Uncovering the value of autonomic signs and seizure detection in epilepsy care

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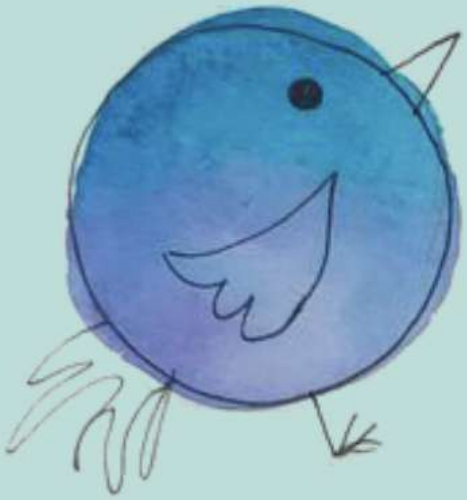

CHAPTER 1

GENERAL INTRODUCTION

INTRODUCTION

Sam was eight years old when he was diagnosed with epilepsy. At first, he experienced only small seizures during the day. He had some difficulties concentrating in school and sometimes fell during soccer practice or for no apparent reason. Two years after the diagnosis, his parents were suddenly awakened at night by a scream from his younger brother. They found their elder son in bed with his eyes wide open, froth on his mouth and having rhythmic jerks in both arms and legs. From that moment, everything changed. Sam's parents could not let go of the image of their child having a large seizure. What would have happened if his younger brother had not alerted them in time? How could they make sure that they would not miss another nocturnal seizure? What would this mean for the future? These are questions that not only Sam's parents, but many parents of children with epilepsy, ask themselves.
As of today, we cannot provide an answer to all these questions and the answers we give are not always reassuring. We can, however, support families like Sam's, by contributing to a safer home environment and improved quality of life through the implementation of seizure detection devices in a suitable manner.

Detecting epileptic seizures automatically

Epilepsy affects around 50 million people globally.[1] Approximately one third of these people continue to have seizures despite treatment.[2] Disability-adjusted life years due to epilepsy have been estimated as thirteen million each year.[3] People with epilepsy have an impaired quality of life (QoL), as do their caregivers.[4-6] Seizures are unpredictable, constitute a loss of control and may cause life-threatening situations through injury, status epilepticus and sudden unexpected death in epilepsy (SUDEP).[7] Convulsive seizures, including focal to bilateral and generalized tonic-clonic seizures, pose the highest mortality risks, especially those occurring at night, as these events are often unwitnessed.[8-10]

Seizure detection devices (SDDs) aim to warn of - potentially dangerous - seizures. A timely alert may enable caregivers to intervene, which might help to reduce seizure-related morbidity and mortality.[9, 11-13] SDDs may help to promote the independence of people with epilepsy, for example by allowing a child to sleep alone. As seizures are often underreported,[14] SDDs also have the potential to provide a more complete documentation of seizure occurrence and thereby improve epilepsy treatment.[15] SDDs may therefore

have a positive impact on the QoL of people with epilepsy and their caregivers, although evidence for this is still lacking.[16]

Preventing risks of SUDEP

The incidence of SUDEP was estimated at around 1 in 1000 adults and 1 in 4500 children with epilepsy per year.[17] Recent studies, however, did not confirm this contrast between age groups and suggested instead that SUDEP rate may be as high in children as in adults.[18, 19]

A high frequency of convulsive seizures and nocturnal unwitnessed events pose the highest SUDEP risk.[7-10] A recent large population-based case control study found a 27-fold increased risk of SUDEP in people who had experienced a convulsive seizure in the preceding year, compared to people with non-convulsive seizures only.[8] The presence of a nocturnal convulsive seizure in the previous year was associated with a 15-fold increased risk of SUDEP and the combination of convulsive seizures and sleeping alone resulted in a 67-fold risk increase.[8] Thus, the most effective way to decrease SUDEP risk appears to be lowering the number of convulsive seizures by optimizing anti-seizure treatment, including use of medication or surgical interventions.[7, 8] An additional strategy is to intensify nocturnal supervision. A case-control study retrospectively compared SUDEP rates in two residential care settings and found a lower SUDEP incidence in the centre with the higher grade of nocturnal supervision, which had implemented an acoustic detection system. [9] Specific recommendations about how to implement use of SDDs to reduce SUDEP risk are still lacking.

Autonomic signs as indicators of seizure

Seizures can provoke changes in autonomic function, including heart rate, respiration, and perspiration[20] Ictal tachycardia is most common, occurring in between 80 and 100% of seizures.[21, 22] Autonomic manifestations present rapidly and may even precede ictal EEG discharges; early-onset tachycardia, for example, is seen in one-third of seizures.[23] Such autonomic parameters therefore provide an interesting tool for early seizure detection. A diverse collection of SDDs is now available using heart rate, heart rate variability, QRS morphology, corrected QT interval, oxygen saturation, electrodermal activity and accelerometry. Currently, however, we do not know which parameters or algorithms perform best to detect seizures.

Seizure-induced tachycardia has not been linked to clinical complications but is often used for seizure detection.[24] In contrast, ictal asystole

(IA; asystole ≥3 seconds preceded by heart rate deceleration) is the most frequent clinically relevant ictal arrhythmia and may predispose to syncope.[24, 25] Post-ictal arrhythmias and apnoea's are more rare but may herald the occurrence of SUDEP.[26] IA is not related to SUDEP, as it has been proved to be self-limiting in all reported cases, presumably because the resulting global cerebral ischemia ends the seizure and thereby the asystole.[24, 27, 28] It may, however, have serious complications, as IA can lead to syncopal loss of consciousness with sudden loss of muscle tone and traumatic falls. IA therefore requires treatment, which can be challenging. Primary treatment focuses on controlling seizures using anti-seizure medication or epilepsy surgery.[29-31] If seizure freedom cannot be obtained, pacemaker implantation may be considered to prevent syncopal falls. Pacing may however fail to prevent ictal syncope,[30-32] presumably because vasodepression, rather than cardioinhibition, is the primary mechanism causing syncope in these cases.[33] Disentangling the relative effects of vasodepression and cardioinhibition would require continuous blood pressure measurements,[34] but these are usually lacking in routine video-EEG recordings. Analysing the relative timing of the onset of syncope versus the beginning of asystole can, however, help provide insight into one aspect of this puzzle.[33] Specifically, if asystole starts after the onset of syncope or within about 3 seconds before syncope (the minimum period in which asystole could conceivably cause loss of consciousness),[34, 35] cardioinhibition is unlikely to be the primary cause of syncope.[33] This analysis of the relative timing could be used in future work to examine the frequency with which pacemaker implantation could prevent syncope in IA.

Validating the performance of seizure detection devices

The most accurate way to detect seizures is by electroencephalography (EEG). Attaching multiple electrodes to the scalp is, however, impractical, obtrusive, and uncomfortable. Various non-EEG based devices to detect seizures at home have become available.[36-38] Apart from autonomic sensors and sensors assessing movement (attached to the bed or worn on the body), other applications include remote sensors using automated video- or audio-based detection algorithms and multimodal devices.[37, 39] Validation studies on SDD performance are heterogeneous, and some devices appeared on the market with no published performance studies.[40] For many available SDDs little is known about their reliability.[40] A meta-analysis on 23 wearable SDDs yielded a mean sensitivity of 91% for the detection of convulsive seizures and an overall false alarm rate (FAR) of 0.08/hour.[38] Sensitivity for the detection of nonmotor

seizures appears low (19-74%), while FARs are extremely high (50-216/day).[37] Almost all SDD studies were based on data from epilepsy monitoring units, where people with epilepsy are mostly restricted to bed.[36-38] These studies include a short follow-up, specific patient groups that are not representative of the epilepsy population, and often lack crucial feedback from user experience.[36, 37] Optimal SDD validation extends beyond performance results and also includes the impact on the family and even larger societal effects. Long-term, home-based trials are therefore critically needed to explore all these contexts and to guide SDD implementation.

NightWatch: a multimodal 'wearable'

Most wearable SDDs measure just one parameter, but evidence is accumulating suggesting that multimodal devices are superior to unimodal ones.[39] The 'NightWatch' is an example of a multimodal SDD with sensors for heart rate (photoplethysmography) and movement (3D-accelerometry). The NightWatch is worn around the upper arm at night to warn of major motor seizures. The device has been prospectively validated in adults with refractory epilepsy living in a residential care setting.[41] Based on 1826 recorded nights from 28 participants, including 809 major seizures, NightWatch showed a median sensitivity of 86% and a median FAR of 0.25 per night.[41] Consecutive validation in a paediatric cohort revealed higher FARs.[42] As a result, the NightWatch algorithm was adjusted to fit better to both children and adults.[42] This improved NightWatch algorithm has not yet been validated prospectively in children living at home. Additional aspects of NightWatch implementation, including the effect on parental sleep, stress and QoL, need further study.

Remote automated video-based detection

Some seizure-related changes, including heart rate and perspiration can only be monitored by body-worn devices. These so-called 'wearables' are not always tolerated well, may require charging, during which time they often cannot detect seizures, or may be damaged during seizures. Remote detection systems may provide a solution to these limitations. Convulsive seizures show a typical pattern of 2-6 Hz movements during the clonic phase, which can be detected using a video-based detection algorithm.[43] Retrospective validation of a real-time video-based seizure detection algorithm in 28 adults living in a residential care setting showed good performance.[44] The algorithm was able to detect all 50 nocturnal convulsive seizures (sensitivity 100%), with a median FAR of 0.78 per night and a latency of ≤10 seconds in 78% of detections.[44] The video detection

algorithm has not yet been studied in children with epilepsy, but would need validation as ictal movement patterns may differ between age groups.

Analysing the value of seizure detection devices

Caring for a child with epilepsy is complex, demanding and has a great impact on parental QoL.[6] Parents must cope with the unpredictability of seizure occurrence, potential complications including hospitalizations, and uncertain long-term outcome. The greatest fear of parents caring for a child with epilepsy is to lose their child. These parents experience high rates of stress, anxiety, and depression.[45, 46] This is mostly influenced by psychological variables, rather than disease-related ones.[47, 48] Adequate seizure detection has the potential to lower seizure-related risks and hereby decrease the burden of seizure monitoring, but little is known about either the value of SDDs for families or the effectiveness from a societal perspective. Evidence-based decisions on effects and costs are increasingly important in health care decision-making,[49, 50] yet so far, no economic evaluations have been performed on the cost-effectiveness of SDDs. This evidence is critically needed as SDDs are costly and often lack reimbursement thus creating health care inequalities.

Developing and implementing seizure detection devices

During the development of SDDs, critical design choices are made that are partly shaped by personal preferences of the designer.[37, 51] Values from designers and physicians may, however, differ from users' preferences. It is therefore important to avoid fixation on opinions about the user and the product. Previous assessments regarding user preferences for SDDs show preferences for highly accurate, comfortable, wearable, and non-stigmatizing devices.[52-59] These studies used methods based on surveys and interviews, which often do not allow for a deeper understanding of user values.[51] For example, little is known about how people evaluate the balance between sensitivity and positive predictive value when accounting for their own seizure frequency. Another important aspect that has not been examined in previous studies is the relative strength of different preferences and how this may influence the user's choice of SDD. In industrial design, the context mapping approach is frequently applied to examine end users' needs and wishes for a product, which enables designers to fit their product into the lives of the users. This qualitative research method explores users' dreams and fears in a creative manner, to clarify the context of the product. A discrete choice experiment (DCE) is a method which quantifies the strength of different attributes influencing user preferences and may also

help to identify contrasting preferences between user groups. Neither research methods have yet been applied to the development of SDDs, but both have the potential to help optimize implementability.

OUTLINE OF THIS THESIS

This thesis focuses on different aspects of seizure detection. First, we concentrate on autonomic manifestations in epilepsy and review how these phenomena can be used to manage clinical emergencies. In **Chapter 2** we systematically review the performance of different devices to detect seizures based on changes in autonomic function, and we discuss the challenges in the management of ictal asystole in **Chapter 3**. The results from a multicentre study on the timing of syncope and IA to provide guidance when considering pacemaker implantation are presented in **Chapter 4**.

Thereafter, we focus on the validation of a wearable and a remote SDD in children. The implementation of NightWatch for children in the home environment is examined in the PROMISE trial: a prospective multicentre home-based study. **Chapter 5** reports on the performance results of this SDD in children and its effect on caregivers. In **Chapter 6** we retrospectively validate a remote video detection algorithm in a cohort of children with refractory epilepsy in a home or residential care setting.

The value of seizure detection devices is the final focus of this thesis. **Chapter 7** gives insight into the cost-effectiveness and cost-utility of NightWatch in children with epilepsy, by performing an economic evaluation from a societal perspective. The value of NightWatch for parents is qualitatively assessed in **Chapter 8** through in-depth interviews with parents participating in the PROMISE study.

Chapter 9 presents a new qualitative research method into epilepsy care: the 'context mapping approach'. We explored latent needs and wishes of informal and professional caregivers of people with epilepsy. The resulting key elements for future nocturnal SDD implementation were tested on a broader scale with an online questionnaire. Results of this survey, including a discrete choice experiment, are presented in **Chapter 10**.

Chapter 11 provides a summary of all results and discusses future perspectives.

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