtaining the largest margin between the two categories. The algorithm does so by mapping the training examples into a higher dimensional space, using a radial basis kernel. A hyperplane that splits the examples as cleanly as possible is then fitted. When being mapped back to the original feature space, the separation boundary becomes nonlinear. Examples from the test set are mapped into that same space and categorized as belonging to a paroxysm or not, according to which side of the boundary they fall on.

To obtain a generic algorithm, we used a triple-repeated fivefold cross-validation, in which each fold contained 16 patients for training the model, and four patients for testing. This method was recommended for evaluations of the algorithm, because it yields very accurate performance estimations [24].

The model was optimized based on the input vectors (containing the detail decomposition levels), which channel to use (tested as both a transversal and longitudinal montage), the width of the kernel-specific parameter ($\gamma = 0.5$, 1, 2, or 4), and the cost factor that determines how errors by the paroxystic electroencephalographic examples (false negatives) outweigh errors by the normal electroencephalographic examples (false positives) ($C = 0.17$, 0.20, 0.23, or 0.26).

After optimizing the model, the best parameters were chosen for each channel. The robustness of this model was evaluated with an addition five repetitions of the fivefold cross-validation, to avoid a biased result.

Results

A typical paroxysm recorded from channel F7-Fp1 is presented in Fig 1, together with its wavelet decompositions. Comparing the decompositions with the original signal, decomposition d1-d3, containing the high frequencies, describes primarily the spikes, whereas decomposition d5-d6 describes the wave portion of the paroxysm. This result indicates that investigating all decomposition levels could be valuable, despite previous reports on the insignificance of detail levels containing high frequencies. Such an analysis is presented in Fig 2. The tendency points toward an advantage of choosing decompositions that include at least level 1 or 2. The optimal performance is obtained using decomposition levels d1-d4. This approach renders a sensitivity of 97.2%, and no false detections. We performed the same investigation on the remaining 31 channel configurations, and the results were similar.

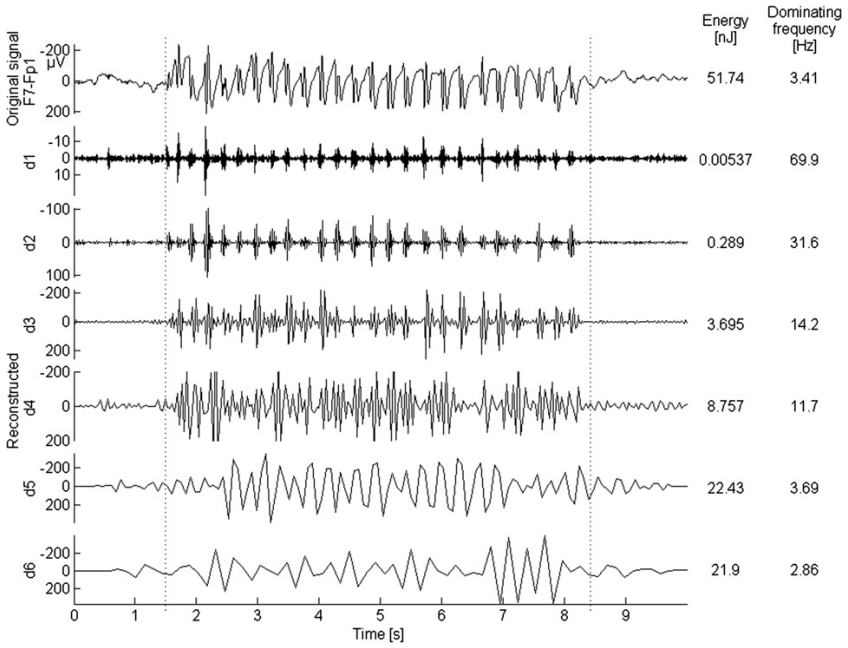


Figure 1. A typical childhood absence epilepsy paroxysm recorded at electrode position F7-Fp1, and its corresponding reconstructed wavelet decompositions. Decompositions d1-d3 primarily describe the spike portion of the paroxysm, whereas d5-d6 explain the wave portion. The energy and dominating frequency of each decomposition band are presented at right.

The remaining 2.9% of paroxysms that went undetected were investigated to assess the shortcomings of the algorithm. Figure 3 depicts both a detected and nondetected paroxysm from the same patient. At left, a normal polyspike-wave paroxysm of approximately 3 Hz is illustrated. The patient manifested 11 such paroxysms during the 32-minute electroencephalogram recording. The problem was that she also manifested three paroxysms similar to the tracings at the right in Fig 3. These paroxysms were identified as paroxysms during dozing, and were the only three paroxysms among all the patients that were not detected by the algorithm.

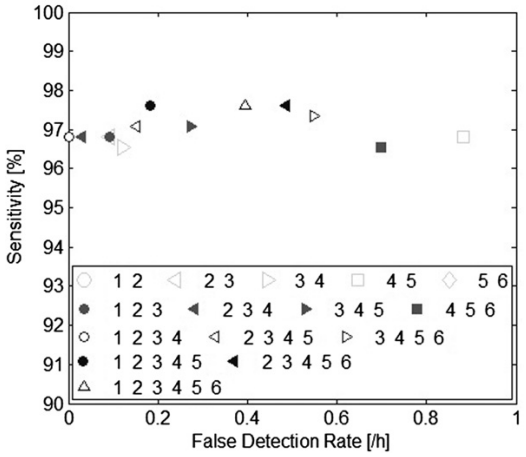


Figure 2. The relationship between performance and the wavelet decomposition bands of channel F7-Fp1. Using d1-d4 produces no false detections, without significantly lowering the sensitivity. Only the results of consecutive detail bands are presented.

Maintaining decompositions d1-d4, we examined the spatial performance for all of the bipolar channels. Figure 4 provides an overview of the sensitivities and false detection rates for channels derived in a transversal and longitudinal montage. Symmetry of the performance across the midline is evident, when dividing the signals from the two hemispheres. Such symmetry is classic in idiopathic generalized epilepsy [25]. Furthermore, the performance is notably better in the anterior part of the brain, with channels F7-Fp1 and Fp2-F8 superior to the remaining bipolar derivations.

All paroxysms registered by the neurophysiologist as longer than 2 seconds exhibited a mean duration of 11.0 seconds, and a standard deviation of 8.1 seconds. The mean duration estimated by the algorithm was 1.4 seconds shorter than those estimated by the neurophysiologist, with a standard deviation of 2.1 seconds. This estimation is considered very accurate. Furthermore, the mean latency from electroencephalogram onset to declared onset by the algorithm was quite reliable. Paroxysms were detected 0.74 second after onset, with a standard deviation of 0.87 second.

Because the clinical relevance of the 2-second cutoff on the duration of paroxysms may be debated, we examined the relationship between cutoff time and detection performance. Figure 5 depicts the relationship between the defined minimum length of paroxysms and sensitivity with no false detections. The performance improved up to a length of 2 seconds, whereupon it stalled. The final improvement up to 100% is not achieved until a length of 8.6 seconds is reached. This result is attributable to the doze paroxysms already mentioned. The problem of raising the defined lower paroxysm length is evident in the graph depicting the number of detected paroxysms per patient: it declines as the lower limit rises. At 2 seconds, the number of detected paroxysms per patient has not yet dropped dramatically.

Table 1 provides an overview of the performance when the algorithm was applied to the ambulatory data. Because data were recorded somewhat differently than at the standard setting in the

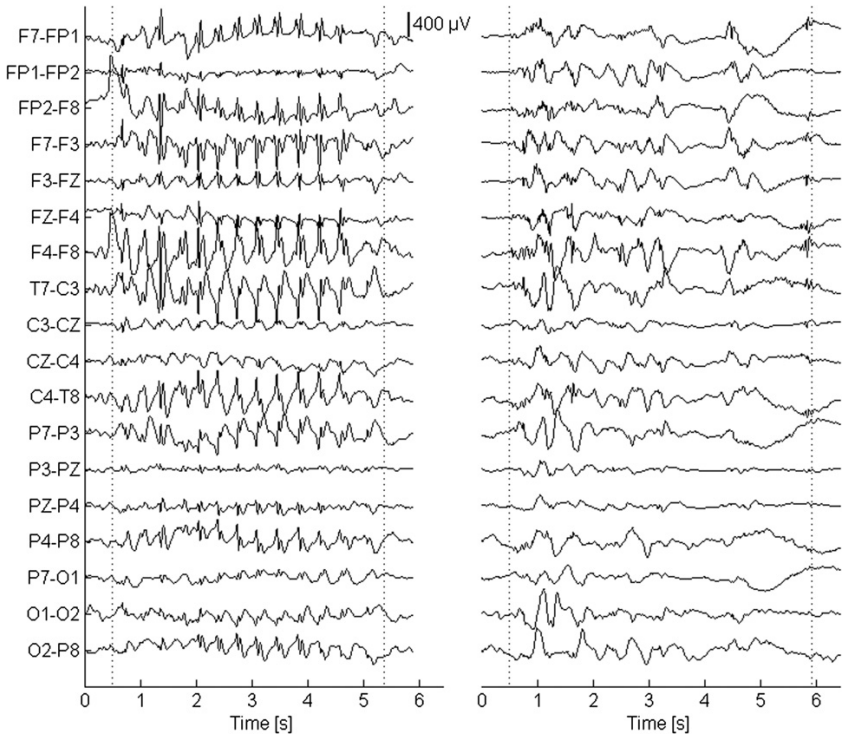


Figure 3. A detected (left) and a nondetected (right) paroxysm for channel F7-Fp1 from the same patient. Both paroxysms were obtained while the patient was dozing. The left paroxysm demonstrates the typical appearance of generalized epilepsy. The right paroxysm is characterized by irregular, diffuse 2-4 Hz activity and spikes, without the typical, regular appearance of generalized epilepsy. This patient manifested three paroxysms similar to the one at the right, which caused the 2.9% false negative detections.

outpatient clinic, we chose to use the first day for training, and the rest for testing. Without further adjustments of the algorithm, we were able to detect 19 of 20 paroxysms (sensitivity of 95%), with only two false detections (false detection rate of 0.037/hour).

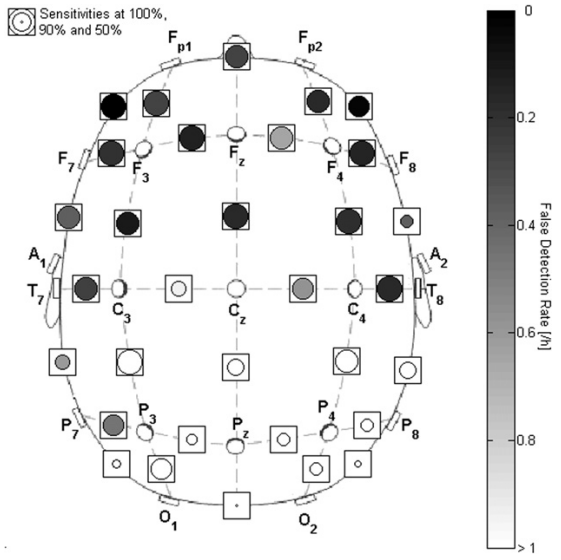


Figure 4. Overall performance of the seizure detection algorithm for all bipolar channel registrations. Frontal channels are superior in detection performance. The symmetry across the midline of the brain was expected. A, auricular point; C, central lobe; F, frontal lobe; O, occipital lobe; P, parietal lobe; T, temporal lobe.

Discussion

Previous findings

Several recent studies focused on the detection of absence seizures [20,26-28]. Adeli et al. [20] analyzed the frequency content and time-related course during two absence seizures. They concluded that the wavelet transform based on a Daubechies 4 mother wavelet is appropriate to describe the spike-wave electroencephalogram signal, and only frequencies below 30 Hz are clinically relevant. Subasi [26] analyzed four channels of electroencephalograms from five patients with absence seizures. He based his detection system on a wavelet transform and an adaptive neuro-fuzzy inference system for classification. Using his database of limited size, he reported a correctly classified epoch performance of 94%. Xanthopoulos et al. [27] studied six patients with absence seizures who were monitored in an ambulatory setting. They applied the wavelet transform on 16 bipolar channels, and classified the epochs based on a sliding variance technique. Discarding paroxysms shorter than 2.1 seconds, their approach resulted in a sensitivity of 97.25% and a false detection rate of 1.0/hour. Finally, in an earlier study [28], our group applied a wavelet transform feature extraction and support vector machine classifier to a single frontal channel from 19 patients with childhood absence epilepsy. Discarding paroxysms shorter than 2 seconds, we obtained a sensitivity of 99.1% and a false detection rate of 0.5/hour.

In the present study, the implementation of a preprocessing step for artifact rejection and a more reliable parameter optimization procedure have especially improved the detection performance in single-channel recordings. Our approach resulted in a sensitivity of 97.2%, with no false detections. The missed paroxysms all

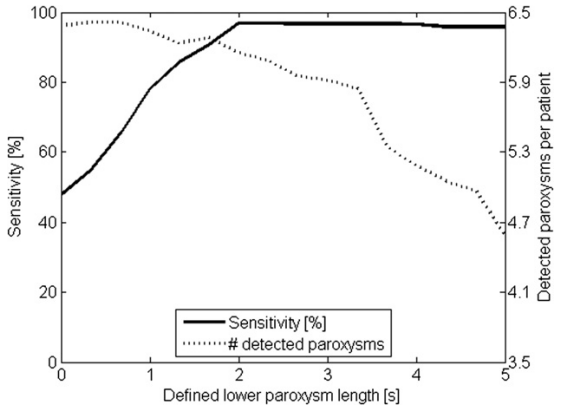


Figure 5. Sensitivity and number of detected paroxysms per patient, as a function of the defined lower paroxysm length. The sensitivity increases up to 2 seconds, whereupon it stalls. Although sensitivity increases as a function of lower paroxysm lengths, the number of detected paroxysms per patient decreases because of fewer paroxysms available for analysis.

originated from the same patient. Figure 3 demonstrates one of the false negative registrations while the patient is dozing. It is characterized by irregular, diffuse 2-4 Hz activity and spikes, without the typical regular appearance of generalized epilepsy. On the other hand, the overall appearance points more toward an epileptic discharge than a normal nonepileptic dozing paroxysm. The electric discharge is especially low on channel F7-Fp1. For that reason, the detection algorithm cannot detect the paroxysm on this channel. When analyzing F4-F8, for example, no problem was evident in detecting this paroxysm, but the channel demonstrated problems with other paroxysms.

The generic approach

The scope of automatic seizure detection based on a single channel suitable for all patients is very ambitious. A *patient-independent* approach to automatic seizure detection is generally described as inferior to a *patient-specific* approach [17,29]. This finding probably also applies to most types of seizures, but the discharges during childhood absence epilepsy are quite homogeneous, both within and between patients. Our detection performance is equal to or better than those in state-of-the-art automatic seizure detection algorithms for multichannel, patient-specific, scalp or intracranial electroencephalograms [30,31].

Levels of detail bands

Despite previous reports, we investigated all decomposition levels from 1-6, containing frequencies from 1.56-100 Hz. We based this approach on visual inspections of reconstructed decompositions, as depicted in Fig 1. Although energy levels were a factor of more than 1000 lower for the detail decomposition d1 compared with d5, the energy still increased during the seizure. As depicted in Fig 2, to include the low levels of decompositions proved beneficial. The best performance was obtained using d1-d4, containing frequencies of 6.25-100 Hz. Because absence seizures are defined as exhibiting a dominating frequency of around 3 Hz, the exclusion of decomposition levels containing the lower frequencies may seem counterintuitive. However, an investigation of the performance for d1-d5 indicated that these features resulted in false detections because of artifacts during heavy eye-blinking, with only a slight increase in true detections (sensitivity, 97.6%; rate of false detections, 0.18/hour). In contradiction to previous reports, we therefore propose that high-frequency decomposition levels are superior to low-frequency levels when used for the automatic detection of seizures in childhood absence epilepsy.

Short paroxysm detection

Our method contains the putative shortcoming that it is designed only to detect paroxysms longer than 2 seconds. This design strengthens the robustness of the algorithm, leading to excellent detection performance. Although brief paroxysms of spike-waves involve a low likelihood of affecting complex tasks [32,33], all spike-wave paroxysms should be treated, regardless of duration [34].

Difficulties arise when seizure frequency and duration are assessed according to an estimate from a parent. When a well instructed parent is asked to note absences of normal duration (4-20 seconds), they report only 6% of them because of very subtle clinical manifestations. When the duration drops below 3 seconds, the clinical signs are likely never to show [11]. Thus parents will be unlikely to recognize paroxysms shorter than 2 seconds. Our method is therefore likely to outperform registrations made by nonprofessionals. With that said, the ability to detect short paroxysms would also allow for evaluations of whether persisting or increased epileptiform abnormalities occur during antiepileptic drug withdrawal. These abnormalities demonstrated a statistically significant association with clinical outcomes in patients with idiopathic generalized epilepsy, and are therefore of utmost interest [35].

Although childhood absence epilepsy is a generalized type of epilepsy, focal paroxysms are known to occur [36,37]. If they originate from areas not included in the analyzed channel, they may not be detected. Mariani et al. investigated the electroencephalograms of 29 patients in which focal abnormalities were observed in 38% of the children, predominantly in the frontal regions in all cases [38]. In general, the frequency of appearances decreased in follow-up electroencephalograms, proportional to the number of typical absences. The presence of abnormalities did not seem to change the benign prognosis of childhood absence epilepsy.

Although focal paroxysmal abnormalities may not be detected by our algorithm, this shortcoming seems of minor importance to the overall medical evaluation. The only approach to avoid these problems involves recording a full international 10-20 system scalp electroencephalogram. The benefits of a small and comfortable device are then eliminated.

Childhood absence epilepsy as one of many epileptic syndromes

Most studies of automatic seizure detection today are evaluated via scalp or intracranial electroencephalogram recordings from adults. Surprisingly few evaluate their algorithms with absence seizures, and those that do often conflate all epilepsy types with typical absence seizures into one group. This practice is not sensible, because the various epileptic syndromes are quite heterogeneous [1]. Such a diverse group of patients cannot be expected to

Table 1. Performance of the algorithm in a real-world ambulatory example

Day	True Positives	False Negatives	False Positives
1	Nine paroxysms used for training		
2	17	1	1
3	2	0	1
4	0	0	0
Total	19	1	2

present the same homogeneous appearance of epileptic paroxysms in electroencephalograms as a group limited to patients with childhood absence epilepsy. We therefore view our investigation as a major leap forward in the research toward better monitoring and drug optimization for patients with childhood absence epilepsy.

Our aims for future work include further testing on ambulatory data. Our proof-of-concept evaluation indicates that applying the algorithm to real-world measurements, based on the setting of the hospital, is highly feasible.

The authors thank the nurses and technicians at the Department of Clinical Neurophysiology, Copenhagen University Rigshospitalet, who performed all the measurements. The authors also thank Hans Hoegenhaven, MD, and Peter Uldall, MD, PhD, for rewarding discussions during preparation of the manuscript.

The Danish Agency for Science, Technology and Innovation has supported the work of Jonas Duun-Henriksen by granting one third of an industrial PhD scholarship. The rest was granted by the company Hypo-Safe A/S. Rasmus E. Madsen and Line S. Remvig are both employed full-time at Hypo-Safe A/S. Drs. Thomsen, Sorensen, and Kjaer do not have any financial interest in Hypo-Safe A/S.

References

[1] Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989;30:389–99.
[2] Bennett TL, Ho MR. The neuropsychology of pediatric epilepsy and antiepileptic drugs. In: Reynolds CR, Fletcher-Janzen E, editors. Handbook of clinical child neuropsychology. Boston: Springer; 2009. p. 505–16.
[3] Olsson I, Hagberg G. Epidemiology of absence epilepsy. III. Clinical aspects. Acta Paediatr Scand 1991;80:1066–72.
[4] Loiseau P, Duché B, Pédespan JM. Absence epilepsies. Epilepsia 1995;36: 1182–6.
[5] Wirrell EC, Camfield CS, Camfield PR, Gordon KE, Dooley JM. Long-term prognosis of typical childhood absence epilepsy: Remission or progression to juvenile myoclonic epilepsy. Neurology 1996;47:912–8.
[6] Camfield C, Camfield P. Management guidelines for children with idiopathic generalized epilepsy. Epilepsia 2005;46(Suppl. 9):112–6.
[7] de Feo MR, Mecarelli O, Ricci G, Rina MF. The utility of ambulatory EEG monitoring in typical absence seizures. Brain Dev 1991;13:223–7.
[8] Duchowny MS. Intensive monitoring in the epileptic child. J Clin Neurophysiol 1985;2:203–19.
[9] Waterhouse E. New horizons in ambulatory electroencephalography. IEEE Eng Med Biol Mag 2003;22:74–80.
[10] Browne T, Dreifuss F, Penry J, Porter R, White B. Clinical and EEG estimates of absence seizure frequency. Arch Neurol 1983;40:469–72.
[11] Keilson MJ, Hauser WA, Magrill JP, Tepperberg J. Ambulatory cassette EEG in absence epilepsy. Pediatr Neurol 1987;3:273–6.
[12] Smith RG, Houge JC, Webster JG. Portable device for detection of petit mal epilepsy. IEEE Trans Biomed Eng 1979;26:445–50.
[13] Quy R, Fitch P, Willison R. High-speed automatic analysis of EEG spike and wave activity using an analogue detection and microcomputer plotting system. Electroencephalogr Clin Neurophysiol 1980;49:187–9.
[14] Koffler DJ, Gotman J. Automatic detection of spike-and-wave bursts in ambulatory EEG recordings. Electroencephalogr Clin Neurophysiol 1985; 61:165–80.
[15] Carrie JR, Frost JD. Clinical evaluation of a method of quantification of generalized spike-wave EEG patterns by computer during prolonged recordings. Comput Biomed Res 1977;10:449–57.
[16] Baier G, Hermann T, Sahle S, Stephani U. Sonified epileptic rhythms. Proc Conf Audit Display; 2006:148–51.
[17] Shoeb A, Edwards H, Connolly J, Bourgeois B, Treves ST, Guttag J. Patient-specific seizure onset detection. Epilepsy Behav 2004;5:483–98.
[18] Gardner AB, Krieger AM, Vachtsevanos G, Litt B. One-class novelty detection for seizure analysis from intracranial EEG. J Mach Learn Res 2006;7:1025–44.
[19] Henriksen J, Remvig LS, Madsen RE, et al. Automatic seizure detection: Going from sEEG to iEEG. Conf Proc IEEE Eng Med Biol Soc; 2010:2431–4.
[20] Adeli H, Zhou Z, Dadmehr N. Analysis of EEG records in an epileptic patient using wavelet transform. J Neurosci Methods 2003;123:69–87.
[21] The MathWorks, Inc. Wavelet toolbox. Version 4.3. Natick, MA: The MathWorks, Inc.; 2008.
[22] Subasi A. Automatic detection of epileptic seizure using dynamic fuzzy neural networks. Expert Syst Appl 2006;31:320–8.
[23] Joachims T. Making large-scale support vector machine learning practical. In: Schölkopf B, Burges CJC, Smola AJ, editors. Advances in kernel methods: Support vector learning. Cambridge, MA: MIT Press; 1999. p. 169–84.
[24] Refaeilzadeh P, Tang L, Liu H. Cross-validation. In: Liu L, Özsu MT, editors. Encyclopedia of database systems. New York: Springer Publishing Company; 2009. p. 512–38.
[25] Gloor P. Generalized epilepsy with spike-and-wave discharge: A reinterpretation of its electrographic and clinical manifestations. The 1977 William G. Lennox Lecture, American Epilepsy Society. Epilepsia 1979;20:571–88.
[26] Subasi A. Application of adaptive neuro-fuzzy inference system for epileptic seizure detection using wavelet feature extraction. Comput Biol Med 2007;37:227–44.
[27] Xanthopoulos P, Rebennack S, Liu C-C, et al. A novel wavelet based algorithm for spike and wave detection in absence epilepsy. Conf Proc IEEE BIBE. 2010:14–9.
[28] Petersen EB, Duun-Henriksen J, Mazzaretto A, Kjaer TW, Thomsen CE, Sorensen HBD. Generic single-channel detection of absence seizures. Conf Proc IEEE Eng Med Biol; 2011:4820–3.
[29] Wilson SB. Algorithm architectures for patient dependent seizure detection. Clin Neurophysiol 2006;117:1204–16.
[30] Minasyan GR, Chatten JB, Chatten MJ, Harner RN. Patient-specific early seizure detection from scalp electroencephalogram. J Clin Neurophysiol 2010;27: 163–78.
[31] Duun-Henriksen J, Kjaer TW, Madsen RE, Remvig LS, Thomsen CE, Sorensen HBD. Channel selection for automatic seizure detection. Clin Neurophysiol 2011;123:84–92.
[32] Goode DJ, Penry JK, Dreifuss FE. Effects of paroxysmal spike-wave on continuous visual-motor performance. Epilepsia 1970;11:241–54.
[33] Opp J, Wenzel D, Brandl U. Visuomotor coordination during focal and generalized EEG discharges. Epilepsia 1992;33:836–40.
[34] Browne TR, Penry JK, Porter RJ, Dreifuss FE. Responsiveness before, during, and after spike-wave paroxysms. Neurology 1974;24:659–65.
[35] Galimberti CA, Manni R, Parietti L, Marchioni E, Tartara A. Drug withdrawal in patients with epilepsy: Prognostic value of the EEG. Seizure 1993;2:213–20.
[36] Caraballo RH, Fontana E, Darra F, et al. Childhood absence epilepsy and electroencephalographic focal abnormalities with or without clinical manifestations. Seizure 2008;17:617–24.
[37] Yoshinaga H, Ohtsuka Y, Tamai K, et al. EEG in childhood absence epilepsy. Seizure 2004;13:296–302.
[38] Mariani E, Rossi LN, Vajani S. Interictal paroxysmal EEG abnormalities in childhood absence epilepsy. Seizure 2011;20:299–304.

A.6
CORRELATION BETWEEN INTRA- AND EXTRACRANIAL BACKGROUND EEG

AUTHORS: Jonas Duun-Henriksen, Troels W. Kjaer, Rasmus E. Madsen, Line S. Remvig, Carsten E. Thomsen, and Helge B.D. Sorensen

JOURNAL: Conf Proc IEEE Eng Med Biol Soc. 2012

YEAR: 2012

PUBLICATION HISTORY: Accepted as poster presentation at the 33nd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), San Diego, USA
Not yet published.

Correlation Between Intra- and Extracranial Background EEG

Jonas Duun-Henriksen[1,2,3], Troels W. Kjaer[2], Rasmus E. Madsen[3], Line S. Remvig[3], Carsten E. Thomsen[4], and Helge B.D. Sorensen[1], *Member, IEEE*

***Abstract*— Scalp EEG is the most widely used modality to record the electrical signals of the brain. It is well known that the volume conduction of these brain waves through the brain, cerebrospinal fluid, skull and scalp reduces the spatial resolution and the signal amplitude. So far the volume conduction has primarily been investigated by realistic head models or interictal spike analysis. We have set up a novel and more realistic experiment that made it possible to compare the information in the intra- and extracranial EEG. We found that intracranial EEG channels contained correlated patterns when placed less than 30 mm apart, that intra- and extracranial channels were partly correlated when placed less than 40 mm apart, and that extracranial channels probably were correlated over larger distances. The underlying cortical area that influences the extracranial EEG is found to be up to 45 cm^2. This area is larger than previously reported.**

I. Introduction

The first human electroencephalography (EEG) was measured by Hans Berger more than 80 years ago but humankind is still striving to understand the physiology behind the curves. Especially the differences between the scalp and cortical EEG have long been observed [1–5]. It is well acknowledged that cortical EEG potentials are of higher amplitude and contain more energy in the high frequency bands [6]. This is due to the property of the skull as a spatial averager which only transmits those components common to and synchronous over large areas of the cortex [1].

Existing research trying to explain the cortical substrates of scalp EEG has either focused on *in vitro* measurements [2], describing the volume conduction based on a realistic head model [7], or used the interictal spikes from epilepsy patients to estimate the area of the substrates [8], [9]. The *in vitro* measurements performed by Cooper et al. [2] has often been accepted as the *de facto* standard for synchronized cortical activity necessary for generation of scalp EEG. They reported that an area of 6 cm^2 was most probably necessary. However, *in vitro* measurements are very approximate to volume conduction *in vivo*. The three or four compartment models used in the realistic head simulations have provided estimations of the underlying source regions to be accurate in the range of perhaps 10 or 20 cm^2 [7]. When the distributed sources are broadly localized, the surface Laplacian method used to estimate the dura surface potentials underestimates the true cortical potentials. It tends to filter out very low spatial frequency sources, as well as low spatial frequency potentials due to volume conduction only. Most important though, is that no matter how complicated the geometric model, the volume conductor model will be severely limited by the lack of information on tissue conductivity. Finally, by visual investigation of interictal spikes, the size of the underlying cortical area needed to produce a scalp potential also resulted in 10-20 cm^2 [8]. This area is probably also an underestimation of the cortical area contributing to scalp EEG, since the interictal epileptiform discharges have larger amplitudes than background EEG. As scalp potentials represent summed voltage field potentials generated at the cortical pyramidal cells, larger amplitude as well as higher synchrony between cells will provide greater probability of the potential being recordable on the scalp.

We investigate to what extend cortical source potentials contribute to extracranial normal wake EEG. We found this area of correlation by constructing an *in vivo* setup with aligned electrodes intra- and extracranially. By calculation of the correlation between channels on either side of the skull, we were able to estimate the distance of which channels still have correlates.

II. Materials and Methods

A. Clinical Data

Six patients admitted to the *epilepsy monitoring unit* at Copenhagen University Hospital Rigshospitalet volunteered to participate in the study, see Table 1. They were all undergoing neurosurgery work up for control of medically refractory seizures. Implantation of subdural grid, strip or depth electrodes was conducted in accordance with established standards, and the insertion of the extracranial strip of electrodes was done after agreement on location between neurophysiologists and neurosurgeons. The project

TABLE I. Patient information

Patient	Sex	Age	Extracranial Electrodes	Intracranial Electrodes	Time Available
#	Male/ Female	Years	C: Contacts	C: Contacts	Hours: Minutes: seconds
1	M	65	2 x 6C strip	1 x 20C grid	00:22:20
2	F	32	2 x 4C strip	1 x 4C strip	00:10:00
3	F	43	1 x 6C strip	1 x 48C grid	00:59:59
4	F	29	1 x 4C strip	1 x 20C grid	00:10:26
5	F	30	1 x 4C strip	1 x 4C strip 2 x 6C strip	00:14:40
6	F	35	1 x 4C strip	1 x 32C grid	00:21:00

Corresponding authors: J. Duun-Henriksen and H.B.D Sorensen (phone: +45 4525 5244; fax: +45 4588 0117; e-mail: [jhe] / [hbs]@elektro.dtu.dk).
[1] Technical University of Denmark, Department of Electrical Engineering, Building 349, Oersteds Plads, 2800 Kgs. Lyngby, Denmark
[2] Department of Clinical Neurophysiology, Copenhagen University Hospital Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark
[3] Hypo-Safe A/S, Diplomvej 381, 2800 Kgs. Lyngby, Denmark
[4] Department of Odontology, University of Copenhagen, Noerre Allé 20, 2200 Copenhagen, Denmark

was approved by The Local Committee on Health Research Ethics. The extracranial strip was placed directly on the skull approximately aligned over the cortical electrodes, see Fig. 1. All electrodes were connected to the same recording system (Stellate Systems, Inc., San Carlos, USA). Data were digitized at a rate of 1000 Hz and band pass filtered with cut-off frequencies at 0.3 and 300 Hz. Postoperatively, the patient was CT scanned to precisely determine the location of the electrodes in a three dimensional coordinate system.

For the correlation analysis, at least 10 min of data were selected from artifact free awake EEG. Data were down sampled to 200 Hz for faster computation; a least-squares error minimization FIR-filter with an order of 10 and low pass cut-off at 90 Hz was applied to avoid aliasing followed by data decimation by selecting every 5th sample.

To avoid issues with a fixed reference electrode that is responsible for most of the correlation, we used bipolar derivations setup for all adjacent electrodes transversally as well as longitudinally. In the correlation analysis we did not compare derivations with electrodes in common to avoid the same problem as a fixed reference that drives the entire correlation. To calculate the Euclidian distance between channels, we defined one channels coordinates as the mean of the two electrodes coordinates.

B. Pearson Product-Moment Correlation Coefficient

We used the Pearson product-moment correlation coefficient as a measure of dependence between data. This method is well suited to measure the waveform and time coupling between two channels [10]. It is obtained by normalizing the covariance of two variables, x and y, by the product of their sample standard deviations, s_x and s_y, which must be nonzero. If we annotate the sample means of x and y as $\bar{x}$, $\bar{y}$ respectively we find the sample correlation coefficient to be:

$$r_{xy} = \frac{cov(x,y)}{s_x s_y} = \frac{\sum_{i=1}^{n}(x_i-\bar{x})(y_i-\bar{y})}{\sqrt{\sum_{i=1}^{n}(x_i-\bar{x})^2 \sum_{i=1}^{n}(y_i-\bar{y})^2}}, \quad (1)$$

where n is the number of samples. The variables x and y are the time series of two different EEG channels. Note that the correlation coefficient is equal to the normalized cross-correlation at lag 0. For analysis and model fitting we used the absolute value of the correlation coefficient, since we did not mind the sign of the derivations. To find the best model fit, we chose the one with the highest r^2-value following the model:

$$f(n) = (an)^p + b \text{ for } \in \mathbb{Z}.$$

where a is the constant of proportionality and b is a constant term that represent the noise or variance.

III. Results

A. Generic Modeling

A total of 5 195 intra- vs. intracranial EEG (i/iEEG), 955 extra- vs. intracranial (e/i), and 39 extra- vs. extracranial (e/e) comparisons were performed. Fig. 2 illustrates all of the correlations for each of the three situations. For all

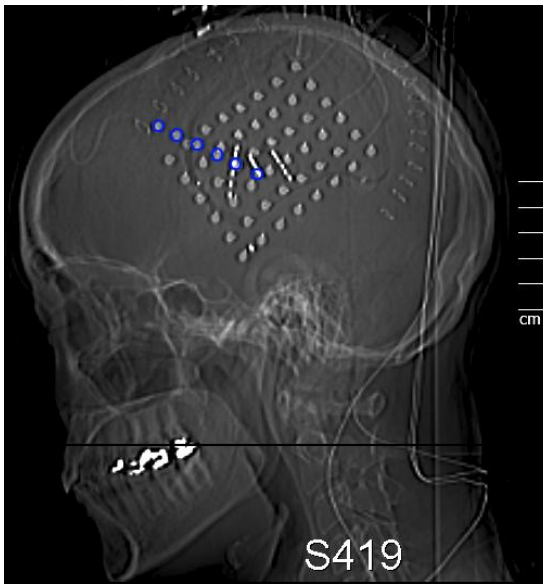


Figure 1. Sagital view of a patient's postoperative CT image. The intracranial electrodes can be seen as light gray dots while the extracranial electrodes are encircled in blue.

comparisons there is a clear tendency that the correlation increases with decreasing distance. For i/iEEG comparisons the best fitted line followed the model:

$$f(n) = (an)^{-2} + b.$$

Best e/iEEG comparisons followed the model:

$$f(n) = (an)^{-1} + b,$$

and best e/eEEG comparisons followed the model:

$$f(n) = an + b.$$

Note that the r^2-values are small.

The lines that represent the mean values are calculated based on a moving average filter that simply finds the mean of N succeeding samples and are plotted at the distance of the center sample. In the i/iEEG analysis this line has leveled out at distances above 30 mm, whereas e/iEEG becomes flat after 40 mm. It is impossible to state for the e/eEEG comparisons due to the limited number of correlations. For the i/iEEG correlation it means that any given channel is partly correlated with surrounding channels in a radius of 30 mm. This corresponds to an area of almost 30 cm^2. The radius of 30 mm is in agreement with the work by Bullock et al. [11]. They reported that the coherence between cortical electrodes is in the millimeter domain, i.e. below 28 mm when analyzing their figures. For the e/iEEG correlation we can use the 40 mm to calculate the size of the underlying area an eEEG channel is influenced by. The interesting distance is the tangential, but the distance between the channels is calculated as the Euclidian distance. For the six patients, the radial distance between intra- and extracranial electrodes was in mean 12 mm. By use of the Pythagorean Theorem we find the tangential distance to be 38 mm. This corresponds to an underlying area of 45 cm^2.

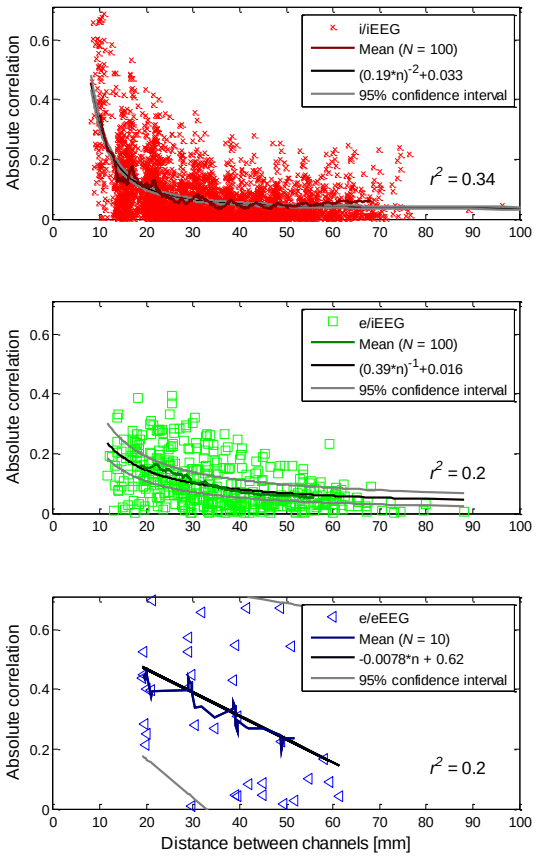


Figure 2. Generic modeling of i/iEEG, e/iEEG and e/eEEG. All comparing samples are used for obtaining the best fitted regression line.

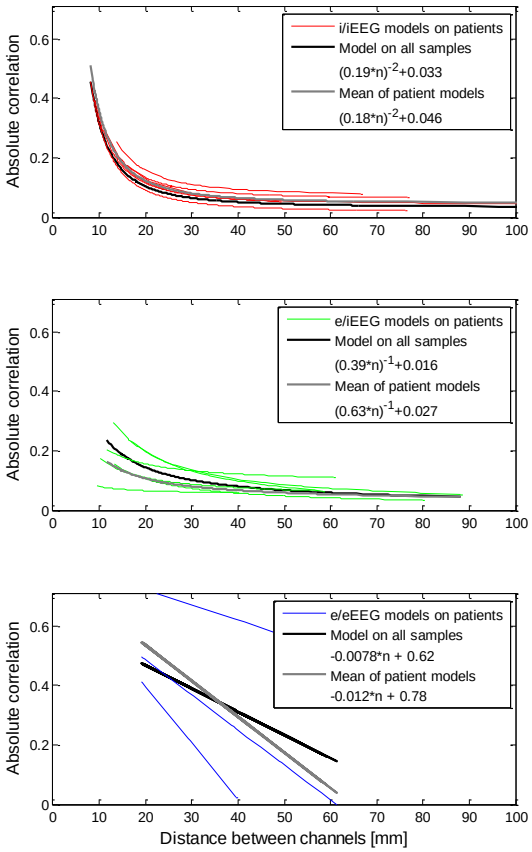


Figure 3. Patient-specific modeling of i/iEEG, e/iEEG and e/eEEG. Especially the i/iEEG comparisons show high similarity. For e/iEEG and e/eEEG all regression lines also have a negative slope, giving credibitily to the model.

B. Patient-Specific Modeling

Based on the results in the generic modeling, data from each patient were fitted with the model that had the best fit for each of the three comparisons. Fig. 3 shows how the i/iEEG models were similar decreasing correlation across patients (red lines). For e/iEEG and e/eEEG all comparisons (i.e. the green and blue lines) also showed a decreasing correlation with increasing distance although the variances between the models were higher. The black lines correspond to the model on all samples in Fig. 2, and the grey lines are calculated based on the mean of the parameters *a* and *b* in the model fittings for each patient.

IV. Discussion

A. Background EEG for Analysis

Our approach of assessing cortical substrates in extracranial EEG based on analysis of background EEG activity is very different from previously published methods. Others based their comparisons on either visual interictal spike analysis [4] or a realistic head model [7]. The first approach is very confined to the high frequencies in spikes and does not take into account how the spikes usually contain high power and thus have a higher probability of propagation through the skull despite a small synchronous cortical area. This aspect suggest a smaller area than if background EEG was used. The approach of realistic head modeling can show interesting properties of volume conduction, but has serious limitations in estimating correct and general conductivities of the brain, cerebrospinal fluid, skull and scalp. Our approach of using awake background EEG also has its limitations and advantages. As opposed to realistic head modeling we will not be able to circumvent the breach effect where cortical brainwaves pass through the craniotomy to the scalp without the moderation by the skull [12]. Another possible technical confound is the Silastic membrane and metal electrode disks of the subdural grid or strip. Both might exhibit an attenuating and blurring effect on the extracranial voltage field, although Tao et al. [8] reported no appreciable amplitude asymmetry in EEG from the two temporal areas where only one was affected by a subdural grid. How much the breach effect and subdural grid/strip influence the correlation will be a subject for further research.

As a non-stationary signal, the EEG will exhibit different power spectra throughout the at least 10 min of recording. As the correlation coefficient does not assume stationarity

this is actually an advantage. It means that we have a broad view of the activity of the brain, and that the underlying cortical area values we estimate are based on common observations. On the other hand, this paper does not distinguish between conductivities at different frequency bands. This will also be subject for further research.

B. Generic vs. Patient-Specific Modeling

We used two different approaches for modeling of the correlation data, both having advantages and downsides. The generic modeling has the advantage of using a lot of sample points to model the data; unfortunately each patient does not contribute with an equal amount of samples. E.g. does patient 3 have a total of 410 different e/iEEG comparisons, while patient 5 only has 39. This means that patient 3 contributes more to the generic model than patient 5. On the other hand, the mean of the patient-specific modeling might put too much emphasis on patients whose model was weak with a large confidence interval due to few sample points. The weak model of patient 5 contributes here equally to the very strong model of patient 3. In Fig. 3 we could compare the model on all samples (generic) and the mean of patient models (patient-specific). It is not possible to conclude which is better.

C. Models for Regression Lines

The models for the different comparisons all had a constant term and a slope in different powers. For the i/iEEG and e/iEEG the power of the slope was negative meaning that this term will approach zero when distance goes to infinity. The constant term is thus the "noise" in the measurement that will exist no matter how far the distance between channels. We assume that the different powers of the slope can be interpreted through Coulomb's law from which it follows that the magnitude of the electric field, E, created by a single point charge, q, at a certain distance, r, is given by:

$$E = \frac{q}{4\pi\varepsilon_0 r^2},$$

where ε_0 is an electric constant that describes the properties of the electric field in relation to its sources. The theorem states that the electric field from a single point charge radiated outward in three-dimensional space is inversely proportional to the square of the distance. Due to Ohm's law, the potential from a given point charge will follow the same relationship as seen in our i/iEEG comparisons.

For the e/iEEG relationship, the geometry is different. An electrical emission will always travel the route with the smallest resistivity. Electrical currents will primarily travel radially through the skull, and tangentially along the scalp or brain due to higher conductivities. This means that the skull will entail a constant attenuation of the correlation independent of distance between channels. The scalp will then primarily be responsible for carrying the electric field. As the spread only occurs in two dimensions, the electric field will be inversely proportion to the distance as our findings also indicated.

The e/eEEG comparisons should theoretically follow the same decline as the e/iEEG comparisons, but it had too large a confidence interval for us to comment on the actual decline.

V. Conclusion

We succeeded in estimating the underlying cortical area correlated with extracranial EEG based on background brain activity from six patients. Using a realistic analysis setup we obtained an estimate of the true area that contributes to an extracranial recording. It was found to be correlated with an underlying cortical area of approximately 45 cm^2. Even though the intracranial channels located directly underneath an extracranial channel are more correlated than those placed on the brink of the field of view, they are still not that similar with correlation coefficients approximately at 0.2.

The 45 cm^2 field of view is larger than previous reported correlates between intra- and extracranial channels that are based on interictal spikes [8] or realistic head modeling [7]. It should be noted though that the scopes are different. For intracranial recordings we found the correlation area to be within a radius of 30 mm corresponding to an area of approximately 28 cm^2. This is in concordance with previous reports [11].

References

[1] M. Delucchi, B. Garoutte, and R. Aird, "The scalp as an electroencephalographic averager☆," *Electroencephalography and Clinical Neurophysiology*, vol. 14, no. 2, pp. 191-196, Apr. 1962.

[2] R. Cooper, A. L. Winter, H. J. Crow, and W. G. Walter, "Comparison of Subcortical, Cortical and Scalp Activity Using Chronically Indwelling Electrodes in Man," *Electroencephalography and clinical neurophysiology*, vol. 18, pp. 217-28, Feb. 1965.

[3] J. S. Ebersole, "Defining epileptogenic foci: past, present, future.," *Journal of clinical neurophysiology*, vol. 14, no. 6, pp. 470-83, Nov. 1997.

[4] J. X. Tao, M. Baldwin, S. Hawes-Ebersole, and J. S. Ebersole, "Cortical substrates of scalp EEG epileptiform discharges.," *Journal of clinical neurophysiology*, vol. 24, no. 2, pp. 96-100, Apr. 2007.

[5] K. Abraham and C. Ajmone Marsan, "Patterns of cortical discharges and their relation to routine scalp electroencephalography.," *Electroencephalography and clinical neurophysiology*, vol. 10, no. 3, pp. 447-61, Aug. 1958.

[6] G. Pfurtscheller and R. Cooper, "Frequency dependence of the transmission of the EEG from cortex to scalp.," *Electroencephalography and clinical neurophysiology*, vol. 38, no. 1, pp. 93-6, Jan. 1975.

[7] P. L. Nunez and R. Srinivasan, *Electric fields of the brain: the neurophysics of EEG*, 2nd ed. New York: Oxford University Press, USA, 2006.

[8] J. X. Tao, A. Ray, S. Hawes-Ebersole, and J. S. Ebersole, "Intracranial EEG substrates of scalp EEG interictal spikes.," *Epilepsia*, vol. 46, no. 5, pp. 669-76, May 2005.

[9] M. Yamazaki et al., "Comparison of dense array EEG with simultaneous intracranial EEG for interictal spike detection and localization.," *Epilepsy research*, vol. 98, no. 2-3, pp. 166-73, Feb. 2012.

[10] M. A. Guevara and M. Corsi-Cabrera, "EEG coherence or EEG correlation?," *International journal of psychophysiology*, vol. 23, no. 3, pp. 145-53, Oct. 1996.

[11] T. H. Bullock, M. C. McClune, J. Z. Achimowicz, V. J. Iragui-Madoz, R. B. Duckrow, and S. S. Spencer, "EEG coherence has structure in the millimeter domain: subdural and hippocampal recordings from epileptic patients.," *Electroencephalography and clinical neurophysiology*, vol. 95, no. 3, pp. 161-77, Sep. 1995.

[12] F. Brigo, R. Cicero, A. Fiaschi, and L. G. Bongiovanni, "The breach rhythm.," *Clinical neurophysiology*, vol. 122, no. 11, pp. 2116-20, Nov. 2011.

A.7
SUBDURAL TO SUBGALEAL EEG SIGNAL TRANSMISSION: THE ROLE OF DISTANCE, LEAKAGE AND INSULATING AFFECTORS

AUTHORS: Jonas Duun-Henriksen, Troels W Kjaer, Rasmus E Madsen, Bo Jespersen, Anne Katrine Duun-Henriksen, Line S Remvig, Carsten E Thomsen, and Helge B D Sorensen

JOURNAL: Submitted to Clinical Neurophysiology

PUBLICATION HISTORY: Submitted October 9th, 2012.

Subdural to subgaleal EEG signal transmission: the role of distance, leakage and insulating affectors

Jonas Duun-Henriksen,[1,2,3] Troels Wesenberg Kjaer,[2] Rasmus Elsborg Madsen,[3] Bo Jespersen,[4] Anne Katrine Duun-Henriksen,[5] Line Sofie Remvig,[3] Carsten Eckhart Thomsen,[6] and Helge Bjarup Dissing Sorensen[1]

[1] Technical University of Denmark, Department of Electrical Engineering, Building 349, Oersteds Plads, 2800 Kgs. Lyngby, Denmark

[2] Department of Clinical Neurophysiology, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen, Denmark

[3] Hypo-Safe A/S, Diplomvej 381, 2800 Kgs. Lyngby, Denmark

[4] Department of Neurosurgery, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen, Denmark

[5] Technical University of Denmark, Department of Informatics and Mathematical Modelling, Building 305, Asmussens Alle, 2800 Kgs. Lyngby, Denmark

[6] Department of Odontology, Copenhagen University, Noerre Allé 20, 2200 Copenhagen, Denmark

Corresponding authors:

Troels Wesenberg Kjaer
Department of Clinical Neurophysiology
Copenhagen University Hospital
Blegdamsvej 9
2100 Copenhagen
Denmark
Telephone: +45 3545 3545
Fax: +45 3545 3264
E-mail: neurology@dadlnet.dk

Jonas Duun-Henriksen
Technical University of Denmark
Oersteds Plads building 349, room 109
2800 Kgs. Lyngby
Denmark
e-mail: jhe@elektro.dtu.dk
cell phone: +45 6178 9966
fax: +45 4588 0117

Keywords:

Intra- and extracranial electroencephalography; transfer function; skull; breach effect; coherence

Financial support

This work was supported by The Danish Agency for Science, Technology and Innovation [08-041638 to J.D.] and The Lundbeck Foundation [282/05 to T.W.K.].

Acknowledgement

The authors thank the nurses and technicians at the Department of neurosurgery and Department of clinical neurophysiology, Copenhagen University Rigshospitalet, who performed all the measurements. A special thank to Lennert Derm, who made a big effort in obtaining the measurements. The authors also thank Hans Hoegenhaven, MD, for reviewing the EEG records and giving considerations in preparation of this paper and Professor Henrik Spliid for considerations and constructive feedback on the statistical analysis.

Explicit statement of any financial or commercial involvement

Jonas Duun-Henriksen is working as an industrial PhD-student. The Danish Agency for Science, Technology and Innovation has paid one third of the scholarship while the company HypoSafe A/S has paid the rest. HypoSafe A/S is developing a small subcutaneous EEG device for prediction of hypoglycaemia in diabetic patients. Rasmus E Madsen and Line S Remvig are also employed by HypoSafe A/S. The rest of the authors are employed by a university or hospital and have no commercial interest in HypoSafe A/S.

Highlights

- During spontaneous awake EEG, a subgaleal EEG channel reflects activity in approximately 31 cm^2 of cortex.
- The Euclidean distance between channels accounts for 75% of the coherence in the 4-15 Hz frequency band. The craniotomy and the silastic membrane of intracranial grids account for 12 and 13%, respectively.
- Transcranial coherence depends on frequency. Frequencies below 16 Hz show similar declines as a function of distance. Between 16 and 30 Hz the decline is steeper, while there is no coherence above 30 Hz at any distance.

Abstract

Objective: To estimate the area of cortex affecting the extracranial EEG signal.

Methods: The coherence between intra- and extracranial EEG channels were evaluated on at least 10 min of spontaneous, awake data from seven patients admitted for epilepsy surgery work up.

Results: Cortical electrodes showed significant extracranial coherent signals in an area of approximately 150 cm^2 although the field of vision was probably only 31 cm^2 based on spatial averaging of intracranial channels taking into account the influence of the craniotomy and the silastic membrane of intracranial grids. Selecting the best cortical channels, it was possible to double the coherence values compared to the single intracranial channel with highest coherence. The coherence seemed to increase linearly with an accumulation area up to 31 cm^2, where 50% of the maximal coherence was obtained accumulating from only 2 cm^2 (corresponding to one channel), and 75% when accumulating from 16 cm^2.

Conclusions: The skull acts as a spatial averager and cause signals to be coherent quite far from the source.

Significance: An empirical assessment of the actual area of cerebral sources generating the extracranial EEG provides better opportunities for clinical electroencephalographers to determine the location of origin of particular patterns in the EEG.

Keywords: Intra- and extracranial electroencephalography; transfer function; skull; breach effect; coherence

Introduction

The surface electroencephalography (EEG) has empirically revealed itself as an efficient diagnostic tool for neurological diseases, despite the fact that the underlying cerebral substrate of the recorded signal is mostly speculative. The best guesses of the actual area of cerebral sources generating the scalp EEG are either found by *in vitro* measurements (Cooper et al., 1965) or by volume conduction calculations based on a realistic head model (Nicolas and Deloche, 1976; Nunez and Srinivasan, 2006). Differences between the scalp and cortical EEG have long been observed (Abraham and Ajmone Marsan, 1958; Delucchi et al., 1962; Ebersole, 1997). Cortical EEG potentials are of higher amplitude than scalp EEG and the power spectrum inclines slower for higher frequencies (Pfurtscheller and Cooper, 1975). The skull is described to be a spatial averager which only transmits components that are common and synchronous over a large area of the cortex (Delucchi et al., 1962), although, as Abraham and Ajmone Marsan, 1958, noted; The amplitude of the "original" discharge and extent of the area involved by the discharge itself are not the only factors responsible for presence or absence of spread to the scalp.

The region of synchronously activated cortex required to produce a recordable scalp EEG event is often quoted as 6 cm^2 (Cooper et al., 1965). In this classical study, the recording and stimulating electrodes were placed on either side of a large piece of fresh wet skull, and a low frequency, low impedance oscillator was connected to estimate the properties of the skull. This investigation is of high relevance to understand the properties of the skull, but the suggested area of 6 cm^2 is probably only a lower limit for the necessary source area generating scalp-recordable spontaneous potentials. The average area of *in vivo* signals is most likely higher due to conduction through the anisotropic cortex as well as blood vessels and cerebrospinal fluid. This is also discussed by the original proposers and others (Ebersole, 1997).

Investigation of epileptiform interictal spikes provides a more direct method to estimate the area of cortical discharges required for scalp recordable potentials (Tao et al., 2007). Comparing spikes simultaneously recorded intra- and extracranially, the cortical area required to generate a recognizable interictal spike or ictal rhythm on the scalp was estimated to 10 to 20 cm^2. This figure is solely based on the high amplitude, high frequency containing spikes, so the cortical substrates in the normal background scalp EEG are still to be unravelled. Multiple research groups have tried to model the volume conduction of cortical dipole currents with a realistic head model (Nunez and Srinivasan, 2006), but they are severely limited by the inaccurate estimates of tissue conductivity and the anisotropy of the skull. When the distributed sources are broadly localized, the "surface Laplacian" used to estimate the dura surface potentials underestimates the true cortical potentials and it tends to filter out low spatial frequency sources and potentials.

The spatial information available in the scalp EEG is severely limited. This is due to the dispersion of the cortically generated electric fields when entering through the cerebrospinal fluid, skull and scalp. Especially the very low conductivity of the skull (often found to be a factor 80 lower than the scalp (Hallez et al., 2007)) blurs the cortical potentials resulting in a poor spatial resolution (Nunez and Srinivasan, 2006). Using a propagation model with general field equations Nicolas and Deloche, 1976 estimated the diameter of the theoretical *field of vision* to be 48 mm for scalp electrodes. To our knowledge, no one has published *in vivo* comparisons between intra- and extracranial resting awake EEG in humans. Previous studies have either focused on animals (Bullock and McClune, 1989; Delucchi et al., 1962) or been limited to specific pathological patterns (Hashiguchi et al., 2007; Tao et al., 2007).

The focus of our study is on the macroscopic volume conduction of electrical signals rather than the biophysical mechanisms that cause the effects observed. We describe the effects of the skull on the electroencephalography. This includes considerations on how well an extracranial channel is coherent with a cortical channel on the opposite side of the skull compared to one further away, how far from a cortical source the extracranial EEG accumulate, how comparable coherence values across patients are, what the effect of the craniotomy and silastic membrane of the electrode grid on the extracranial channels is, and

the possibility to establish a system of relations that can predict the extracranial EEG given multiple intracranial channels.

Materials and methods

Experimental design

After approval by The Local Committee on Health Research Ethics, patients admitted to the *epilepsy monitoring unit* at Copenhagen University Hospital Rigshospitalet for neurosurgery work up of medically refractory epileptic seizures were asked if they would participate in our study. Seven patients admitted from September 2010 to April 2012, see Table 1, were found suitable to participate in the study and agreed to be enrolled. Implantation of subdural grid, strip or depth electrodes was conducted in accordance with the clinical needs according to established standards, while the insertion of subgaleal strip(s) of electrodes was done after agreement on location between neurophysiologists and neurosurgeons. The extracranial strip(s) was placed on the skull under the galea with some contacts over the grids and some outside, see Figure 1. All electrodes were connected to the same recording system (Stellate Systems, Inc., San Carlos, USA). Postoperatively, the patient was CT scanned to determine the precise location of the electrodes in a three dimensional coordinate system. Data were recorded for several days (3 days 5 hours ± 1 days 0 hours) whereupon decision on possible resective surgery was made. Only the intracranial electrodes were used for this decision.

Table 1: Characteristics of the experimental setup for each study volunteer. Electrodes in parenthesis were not near the extracranial electrodes and thus not included in the analysis.

Patient no. #	Gender Male/ Female	Age Years	Subgaleal electrodes C: Contacts	Intracranial electrodes C: Contacts	Electrode placement Lobe
1	M	65	2 1x6 C strip	4x5 C grid (2 1x4 C strip)	Parietal
2	F	32	2 1x4 C strip	1x6 C strip 1x4 C strip (1x6 C strip) (1x4 C strip) (2 1x4 C depth) (2 1x6 C depth)	Temporal – frontal
3	F	43	1x6 C strip	6x8 C grid	Temporal – parietal
4	F	29	1x4 C strip	4x5 C grid (2 1x6 C strip) (2 1x4 C depth)	Temporal
5	F	30	1x4 C strip	1x4 C strip 2 1x6 C strip (1x4 C strip) (1x6 C strip) (2 1x6 C depth) (1x10 C depth)	Frontal
6	F	35	1x4 C strip	4x8 C grid (4 1x6 C strip)	Temporal

7	F	28	2 1x4 C strip	4x8 C grid (4x8 C grid) (5 1x6 C grid) (1x6 C depth)	Frontal – parietal

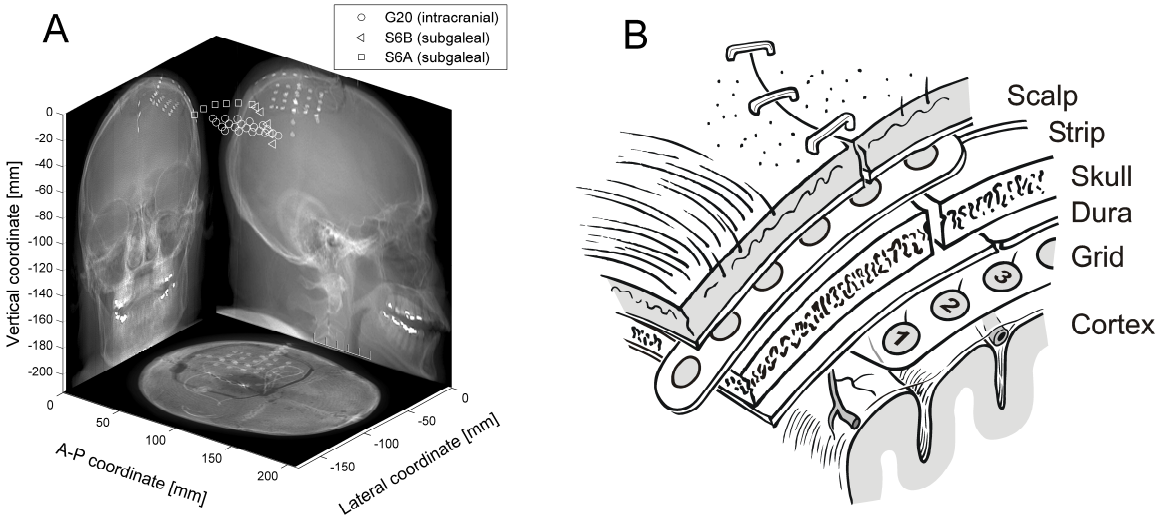


Figure 1: A) Planar projections of postoperative CT scan of patient 1 with electrodes implanted. The G20 electrodes are situated subdurally, while S6A and S6B are extracranial electrodes in the subgaleal space. The location of the craniotomy was also mapped based on these images. B) An illustration of the placement of intra- and extracranial electrodes. It can be inferred that the silastic membrane containing the intracranial electrodes will attenuate the cortical potential, while some electrical current might escape through the skull defect with less attenuation than the skull.

Data processing

Data were digitized at a rate of 1000 Hz and bandpass filtered with cut-off frequencies at 0.3 and 300 Hz. At least 10 min of spontaneous EEG were selected for each patient from awake periods free of obvious artefacts. Data were downsampled to 200 Hz for faster computation; a least-squares error minimization FIR-filter with an order of 10 and low pass cut-off at 90 Hz was applied to avoid aliasing. This was followed by data decimation by selection of every 5th sample.

To avoid issues with a fixed reference electrode that is responsible for most of the coherence (Zaveri et al., 2000) or a common reference that confounds the spectral power in the signal (Fein et al., 1988), we used a bipolar derivation setup for all adjacent electrodes transversally as well as longitudinally. To avoid the same problem as a fixed reference that drives the entire correlation, we did not compare derivations with electrodes in common. For calculation of the Euclidean distance between channels, we defined the coordinates of one channel as the mean of the two electrodes' coordinates.

Magnitude squared coherence

To be able to compare the EEG signals recorded intra- and extracranially (*x* and *y* respectively), we use the magnitude squared coherence estimate, $C_{xy}(f)$, from now on called the coherence. It quantifies linear correlations in frequency domain and is well suited for our purpose as it is excellent in describing the stability of the relationship between two recording sites including both power asymmetries and

morphology (Guevara and Corsi-Cabrera, 1996). The coherence is a function of the power spectral densities $P_{xx}(f)$ and $P_{yy}(f)$ and the cross power spectral density $P_{xy}(f)$:

$$C_{xy}(f) = \frac{\left|P_{xy}(f)\right|^2}{P_{xx}(f)P_{yy}(f)} \quad (1)$$

The coherence spectrum will always contain values between 0 and 1, the former indicating no correlation between the signals *x* and *y*, while the latter denotes full cross power spectral correlation. The power spectral densities are found using Welch's averaged, modified periodogram method with a moving Hamming window of 1024 samples (5.12 s), each overlapping 512 samples with the former.

For some of the investigations conducted in the present paper we divide data into the following standard frequency bands: δ = 0-4 Hz, θ = 4-8 Hz, α = 8-12 Hz, β_{low} = 12-16 Hz, β = 16-20 Hz, β_{high} = 20-30 Hz, and γ = 30-70 Hz. The coherence values within each band, C_{φ}, are based on the following formula:

$$C_{\varphi} = \frac{1}{N}\sum_{n=\varphi_1}^{\varphi_N} C_{xy}(n) \quad (2)$$

where $n=\varphi_1 \ldots \varphi_N$ contains the *N* discrete values within a given frequency band, φ, defined above. If nothing else is stated the coherence value is calculated based on the φ = 4-15 Hz band where all patients showed significant coherence amplitudes. This value will be called the *coherence scalar*.

Surrogate data

For any non-infinite random signal, the coherence will on average be non-zero. We tested this offset by shifting data for each channel five seconds compared to the former channel, and then calculated the coherence scalars. These values were found to be normally distributed with $N(\mu_{nb}, \sigma_{nb}^2)$, where μ_{nb} is the mean and σ_{nb}^2 the variance of the surrogate coherence scalars. Values close to μ_{nb} can be expected to be non-coherent. According to the normal distribution, everything below three standard deviations from the mean accounts for 99.9% of all values in the surrogate data. This value is fixed as the discriminative threshold between significant coherence and random coherence. We thus set the noise bias, *nb*, to

$$nb = \mu_{nb} + 3\sigma_{nb}. \quad (3)$$

Intracranial subset selection

In the introduction it was mentioned that the skull is considered a spatial averager. This means that extracranial EEG is believed to originate from a wide intracranial area. It can be tested by averaging of multiple intracranial EEG channels. If this results in a higher coherence with the extracranial channels the skull *is* a spatial averager. Two methods for inclusion of intracranial channels were used: linear forward selection based on distance, and greedy forward selection based on coherence values.

Linear forward selection

For each extracranial EEG-channel, the nearest intracranial channel in the Euclidean space was selected for coherence analysis. Then the two closest channels were averaged and coherence was calculated. For each repetition, the nearest unused channel was included in the averaging of the intracranial channels. The included channels were all weighted equally. This continued until all intracranial channels were included.

Greedy forward selection

Since the potential from some intracranial channels might contribute negatively to the coherence, we implemented a greedy forward selection method that only included the channels contributing positively. The calculated coherence values of all intracranial channels against a specific extracranial channel were used in this selection method. First, the intracranial channel with the highest coherence to the extracranial channel was selected. Every remaining intracranial channel was then averaged together with the first selected channel one at a time, and coherence values calculated. The configuration of two intracranial channels with the highest coherence to the extracranial channel was selected. Again, all remaining intracranial channels were averaged with the two first channels one at a time, coherence values calculated and the channel contributing to the highest coherence scalar was selected. This loop continued until no extra intracranial channels contributed to a higher coherence.

Results

Coherence estimates

The coherence spectra found by equation 1 showed to be diverse across patients, see Figure 2. We found the individual coherence spectra to be comparable with the patient's intracranial power spectra; if the patient had an increase in e.g. alpha activity at around 10 Hz, the coherence spectra would display a corresponding increase in the same frequency band. The coherence in the delta band, on the other hand, usually did not show the same increase as the scalp EEG power spectra. Above 25 Hz, coherence was below the noise level, *nb*. All patients had significant coherence values within the 4-15 Hz frequency band.

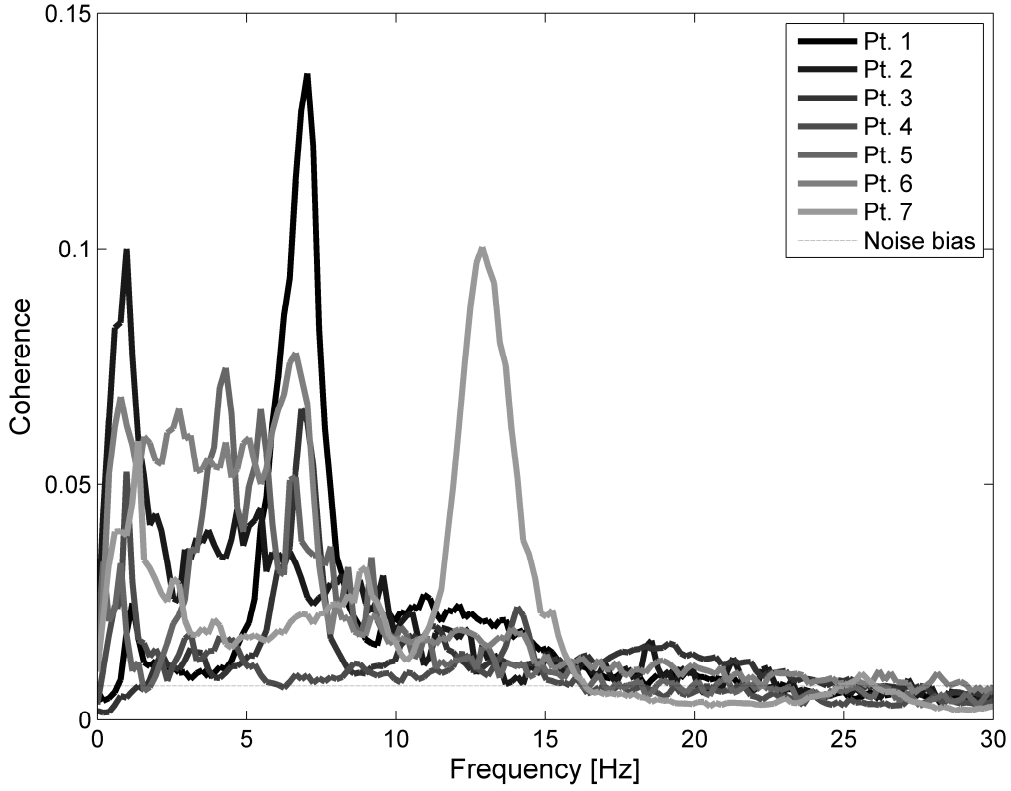


Figure 2: Mean coherence spectra for each patient. The dominant coherence frequencies are diverse across patients, although all patients have significant components between 4 and 15 Hz.

When we compute the coherence scalar in the 4-15 Hz band based on equation 2 and compare the results to the Euclidean distance between all combinations of channels, we obtain Figure 3A. Comparisons between intracranial EEG channels (i/iEEG), subgaleal EEG channels (e/eEEG), and between subgaleal and intracranial EEG channels (e/iEEG) are all shown. The i/iEEG coherences follow the tendency reported by Bullock et al., 1995, who stated that the coherence declines quickly with distance for the first 15 mm whereupon it declines more slowly until it falls below the noise bias level at 40 mm. The e/eEEG comparisons show coherence scalars larger than the i/iEEG comparisons. This is consistent with the premise that the skull is a spatial averager (Delucchi et al., 1962), however there are too few e/eEEG comparisons for us to comment on the behaviour of the decline with distance.

In the present paper we have focused on the e/iEEG comparisons. Their coherence scalars are smaller than the other comparisons for short distances but show a similar decline with distance. This decay was present for every individual patient. Figure 3B shows a zoom on the e/iEEG coherences with a moving average. The moving average is calculated by taking the mean of *N* succeeding coherence scalars, and plotted against the Euclidean distance for the mean of the corresponding distances. At 70 mm the moving average crosses the noise bias. This point expresses the distance at which the cortical neurons no longer contribute to the extracranial EEG. This results in an area with significant coherence of approximately 150 cm^2.

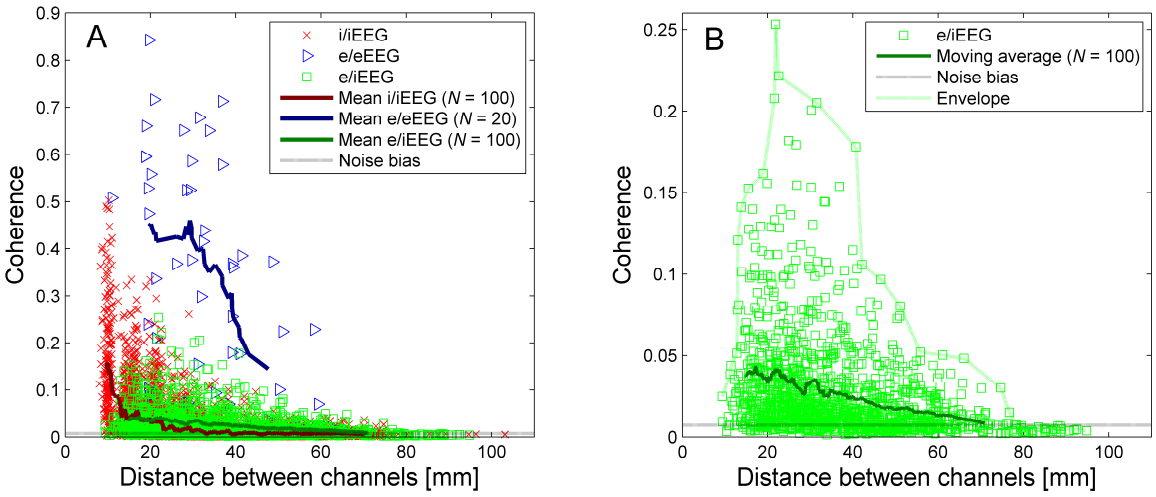


Figure 3: A) Coherence as a function of Euclidean distance between channels. The comparisons between extracranial electrodes (e/eEEG: blue triangles) have higher coherence than comparisons between intracranial electrodes (i/iEEG: red crosses) and between extra- and intracranial electrodes (e/iEEG: green squares). All comparisons show a decrease in coherence at higher distances. B) Coherence between intra- and extracranial channels as a function of Euclidean distance between the channels.

To evaluate the contribution to the coherence from each of the three affectors (the Euclidean distance between channels, d_{Eu}, the extracranial channel distance to the craniotomy, d_{Cran}, and the intracranial channel distance to the edge of the silastic membrane, d_{Edge}) we created a model to describe these effects. The e/iEEG coherence scalars were found to be gamma distributed, and thus we used a generalized linear model based on this distribution. The patient number was included as a factor to prevent the physiological variance between patients to influence the statistics. The three affectors were all improving the model with statistical significance (*p-value* < 0.01 based on the generalized linear model and *p-value* < 0.001 on an analysis of deviance table with a χ^2-test). The best generalized linear model was:

$$C_{\varphi}(d_{Eu}, d_{Cran}, d_{Edge}) = \frac{1}{0.0308 \cdot d_{Eu}^{\ 2} - 1.13 \cdot d_{Eu} + 0.348 \cdot d_{Cran} + 1.64 \cdot d_{Edge} + 17.7} \quad (4)$$

We obtain the fitted lines in Figure 4 by varying one affector in its range and setting the other two to zero. The change in coherence due to each affector is found by taking the maximum coherence value and subtracting the minimum. The Euclidean distance between channels was accountable for 75% of the coherence, the extracranial channel distance to craniotomy was accountable for 12% and the intracranial channel distance to edge of silastic membrane was accountable for 13%. This means, e.g. for the latter, that a channel placed on the outermost edge of the grid, in mean, results in a 13% higher coherence with the extracranial channels than one with a distance of 24 mm to the edge.

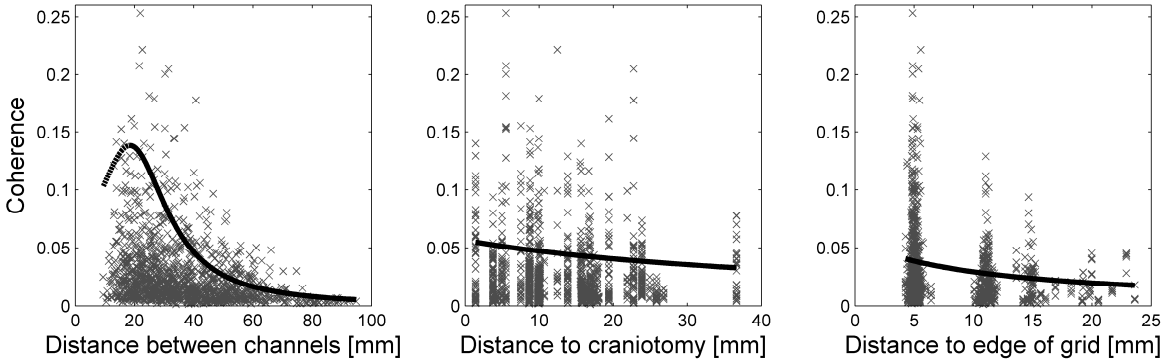


Figure 4: Coherence as a function of the three affectors: Euclidean distance between channels (left), the extracranial channel distance to the craniotomy (middle), and the intracranial channel distance to the edge of the silastic membrane. Based on a gamma distribution, the fitted lines are generated from a generalized linear model where the non-displayed affectors are set to zero. The most contributing factor is the Euclidean distance between channels which is accountable for 75% of the total coherence. The dashed part in the fitted line for the distance between channels is due to an edge effect.

Coherence in different frequency bands

Using equation 2, we found the mean of the different frequency bands defined in the method section, see Figure 5. We observed that the frequency bands containing components below 16 Hz all decline with distance at approximately the same rate. The β and β_{high} bands decline quicker while the γ-band has rarely any coherence at any distances as we also showed in Figure 2.

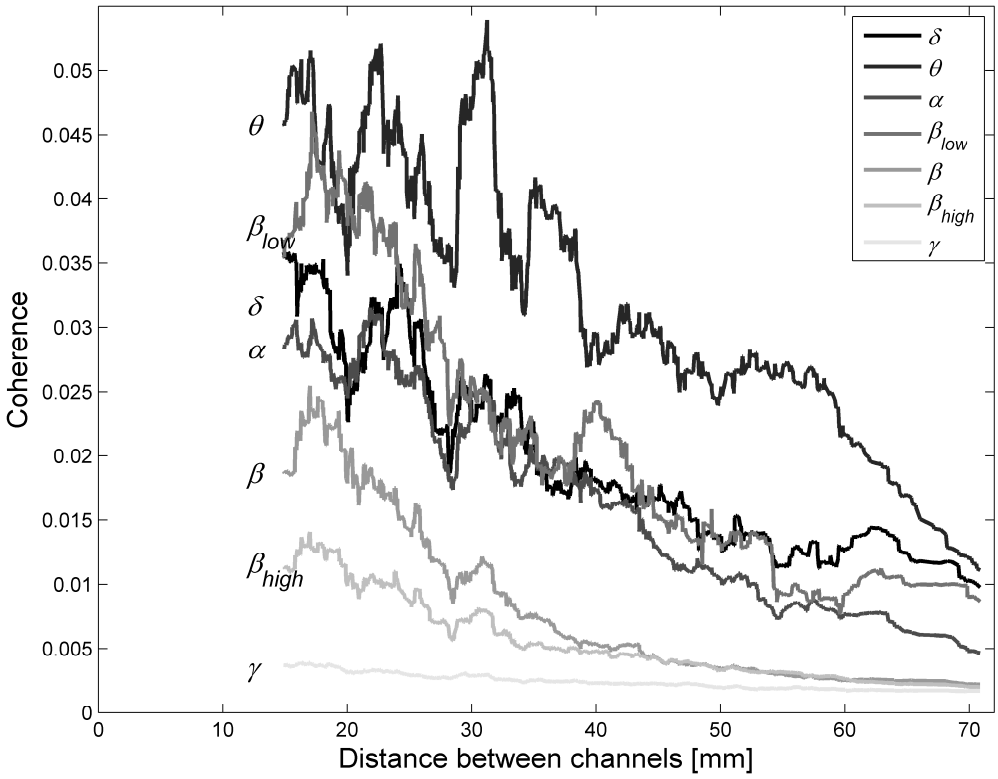


Figure 5: Coherence of different frequency bands as a function of Euclidean distance between channels. δ, θ, α and β_{low} bands all seem to decline with the same rate, while β and β_{high} bands decay faster. There is practically no coherence for the γ-band.

Using multiple intracranial channels

To test whether the skull acts as a spatial averager, we computed the mean of the potentials of multiple intracranial channels. The first scheme applied the linear forward selection method. In Figure 6 we see the results for the subgaleal channel S6A1 – S6A2 of patient 3. The uppermost line in the figure is the coherence spectrum when only the nearest channel is used. As more and more channels are included, the coherence spectrum changes and the coherence scalar reach an optimum at the inclusion of 28 channels. Including more than 28 intracranial channels will in this case render a lower coherence. Across all patients with a subdural grid implanted we found the maximum coherence to be at the inclusion of 23.8 ± 16.7 intracranial channels. If we assume that the distance to the outmost channel that contributed to a higher coherence represent the side length of a cone with apex at the subgaleal channel, and that the height of the cone is equal to the distance between the intracranial grid and extracranial strip (12 mm in mean), the area of the base of the cone is 32.0 cm^2. This is the cortical area that contributes to the highest coherence.

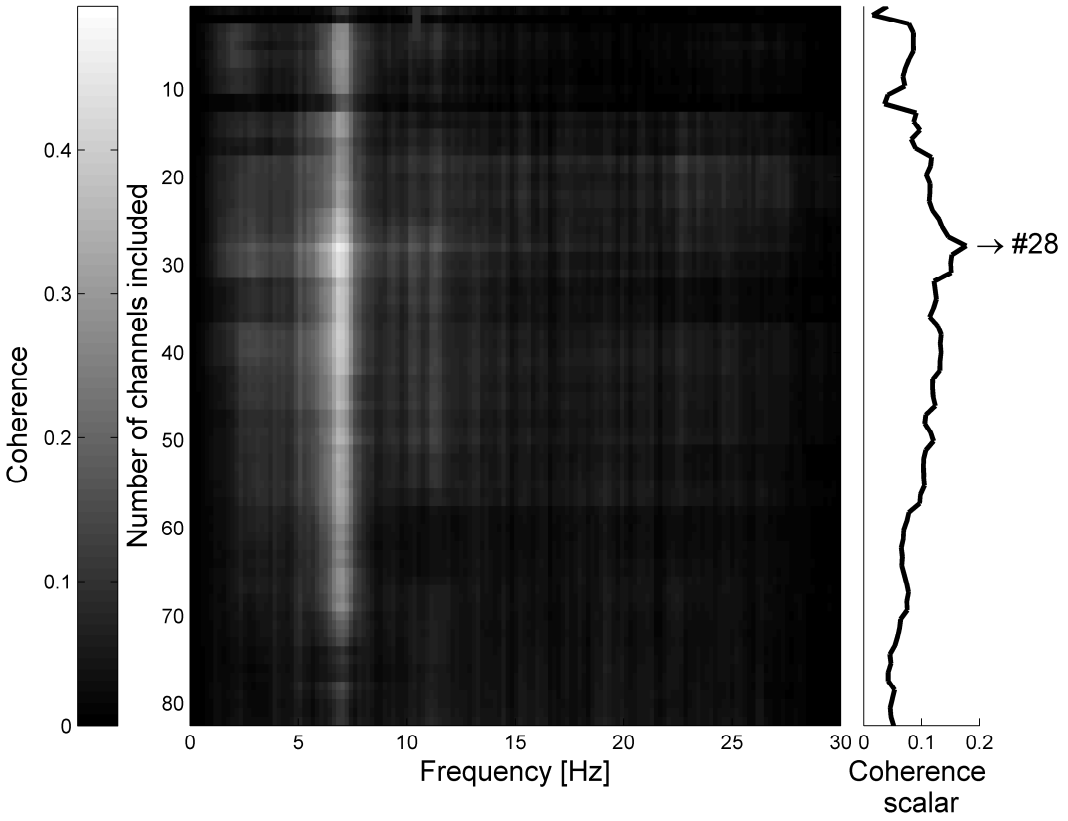


Figure 6: Coherence spectra for patient 3 channel S6A1 – S6A2. The intracranial channel constitute the mean of intracranial channels linearly included based on the distance from the extracranial channel. The largest coherence is found at inclusion of 28 channels. The coherence declines subsequently since extra channels only add noise.

Applying the scheme with greedy forward selection of channels, we find that only 8.8 ± 4.5 channels are needed for maximum coherence. Every single extracranial channel showed higher obtainable coherence scalar value for the greedy forward inclusion compared to the linear inclusion. The area was found to be 31.2 cm^2 by means of the same method as above to estimate the area of cortex contributing to the maximum coherence value. The highest obtainable coherence is in mean 0.25 ± 0.09 for all subgaleal channels. This is a doubling compared to selecting only the most coherent single intracranial channel.

Discussion

For the clinical electroencephalographer, the principal task is to recognize particular patterns of diagnostic significance and to determine their location of origin. This is a task that requires training as well as understanding of the basic principles of electrophysiology. The electric fields from the brain are primarily generated by synaptic potentials in vertically oriented pyramidal neurons in the cortex. An intuitive way to grasp how the pyramidal neurons contribute to the EEG is by the solid angle concept of volume conductor theory (Gloor, 1985). Unfortunately, this concept does not state the area of which the extracranial EEG is accumulated over. Neither does it provide an answer to the transmission properties of different frequency components. Using an *in vivo* setup of spontaneous EEG measurements, we were able to make realistic assessments of this.

Extracranial accumulation of cortical EEG

The coherence between extra- and intracranial EEG was found significant as far away as 70 mm from each other in the 4-15 Hz frequency band corresponding to an underlying cortical area of 150 cm^2. The nearest channels were usually more coherent than those further away. Coherences for frequencies between 0 and 16 Hz all seemed to decay equally fast with distance, while the 16-30 Hz frequencies decayed faster. There was practically no coherence for frequencies above 30 Hz. This is in concordance with previous results from Pfurtscheller and Cooper, 1975, who showed that cortical power is not attenuated substantially on the scalp for oscillations below 15 Hz, while 15-30 Hz components showed clear attenuation. We emphasize that this investigation relates to spontaneous normal EEG, while the often higher frequency content during e.g. an epileptic seizure would probably yield significant coherence for frequencies above 30 Hz as well (Duun-Henriksen et al., 2012).

Although coherence was significant in an accumulation area of 150 cm^2, it is not given that intracranial channels within this area contribute positively if we compute the coherence based on the mean amplitude of all channels. We showed this by using two different selection criteria for multiple intracranial channels. Both the linear and the greedy forward selection method revealed that only channels within an accumulation area of approximately 30 cm^2 would increase the coherence. Channels outside this area contributed with more noise than coherent signal. The maximal coherence obtained in this *field of vision* was 0.25 ± 0.09. Since this is the double of the single most coherent intracranial channel across patients, it is a clear indication that the human skull acts as a spatial averager as hypothesized and shown on cats (Delucchi et al., 1962). The coherence seemed to increase linearly with an accumulation area up to 31 cm^2, where 50% of the maximal coherence was obtained accumulating from only 2 cm^2 (corresponding to one channel), and 75% when accumulating from 16 cm^2. This is consistent with the distance having an inversely squared proportionality with coherence found in equation (4) since the area is the distance squared.

Instead of using all approximately 24 channels in the accumulation area, the greedy forward selection method showed that only an average of 8.8 contributed positively. Since only a fraction of the cortical channels contribute, we conclude that the cortical areas responsible for the spontaneous coherence are “patchy”. We were not able to uncover any distinctive properties for these channels compared to the rest.

The coherence scalar values were found to be gamma distributed. This means that a lot of the comparisons showed none or only little coherence. We did not succeed in explaining the difference between “silent” and coherent channels. There was no correlation between a higher power in the intracranial channel and the coherence with the extracranial channels, although this might have been expected. What we did find, was that often the intracranial channels showing the highest coherence to the extracranial channels were situated next to each other. This could be an indication that they were placed optimally on a gyrus for the purpose of recording tangentially electrical fields that pass through the skull. An electrode-gyri localization assessment by fusion of pre-operational MR and post-operational CT images was outside the scope of this paper.

The effect of the craniotomy and silastic membrane

By modelling the coherence scalars with a generalized linear model based on a gamma distribution, we found the Euclidean distance between channels to be accountable for 75% of the coherence, the craniotomy 12%, and the silastic membrane of the grid 13%. Even though the Euclidean distance between channels by far is the most important affector, the craniotomy and silastic membrane affect the coherence of the spontaneous EEG with a non-negligible part.

A well documented effect of the craniotomy is the *breach rhythm* (Brigo et al., 2011). It is defined as an increase in amplitude activity of alpha and beta rhythms close to the area of a bony skull defect (Cobb et al., 1979). The sharply contoured morphology of breach rhythms may be considered as epileptiform

abnormality and should thus be interpreted carefully. While some reported an increase of 150% in mean ratio between EEG amplitudes over the defect and the homologous contralateral area (Brigo et al., 2011), others found no difference (Tao et al., 2005). The 2005 investigation used simultaneous intracranial grid electrodes and scalp EEG recordings. Since we found the craniotomy and silastic membrane to be accountable for approximately same part of the coherence, these two affectors may have balanced each other out. Application of a contoured grid with slits and holes instead of solid ones would most likely have rendered different results. As the coherence scalars were only computed for the 4-15 Hz frequency band, the often more high frequent and burst related breach rhythm will only be of importance in discreet short windows. An averaging over at least 10 min of EEG might then attenuate this effect.

Only the Euclidean distance between channels showed an inversely squared proportionality with coherence. The expected potential field based on a modelled current dipole would theoretically also show an attenuation of $1/d^2$, where d is the distance (Hallez et al., 2007). The positive increase of coherence for a Euclidean distance of up to 20 mm seen in Figure 4 is on the other hand counter intuitive. We ascribe this odd appearance as an edge effect due to physiological differences between patients such as the fact that the intra- and extracranial electrodes were placed closer to each other for patient 4 than the others. This patient showed in general a lower coherence, which produced some low coherence values for short Euclidean distances.

Study limitations

We acknowledge some limitations of our study. First of all we are challenged by the inhomogenity in matrix size of intra- and extracranial strips and grids, channel distances and physiological covered area. Due to ethical issues, our experiment setup is only possible on humans already admitted for implantation of intracranial electrodes. Thus we will have to consider pathological issues prior to experimental issues when placing the intracranial electrodes. It is not given that the cortical area covered with electrodes used in our analysis is diseased. This was examined as a part of the neurosurgery work up.

Periods containing paroxysm were not included for analysis in the present setup. Since some of the covered cortical areas represent diseased tissue, a few interictal spikes have been included. A spike with high amplitude originating from a spatially well defined small area will probably contribute equally to the extracranial EEG as a source with wider spatial origin but lower amplitude. Since we chose our data to contain spontaneous awake EEG without obvious visual artefacts, the present spikes will only contribute minimally compared to the normal EEG.

An assumption which may also be challenged is whether the intracranial EEG recordings provide a fair representation of the true cortical generators. The spatial sampling of one cm might leave out important generators. Bullock et al., 1995a, and Duun-Henriksen et al., 2012, have previously shown that the coherence and correlation between intracranial channels are high for very short distances (< 10 mm). Therefore we believe that cortical generators between electrodes radiate most of their electrical discharges to the nearest intracranial electrodes. If a fixed current stimulation of considerably higher voltage amplitude than the spontaneous EEG was applied and measured, we would know the true source and be able to give good approximations of signal volume conduction and the influence of the craniotomy. Subdural current stimulation was used for three of our included patients. Unfortunately, it was not possible to extract meaningful data from these periods as the stimulation induced too much noise.

Finally, the source orientation of the electric field generator is important. An electrode pair placed directly above a cortical generator does not necessarily record the maximum voltage. An optimal orthogonal and radial field is only produced if the net orientation of the active cortical area is parallel to the skull (Ebersole, 1997). The gyri and sulci of the brain make this far from the reality for all neurons. This might also be part

of the reason for the initial increasing coherence values as function of Euclidean distance between channels in Figure 4.

This paper represents a comprehensive although not all-embracing analysis. We will for future research try to understand which intracranial channels that contributes with high coherence, and how amplitude differences might come into play, together with an investigation of whether a time delay between intra- and extracranial channels might be dependent on the distance between channels, craniotomy and silastic

References

Abraham K, Ajmone Marsan C. Patterns of cortical discharges and their relation to routine scalp electroencephalography. Electroencephalogr Clin Neurophysiol 1958; 10: 447–61.

Brigo F, Cicero R, Fiaschi A, Bongiovanni LG. The breach rhythm. Clin Neurophysiol 2011; 122: 2116–20.

Bullock TH, McClune MC. Lateral coherence of the electrocorticogram: a new measure of brain synchrony. Electroencephalogr Clin Neurophysiol 1989; 73: 479–98.

Bullock TH, McClune MC, Achimowicz JZ, Iragui-Madoz VJ, Duckrow RB, Spencer SS. EEG coherence has structure in the millimeter domain: subdural and hippocampal recordings from epileptic patients. Electroencephalogr Clin Neurophysiol 1995; 95: 161–77.

Cobb WA, Guiloff RJ, Cast J. Breach rhythm: the EEG related to skull defects. Electroencephalogr Clin Neurophysiol 1979; 47: 251–71.

Cooper R, Winter AL, Crow HJ, Walter WG. Comparison of Subcortical, Cortical and Scalp Activity Using Chronically Indwelling Electrodes in Man. Electroencephalogr Clin Neurophysiol 1965; 18: 217–28.

Delucchi M, Garoutte B, Aird R. The scalp as an electroencephalographic averager. Electroencephalogr Clin Neurophysiol 1962; 14: 191–196.

Duun-Henriksen J, Madsen RE, Remvig LS, Thomsen CE, Sorensen HBD, Kjaer TW. Automatic detection of childhood absence epilepsy seizures: toward a monitoring device. Pediatr Neurol 2012; 46: 287–92.

Ebersole JS. Defining epileptogenic foci: past, present, future. J Clin Neurophysiol 1997; 14: 470–83.

Fein G, Raz J, Brown FF, Merrin EL. Common reference coherence data are confounded by power and phase effects. Electroencephalogr Clin Neurophysiol 1988; 69: 581–4.

Gloor P. Neuronal generators and the problem of localization in electroencephalography: application of volume conductor theory to electroencephalography. J Clin Neurophysiol 1985; 2: 327–54.

Guevara MA, Corsi-Cabrera M. EEG coherence or EEG correlation? Int J Psychophysiol 1996; 23: 145–53.

Hallez H, Vanrumste B, Grech R, Muscat J, De Clercq W, Vergult A, et al. Review on solving the forward problem in EEG source analysis. J Neuroeng Rehabil 2007; 4: 46.

Hashiguchi K, Morioka T, Yoshida F, Miyagi Y, Nagata S, Sakata A, et al. Correlation between scalp-recorded electroencephalographic and electrocorticographic activities during ictal period. Seizure 2007; 16: 238–47.

Nicolas P, Deloche G. Convolution computer processing of the brain electrical image transmission. Int J Biomed Comput 1976; 7: 143–59.

Nunez PL, Srinivasan R. Electric fields of the brain: the neurophysics of EEG. 2nd ed. New York: Oxford University Press, USA; 2006.

Pfurtscheller G, Cooper R. Frequency dependence of the transmission of the EEG from cortex to scalp. Electroencephalogr Clin Neurophysiol 1975; 38: 93–6.

Tao JX, Baldwin M, Hawes-Ebersole S, Ebersole JS. Cortical substrates of scalp EEG epileptiform discharges. J Clin Neurophysiol 2007; 24: 96–100.

Tao JX, Ray A, Hawes-Ebersole S, Ebersole JS. Intracranial EEG substrates of scalp EEG interictal spikes. Epilepsia 2005; 46: 669–76.

Zaveri HP, Duckrow RB, Spencer SS. The effect of a scalp reference signal on coherence measurements of intracranial electroencephalograms. Clin neurophysiol 2000; 111: 1293–9.

APPENDIX

B

ETHICAL COMMITTEE APPLICATIONS

B.1
REPEATED LONG-TERM-EEG MEASUREMENTS IN CHILD EPILEPSIES

RECORD NO.: H-3-2011-054

FORSØGSPROTOKOL

Gentagne langtids-EEG-målinger ved børneepilepsier.

Overlæge Troels Wesenberg Kjær, MD, Ph.D., Rigshospitalet.

Projektets hovedformål

Formålet med undersøgelsen er at udføre gentagne langtids-EEG-målinger hos patienter med børneepilepsi. Ved at sammenligne hyppigheden og varigheden af anfaldsaktivitet fundet ved disse målinger med pårørendes observationer og observationer foretaget ved standard-EEG-målinger kan vi se om en øget monitorering af patienterne vil ændre lægens medicinering af patienten.

Hypoteser

1. Langtids-EEG-målinger giver mere detaljerede oplysninger om hyppighed og varighed af anfaldsaktivitet, end der kan opnås ved indberetning fra pårørende eller standard-EEG-målinger.
2. Præcis viden om hyppighed og varighed af anfaldsaktivitet resulterer i bedre oplevet sygdomskontrol og sygdomsindsigt hos patient/pårørende.
3. Behandlende læge ændrer medicinering som følge af langtids-EEG-målingerne.

Baggrund

Specielt blandt børneepilepsier synes der at være en direkte sammenhæng mellem paroxystisk aktivitet i EEG'et og patientens prognose. Samtidig er denne patientgruppe specielt påvirkelige af anti-epileptiske medikamenter, således at en op- eller nedregulering af medicindosis påvirker anfaldsaktiviteten. Desværre har alle eksisterende medicinske behandlingsformer af epilepsi betragtelige bivirkninger, hvilket gør at en så lille medicinsk dosis som mulig ønskes.

Mange børneepilepsier er kendetegnet ved, at de elektriske signaler i hjernen begynder at svinge i takt over hele hjernen samtidig. Dette kan måles med elektroencephalographi (EEG) optagelser. Disse EEG optagelser benyttes ofte af de behandlende læger til at få en bedre forståelse af anfaldsfrekvens og –varighed. Normalt stilles diagnosen epilepsi ud fra en klinisk vurdering kombineret med 30 minutters overflade-EEG. Dette betegnes standard-EEG. Visse typer af epilepsi har dog så diskrete symptomer at behandlingen primært udføres på det målte EEG. Inden for dette projekt ønsker vi at kigge på disse typer af epilepsi med speciel fokus på børneabsenceepilepsi (eng.: Childhood absence epilepsy (CAE)).

Børneabsenceepilepsi

CAE står for cirka 5 % af alle tilfælde af epilepsi startende i barndommen. Årligt får omkring 350 danske børn i alderen 4-10 år stillet diagnosen. CAE er klinisk karakteriseret ved mange daglige, men kortvarige fjernhedsperioder. Der kan være øjendrejning og nik med hovedet. Derimod er der normalt ikke kramper, fald til jorden eller andre voldsomme fænomener, som kan henlede omgivelsernes opmærksomhed på anfaldet, som derfor ofte går upåagtet hen.

Patienter kan have flere hundrede anfald dagligt, specielt hvis de er under- eller ubehandlede. Børnene oplever ikke selv anfaldene som typisk varer mellem 4 og 20 sekunder, men det medfører opmærksomhedsproblemer og dermed indlæringsvanskeligheder. Da patienterne ikke er ved bevidsthed under anfaldet, taber de tråden og skal bruge tid på efterfølgende reorientering. Ved

medicinsk behandling kan de fleste børn blive anfaldsfrie ved korrekt diagnose og behandling. Efter nogle år kan omkring 80-90 % blive trappet ud af behandling uden tilbagevendende anfald. Der er en direkte sammenhæng mellem hvor succesfuld den medicinske behandling er og hvor god patientens chance er for at blive anfaldsfri uden medicin efter et par år.

Normalt stilles diagnosen børneabsenceepilepsi ud fra en klinisk vurdering kombineret med 30 minutters overflade-EEG. Hos patienter med børneabsenceepilepsi er EEG'et karakteriseret ved højamplitude "spike-and-wave"-mønstre i hele anfaldets varighed. Ved overflade EEG måles typisk fra 19-21 EEG-elektroder placeret på hovedet som små plader eller små nåle. Patienten får stillet diagnosen efter første EEG registrering, og begynder derefter behandling. Afhængig af efterfølgende klinisk vurdering, kan den behandlende læge bestille ekstra EEG-målinger for at vurdere medicinens virkning. Når patienten udtrappes af medicinen efter nogle år, anbefales det at det gøres under EEG-overvågning for at verificere at anfaldsaktiviteten er stoppet.

Andre børneepilepsityper
To grupper af patienter som på nogle områder ligner børneabsencepatienterne er juvenil absence epilepsi (JAE) og juvenil myoklon epilepsi (JME). Disse patientgrupper får som oftest deres første anfald i alderen 10-17 år, men i modsætning til CAE patienterne, er anfaldene sjældent ligeså homogene i deres manifestation. JAE og JME er desuden ofte kroniske epilepsiformer hvor patienten ikke så ofte kan trappe ud af medicineringen allerede efter få år. Det må dog forventes at patienternes livskvalitet er direkte sammenhængende med hvor godt de er medicinerede.

En anden type af epilepsi, som ligeledes behandles ud fra EEG'et er continuous spikes and waves during slow sleep (CSWS). Denne epilepsitype manifestere sig hos børn i alderen 2-9 år ved kun at være dominerende om natten. Hovedsymptomet er pludselig stilstand i udviklingen eller direkte tab af intellektuelle, sproglige og praktiske færdigheder, oftest i kombination med svære adfærdsforstyrrelser i form af ukoncentreret og planløs adfærd, hyperaktivitet og uforudsigelig eksplosiv adfærd, uden nogen relation til anfaldene. I dag udføres 1-2 årlige 1-døgns EEG-registreringer under indlæggelse, som giver den behandlende læge et indblik i medicinens virkning. Også her arbejder lægerne ud fra en hypotese om at en mere tæt regulering af patienterne giver en bedre prognose.

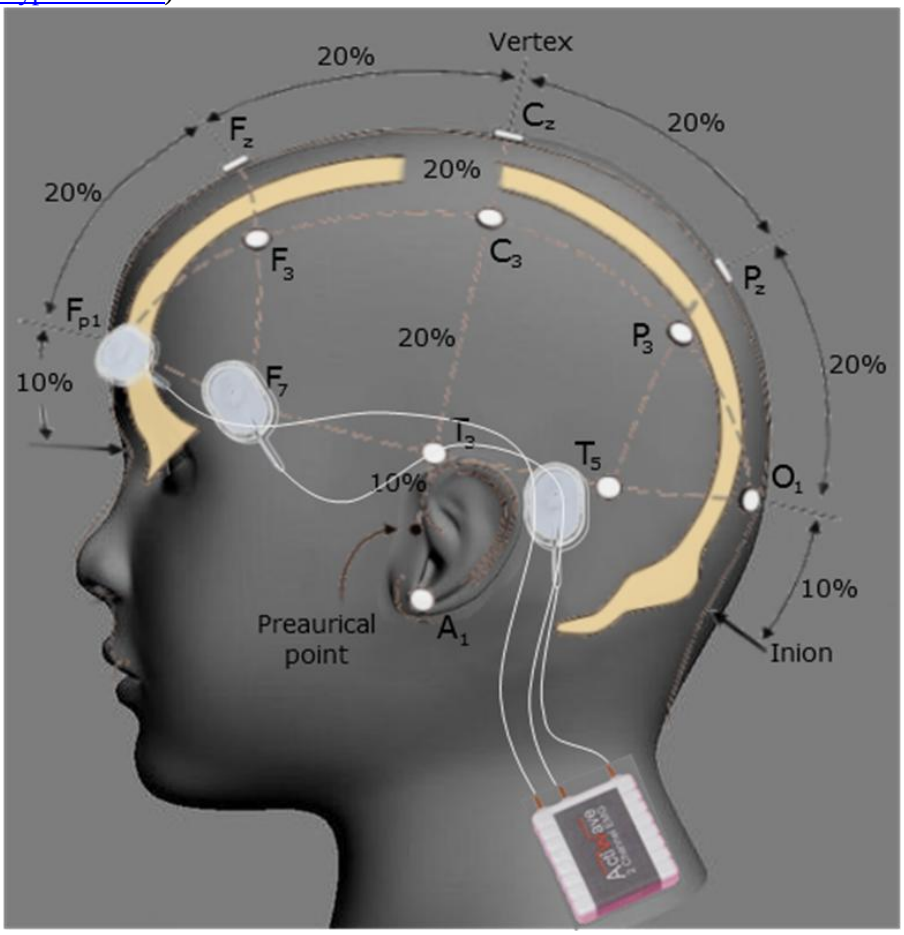
Behandlingen
På trods af at størstedelen af børn med ovenstående epilepsityper bliver anfaldsfrie på medicinsk behandling, kan optimering og valg af det rette medikament til tider være udmattende for patient og pårørende, da den kliniske vurdering kan være svær. Dette skyldes at anfald, hvis de overhovedet ses, er kortvarige og diskrete uden synlige kramper eller fald. Dertil kommer, at anfald kan ses på alle tider af døgnet - også om natten hvor patienten ikke observeres. Et andet problem for patient og pårørende er de hyppige kontakter til sundhedsvæsenet. Og for patienten kan bivirkning ved overmedicinering også give anledning til problemer.

Det må forventes at være optimalt, hvis man kører en tæt op- og nedtrapning af medicineringen, som følger fundene fra EEG'et. Ved at lave gentagne langtids-EEG-målinger vil patienten kunne monitoreres døgnet rundt i en længere perioder, og man får et mere præcis mål for patientens anfaldsaktivitet. Dette svarer på mange måder til den udvikling der er sket inden for kardiologien, hvor der udføres en såkaldt Holter-monitorering for analyse af hjerterytmeabnormaliteter. Ligesom anfaldsaktivitet hos epilepsipatienter, kan

hjerterytmeabnormaliteter forekomme tilfældigt eller spontant, hvorfor længerevarende registreringer er nødvendige.

For at gøre de gentagne langtids-EEG-målinger brugervenlige vil registreringerne typisk være begrænset til ganske få kanaler (typisk 2) svarende til 3 plasterelektroder som klistres på hovedet, se Figur 1. Der benyttes standard CE-godkendte EEG-elektroder som forbindes til et lille CE-godkendt monitoreringsapparat på størrelse med en lille tændstikæske. Elektroderne er designet til længerevarende målinger i ansigtet. Monitoreringsapparat vil blive fastgjort til huden ved hjælp af medicinsk godkendt tape. Al dataopsamling vil foregå i apparatet, hvorefter det kan udtrækkes offline for analyse. Vi råder over sådanne EEG-monitoreringsapparater, som er blevet stillet til rådighed af firmaet HypoSafe. HypoSafe vil ligeledes betale udgifter til elektroderne. Apparaterne har en stykpris på 19.200 kr, men er genanvendelige. Elektroderne er til engangsbrug og koster omkring 8 kr pr. styk. Udstyret har været anvendt i en række studier inden for søvnforskning.

Projektet er opstartet på initiativ af undertegnede (TWK). I projektgruppen indgår ud over personale på Rigshospitalet, forskere på DTU (www.dtu.dk) og ingeniører fra firmaet HypoSafe A/S (www.hyposafe.com).

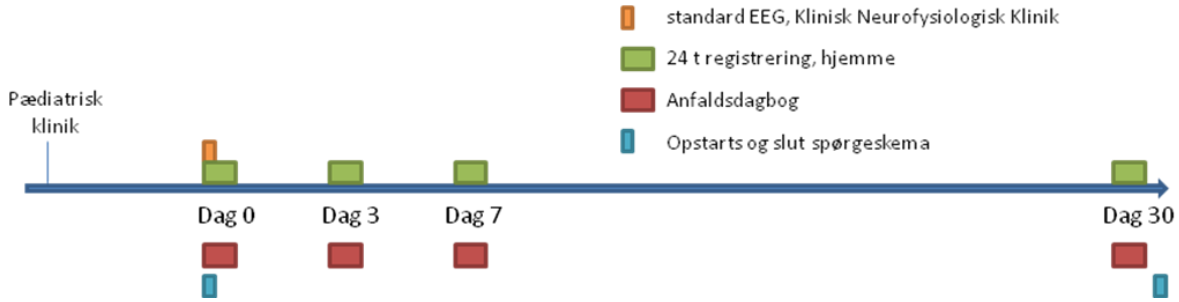


Figur 1: Eksempel på hvorledes de ekstra plasterelektroder kan tænkes påsat til 24 timers monitorering af patientens EEG. Monitoreringsapparatet er CE-godkendt og mindre end en lille tændstikæske.

Metode

Patienter informeres om projektet i forbindelse med besøg i børneambulatoriet på Rigshospitalet. Såfremt det er nødvendigt for at få nok patienter i projektet vil det blive muligt at inkludere patienter fra andre hospitaler eller praktiserende speciallæger i regionen. Hvis patienten og indehaver af forældremyndigheden udviser interesse, vil den henvisende læge, samtidig med at der bestilles tid til standard EEG på Klinisk Neurofysiologisk Klinik, Rigshospitalet, gøre de forsøgsansvarlige opmærksomme på, at det kan være en kandidat til forsøget. Patient og forældre får informationsmateriale med hjem. Ønsker patienten stadig at deltage ved ankomst til undersøgelse på Klinisk Neurofysiologisk Klinik, bedes erklæring om informeret samtykke underskrevet, og den normale procedure for registrering af standard-EEG, vil begynde. Der vil i denne forbindelse blive påsat op til fem ekstra plasterelektroder fra langtids-EEG-monitoreringsudstyret. Pt. overvåges efter afdelingens vanlige procedurer. Efter tilfredsstillende EEG-registrering afsluttes den indledende undersøgelse som normalt og standard-EEG udstyret tages af, mens de op til fem elektroder fra langtids-EEG-apparatet bliver siddende. Det kan formodes at der forekommer et ekstra lille ubehag for patienten i relation til at bære apparatet ud over de i forvejen placerede elektroder. Dette udgør dog en mindre del i forhold til den i forvejen gennemførte rutine procedure.

Efter standard-EEG målingen vil det tændstikæske-store apparat (37 mm x 27 mm x 9 mm) blive fastgjort til nakke/skulder med medicinsk godkendt tape. Pt. skal bære dette udstyr de følgende 24 t. Efter 3-4 dage skal pt. igen gå med apparatet i 24 t, og igen efter ca. 7 dage og 1 måned. I alt skal pt. gå med det ekstra udstyr i 4 x 24 t, se Figur 2. Pt. og pårørende vil blive instrueret i påsætning af elektroder, således at de kan gøre dette selv. Det må formodes at der forekommer et lille ubehag for patienten i relation til at bære apparatet i 4 x 24 t, men dette forventes at blive opvejet af den mulige forbedrede diagnostik (se uddybelse under Etiske overvejelser). Forældre vil blive bedt om at udfylde en anfaldsdagbog som angiver hvor mange anfald de mener barnet har de dage hvor der monitoreres.



Figur 2: Tidslig illustration af forsøgsgangen for patienten. Ved første besøg på pædiatrisk klinik vil patient og pårørende blive informeret om forsøget samtidig med at der bestilles tid til standard-EEG, som det vanligvis er procedure. Ønsker patienten/værge at deltage vil samtykke blive givet til Jonas Duun-Henriksen eller undertegnede i forbindelse med at standard EEGet optages. Patienten opstarter herefter undersøgelse med et lille EEG-monitoreringsapparat i 4 perioder á 24 timers varighed.

Apparatet indeholder en mikroprocessor som konverterer den analoge EEG måling til digitalt format som derefter vil blive lagret. Den matematiske bearbejdning vil ikke ske umiddelbart, men foregå på gemt data. I første omgang vil patienternes EEG blive opsamlet, for efterfølgende at blive lægeligt vurderet med hensyn til hvad der er anfald, og hvad der er artefakter. Opsamlet data vil blive anonymiseret, således at alle data som forlader Rigshospitalet ikke er personhenførbart. Alle fortrolige oplysninger vedrørende patienterne opbevares forsvarligt aflåst på Rigshospitalet. Data

vil blive slettet, såfremt det vurderes, at der ikke længere kan produceres forskningsresultater fra dem, eller såfremt forsøgspersonerne eller indehaver af forældremyndigheden ønsker dem slettet.

I forbindelse med undersøgelsen vil forældrene modtage to spørgeskemaer. Et som omhandler forældrenes og eventuelt børnenes forventninger til undersøgelsen inden igangsættelse, og et som omhandler en evaluering af forsøgsgangen efter sidste måling. Der vil herunder blive spurgt til, om de fik det ud af undersøgelsen som de havde forventet, samt en evaluering af hvor besværligt det har været for børn og forældre at benytte monitoreringsapparatet. Dette vil give os indblik i, om proceduren er berettiget i forbindelse med øget ubehag imod forbedret prognose. Spørgeskemaer er vedhæftet ansøgningen.

Patient og indehaver af forældremyndigheden informeres mundtligt og skriftligt om forsøget og får udleveret folderen "Før du bestemmer dig" samt tillægget vedrørende rettigheder som forsøgsperson i et biomedicinsk forskningsprojekt. Kun patienter og/eller indehavere af forældremyndigheden som accepterer og underskriver den informerede samtykke (vedlagt) efter at have haft lejlighed til at gennemlæse patientinformationen vil blive inkluderet i undersøgelsen. Patient og indehaver af forældremyndigheden kan selv vælge om de vil have indblik i eventuelle ekstra fund på baggrund af den ekstra procedure.

Forsøgspersoner herunder inklusions- og eksklusionskriterier

I forsøget forventes indrulleret 100 patienter over 5 år med formodet eller sikker epilepsi.

Inklusionskriterier:

- Patienter med diagnosticeret eller mistanke om børneepilepsi.
- Kun patienter over 5 år vil blive indrulleret, og kun efter mundtlig og skriftligt samtykke fra forældremyndighedens indehaver(e).

Eksklusionskriterier:

- Patienter med svær systemisk sygdom.
- Patienter med svær retardering eller anden sygdom som gør at de skønnes uegnede til at bære elektroder over en længere periode.
- Det vil være muligt for den forsøgsansvarlige at udelukke en inkluderet patient for yderligere forsøg, hvis det efter en eller flere målinger skønnes at apparatet ikke bliver båret korrekt. Dette vil dog foregå i dialog med patienten/forældremyndigheden hvor vi først vil se om vi kan afhjælpe problemet.

Forsøgspersonerne vil først blive inkluderet efter de og/eller indehaver af forældremyndigheden har afgivet mundtlig og skriftlig samtykke. De kan til enhver tid trække deres samtykke tilbage.

Overvejelser angående inklusion af personer under 18 år er grundigt beskrevet i afsnittet Etiske overvejelser. Jævnført Den Centrale Videnskabsetiske Komités vejledning om anmeldelse m.v. af et biomedicinsk forskningsprojekt skal der ifølge afsnit 4.2.1.1e anføres under hvilke forhold forsøget kan godkendes. Både begrundelse B og C gør sig gældende i indeværende forsøg:

B) Projektet ikke med tilsvarende nytte kan gennemføres ved at inddrage myndige, habile forsøgspersoner, og projektet har udsigt til direkte at gavne barnet eller den unge.

C) Projektet alene kan gennemføres ved at inddrage personer, der er omfattet af den pågældende aldersgruppe, sygdom eller tilstand, og projektet har direkte udsigt til at kunne overføre meget store

fordele til den patientgruppe, som omfattes af samme aldersgruppe, sygdom eller tilstand som forsøgspersonen, og projektet indebærer minimale risici og gener for barnet eller den unge.

Styrkeberegning
Da dette er et deskriptivt studium er vi først og fremmest interesserede i kvalitative data vedrørende metodens brugbarhed. Vi skønner at der kan være en del tekniske problemer hos børn, lige som det reducerede elektrodeantal ved registreringerne kan have betydning for udfaldet af målingerne hos de enkelte patienter. Ved at søge om tilladelse til at undersøge 100 patienter over en 5-årig periode, mener vi at kunne få nok data fra flere patientgrupper til at kunne lave statistiske valide resultater. De 100 patienter forventes at inkludere 20 patienter med børneabsenceepilepsi (CAE), 20 patienter med juvenil absence epilepsi (JAE), 20 patienter med juvenil myoklon epilepsi (JME), 10 patienter med Continuous Spikes and Waves during slow Sleep (CSWS) og op til 30 patienter med anden form for epilepsi.

Deltagerinformation
Deltagerne vil blive informeret både mundtligt og skriftligt, og kan til enhver tid trække deres tilsagn om deltagelse tilbage, uden at det ændrer deres behandlingsmuligheder nu eller i fremtiden. Informationen vil blive givet i forbindelse med, at patienten alligevel kommer til undersøgelse eller udredning. Denne information gives af den behandlende læge som har fuldt kendskab til projektet. Det vil foregå i et dertil indrettet rum bag lukkede døre. Lægen vil i kraft af sin daglige omgang med mindreårige patienter have den nødvendige pædagogiske forudsætning og forståelse for kommunikation med dem.

Inden den mundtlige information gives, vil patienten have modtaget en skriftlig information, hvori det også forklares, at patienten har mulighed for at have en bisidder med til den mundtlige orientering. For børn kræves det, at indehaver af forældremyndigheden også deltager under den mundtlige information. Patienten gives mindst 3 dages betænkningstid inden samtykkeerklæringen skal underskrives. Forsøgspersonens tilkendegivelser i forhold til forsøgsdeltagelse tillægges relevant betydning.

Både i den mundtlige og skriftlige information vil det blive understreget at manglende deltagelse i undersøgelsen, eller afbrydelse af forløbet ikke vil have nogen indflydelse på patientens behandling i øvrigt.

Patienter mellem 15 til 17 år kan få udleveret samme patientinformation som indehaveren af forældremyndigheden, hvis de ønsker dette. Det skønnes at den skriftlige patientinformation er skrevet forståeligt for denne aldersgruppe.

Bivirkninger, risici og ulemper
Bivirkninger, risici og ulemper forbundet med denne type optagelse forventes kun øget i ringe grad. Ved at gå med elektroder over længere perioder, kan der opstå en mindre irritation af huden i området hvor elektroden er klistret fast. Dette kan resultere i lidt kløe. Denne kløe vil normalt ophøre umiddelbart efter elektroden fjernes.

Da patienten skal bære apparatet i 4 x 24 t, vil dette kunne være til lille gene. Apparatet er dog ikke større end 37 mm x 27 mm x 9 mm og vejer under 10 g. Det kan bæres under alle normale aktiviteter, men skal dog fjernes under badning.

Etiske overvejelser
Eftersom barnet skal gå med apparatet i 4 x 24 t, vil det være umuligt ikke at tildrage nogen opmærksomhed. Dette vil kunne medføre en sygeliggørelse som kan betyde både mobning og afstandstagen fra andre børn. Projektets opsætning er dog planlagt således at de fleste registreringer

kan foretages på weekenddage hvor barnet ikke skal i skole eller på institution. Det er dog en patientgruppe som inden udredning i forvejen har været stærkt mærket af deres symptomer. Det må forventes at undersøgelsen kan være med til at optimere behandlingen for patienten. Dog er det muligt at enkelte patienter ikke opnår nogen umiddelbar gevinst ved at deltage i forsøget.

Grunden til at forsøget skal foregå på børn er, at det netop er denne aldersgruppe som har den type generaliseret epilepsi, hvor der er en tæt sammenhæng mellem behandling og EEG. På trods af at børnene ofte ikke selv oplever de epileptiske anfald, er det en stærkt invaliderende sygdom. Den konstante kliniske monitorering og udredning for progressionen af sygdommen er desuden hård for barn og forældre. Da det forventes at undersøgelsen kan føre til en forbedret udredning for epilepsien samtidig med at den ikke forventes at påføre patienterne betragtelige gener, findes det fuldt etisk forsvarligt at udføre de ekstra målinger, som protokollen omfatter. Selvom nogle børneepilepsier diagnosticeres inden barnet er fyldt 5 år, har vi valgt at sætte denne grænse som inklusionskriterie. Dette er gjort for at skåne de yngste, samtidig med at vi mener at børn fra denne alder vil kunne forstå hvorfor de skal bære de ekstra ledninger, og ikke må rive dem af.

Med baggrund i tidligere udførte målinger forventes det ikke at forsøgene påfører patienterne betragtelige gener og smerter. Elektroderne er CE-mærkede til langtidsmålinger og anvendelse i ansigtet. Hvert enkelt optageapparat er testet af leverandøren. Strømforsyningen er almindelig batteri med lav spænding.

Alle patienter/forældremyndighedsindehavere skal give informeret samtykke. Personlige oplysninger vil kun være tilgængeligt for projektgruppen og vil ikke blive videregivet til tredjepart. Kun anonymiseret data vil kunne blive delt med Rigshospitalets samarbejdspartnere. Alle fortrolige oplysninger vedrørende patienterne vil blive destrueret ved projektets afslutning.

Forsøgspersonerne kan til enhver tid, uden nogen form for begrundelse, trække deres samtykke om deltagelse tilbage, uden at dette vil ændre deres mulighed for nuværende eller fremtidig behandling. Oplysninger om forsøgspersonerne vil blive behandlet med fuld diskretion. Ingen fortrolige oplysninger vil være tilgængelige for tredjeparter.

Anmeldelse af projektet til Datatilsynet

Projektet vil blive udført under Rigshospitalets paraplygodkendelse fra Datatilsynet. Det er blevet anmeldt jf. Region Hovedstadens gældende regler for Anmeldelse af behandling af Data. De ekstra EEG-kanaler som bliver opsamlet vil blive behandlet ifølge loven om behandling af personoplysning ligesom resten af det EEG som i forvejen bliver opsamlet på Rigshospitalet. Eventuelle data som forlader Rigshospitalet vil blive anonymiseret inden det bliver udtrukket således, at det ikke vil være personhenførbart.

Økonomiske forhold

Forsøget udføres som en del af et forskningsprojekt for erhvervs-Ph.D.-studerende Jonas Duun-Henriksen med titlen ”Detektion og prædiktion af epileptiske anfald”. Jonas Duun-Henriksen er som Ph.D.-studerende indskrevet ved DTU og projektet er initieret i samarbejde mellem DTU og Rigshospitalet. Jonas Duun-Henriksens ansættelsesform er i en projektbegrænset funktionærstilling via et erhvervs-Ph.D stipendium i firmaet Hypo-Safe A/S som står for afholdelse af udgifter til projektet samt 2/3 af Ph.D.-afgift og løn til Jonas Duun-Henriksen (sidste tredjedel er fra videnskabsministeriet). Jonas’ løn udgør 35.000 kr/måned hvor videnskabsministeriet giver 14.500 kr/måned i løntilskud. Udgifter til projektet består af 2 EEG-monitoreringsapparater med en

stykpris på 19.200 kr., samt elektroder med stykpris på ca. 8 kr. Total elektrodepris vil beløbe sig i 5 elektroder * 4 dage * 100 patienter * 8 kr/elektrode = 16.000 kr. Derudover er der en udgift til renseservietter til klargøring af elektrodepåsætning på 200 kr. Samlede udgifter bliver dermed 54.600 kr. Udgifter vil blive indbetalt på forskningskonto 959585865 tilknyttet Rigshospitalet som et vederlag pr. forsøgsperson af HypoSafe.

Professor, overlæge, Peter Uldall, neuropædiatrisk enhed står får den kliniske del af projektet. Han har ingen økonomisk interesse i Hypo-Safe A/S. Jonas Duun-Henriksen står for analysen af data. Han har heller ingen økonomisk interesse i Hypo-Safe A/S. For den parakliniske del af projektet står overlæge Troels W. Kjær fra Klinisk Neurofysiologisk Klinik og ekstern lektor ved Københavns Universitet. Han er desuden Ph.D.-vejleder for Jonas Duun-Henriksen, men har ingen økonomisk interesse i Hypo-Safe A/S. I den tekniske del vil lektor Helge B.D. Sørensen, DTU Elektro, være behjælpelig med signalbehandlingen. Helge fungerer samtidig som hovedvejleder for Jonas. Helge B.D. Sørensen har heller ingen økonomisk interesse i Hypo-Safe A/S.

Afhængigt af resultaterne i projektet er det muligt at Hypo-Safe A/S ønsker at videreudvikle deres eget udstyr til automatisk anfaldsdetektion. Dette vil i givet fald ske uafhængigt af dette projekt.

Tilgængeligheden af oplysninger

Det er under hele projektet muligt at kontakte:

Overlæge, Ph.D. Troels W. Kjær på Klinisk Neurofysiologisk Klinik, Rigshospitalet, Blegdamsvej 9, 2100 København Ø; Tlf. 3545 3266, e-mail: neurology@dadlnet.dk

Professor, overlæge, dr. med, Peter Uldall, Pædiatrisk Klinik, Rigshospitalet, Blegdamsvej 9, 2100 København Ø; Tlf. 3545 1740, e-mail: peter.uldall@rh.regionh.dk

Ph.D-studerende cand. polyt, Jonas Duun-Henriksen, DTU Elektro, Ørsteds Plads bygn. 349, rum 109, 2800 Kgs. Lyngby; Tlf. 6178 9966, e-mail: jhe@elektro.dtu.dk.

Offentliggørelse af resultater

Projektet vil resultere i en eller flere artikler, som vil blive publiceret i peer reviewede internationale videnskabelige tidsskrifter. Både positive såvel som negative resultater vil blive publiceret. Hvis publikation ikke lykkes, vil der ske offentliggørelse på anden vis. Her sigtes der på præsentation på konference.

B.2
CONTINUOUS SUBCUTANEOUS EEG MEASUREMENTS FOR DETECTION AND PREDICTION OF EPILEPTIC SEIZURES

RECORD NO.: H-1-2009-140

FORSØGSPROTOKOL

Kontinuerte subkutane EEG-målinger med henblik på detektion og prædiktion af epileptiske anfald.

Troels Wesenberg Kjær, MD, Ph.D.,

Projektets hovedformål
Formålet med undersøgelsen er at detektere og prædiktere epileptiske anfald ved hjælp af subkutane elektroder. En række epilepsiformer giver ingen eller få kliniske symptomer og det er derfor svært for den behandlende læge, de pårørende og patienten selv at vide hvornår og hvor ofte der er anfaldsaktivitet i hjernen. Dette projekt har til formål at vurdere forekomsten af anfaldsaktivitet hos disse patienter, og muligheden for at forudsige de enkelte anfald.

Detektion af epilepsianfald i real-time relateret til advarsel af tredjeperson
Projektmålet omhandler patienter med lokalisationsrelateret epilepsi. De fleste patienter bliver anfaldsfrie på medicinsk behandling, men en mindre gruppe bliver ikke anfaldsfrie trods intensiv medicinsk behandling. Disse patienter kan tilbydes operation, hvor man fjerner det område, hvor epilepsien starter. Hvis patienten i stedet kunne få detekteret sine anfald, kunne en tredjeperson få tilsendt en advarsel mens de står på. Han eller hun kan derefter tjekke op på om patienten var kommet over anfaldet uden men. Undersøgelsen skal dermed klarlægge om subkutane elektroder kan benyttes til detektion af epilepsianfald. Der er tale om patienter mellem 18 og 70 år. Der forventes at blive inkluderet 50 pt.

Prædiktion af Epilepsianfald i real-time relateret til advarsel af patienten selv
Anfaldsprædiktion er et forholdsvist nyt forskningsområde og forventes at kunne inkorporeres som advarselsmetode for patienten på længere sigt. Muligheden for prædiktion vil blive undersøgt på samme patientgruppe som ovenstående, hvormed der ikke kræves yderligere patienter til dette.

Hypotese
Vores hypotese er, at synkroniseringen af fyringsfrekvensen for hjernecellerne under et epileptisk anfald er så udtalt, at det er muligt at detektere automatisk via EEG-data.
Derudover forventes det, at de elektriske forandringer på EEG'et starter noget tidligere end det kliniske anfald forekommer. Information gemt i EEG-signalet kan dermed medføre en prædiktion af det forestående anfald. Dette vil lette hverdagen for mange patienter, da de så ville kunne undgå den evige frygt for et pludseligt anfald og derudover undgå diverse farlige situationer.

Baggrund
Epilepsipatienter angiver tit, at den største ulempe ved at have epilepsi er det kontroltab man oplever, når der kommer uventede anfald. For forældre er det også svært at lade børn med epilepsi sove alene af frygt for uopdagede natlige anfald. Formålet med forsøget er at give disse mennesker en større følelse af tryghed og kontrol i hverdagen med automatisk detektion og evt. prædiktion af epilepsianfald.

I dag indlægges omkring 200 patienter om året i en *Epilepsy Monitoring Unit* (EMU) på Rigshospitalet. De fleste er indlagt med diagnostiske formål, mens 40-50 er til udredning for, om de vil kunne have gavn af epilepsikirurgi. Omkring 15 af disse patienter får indlagt intrakranielle

elektroder på hjernen ved det formodede epileptogene område, hvorefter hullet i kraniet lukkes. Efter nogle dages monitorering fjernes elektroderne, og det vurderes om patienten kan få fjernet epileptogent hjernevæv.

Vi ønsker at supplere disse målinger med elektroder som placeres udenpå kraniet, men under huden, i det subkutane hulrum som alligevel dannes af lægen i forbindelse med operationen. Denne procedure vurderes til ikke have nogen gene for patienten, og vil maksimalt udvide operationstiden med 5 minutter. Elektroderne vil blive fjernet i forbindelse med fjernelse af de øvrige elektroder.

Basis for dette projekt er at etablere en tilstrækkelig stor bank med EEG-data fra både de interiktale (mellem anfald), præiktale (inden anfald) og iktale (under anfald) perioder til statistisk analyse. I første omgang vil patienternes EEG blive opsamlet, for efterfølgende at blive lægeligt vurderet med hensyn til hvad der er anfald, og hvad der er artefakter.
Kun patienter som har indvilliget i at lade os opsamle deres EEG, efter informeret samtykke (vedlagt), bliver inkluderet. Opsamlet data vil blive anonymiseret, således at alt data som forlader Rigshospitalet ikke er personhenførbart. Alle fortrolige oplysninger vedrørende patienterne opbevares forsvarligt aflåst på Rigshospitalet. Personhenførbart data vil blive slettet, såfremt det vurderes, at der ikke længere kan produceres forskningsresultater fra dem, eller såfremt forsøgspersonerne ønsker dem slettet. Det ønskes at dele det anonymiserede EEG-data med nogle af Rigshospitalets samarbejdspartnere, hvorfor kopier af dette vil kunne blive sendt til andre hospitaler eller universiteter i Danmark eller udlandet.

Metode
Patienterne informeres mundtligt og skriftligt om forsøget og får udleveret folderen "Før du bestemmer dig" samt tillægget vedrørende rettigheder som forsøgsperson i et biomedicinsk forskningsprojekt. Patienterne underskriver informeret samtykke efter at have haft lejlighed til at gennemlæse ovenstående. Hvis forsøgspersonen ikke er myndig, vil indehaveren af forældremyndigheden, sammen med patienten, få al mundtlig og skriftlig information, og skal derefter give sit informerede samtykke.

Under den normale procedure for indlæggelse af elektroder intrakranielt placeres et grid eller en strip af elektroder subduralt, dvs. under den hårde hjernehinde. Derefter syes dura sammen, og den del af knoglen som er blevet fjernet for at kunne anlægge de intrakranielle elektroder, fikseres igen til kraniet. Denne undersøgelse ønsker derefter at anlægge nogle tilsvarende elektroder udenpå kraniet, men under huden inden denne syes sammen. Undersøgelsen vil blive gennemført med subkutant placerede, kommercielt tilgængelige CE-godkendte elektroder. De ekstra elektroders proksimale del, vil blive forbundet med det udstyr som allerede benyttes på Rigshospitalet til indsamling af de intrakranielle EEG-data. Den matematiske bearbejdning vil ikke ske umiddelbart, men foregå på gemt data.

Forsøgspersoner herunder inklusions- og eksklusionskriterier

Inklusionskriterier:
- Voksne patienter med epilepsi indlagt til udredning for mulighed for epilepsikirurgi.
- 50 patienter mellem 18 og 70 år med epilepsi.

Eksklusionskriterier:
- Patienter med anden svær systemisk sygdom.
- Pt. som har øget infektionsrisiko.
- Pt. hvor det ikke skønnes sikkert at placere måleelektroden.

- Gravide og ammende.

Forsøgspersonerne vil først blive inkluderet efter de har afgivet mundtlig og skriftlig samtykke og kan til enhver tid trække deres samtykke tilbage.
Antallet af inkluderede patienter er valgt ud fra følgende styrkeberegning: Indeværende forsøg vil ikke ændre den eksisterende protokol for udredning af epilepsikirurgi i monitoreringsenheden. Således vides det at ca. halvdelen af patienterne bliver overført til epilepsikirurgi inden de har haft 4 eller flere anfald hvilket er nødvendigt før vi kan generalisere over udseendet af EEG'et under deres anfald. Af de resterende 25 patienter forventes det at ca. 20% vil have preictale mønstre som kan benyttes til forudsigelse af anfald. Dette giver 5 patienter hvilket er nødvendigt for at vi med statistisk signifikans kan sige at vi uden tilfældighed kan prædiktere anfald.

Deltagerinformation
Deltagerne vil blive informeret både mundtligt og skriftligt, og kan til enhver tid trække deres tilsagn om deltagelse tilbage, uden at det ændrer deres behandlingsmuligheder nu eller i fremtiden. Informationen vil blive givet i forbindelse med, at patienten alligevel kommer til undersøgelse eller udredning. Denne information gives af den ansvarshavende læge. Det vil foregå i et dertil indrettet rum bag lukkede døre.
Inden den mundtlige information gives, vil patienten have modtaget en skriftlig information, hvori det også forklares, at patienten har mulighed for at have en bisiddende med til den mundtlige orientering. Den skriftlige information vil blive udsendt sammen med oplysninger om patientens operationsmuligheder. Patienten gives 3 dages betænkningstid inden samtykkeerklæringen skal underskrives.

Bivirkninger, risici og ulemper
Bivirkninger, risici og ulemper forbundet med denne type operation forventes kun øget i ringe grad ved anlæggelse af subkutane elektroder. Anlæggelsen består blot af at anbringe elektroder umiddelbart under huden under en operation som alligevel foretages. Anlæggelsen af elektroder er forbundet med en let øget blødningsrisiko svarende til området, hvor elektroderne anlægges. Der anlægges kun ét elektrodearray. Ved anlæggelse kan lægen direkte se om der er blødning, og dermed stoppe denne. Anlæggelsen forventes at vare under 5 minutter. Ethvert fremmedlegeme i kroppen er forbundet med en infektionsrisiko, som dog anses for at være minimal i denne situation. Patienten er indlagt på Rigshospitalet i hele forløbet og er under løbende overvågning.

Etiske overvejelser
Alle patienter vil give informeret samtykke. Personlige oplysninger vil kun være tilgængeligt for projektgruppen og vil ikke blive videregivet til tredjepart. Kun anonymiseret data vil kunne blive delt med Rigshospitalets samarbejdspartnere. Alle fortrolige oplysninger vedrørende patienterne vil blive destrueret ved projektets afslutning.

Videnskabsetisk redegørelse
Det forventes ikke at forsøgene påfører patienterne unødvendige gener og smerter. Der er ikke nogen umiddelbar gevinst for patient eller familie ved at deltage i forsøget.

Elektroderne er CE-godkendte til subkutan anlæggelse og anvendelse. Disse fungerer og benyttes allerede sammen med Rigshospitalets standard-måleudstyr.

Forsøgspersonerne kan til enhver tid, uden nogen form for begrundelse, trække deres samtykke om deltagelse tilbage, uden at dette vil ændre deres mulighed for nuværende eller fremtidig behandling. Oplysninger om forsøgspersonerne vil blive behandlet med fuld diskretion. Ingen fortrolige oplysninger vil være tilgængelige for tredjeparter.

Da forsøget ikke forventes at påføre patienterne yderligere gener end hvad der kan forventes under det indgreb de i forvejen skal undergå, findes det fuldt etisk forsvarligt at udføre de ekstra målinger, som protokollen omfatter.

Anmeldelse af projektet til Datatilsynet
Projektet vil ikke blive anmeldt til Datatilsynet. De ekstra EEG-kanaler som bliver opsamlet vil blive behandlet ifølge loven om behandling af personoplysning ligesom resten af det EEG som i forvejen bliver opsamlet på Rigshospitalet. Eventuel data som forlader Rigshospitalet vil blive anonymiseret inden det bliver udtrukket således at det ikke vil være personhenførbart.

Økonomiske forhold
Forsøget udføres som en del af et forskningsprojekt for PhD-studerende Jonas Henriksen med titlen "Detektion og prædiktion af epileptiske anfald". Jonas Henriksen er PhD-studerende ved DTU og projektet er initieret i samarbejde mellem DTU og Rigshospitalet. Jonas Henriksens ansættelsesform er i et erhvervs-PhD stipendium i firmaet Hypo-Safe A/S som står for afholdelse af udgifter til projektet samt 2/3 af Ph.D-afgift og løn til Jonas Henriksen (sidste tredjedel er fra videnskabsministeriet). Udgifter til projektet består af 50 ekstra elektroder med stykpris på 5000 kr hvilket beløber sig til samlet udgift på 250.000 kr.

Jonas Henriksen står for analysen af data. For den kliniske del af projektet står overlæge Troels W. Kjær, ekstern lektor Københavns Universitet. Han er desuden Ph.D.-vejleder for Jonas Henriksen, men har ingen økonomisk interesse i Hypo-Safe A/S. I den tekniske del er Lektor Helge Sørgensen, DTU, hovedvejleder. Han har heller ingen økonomisk interesse i Hypo-Safe A/S.

Afhængigt af resultaterne i projektet er det muligt at Hypo-Safe A/S ønsker at videreudvikle deres eget udstyr til automatisk anfaldsdetektion. Dette vil i givet fald ske uafhængigt af dette projekt.

Tilgængeligheden af oplysninger
Det er under hele projektet muligt at kontakte overlæge, Ph.D. Troels W. Kjær på Klinisk Neurofysiologisk Klinik, Rigshospitalet, Blegdamsvej 9, 2100 København Ø; Tlf. 3545 3266, e-mail: neurology@dadlnet.dk

Offentliggørelse af resultater
Projektet vil resultere i en eller flere artikler, som vil blive publiceret i internationale videnskabelige tidsskrifter.

APPENDIX

C

PERSONAL CORRESPONDENCE

Jonas Duun-Henriksen

From: ardalan aarabi [ardalan_aarabi@yahoo.com]
Sent: 17. december 2009 20:09
To: Jonas Henriksen
Subject: Re: Epileptic seizure detection

Dear Mr. Henriksen,

There were a few problems. First of all, the quality of EEG recordings in some patients was not good enough for any analysis. Then, there were some false seizures that were wrongly determined as seizures. After verifying them with our EEG expert, We asked epileptologists in the Epilepsy Center of the University Hospital of Freiburg, Germany, nobody answered, so we had to discard them from our analysis.

regards,

Ardalan

Ardalan Aarabi, PhD
Postdoctoral Fellow
Department of Electrical and Computer Engineering
Faculty of Engineering
University of Manitoba

From: Jonas Henriksen <jhe@elektro.dtu.dk>
To: aarabi@EE.UManitoba.CA
Sent: Wed, December 16, 2009 9:28:48 AM
Subject: Epileptic seizure detection

Dear Mr. Aarabi

I am a Ph.D.-student from Denmark who works with automatic seizure detection. It was with great interest that I read you recent paper in Clinical Neurophysiology: A fuzzy rule-based system for epileptic seizure detection in intracranial EEG.
I am also using the FSPEEG database for evaluation of my algorithm, but the amount of seizures for each patient is not the same as yours. Can you tell me why and which seizures you have chosen not to analyze?

Best regards
Jonas Henriksen
Technical University of Denmark

www.elektro.dtu.dk

Department of Electrical Engineering
Biomedical Engineering
Technical University of Denmark
Ørsteds Plads
Building 348
DK-2800 Kgs. Lyngby
Denmark
Tel: (+45) 45 25 38 00
Fax: (+45) 45 93 16 34
Email: info@elektro.dtu.dk

ISBN 978-87-92465-62-7