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

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

De waarde van autonome symptomen en aanvalsdetectie in de epilepsiezorg onthuld

(met een samenvatting in het Nederlands)

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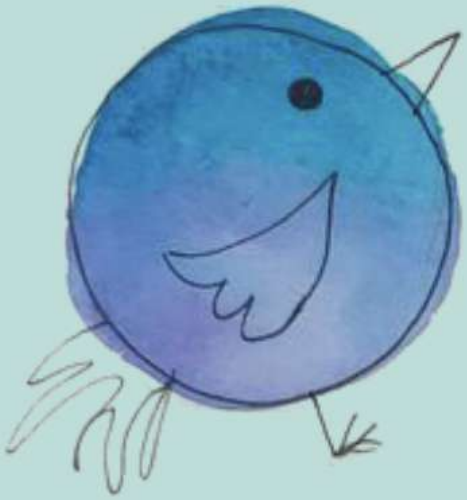

CHAPTER 1

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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CHAPTER 2

Ictal autonomic changes as a tool for seizure detection: a systematic review

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Van Huffel S, Thijs RD

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ABSTRACT

Introduction

Adequate epileptic seizure detection may have the potential to minimize seizure-related complications and improve treatment evaluation. Autonomic changes often precede ictal electroencephalographic discharges and therefore provide a promising tool for timely seizure detection. We reviewed the literature for seizure detection algorithms using autonomic nervous system parameters.

Methods

The PubMed and Embase databases were systematically searched for original human studies that validate an algorithm for automatic seizure detection based on autonomic function alterations. Studies on neonates only and pilot studies without performance data were excluded. Algorithm performance was compared for studies with a similar design (retrospective vs. prospective) reporting both sensitivity and false alarm rate (FAR). Quality assessment was performed using QUADAS-2 and recently reported quality standards on reporting seizure detection algorithms.

Results

Twenty-one out of 638 studies were included in the analysis. Fifteen studies presented a single-modality algorithm based on heart rate variability (n = 10), heart rate (n = 4), or QRS morphology (n = 1), while six studies assessed multi-modal algorithms using various combinations of HR, corrected QT interval, oxygen saturation, electrodermal activity, and accelerometry. Most studies had small sample sizes and a short follow-up period. Only two studies performed a prospective validation. A tendency for a lower FAR was found for retrospectively validated algorithms using multimodal autonomic parameters compared to those using single modalities (mean sensitivity per participant 71-100% vs. 64-96% and mean FAR per participant 0.0-2.4/h vs. 0.7-5.4/h).

Conclusions

The overall quality of studies on seizure detection using autonomic parameters is low. Unimodal autonomic algorithms cannot reach acceptable performance as false alarm rates are still too high. Larger prospective studies are needed to validate multimodal automatic seizure detection.

INTRODUCTION

Epileptic seizures are potentially dangerous as they can lead to complications, including injury, status epilepticus, and sudden unexpected death in epilepsy (SUDEP).[1] Adequate seizure detection may have the potential to minimize these complications and to ameliorate treatment evaluation, as seizures — particularly those at night — are often underreported.[2-5] Detection devices may also help to improve the independence and quality of life of people with epilepsy and their caregivers.[3,6]

Several parameters, including movement, sound, and autonomic nervous system changes, can be used to detect seizures. This review focuses on changes in autonomic function, including cardiovascular, respiratory, and transpiration changes.[7] Seizures can alter autonomic function, particularly if the central autonomic network is involved. The most common expression is a sudden increase in sympathetic tone.[7, 8] Ictal tachycardia (IT) is a very frequent sign, with prevalence rates ranging from 80 to 100%.[9, 10] IT is a hallmark of convulsive seizures (i.e., focal to bilateral tonic-clonic as well as generalized tonic-clonic seizures), and more common in temporal lobe vs. extratemporal lobe seizures.[9] Changes in autonomic function can precede ictal electroencephalographic (EEG) discharges by several seconds.[10-12] Preictal tachycardia has an incidence rate of approximately one-third of seizures.[13] Autonomic alterations may therefore provide an adequate tool for early seizure detection and facilitate timely interventions. Ictal arrhythmias and desaturations are more common but are thought to be self-limiting, while postictal arrhythmias and apneas may lead to SUDEP.[14-17] SUDEP usually occurs several minutes after a convulsive seizure (mean 10 min, range 2-17 min).[18] Raising an alarm at seizure onset may be sufficient to allow timely intervention.

We aimed to systematically review different seizure detection algorithms based on autonomic function changes.

METHODS

This systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline.[19] The PubMed and Embase databases were systematically searched through May 2018 for original studies validating an algorithm for automatic seizure detection based on heart rate (HR), heart rate variability (HRV), oxygen saturation (SpO2), electrodermal activity (EDA, reflecting changes in transpiration), or a

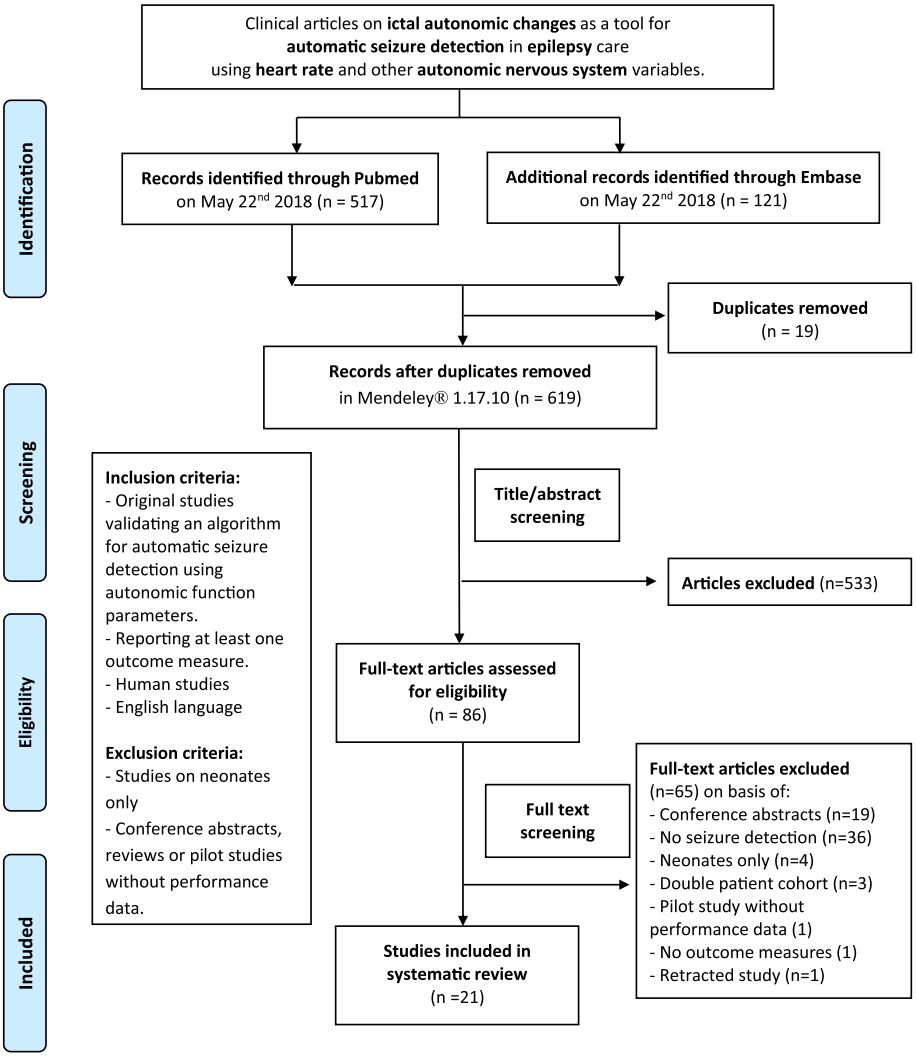

Figure 1 Flowchart of the search for applicable studies

combination of the aforementioned. A sequence of synonyms for 'autonomic variables,' 'seizures,' and 'detection' were used as search terms. Studies were included if they met the following criteria: (1) human studies; (2) written in English; (3) reporting on children or adults with any type of epilepsy; (4) validating an algorithm for automatic seizure detection using autonomic parameters; (5) reporting at least one performance measure [sensitivity, positive predictive value (PPV), false alarm rate (FAR), or detection latency (DL)]. Studies on neonates only were excluded, because both seizure and autonomic

function characteristics differ greatly at this age compared to older age. Pilot studies lacking performance data, as well as conference abstracts and reviews were also excluded (Fig. 1).

One author (AvW) screened all titles and abstracts, as well as the full texts of the remaining studies. For each article included, the following parameters were recorded: method of automatic seizure detection, type of autonomic variable, individual characteristics, number and types of seizures analyzed, prospective or retrospective validation, total recording time and performance of the algorithm (including sensitivity, PPV, FAR, and DL). We compared algorithm performance using multimodal autonomic parameters versus those using single modalities, provided that the studies (1) had a similar design (prospective vs. retrospective) and (2) reported both sensitivity and FAR.

The quality of the included studies was evaluated using the QUADAS-2.[20] This tool consists of four domains (patient selection, index test, reference standard, and flow and timing) and different signaling questions to assist in judgments of the risk of bias and applicability. Additionally, we assessed all included studies according to the recently proposed standards for clinical validation of seizure detection devices (SDDs).[21]

RESULTS

Out of the 638 articles identified, 86 studies were selected based on title and abstract. After full-text screening, 21 studies were included for further analysis. Most of the excluded articles lacked the validation of a seizure detection algorithm (Fig. 1). The characteristics of the included studies are summarized in Table 1. Most of the studies (n = 15) focused on ictal cardiac changes as a tool for seizure detection algorithms, including HRV (n = 10),[8, 22-30] HR (n = 4),[31-34] and changes in QRS morphology (n = 1).[35] Six studies used multimodal algorithms, including combinations of HR, corrected QT interval (QTc), SpO2, EDA, and accelerometry (ACC).[2, 36-40] None of the included studies validated an algorithm based on oxygen saturation or EDA alone. Most studies were conducted in adults, but two studies included a pediatric population,[23, 40] and six studies included both children and adults.[22, 25, 35-37, 39] Fourteen studies prospectively enrolled their participants,[8, 22, 23, 26, 28, 30-33, 36-40] but only two studies prospectively validated their algorithm.[31, 33] Most studies had small sample sizes (median population size 14, IQR 7-26). The number of seizures analyzed per patient tended to be low (median number of seizures per participant 3, IQR 2-7). The total recording time used to validate the algorithm varied from 7 min to 158

h per person (median recording time per participant 34 h, IQR 3-86 h), but was not specified in two studies. Seizure onset was mostly focal (n = 14),[8, 22, 24-26, 28, 30, 31, 33, 34, 37, 39, 40, 42] but was focal and generalized in some (n = 4)[2, 23, 35, 42] or not specified in others (n = 3).[32, 36, 38] All four performance measures (sensitivity, PPV, FAR, and DL) were only reported in three out of 21 studies;[22, 33, 39] eight studies reported three,[2, 23-25, 28, 30, 31, 42] eight studies reported two,[8, 26, 34, 36-38, 40, 43] one study reported one,[41] and one study only reported sensitivity and PPV data for some of the subjects.[32]

Heart rate analysis

Heart rate was monitored using single or multiple lead electrocardiography (ECG) in 14 of 18 studies,[8, 22-26, 28, 32, 34-37, 42, 43] Alternative methods included photoplethysmography (PPG) in a wearable sensor (n = 2)[2, 30] and an implanted heart rate sensor (AspireSR) (n = 2).[31,33]

Heart rate measurement was done using various methods of R-peak detection, including those proposed by Pan and Tompkins,[30, 41] Kohler,[28] Yeh and Wang,[22-24] or unspecified methods.[8, 25, 26, 31-34, 42] Some studies applied noise filtering techniques to diminish false R-peak detection, including high- and low-pass noise filters[8, 22-24, 26, 30] or a specific algorithm (baseline estimation and denoising with sparsity).[42] One case study prospectively assessed a HR algorithm using a vagal nerve stimulation (VNS) device with a fixed HR sensitivity threshold.[33] Alarms were generated when the HR augmentation exceeded 50% of the baseline HR. Eleven out of twelve seizures were detected (sensitivity 92%), together with 128 false alarms (FAR 1.88/h; 68 h recordings). A second prospective validation study of the same VNS device compared different HR thresholds (≥ 20%, ≥ 40%, and ≥ 60% increases from baseline) in 16 adults with refractory epilepsy.[31] Lower thresholds resulted in higher sensitivity and higher FAR than higher thresholds (e.g., sensitivity 59.3% and FAR 7.2/h for threshold ≥ 20% vs. sensitivity 18.8% and FAR 0.5/h for thresholds ≥ 60%). Similar effects of varying the thresholds (for both the relative HR increase and the duration of HR increase) were reported in two studies on retrospectively validated HR algorithms.[32, 34] A follow-up using the same dataset examined different factors that may influence the probability of seizure detection.[44] The best regression model was created with variables including age, gender, etiology, seizure class, and years with epilepsy.

Table 1 Characteristics of included studies

Study	Autonomic parameter	Measure-ment	Device	Algorithm	Prospective/ retrospective validation	Population (n)	No. of seizures/ TRT[a]	Type of seizures (n)	Mean age (y) [range]	Performance (mean of values per patient)
De Cooman et al.[22]	Cardiac	HRV	Single-lead ECG	*Noise filtering:* High- and low-pass Butterworth filters. HRI-extract algorithm and HRI feature extraction with patient-indepen-dent SVM classifier: LOPO CT. Fastened HRI-SVM seizure detection	Retrospective	Refractory temporal lobe epilepsy (17)	127/ 918 h	FOIA, FOBTC	33.5 [9-54]	Sens: 83.2% [50-100%] (overall: 81.9%) PPV: 7.9% [0.4-21%] (overall: 5.4%) FAR: 2.01/h [0.88-3.52/h] (overall: 1.97/h) DL: 13.3 s [− 18.2-54.3] (overall:17.8 s)
De Cooman et al.[23]	Cardiac	HRV	Single-lead ECG	See De Cooman[22], Patient-specific heuristic adaptive classifier	Retrospective	1) Children (14) 2) Other group of children (14)	107/ 695 h	GOS (30), FOS (77)	NA	Patient-independent: Sens: (overall:81.3%) PPV: NA FAR (overall: 0.75/h) DL: NA Patient-specific: Sens: (overall: 77.6%) PPV: (overall: 30.7%) FAR (overall: 0.33/h) DL: 19.1 s
De Cooman et al.[24]	Cardiac	HRV	Single-lead ECG	See De Cooman[22], Patient-specific heuristic adaptive classifier and real-time adaptive classifier	Retrospective	Temporal lobe epilepsy (19)	153/ 2833 h	FOS, FOIA, FOBTC, U, sub-clinical	NA	Patient-independent: Sens: (overall: 78.4%) PPV: (overall: 2.4%) FAR: (overall: 1.73/h) DL: NA Patient-specific: Sens: (overall: 76.5%) PPV: (overall: 3.7%) FAR: (overall: 1.09/h) DL: NA Adaptive: Sens: (overall: 77.1%) PPV: (overall: 3.3%) FAR: (overall: 1.24/h) DL: NA

Table 1 (Continued)

Study	Autonomic parameter	Measure-ment	Device	Algorithm	Prospective/ retrospective validation	Population (n)	No. of seizures/ TRT[a]	Type of seizures (n)	Mean age (y) [range]	Performance (mean of values per patient)
Fujiwara et al.[25]	Cardiac	HRV	ECG	*Time domain analysis*: mean NN, SDNN, RMSSD, TP, NN50. *Frequency domain analysis*: LF, HF, LF/HF. Analysis over 2-5 min. *Algorithm 2*: T^2 and Q statistics exceed limit > 10 s continuously	Retrospective	Refractory focal epilepsy (14)	11/ 69 h	FOS, awakening seizures (11)	30.6 [14-63]	T^2 (Overall): Sens: 55% PPV: NA FAR: 1.2/h DL: − 524 ± 216 s Q (Overall): Sens: 91% PPV: NA FAR: 0.7/h DL: − 494 ± 262 s
Jeppesen et al.[26]	Cardiac	HRV	Single-lead ECG	*Noise filtering*: High- pass filter + manual edit. Automatic R-peak detection. *Lorenz plot[b] analysis*: SD1, SD2, CSI, mCSI, CVI	Retrospective	Temporal lobe epilepsy (19)	11/ 13 h	FOIA (11)	NA	Sens: 88% (CSI-30), (overall: 73%, CSI-30, mCSI-50) PPV: NA FAR: NA DL: − 5-60 s
Jeppesen et al.[a]	Cardiac	HRV	Single-lead ECG	*Noise filtering*: High- pass filter + manual edit. Automatic R-peak detection. *Frequency domain analysis*: HF-power (using FFT) HR-diff. *Lorenz plot[b] analysis*: CSI, mCSI	Retrospective	Focal epilepsy (17)	47/ ±27 h	FOS (44), FOBTC (3)	39 [20-55]	Sens: 81% (mCSI-100) (overall: 74%, mCSI 100) PPV: NA FAR: NA DL: 16 s [6-50]

Table 1 (Continued)

Study	Autonomic parameter	Measure-ment	Device	Algorithm	Prospective/ retrospective validation	Population (n)	No. of seizures/ TRT[a]	Type of seizures (n)	Mean age (y) [range]	Performance (mean of values per patient)
Moridani et al.[27]	Cardiac	HRV	ECG	R-peak detection by Pan & Tompkins' algorithm *Time domain analysis*: SDNN, RMSSD, NN50, pNN50 *Frequency domain analysis*: LF, HF, VLF, LF/HF *Poincaré plot analysis*: SD1, SD2, SD2/SD1	Retrospective	Focal epilepsy (7)	11/±6 h	NA	NA	Sens: (overall: 88.3%) PPV: NA FAR: NA DL: NA
Pavei et al.[28]	Cardiac	HRV	ECG	*Noise filtering*: Visual artifact inspection, high- and low-pass Butter-worth filters. QRS detec-tion algorithm by Kohler. *Time domain analysis*: SDNN, RMSSD *Frequency domain analysis*: LF, HF (with FFT) *SampEn*:Entropy changes. Lorenz plot analysis: CSI, CVI	Retrospective	Temporal lobe epilepsy (12)	34/171 h	FOIA (34)	34.5 SD 7.5	Sens: (overall: 94.1%) PPV: (overall: 95.6%) FAR: (overall: 0.49/h) DL: NA
Qaraqe et al.[24]	Cardiac	HRV	Single-lead ECG	*Noise filtering*: Baseline estimation and de-noising with sparsity. QRS detection algorithm. Outlier removal, linear interpolation. *Time frequency analysis*: MP-WVD algorithm. SVM classifier for EEG features.	Retrospective	Focal epilepsy (7)	68/NA	FOA, FOIA, FOBTC	43.6 [26-65]	ECG: Sens: 96.4% [75-100%] PPV: NA FAR: 5.4/h [1.5-9.5/h] DL: 13.1 s [8-20.5] ECG + EEG: Sens: 100% PPV: NA FAR: 1.6/h [0-3.5/h] DL: 12.3 s [3-26]

Table 1 (Continued)

Study	Autonomic parameter	Measurement	Device	Algorithm	Prospective/ retrospective validation	Population (n)	No. of seizures/ TRT[a]	Type of seizures (n)	Mean age (y) [range]	Performance (mean of values per patient)
Vandecasteele et al.[30]	Cardiac	HRV/ PRV	180[b] eMotion Faros and Empatica E4 smartwatch	R-peak detection by Pan-Tompkins' algorithm. HRV analysis: Method of Varon. PRV analysis: Method of Lázaro. Seizure detection algorithm with SVM classifier by de Cooman. *Feature extraction*: HR_{peak}, HR_{base}, and $STDHR_{base}$	Retrospective	Temporal lobe epilepsy (11)	47/701 h	NA	42.7 [19-67]	Wearable ECG: Sens: 64% (overall: 70%) PPV: 2.03% (overall: 2.15%) FAR: 2.35/h (overall 2.11/h) DL: NA Hospital ECG: Sens: 57% (overall: 57%) PPV: 2.22% (overall: 1.93%) FAR: 2.05/h (overall: 1.92/h) DL: NA PPG: Sens: 33% (overall:32%) PPV: 1.43% (overall: 1.12%) FAR: 1.88/h (overall:1.80/h) DL: NA
Varon et al.[43]	Cardiac	QRS morphology	Single-lead ECG	R-peak detection via Pan-Tomkins' algorithm. *Algorithm 1*: principal component analysis for changes in QRS morphology. *Algorithm 2*: ictal acceleration of HR quantified by using phase-rectified signal averaging (PRSA)	Retrospective	1) Children with refractory epilepsy (37) 2) Women with epilepsy (5)	1) 98 2) 10/ ±5 h[c]	1) FOS (48) (28 frontal, 20 temporal) GOS (50) (29 T/TC, 11 MC, 10 absences) 2) FOS (10)	1) 9.2 [3-16] 2) [31-48]	Algorithm 1[d]: Sens: 89.5% (F1), 86% (G1), 100% (F2) PPV: 85.7% (F1), 57.3% (G1), 52.6% (F2) FAR: NA DL: NA Algorithm 2: Sens: 100% (F1), 90% (G1), 100% (F2) PPV: 90.5% (F1), 77.5% (G1), 71.4% (F2) FAR: NA DL: NA

Table 1 (Continued)

Study	Autonomic parameter	Measure-ment	Device	Algorithm	Prospective/ retrospective validation	Population (n)	No. of seizures/ TRT[a]	Type of seizures (n)	Mean age (y) [range]	Performance (mean of values per patient)
Elmpt, van et al.[32]	Cardiac	HR	2-lead ECG	R identification (increase signal > 250 μV in 10 ms). *HR*: baseline (60 s before increase), periictal period (120 s after), SD, min and max. *Detection threshold*: +2SD from baseline for ≥ 5QRS complexes. Curve-fitting algorithm and onset detection algorithm	Retrospective	Severe epilepsy (10)	104/9 h	T, TC, MC, atypical absences	34.1 [21-50]	Sens: NA PPV: NA FAR: NA DL: NA HR increase in 48.1% of seizures. Great variability in sensitivity and PPV. Better performance when combined with ACC
Osorio et al.[34]	Cardiac	HR	ECG	True beat range determined (30-180 bpm). *5 s moving window:* RRI determination. *Time of beat sequence* (TOBS): RHR, 4 threshold values (T) and 3 duration values (D)	Retrospective	Focal onset epilepsy (81) Dataset 1 (41) 2 (40)	241/ 6935 h	FOS	NA	Lowest settings T, D Sens: 98.8% PPV: NA FAR: 9.5/h (1), 7.2/h (2) DL: NA Highest settings T, D Sens: 85.5% PPV: NA FAR: 1.1/h (1), 0.7/h (2) DL: NA

Table 1 (Continued)

Study	Autonomic parameter	Measure-ment	Device	Algorithm	Prospective/ retrospective validation	Population (n)	No. of seizures/ TRT[a]	Type of seizures (n)	Mean age (y) [range]	Performance (mean of values per patient)
Boon et al.[31]	Cardiac	HR	VNS-AspireSR	Relative HR increase > 1 s above threshold (≥ 20%, ≥ 40%, ≥ 60% above baseline HR)	Prospective	Refractory epilepsy (16)	66/NA	FOS (8), FOA (26), FOIA (31), FOBTC e (17), U (5)	39.6 SD 13.4 [19-66]	Threshold > 20%: Sens: 16/27 = 59.3% PPV: NA FAR: 7.2/h [95%CI 5.31-9.94] DL: 6.0 s [— 112-105] Threshold > 40%: Sens: 8/23 = 34.8% PPV: NA FAR: 2.7/h [95%CI 1.70-3.91] DL: 27.5 s [0-57] Threshold > 60%: Sens: 3/16 = 18.8% PPV: NA FAR: 0.5/h [95%CI 0.20-0.96] DL: 35.0 s [4-40]
Hampel et al.[33]	Cardiac	HR	VNS-AspireSR	Heartbeat sensitivity threshold 50% compared to baseline	Prospective	Refractory epilepsy (1)	12/68 h	FOS with hyperkinetic movements	29	Sens: 92% PPV: 8% FAR: 1.88/h (n = 128) DL: 7.4 s (±5)
Andel, van et al.[36]	Combined	HR, ACC	Shimmer sensor (chest ECG+3D ACC)	*Algorithm 1*: No. of s in which summed waveform length>fixed threshold within a fixed window. Detection if no. > window length/4. *Algorithm 2*: HR > threshold. *Algorithm 3*: combination of summed waveform length OR HR	Retrospective	Epilepsy (43)	86/402 h[f]	Major motor (86) (18 TC, 41 T, 18 HM, 9 Cluster)	Median 15 [2-65]	All seizures: Sens: 60% (A1), 56% (A2), 71% (A3) PPV: NA FAR: 0.5/h (A1), 0.3/h (A2), 0.7/h (A3). DL: NA Clinically urgent seizures: Sens: 74% (A1), 71% (A2), 87% (A3) PPV: NA FAR: 0.6/h (A1), 0.3/h (A2), 0.8 (A3). DL: NA

Table 1 (Continued)

Study	Autonomic parameter	Measurement	Device	Algorithm	Prospective/ retrospective validation	Population (n)	No. of seizures/ TRT[a]	Type of seizures (n)	Mean age (y) [range]	Performance (mean of values per patient)
Cogan et al.[2]	Combined	HR, SpO2, EDA	Affectiva Q-curve & Nonin WristOx2 sensor	Seizure pattern analysis (HR↑, SpO2↓, EDA↑). Biosignal algorithm. Personalized parameters (*P*)	Retrospective	Focal epilepsy (10)	26/ 340 h	FOIA (23), FOBTC (2), GTCS (1)	41.8 [21-64]	3 Sensors (n = 6): Sens: 100%, 100% (P) PPV: 86%, 100% (P) FAR: 0.015/h, 0.000/h (P) DL: NA
Goldenholz et al.[37]	Combined	HR, QTc, SpO2	Single-lead ECG, Radical-7	*SpO2*: ictal drop, provided it remained > 50%. Optimal balance 80-86%. Calculation of HR and QTc by Bazette method	Retrospective	Refractory epilepsy (45)	151/ 7104 h	FOS (119), FOBTC (32)	40 [14-68]	Sens: (overall: 81-94% (FOBTC), 25-36%(FOS)) PPV: NA FAR: (overall: 0.4-2.4/h) DL: NA
Heldberg et al.[38]	Combined	EDA, ACC	Empatica E3 wristband	*EDA*: low-pass filter, cutoff frequency of 1.5 Hz. *Time windows*: 10 s 50% overlap and 5 min 80% overlap. Decomposing signal (Ledalab algorithm). Feature extraction (56) of EDA and ACC. kNN (11 features) and random forest (26 features) classifiers	Retrospective	Epilepsy (8)	55/ 540 h	Motor seizures (21), nonmotor (34)	NA	kNN classifier: Sens: 76.2% (M), 97.1% (n-M) PPV: 4.6% (M), 9.7% (n- M) FAR: NA DL: NA Random forest: Sens: 90.5% (M), 85.3% (n-M) PPV: 5.6% (M), 12.3% (n-M) FAR: NA DL: NA
Onorati et al.[39]	Combined	EDA, ACC	Empatica E3, E4, iCALM	10 s sliding epochs (75% overlap), feature extraction, classifier, decision thresholds. (3 sets: Poh's (19), larger (46), reduced (25))	Retrospective	Epilepsy (69) (24 children, 45 adults)	55/ 5928 h	FOBTC (49), FOTC (6)	Median 14/37 [4-60]	Sens: 83.6% (C1), 92.7% (C2), 94.6 (C3) PPV: 39% (C1), 50% (C2), 51% (C3) FAR: 0.29/day (C1), 0.21 (C2), 0.20 (C3) DL: 31.2 s (C1), 29.3 s (C2), 29.3 s (C3)

Table 1 (Continued)

Study	Autonomic parameter	Measure-ment	Device	Algorithm	Prospective/ retrospective validation	Population (n)	No. of seizures/ TRT[a]	Type of seizures (n)	Mean age (y) [range]	Performance (mean of values per patient)
Poh et al.[46]	Combined	EDA, ACC	Custom-built wrist-worn biosen-sors	10 s epochs, sliding window with 75% overlap, preproces-sing, 19 time, fre-quency, and nonlinear features extracted to form feature vectors. SVM to classify vec-tors as (non) seizure. Cross- validation	Retrospective	Focal epilepsy (7)	16/ 688 h[h]	FOBTC (16)	10 SD 4.6	Nonpatient-specific: Sens: 14/16 = 88% PPV: NA FAR: 0.04/h (*n* = 28) DL: NA Semi-patient specific: Sens: 15/16 = 94% PPV: NA FAR: 0.04/h DL: NA

ACC accelerometry, *CSI* cardiac sympathetic index (SD2/SD1), *CVI* cardiac vagal index (log10(SD2xSD1)), *DL* detection latency, *ECG* electrocardiogram, *EDA* electrodermal activity, *EEG* electroencephalography, *FAR* rate false alarm rate, *FFT* fast-Fourier transformation, *FN* false negative, *FOA* focal onset aware seizures, *FOBTC* focal onset to bilateral tonic–clonic, *FOIA* focal onset with impaired awareness, *FOS* focal onset seizures, *FOTC* focal onset tonic–clonic, *GOS* general onset seizures, *GTC* generalized tonic–clonic, *HF* high frequency (0.15–0.4 Hz), *HR* heart rate, HR_{base} average HR over the 60 s before the start of the HR increase, HR_{diff} heart rate differentiation, HR_{peak} peak HR at the end of the HR increase, *HRV* heart rate variability, *IHR* instantaneous heart rate (inverse of RRI), *LF* low frequency (0.04–0.15 Hz), *LO(P)O-CT* leave-one-(patient)-out crosstesting, *mCSI* modified CSI (SD2^2/SD1), *MC* myoclonic, *MP-WVD* algorithm matching pursuit and Wigner–Ville distribution algorithm, *NA* not applicable, *No.* number, *NPS* non-patient-specific, *PPG* photoplethysmography, *PRV* pulse rate variability, *RHR* relative heart rate, *RRI* R–R interval, *RMSSD* root mean square of difference in adjacent RRIs, *SampEn* sample entropy, s seconds, *SD* standard deviation, *Sens* sensitivity, *SPS* semi-patient-specific, $STDHR_{base}$ standard deviation of the HR over the 60 s before the start of the HR increase, *SVM* support vector machine, *TP* total power, *TRT* total recording time, *T/TC* tonic or tonic–clonic, U unknown, *VHF* very high frequency (0.4–0.5 Hz), *VLF* very low frequency (0.0001–0.04 Hz), *VNS* vagus nerve stimulation, *y* years

[a]Data used for validation
[b]Lorenz plot=Poincaré plot
cData used for validation
[d]F1 focal seizures in children, G1 generalized seizures in children (F1+G1=training set), F2 focal seizures adult, used for validation
[e]Specified for all seizures, only 66 analyzed
[f]Training and test data combined
[g]Percentage of evaluable data
[h]3525 h without seizures were also tested for false positives

Heart rate variability (HRV)

All the HRV-focused studies performed retrospective validations.[8, 22-26, 28, 30, 41, 42] Different HRV features were selected and specific feature thresholds were classified as 'ictal' or 'interictal.' Nine out of ten HRV studies applied linear analysis[8, 22-25, 28, 30, 41, 42] using time domain[22-25, 28, 30, 41, 42] and frequency domain[8, 25, 28, 41, 42] features. Time domain analysis focuses on the instantaneous HR; the interval between two normal QRS complexes, abbreviated to 'NN.' Different time domain features, such as the mean NN interval or the distribution of NN have been used for seizure detection. Four studies extracted and classified these time domain features using a support vector machine (SVM) classifier and validated the same HRV algorithm in different populations.[22-24, 30] The first retrospective study of seventeen people with temporal lobe epilepsy found a mean sensitivity of 83.2% with a FAR of 2.01/h.[22] The second study extracted ECG or PPG data from three different heart rate sensors worn by eleven adults with temporal lobe epilepsy.[30] The best performance was obtained using a wearable ECG device, with a sensitivity of 64% and a FAR of 2.35/h. A third study tested the algorithm in 28 children and showed a higher overall sensitivity (81.3%) and a lower FAR (0.75/h).[23] Performance, particularly FAR, improved when applying a patient-specific heuristic classifier. The latter was confirmed in the fourth study of data from nineteen people with temporal lobe epilepsy from a pre-existing epilepsy database.[24] The authors also proposed an adaptive seizure detection algorithm, and showed that similar results were obtained with simulated 'real-time' user feedback.

Frequency domain analysis is used to extract the frequency components of the HR signal, each with its own physiological footprint: low frequency (LF 0.04-0.15 Hz), high frequency (HF 0.15-0.40 Hz), very low frequency (VLF 0.0001-0.04 Hz), and very high frequency (VHF 0.4-0.5 Hz). Different frequencies were identified by power spectral density analysis of HRV in four studies,[8, 25, 28, 41] and two studies sped up this process by applying an efficiency algorithm [fast Fourier transform (FFT)].[8, 28] The LF/HF ratio, reflecting the balance of sympathetic and parasympathetic function, was examined in two studies.[25, 41] One of these studies tested a seizure detection algorithm combining both time and frequency domain features on eleven focal seizures upon awakening.[25] Ten of the eleven seizures were detected prior to seizure onset (sensitivity 91%, DL − 494 ± 262 s). Another study of seven adults with focal epilepsy that used time-frequency analysis of HRV based on a combination of the matching-pursuit and Wigner-Ville distribution algorithms reported a sensitivity of 96.4% with high

FAR (5.4/h).[42] Combining ECG and EEG algorithms yielded better performance (sensitivity 100%, FAR 1.6/h).

To assess the dynamic properties of ictal HR changes, nonlinear analysis can be applied, such as a Lorenz (or Poincaré) plot. This method plots the current R-R interval against the next R-R value. Standard deviations in the transverse (SD1) and longitudinal (SD2) directions of these plots can be calculated, and higher ratios of SD2/SD1 reflect increased sympathetic tone. These ratios can be used in seizure detection algorithms, since an increase in sympathetic tone is often seen during the preictal and early ictal phases. One small retrospective study proposed the modified cardio sympathetic index (mCSI) as a new measure in seizure detection that reflects the sympathetic tone.[26] A seizure detection algorithm based on changes in mCSI yielded a sensitivity of 88% in five people with temporal lobe epilepsy (FAR not reported). A larger follow-up study of adults with focal epilepsy compared frequency domain analysis with Lorenz plot analysis.[8] mCSI appeared more sensitive, but FARs were not reported.

The two remaining studies of HRV combined linear and nonlinear analysis.[28, 41] The first retrospective study of seven people with focal epilepsy reported an overall sensitivity of 88.3% with a specificity of 86.2% after selecting an optimal performance threshold for each patient.[41] The second study combined time-frequency and Lorenz plot analysis with a second nonlinear analysis of 'sample entropy'.[28] This parameter quantifies the regularity and complexity of a time series, and entropy decreases can be seen during the ictal phase. Applying all these methods together to ECG data from twelve temporal lobe epilepsy patients resulted in overall sensitivity of 94.1% with a FAR of 0.49/h.

Another retrospective study reported two different seizure detection algorithms based on changes in QRS morphology (algorithm 1) and cardiorespiratory interactions (algorithm 2).[35] The first algorithm captured five consecutive QRS complexes, aligned them with respect to the R peak, and assembled them into one QRS matrix. Principal component analysis was used to select different features from this QRS matrix. This process was repeated for every heart beat, which resulted in a sensitivity of 89.5-100% for detecting focal onset seizures and 86% for generalized onset seizures. The second algorithm was based on the well-known modulatory effects of respiration on HRV. These cardiorespiratory changes were quantified using phase-rectified signal averaging — a methodology used to detect quasi-periodicities in nonstationary signals such as the resampled RR interval time series — and were used for

seizure detection. Slightly better performance was achieved by the second algorithm, which yielded a sensitivity of 100% for focal onset seizures and 90% for generalized onset seizures. In this study, 10.4-90% of the generated alarms were false, and this percentage was lower for the second algorithm.

Combining autonomic parameters

All multimodal autonomic algorithms were retrospectively validated. A combination of three biosignals, measured by two different devices, was used for seizure detection in a study of ten subjects with focal epilepsy.[2] An algorithm based on a specific seizure pattern of increased HR, decreased SpO2, and increased EDA was able to detect all seizures in six out of ten patients with a low FAR of 0.015/h. Specific thresholds of HR, QTC, and SpO2 were combined in an algorithm tested on a larger study population of 45 people with refractory epilepsy.[37] Only half of the collected data was used for analysis, and a sensitivity of 81-94% was found for focal to bilateral tonic-clonic seizures, while focal seizures without bilateral spreading showed worse performance, with a sensitivity of 25-36%. Overall FAR ranged from 0.4-2.4/h.

Three other retrospective validation studies combined EDA and accelerometry (ACC), measured with one device.[28-40] Different classifiers were used to select features of EDA and ACC. The first study tested two machine learning algorithms, the k-nearest neighbor (kNN) and random forest classifiers. The kNN classifier achieved the best results with eleven features and was most sensitive for nonmotor seizures (sensitivity 97.1%, FAR not reported). The random forest classifier selected 26 features and showed its best performance with motor seizures (sensitivity 90.5%, FAR not reported). A second study used a SVM classifier to extract 19 features (16 ACC and 3 EDA).[40] Fourteen out of sixteen focal onset seizures with bilateral spreading were detected (sensitivity 88%) and FAR was 0.04/h. The same feature set was used in the third study and compared to a larger (40 ACC and 6 EDA) and a reduced (22 ACC and 3 EDA) feature set.[39] Retrospectively tested on 24 children and 45 adults with focal epilepsy, the reduced set showed the best performance (sensitivity 94.6%, FAR 0.20/ day).

A multicenter study combined HR and ACC measures in 95 people with nocturnal major motor seizures.[36] Data from only 23 patients could be used to retrospectively validate three different algorithms based on changes in HR, ACC, and ‘HR or ACC.’ Clinically urgent seizures were detected well (sensitivity 71-87%), but FAR was relatively high (2.3-6.3/night), with wide variation between subjects.

Table 2 Quality of the included studies according to QUADAS-2

Study	Risk of Bias				Concerns regarding applicability		
	Patient selection	Index tests	Reference standard	Flow and timing	Patient selection	Index tests	Reference standard
Van Andel et al.[36]	●	●	●	●	●	●	●
Boon et al.[31]	●	●	●	●	●	●	●
Cogan et al.[2]	●	●	●	●	●	●	●
De Cooman et al.[22]	●	●	●	●	●	●	●
De Cooman et al.[23]	●	●	●	●	●	●	●
De Cooman et al.[24]	●	●	●	●	●	●	●
Elmpt, van et al.[32]	●	●	●	●	●	●	●
Fujiwara et al.[25]	●	●	●	●	●	●	●
Goldenholz et al.[37]	●	●	●	●	●	●	●
Hampel et al.[33]	●	●	●	●	●	●	●
Heldberg et al.[38]	●	●	●	●	●	●	●
Jeppesen et al.[26]	●	●	●	●	●	●	●
Jeppesen et al.[8]	●	●	●	●	●	●	●
Moridani et al.[27]	●	●	●	●	●	●	●
Onorati et al.[39]	●	●	●	●	●	●	●
Osorio et al.[34]	●	●	●	●	●	●	●
Pavei et al.[28]	●	●	●	●	●	●	●
Poh et al.[40]	●	●	●	●	●	●	●
Qaraqe et al.[29]	●	●	●	●	●	●	●
Vandecasteele et al.[30]	●	●	●	●	●	●	●
Varon et al.[43]	●	●	●	●	●	●	●

● low risk of bias ● unclear risk of bias ● high risk of bias.

Quality of the included studies

According to the QUADAS-2 criteria, the overall quality of the included studies was medium-high (Table 2). Seventeen out of 21 studies were at risk of bias,

mainly due to an undefined patient selection process and fitting of the algorithm.[2, 8, 22-26, 30, 32, 34, 37-43] There was concern regarding the applicability of the selected patients in three studies, because the populations consisted of children only and/or were not well described.[23, 25, 33] Concerns about the applicability of the index test (i.e., the tested algorithm) arose in nine studies, mainly because the algorithm was fitted to one dataset.[2, 8, 23, 25, 28, 30, 32, 36, 37]

Based on the standards for the clinical validation of SDDs proposed by Beniczky and Ryvlin,[21] most studies were classified as phase 1 proof-of-principle studies, whereas three were classified as phase 0 initial studies,[34, 41, 42] and only one as a phase 2 study on a dedicated SDD[31](Table 3). Seven other studies also tested a dedicated device but included small population sizes or did not address the safety of the device and were therefore classified as phase 1.[2, 30, 33, 36, 38-40] Ten studies trained and tested their algorithm on the same dataset,[2, 8, 22, 26, 32, 34, 37, 40-42] and only four used a predefined algorithm or cutoff values.[30, 31, 33, 36] Eighteen studies used video-EEG as reference standard; the remaining three used EEG or ECoG without video recordings.[34, 41, 42]

DISCUSSION

The overall quality of studies on seizure detection using autonomic parameters is low. Small population sizes, short follow-up periods, and high study heterogeneity raise concerns about the applicability of the results. Available studies are mainly initial or proof-of-principle studies that lack long-term and real-time ambulatory monitoring, which is needed to obtain more reliable performance data and usability outcomes.

HR- or HRV-based algorithms are most frequently applied, but it is hard to compare the results of different studies due to wide variation in the detection techniques used and a lack of FAR data (Table 4). Additionally, FAR, when mentioned, is high for these studies and exceeds acceptable limits for daily practice. We could not compare the performance of HR- and HRV-based algorithms due to the wide variety of study designs employed. HRV-based algorithms seem attractive given their short detection latency, but they still require prospective validation. HRV is, however, situation dependent and affected by exercise, stress, respiration, and sleep stage.[45-47] These confounding factors make it more challenging to distinguish ictal patterns from non-ictal ones, resulting in lower accuracy.[48] Also, similar activation of the autonomic nervous system can occur before physiological arousal or other sleep-related movements.[49] Multimodal algorithms might help to lower FARs.

Table 3 Quality of validation studies of seizure detection, as assessed using standards proposed by Beniczky and Ryvlin

Study	Subjects			Recordings					Analysis & alarms				Reference standard		
	Simulation/ healthy subjects	No. of people with seizures	No. of seizures	Conventional methods	Dedicated device	Continuous	Multicenter	Offline/ retrospective	Training and testing using the dataset	Predefined algorithm & cutoff values	Real time	Blinded	Video or video-EEG recordings	Information from pt & caregivers	Study phase
Van Andel et al.[36]	-	20-50	≥75	-	+	+	+	+	-	+	-	-	+	-	1
Boon et al.[31]	-	10-20	30-75	-	+	+	+	-	-	+	+	-	+	+	2
Cogan et al.[2]	-	10-20	15-30	-	+[a]	+	-	+	+	-	-	-	+	-	1
De Cooman et al.[22]	-	10-20	≥75	+	-	+	-	+	+	-	-	-	+	-	1
De Cooman et al.[23]	-	20-50	≥75	+	-	+	+	+	-	-	-	-	+	-	1
De Cooman et al.[24]	-	10-20	≥75	+	-	+	-	+	-	-	-	-	-[b]	-[c]	1
Van Elmpt et al.[32]	-	10-20	≥75	+	-	+	-	+	+	-	-	-	+	-	1
Fujiwara et al.[25]	-	10-20	1-15	+	-	-	+	+	-	-	-	-	+	-	1
Goldenholz et al.[37]	-	20-50	≥75	+	-	+	-	+	+	-	-	-	+	-	1
Hampel et al.[33]	-	≥1	1-15	-	+	+	-	-	-	+	+	-	+	+	1
Heldberg et al.[34]	-	1-10	30-75	-	+	+	-	+	-	-	-	-	+	-	1
Jeppesen et al.[26]	-	1-10	1-15	+	-	-	-	+	+	-	-	-	+	-	1

Table 3 (Continued)

Study	Subjects			Recordings					Analysis & alarms				Reference standard		
	Simulation/ healthy subjects	No. of people with seizures	No. of seizures	Conventional methods	Dedicated device	Continuous	Multicenter	Offline/ retrospective	Training and testing using the dataset	Predefined algorithm & cutoff values	Real time	Blinded	Video or video-EEG recordings	Information from pt & caregivers	Study phase
Jeppesen et al.[8]	–	10-20	30-75	+	–	–	–	+	+	–	–	–	+	–	1
Moridani et al.[37]	–	1-10	1-15	+	–	+	–	+	+	–	–	–	–[b]	–	0
Onorati et al.[39]	–	≥50	30-75	–	+	+	+	+	–	–	–	–	+	–	1
Osorio et al.[34]	–	≥50	≥75	+	–	+	+	+	+	–	–	–	–[d]	–	0
Pavei et al.[28]	–	10-20	30-75	+	–	–	–	+	–	–	–	–	+	–	1
Poh et al.[40]	–	1-10	15-30	–	+	–	–	+	+	–	–	–	+	–	1
Qaraqe et al.[29]	–	1-10	30-75	+	–	–	–	+	+	–	–	–	–[b]	–	0
Vandecasteele et al.[30]	–	10-20	30-75	+	+	+	–	+	–	+	–	–	+	–	1
Varon et al.[43]	–	20-50	≥75	+	–	–	–	+	–	–	–	–	+	–	1

Phase 0: initial studies performed when initiating or developing a novel method. Phase 1: proof-of-principle studies. Phase 2: studies of a dedicated seizure detection device. Phase 3: studies allowing the final confirmation of safety and accuracy. Phase 4: in-field studies of seizure detection devices in the home environments of the patients, addressing aspects related to usability

No. number, *pt* patient

[a]Two different devices combined

[b]Available database with EEG recordings

[c]Simulated real-time feedback on detections

[d]ECoG without video

Table 4 Performance of seizure detection algorithms grouped according to dataset size

Study	Validation of algorithm				Performance of algorithm			
	No. of subjects	No. of seizures/ TRT	Type of seizures	Algorithm	Sensitivity (%)	FAR	PPV (%)	DL (s) [range]
Large datasets								
Andel, van et al.[36]	23	86/ 402h[a]	All major motor[*b]	Heart rate	60	0.5/h	NA	NA
				Movement	56	0.3/h	NA	NA
				Hart rate or movement	71	0.7/h	NA	NA
		59	Clinically urgent seizures[c]	Heart rate	74	0.6/h	NA	NA
				Movement	71	0.3/h	NA	NA
				Hart rate or movement	87	0.8/h	NA	NA
De Cooman et al.[22]	17	127/ 918h	FOS, including TCs		83.2 [50-100]	2.01/h [0.88-3.52/h]	7.9 [0.4-21]	13.3 [-18.2 to 54.3]
De Cooman et al.[23]	28	107/ 695h	Convulsive and clinical subtle seizures	Patient-independent	Overall:81.3	Overall: 0.75/h	NA	NA
				Patient-specific	Overall: 77.6	Overall: 0.33/h	Overall: 30.7	19.1
De Cooman et al.[24]	19	153/ 2833h	FOS, including TCs (only clinical seizures)	Patient-independent	Overall: 78.4	Overall: 1.73/h	Overall: 2.4	NA
				Patient-specific	Overall: 76.5	Overall: 1.09/h	Overall: 3.7	NA
				Adaptive	Overall: 77.1	Overall: 1.24/h	Overall: 3.3	NA
Goldenholz et al.[37]	45	151/ 7104h	FOS, including TCs		Overall: 81-94 (FOBTC) 25-36(FOS)[d]	Overall: 0.4-2.4/h	NA	NA
Onorati et al.[39]	69	55/ 5928h	FOS, all TCs	Classifier 1	83.6	0.29/day	39	31.2
				Classifier 2	92.7	0.21/day	50	29.3
				Classifier 3	94.6	0.20/day	51	29.3
Medium datasets								
Boon et al.[31]	16	66/ NA	Different types of FOS, including TCs	Threshold >20%	59.3	7.2/h [95% CI 5.31-9.94]	NA	6.0 [-112 to 105]
				Threshold >40%	34.8	2.7/h [95%CI 1.70-3.91]	NA	27.5 [0- 57]
				Threshold >60%	18.8	0.5/h [95%CI 0.20-0.96]	NA	35.0 [4-40]
Heldberg et al.[38]	8	55/ 540h	Motor (M) and non-motor (nM) seizures	kNN classifier	76.2 (M) 97.1 (nM)	NA	4.6 (M) 9.7 (nM)	NA
				Random Forest	90.5 (M) 85.3 (nM)	NA	5.6 (M) 12.3(nM)	NA
Jeppesen et al.[8]	17	47/ ±27h	FOS, including TCs		81:(mCSI-100) (Overall: 74, mCSI-100)	NA	NA	16 [6-50]
Osorio et al.[34]	81	241/ 6935h	FOS	Lowest settings T,D Dataset (1) & (2)	98.8	9.5/h (1) 7.2/h (2)	NA	NA
				Highest settings T,D Dataset (1) & (2)	85.5	1.1/h (1) 0.7/h (2)	NA	NA

Table 4 (Continued)

Study	Validation of algorithm				Performance of algorithm			
	No. of sub-jects	No. of seizures/ TRT	Type of seizures	Algorithm	Sensitivity (%)	FAR	PPV (%)	DL (s) [range]
Pavei et al.[28]	12	34/ 171h	FOIA		Overall: 94.1	Overall: 0.49/h	Overall: 95.6	NA
Poh et al.[40]	7	16/ 688h[c]	FOS, all TCs	Non-patient specific	88	0.04/h (n=28)	NA	NA
				Semi-patient specific	94	0.04/h	NA	NA
Qaraqe et al.[29]	7	68/ NA	FOS, including TCs	ECG	96.4 [75-100]	5.4/h [1.5-9.5 /h]	NA	13.1 [8-20.5]
				ECG+EEG	100	1.6/h [0-3.5/h]	NA	12.3 [3-26]
Vande-casteele et al.[30]	11	47/ 701h	FOIA	Wearable ECG	64 (Overall: 70)	2.35/h (Overall: 2.11/h)	2.03 (Overall: 2.15)	NA
				Hospital ECG	57 (Overall: 57)	2.05/h (Overall: 1.92/h)	2.22 (Overall: 1.93)	NA
				PPG	33 (Overall:32)	1.88/h (Overall: 1.80/h)	1.43 (Overall: 1.12)	NA
Small datasets								
Cogan et al.[2]	6	10/ 340h	FOIA and TCs	3 Sensors	100	0.015/h	86	NA
				Personalized	100	0.000/h	100	NA
Elmpt, van et al.[32]	10	104/ 9h	Motor seizures (T, TC, MC) & atypical absences		NA[f]	NA	NA	NA
Fujiwara et al.[25]	14	11/ 69h	FOS (awake)	T^2 statistics	Overall: 55	Overall: 1.2/h	NA	- 524 ± 216
				Q statistics	Overall: 91	Overall: 0.7/h	NA	- 494 ± 262
Hampel et al.[33]	1	12/ 68h	FOS with hyperkinetic movements		92	1.88/h	8	7.4 (±5)
Jeppesen et al.[26]	5	11/ 13h	FOIA		88 (CSI-30) (Overall: 73, CSI-30, mCSI-50)	NA	NA	-5 to 60
Moridani et al.[27]	7	11/ ±6h	FOS		Overall: 88.3	NA	NA	NA
Varon et al.[43]	42	108/ ±5h	FOS and GOS, including T, TC, MC and absences	Algorithm 1[g]	89.5 (F1) 86 (G1) 100 (F2)	NA	85.7 (F1) 57.3 (G1) 52.6 (F2)	NA
				Algorithm 2[g]	100(F1) 90(G1) 100(F2)	NA	90.5 (F1) 77.5 (G1) 71.4 (F2)	NA

CSI cardiac sympathetic index, *DL* detection latency, *ECG* electrocardiogram, *EEG* electroencephalography, *FAR rate* false alarm rate, *FOBTC* focal onset to bilateral tonic–clonic, *FOIA* focal onset with impaired awareness, *FOS* focal onset seizures, *h* hour, *MC* myoclonic, *mCSI* modified cardiac sympathetic index, *NA* not applicable, *No.* number, *PPG* photoplethysmography, *s* seconds, *T* tonic, *TCs* tonic–clonic seizures, *TRT* total recording time.

Table 4 (Continued)
[a]Training and test set combined.
[b]Including tonic-clonic, tonic, hypermotor and cluster (series of at least five tonic or myoclonic spasms within 3 min).
[c]When attendance or intervention was deemed necessary, based on seizure severity, postictal arousal state, breathing difficulties, and distress.
[d]Percentage of evaluable data.
[e]Also 3525 hours without seizures tested for False positives.
[f]Great variability in sensitivity and PPV.
[g] F1: Focal seizures children, G1: generalized seizures children (F1 +G1 = training set), F2: focal seizures adult, used for validation.

A retrospective study of seven children with tonic-clonic seizures validated different unimodal and multimodal algorithms on the same dataset. All combinations of multimodal sensors, including ECG, EMG, and ACC, showed at least 75% lower FAR.[50] Studies differentiating outcome according to seizure type showed diverse results, indicating that that different seizure types may require different detection techniques. Multimodal techniques can provide a solution to this problem.[51] Another solution could be personalizing or tailoring the algorithm. One study group studied two different personalization strategies and calculated the number of seizures required for accurate tailoring.[52] The authors proposed an initialization phase to tailor an existing predefined algorithm to a patient-specific algorithm. Six to eight seizures seemed sufficient to set individual thresholds.[52] Another retrospective multicenter study proposed an automatic adaptive HRV algorithm and tested it on a database of 107 nocturnal seizures from 28 children.[23] After an initialization phase of five seizures, the personalized algorithm resulted in lower FARs compared to those obtained with the patient-independent algorithm. A follow-up study proposed an adaptive classifier with real-time user feedback that presented similar performance; this method might be better accepted in daily practice.[24]

CONCLUSION

Autonomic function alterations seem to represent an attractive tool for timely seizure detection. Unimodal autonomic algorithms cannot, however, reach acceptable performance: while most algorithms are quite sensitive, false alarm rates are still too high. Multimodal algorithms and personalization of the algorithm are important strategies to improve performance. Larger, prospective, home-based studies with long-term follow-up are needed to validate these methods and to demonstrate the added value of SDDs in clinical care.

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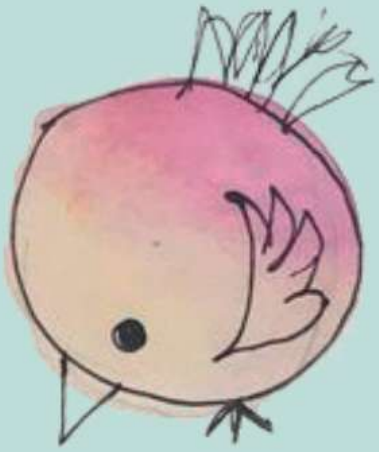

CHAPTER 3

Ictal asystole: how to unveil the hidden ties between the brain and the heart

van Westrhenen A, Thijs RD

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Ictal asystole (IA) can be a challenging diagnosis. It requires recognition of both epileptic and syncopal phenomena and symptoms can be ambiguous.[1, 2] Clinical suspicion must therefore be confirmed by simultaneous video-EEG and ECG recordings.[2] IA seems a rare event in a clinical setting (mean prevalence of 0.32% in people with refractory epilepsy who underwent video-EEG monitoring), but the incidence in the field might be underestimated.[3] It can have devastating consequences, since IA may provoke sudden loss of muscle tone, causing traumatic falls. It is likely that syncope due to epilepsy is even more hazardous than syncope due to vasovagal mechanisms, as IA is typically preceded by focal seizures impairing awareness. As a result, subjects are not warned by the symptoms of an impending faint and consequently do not anticipate the fall. IA therefore necessitates an aggressive treatment, especially since short-term recurrence risk is high.[4] Those refractory to conventional epilepsy treatment could benefit from pacemaker implantation.[5] To optimize management of IA, it is important to increase awareness among neurologists and cardiologists.

Sanchez-Borque and colleagues presented seven cases with a definite diagnosis of IA.[6] The ictal asystolic events were recorded during video-EEG and showed an RR interval over 3 s, due to either sinus pause (n = 6) or paroxysmal atrioventricular block (n = 1). Five cases were previously diagnosed with focal seizures with impaired awareness and presented with recurrent seizures and sudden falls. The two remaining cases revealed asystole during cardiac monitoring, without suspicion of epilepsy at that time. A pacemaker was implanted but failed to prevent future events. Subsequent video-EEG recordings of these episodes unveiled the diagnosis of focal epilepsy. Simultaneous pacemaker activation provided a final proof of IA.

IA usually starts more than one year after epilepsy onset, but earlier onset has also been described.[7] It may be difficult to diagnose IA in these early-onset cases, since epilepsy might not yet be suspected, as illustrated by the two cases mentioned above. In those with recurrent syncope without previous diagnosis of epilepsy, the clinician should search for specific clues. IA events are typically initiated by focal seizures, usually characterized by temporal lobe involvement.[3] It is hard to distinguish symptoms and signs of temporal lobe epilepsy from syncope, since both paroxysmal events may present with pallor, oral automatisms, sweating and staring.[2] Probably the most helpful clues for focal epilepsy include the presence of postictal confusion, the onset of symptoms in supine position (making a vasovagal cause unlikely) or the

occurrence of longer lasting episodes without syncope, as presyncope usually lasts <1 min.[8] Long term recordings in those presenting with IA indicate that not all focal seizures are accompanied by asystole.[3, 4]

To confirm IA diagnosis, Sanchez-Borque and colleagues suggest withdrawal of anti-seizure medication and long-term ECG-Holter to record the event when suspicion is high. We would not favor such an approach as medication withdrawal is not without risk in people with epilepsy. In our opinion, this should only be considered if the epilepsy diagnosis is uncertain. In that case long-term video-EEG recording would be more appropriate to confirm or rule out the diagnosis of epilepsy. In those with a definite or highly likely diagnosis of epilepsy and a suspicion of IA, implantable loop recorders may help to document subsequent episodes of asystole.

Pacemaker implantation may prevent complications of IA.[5] In some cases syncope will disappear following pacemaker implantation, but a contrasting scenario is also possible. Different mechanisms of syncope in IA have been identified; it can be provoked by cardioinhibition, vasodepression or a combination of both.[1, 9] In cases where vasodepression predominates, the benefit of cardiac pacing may be limited. This scenario is important to consider since pacemaker implantation does not have a negligible risk.

All reported cases of IA were self-limiting and thus contrast with the postictal asystole that is associated with sudden unexpected death in epilepsy (SUDEP).[3] It is even suggested that cerebral hypoperfusion due to syncope favors seizure termination in IA.[3, 10] The greatest risk of IA is the associated traumatic falls, due to sudden loss of muscle tone. Controlled prospective studies on IA are still lacking. Available evidence suggests that apart from pacemaker implantation, anti-seizure medications or other epilepsy treatments (e.g., epilepsy surgery) could all prevent complications of IA. The selection of choice should depend on various factors, including the chances of seizure recurrence, the impact and length of the asystole, and whether cardioinhibition is the dominant mechanism provoking syncope.[5] Increasing awareness among neurologists and cardiologists of the hidden ties between brain and heart may facilitate early IA diagnosis and help to prevent complications.

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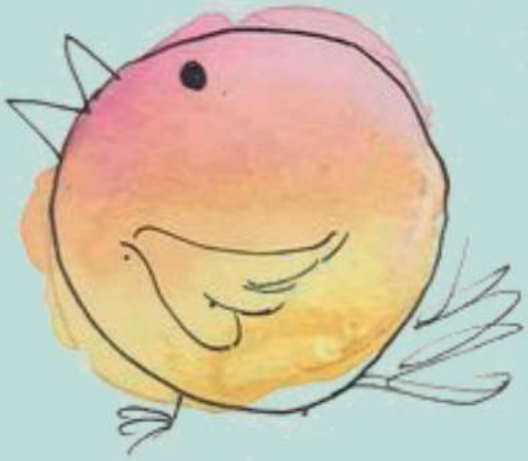

CHAPTER 4

Timing of syncope in ictal asystole as a guide when considering pacemaker implantation

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ABSTRACT

Introduction

In patients with ictal asystole (IA) both cardioinhibition and vasodepression may contribute to syncopal loss of consciousness. We investigated the temporal relationship between onset of asystole and development of syncope in IA, to estimate the frequency with which pacemaker therapy, by preventing severe bradycardia, may diminish syncope risk.

Methods

In this retrospective cohort study, we searched video-EEG databases for individuals with focal seizures and IA (asystole ≥ 3 s preceded by heart rate deceleration) and assessed the durations of asystole and syncope and their temporal relationship. Syncope was evaluated using both video observations (loss of muscle tone) and EEG (generalized slowing/flattening). We assumed that asystole starting ≤3s before syncope onset, or after syncope began, could not have been the dominant cause.

Results

We identified 38 seizures with IA from 29 individuals (17 males; median age: 41 years). Syncope occurred in 22/38 seizures with IA and was more frequent in those with longer IA duration (median duration: 20 [range: 5-32] vs. 5 [range: 3-9] s; $p<.001$) and those with the patient seated vs. supine (79% vs. 46%; $p=.049$). IA onset always preceded syncope. In 20/22 seizures (91%), IA preceded syncope by >3 s. Thus, in only two instances was vasodepression rather than cardioinhibition the dominant presumptive syncope triggering mechanism.

Conclusions

In IA, cardioinhibition played an important role in most seizure-induced syncopal events, thereby favoring the potential utility of pacemaker implantation in patients with difficult to suppress IA.

INTRODUCTION

Ictal asystole (IA) is a seizure manifestation affecting 0.3%-0.4% of people with refractory focal epilepsy admitted for video-EEG monitoring, and mostly occurs in the context of temporal lobe epilepsy.[1,2] IA appears to occur exclusively in focal impaired awareness seizures and is often misdiagnosed as a primary cardiologic phenomenon due to ECG documentation of marked bradyarrhythmia. Seizure-induced asystole may, therefore, be considerably underreported and a substantial proportion of people with IA may not receive optimal treatment.[3-5]

It is thought that IA seizures are self-limited as the resulting global cerebral ischemia induced by the asystole ends the seizure.[1,2,4,6] Nonetheless, dangerous traumatic falls may occur due to sudden loss of muscle tone.[7] Consequently, treatment is essential, and primary treatment should focus on optimizing seizure control with antiseizure medication or if necessary epilepsy surgery.[5,7-9] However, pacemaker implantation may be considered if the primary treatment approach fails.

The mechanism of syncopal loss of consciousness (LOC) in IA is believed to be similar to that of reflex syncope, involving overactivity of autonomic reflex pathways.[7,10,11] In reflex syncope, cardioinhibitory (i.e., vagal lowering of heart rate), as well as vasodepressive (i.e., blood pressure [BP] lowering independent of heart rate) pathways together lower BP. These two actions may occur in concert, and to varying degrees, each may be responsible for hypotension and the resulting transient LOC.[10,11] In cases in which cardioinhibition is the primary mechanism causing syncope in IA, and seizure freedom cannot be obtained by conventional epilepsy treatments, cardiac pacing may be beneficial.[7,10,11] However, several reports suggest that syncope in IA may also be principally the result of vasodepression (i.e., vasodilatation); this may explain why pacing sometimes fails to prevent syncope recurrences.[8,9,12]

Disentangling the relative effects of cardioinhibition and vasodepression requires continuous BP measurement during the evolution of IA,[13] a tool that is lacking with current routine video-EEG recordings. However, we hypothesized that by analyzing the relative timing of the onset of syncope versus the beginning of asystole, we could provide insight into one aspect of the puzzle.[10] Specifically, if asystole starts after onset of syncope or within about 3s before syncope (a period in which it is generally accepted that the brain has sufficient metabolic reserve),[13,14] cardioinhibition is unlikely to be the primary cause.[10] Consequently, the current study examined the temporal relationship between IA

initiation and syncope onset with the objective, based on the 3 s threshold, of estimating how often cardioinhibition was unlikely the primary syncope mechanism in IA, and thereby how often pacemaker implantation may be beneficial in IA refractory to conventional antiseizure therapy.

METHODS

We searched video-EEG databases of five participating centers (Stichting Epilepsie Instellingen Nederland; Department of Epileptology Bonn; National Hospital for Neurology & Neurosurgery, London; New York University, Department of Neurology; University Medical Center Utrecht, Department of Neurophysiology) for focal seizures with IA, simultaneously recorded on video and EEG. IA was defined as any R-R interval of ≥3 s preceded by heart rate slowing coinciding with ictal activity on EEG. Recordings with continuous video, EEG and one or two ECG leads were included. Multiple seizures with IA per person could be included. For every included subject, we listed all recorded seizures to derive an indication of the percentage of IA recurrence. Three authors in pairs of two (Roland D Thijs + Sharon Shmuely or Roland D Thijs + Anouk van Westrhenen) examined all IA recordings and checked whether the events met diagnostic criteria. IA timing and duration were derived from the ECG signal. Video recordings were reviewed for clinical expressions of loss of muscle tone (e.g., head dropping) to determine syncope onset time[14] and duration, and body position (standing, seated or supine) during IA onset. Both researchers were blinded to the EEG and ECG signal during video evaluation. When the onset of unconsciousness could not be reliably determined from the video (e.g., if the individual was supine throughout), the classical EEG pattern during syncope, that is, generalized EEG slowing and/or flattening, was used to time syncope (Figure 1).[15,16]

We applied previously defined criteria to classify the temporal relationship of IA to syncope onset,[9] creating the following groups: (A) asystole starting after syncope; (B) asystole starting ≤3 s before syncope; (C) asystole starting >3 s before syncope, and (D) asystole without syncope. We assumed that cardiac bradycardia could not have been the dominant cause of syncope in Groups A and B.[10]

Data are presented as means ± standard deviation or median and range where appropriate. Differences between groups were analyzed using $\chi 2$ statistics for categorical and the Mann-Whitney U test for unpaired continuous, not normally distributed data.

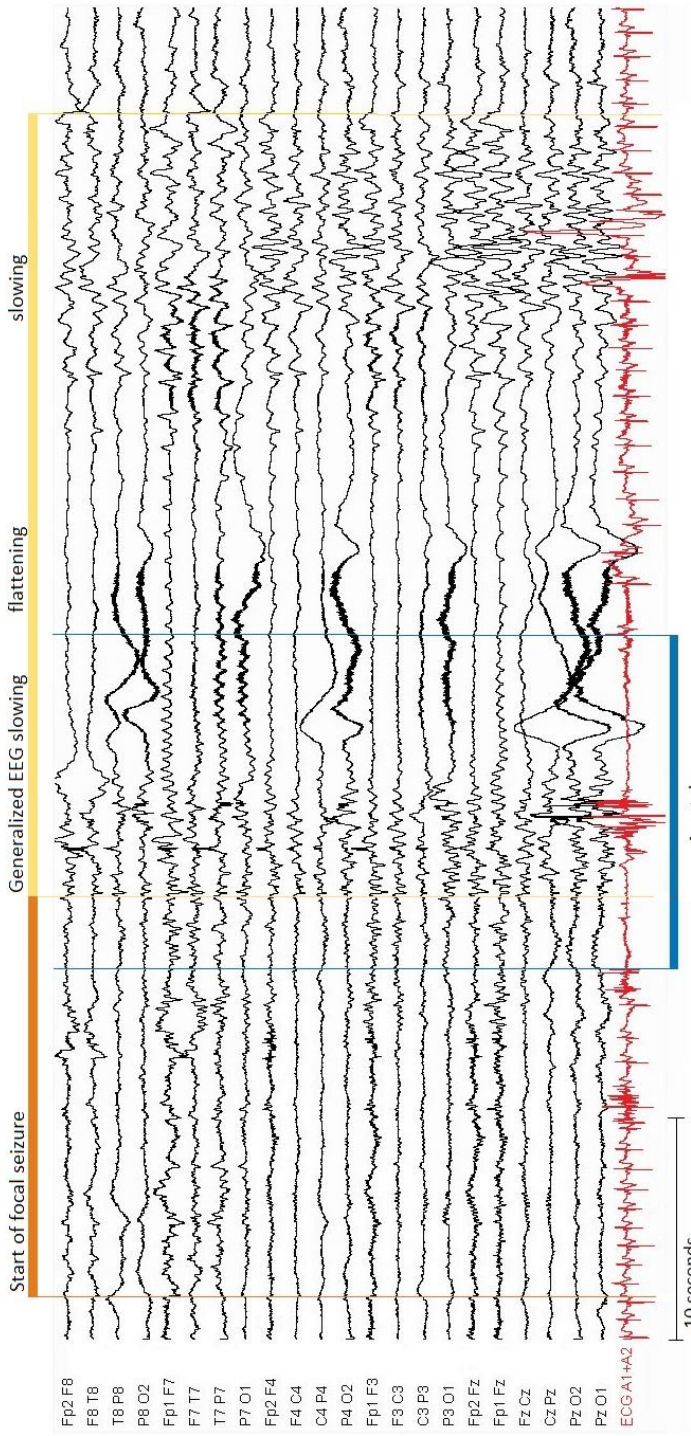

Figure 4 Typical EEG pattern during syncope in ictal asystole. Example of a 60 s EEG recording (filters 0.16–10 Hz, sensitivity 100 mV/cm) of a focal seizure originating in the left temporal lobe (orange bar) with ictal asystole (blue bar; duration 15 s) followed by syncope (yellow bar; duration 34 s). Syncope coincides with a slow-flat-slow pattern in the EEG (yellow bar; duration 34 s)[15,16]

The medical ethics committee of the Leiden University Medical Center declared that the Medical Research Involving Human Subjects Act (in Dutch, the “WMO”) did not apply to this study as all data were acquired during routine clinical care. The data underlying this article cannot be shared publicly for the privacy of individual subjects. The data will be shared on reasonable request to the corresponding author.

RESULTS

We identified 38 focal seizures with IA in 29 individuals (17 male, median age: 41 years [range: 15-71 years]) who underwent evaluation from May 2001 to August 2018. Six had more than one seizure with IA (Table 1). As expected from a previous study,[17] the risk for IA recurrence was relatively high and amounted to 27% in those who had had IA but who also had more than one recorded seizure. Syncope onset and end could not be determined using video in five seizures; in another seven seizures, only syncope end could not be determined. In these 12 cases, we used the EEG to determine syncope timing. The median IA duration was 8 s (range: 3-32 s) and the mean syncope duration was 25 ± 9.4 s (Figure 2A). In seven seizures, there was more than one asystole period within one seizure. Two individuals experienced these sequential IAs in two different seizures, suggesting that some individuals might be more prone to this phenomenon (Table 1, nos. 2 and 21).

Syncope occurred in 22 out of 38 seizures with IA (58%). All IA events preceded syncope (Figure 2B); consequently, none was classified as belonging to Group A (0%). In two seizures, IA started ≤3 s before syncope (Group B, 5%) and in 20 seizures IA started >3 s before syncope (Group C, 53%). Sixteen seizures (42%) fell in Group D (asystole without syncope).

Seizures with syncope had a longer asystole than those without (median duration: 20 [range: 5-32] vs. 5 [range: 3-9] s; $p < .001$). Syncope occurred in all 20 IA events of ≥10 s and in only 2 of 18 IA events of <10 s. In only one of these events did the temporal sequence of IA and syncope meet the criteria of Group B (31 s of syncope, starting <3 s after onset of an IA lasting only 6 s), while another presented with two short sequential IA events (5 and 3 s) followed by 15 s of syncope >3 s after IA onset (Figure 2, marked by asterisk). The temporal sequence in both cases argues against a mainly cardioinhibitory mechanism as the dominant cause of syncope. One individual (Table 1, no. 2) had two seizures including multiple consecutive IAs of <10 s without syncope (Group B), as well as one seizure with asystole of 16 s followed by syncope, starting 6 s after IA

Table 1 Characteristics of included individuals

Individual no.	Age/sex	Epilepsy etiology	Seizure type, onset zone	Total no. of recorded seizures	% IA occurrence[a]	IA duration (s)	Syncope duration (s)	Time between start IA and start syncope (s)	Body position	PM	Follow-up duration	Syncope recurrence
Group B												
15	63/M	Structural	FIA, Bi-Temporal	3	33	6	31[b]	2	Seated	No	5 years	No (seizure free after epilepsy surgery)
22	58/M	Unknown	FIA, Temporal L	1	100	15	31	3	Supine	No	5.5 years	No (seizure free with AED)
Group C												
1	61/F	Infectious	FIA, Temporal L	1	100	30	29	15	Supine	Yes	9 years	No
2	50/F	Structural	FA, Extratemporal R	15	20	16	na[c]	6	Supine	Yes	14 years	No
3	41/M	Unknown	FIA, Temporal L	1	100	24	29	10	Supine	Yes	8.5 years	No
5	41/F	Unknown	FIA, Temporal R	1	100	14	12	10	Supine	Yes	3 years	No (seizure free)
6	71/M	Unknown	FA, Temporal L	1	100	20	11	15	Supine	Yes	2 months	No
8	54/M	Infectious	FIA, Temporal L	1	100	5; 3[d]	15	11	Seated	Yes	1 year	No (seizure free)
9	15/F	Unknown	FIA, Temporal L	1	100	27	33	10	Supine	Yes	3 years	No
10	21/F	Unknown	FIA, Temporal R	2	50	26	37	9	Seated	Yes	8 years	No
11	23/M	Structural	FIA, Temporal R	1	100	20	27	17	Supine	No	3 years	Seizure recurrence without syncope 6 months after epilepsy surgery
12	36/F	Unknown	FIA, Temporal L	1	100	29	25	10	Supine	Yes	10 years	No
16	41/M	Unknown	FIA, Temporal R	1	100	32	43	9	Supine	Yes	None	na
18	57/F	Immune	FIA, Bi-Temporal	2	100	26	33	10	Seated	Yes	4 years	Yes, but less falls after PM implantation
			FIA, Temporal L			19	15	10	Seated			
19	33/M	Unknown	FIA, Temporal L	1	100	13	14	10	Seated	No	None	na
23	27/M	Structural	FIA, Temporal L	1	100	20	30	10	Seated	No		No (seizure free after epilepsy surgery)
24	56/F	Unknown	FIA, Temporal R	2	50	17	20	12	Seated	Yes	8 years	No
25	28/M	Unknown	FIA, Temporal R	2	50	12	11	10	Seated	Yes	11.5 years	Seizure recurrence without syncope after epilepsy surgery
27	48/M	Structural	FIA, Temporal L	2	50	11	23	4	Seated	Yes	8 years	No (seizure free after epilepsy surgery)
28	27/M	Unknown	FIA, Extratemporal R	2	50	23	26	9	Supine	Yes	2 years	No

Table 1 (Continued)

Individual no.	Age/sex	Epilepsy etiology	Seizure type, onset zone	Total no. of recorded seizures	% IA occurrence[a]	IA duration (s)	Syncope duration (s)	Time between start IA and start syncope (s)	Body position	PM	Follow-up duration	Syncope recurrence
29	41/M	Structural	FIA, Temporal L	2	50	24	37	9	Seated	Yes	4 years	No (seizure free after epilepsy surgery)
Group D												
2	50/F	Structural	FA, Extratemporal R	15	20	3; 3; 3; 3[d]	-	-	Supine			
			FA, Extratemporal R			4; 3[d]	-	-	Supine			
4	49/M	Structural	FBTC, Temporal L	3	67	9	-	-	Seated			
			Focal onset tonic[e], Temporal L			8; 4[d]	-	-	Supine			
7	28/F	Unknown	FIA, Extratemporal L	4	25	3	-	-	Supine			
13	22/F	Unknown	FIA, Temporal R	3	33	8	-	-	Supine			
14	40/M	Unknown	FIA, Temporal R	2	50	9	-	-	Supine			
17	47/F	Unknown	FIA, Temporal R	1	100	4; 4[d]	-	-	Supine[f]			
20	16/M	Unknown	FIA, Bi-Temporal	2	100	5	-	-	Supine			
			FIA, Temporal R			5	-	-	Supine			
21	16/M	Unknown	FIA, Temporal R	4	100	8; 3[d]	-	-	Supine			
			FIA, Bi-Temporal			9	-	-	Supine			
			FIA, Bi-Temporal			8	-	-	Supine			
			FIA, Temporal L			5; 8[d]	-	-	Supine			
26	21/F	Structural	FIA, Temporal L	2	100	5	-	-	Seated			
			FIA, Temporal L			5	-	-	Seated			

Note: Characteristics of included individuals with IA, divided per group. Group (B) asystole starting ≤3 s before syncope; (C) asystole starting >3 s before syncope and (D) asystole without syncope. *B* bilateral, *F* female, *FA* focal onset aware, *FBTC* focal to bilateral tonic-clonic, *FIA* focal onset impaired awareness, *IA* ictal asystole, *L* left, *M* male, *Na* not available, *No.* number, *PM* pacemaker, *R* right, *s* seconds.

[a]IA recurrence during video-EEG monitoring defined as a percentage of recurrent seizures with IA in those who had more than one recorded seizure.

[b]Possibly facilitated by β-blocker.

[c]Syncope end could not be determined using video. The EEG recording was not available.

[d]These numbers reflect multiple asystolic events within one seizure.

[e]Awareness could not be assessed, because the individual was covered by a blanket.

[f]Closed curtain blocked the view of the individual at the beginning of the seizure. When the curtain was moved aside, the individual was lying down.

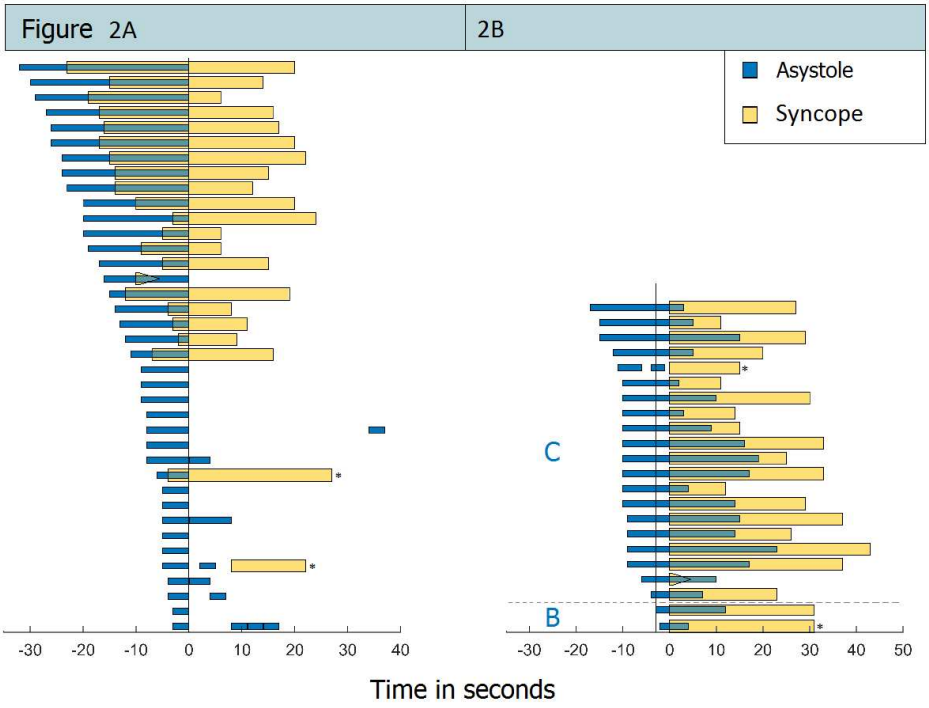

Figure 2 Relative timing of ictal asystole (IA) to onset of syncope. The horizontal bars represent one seizure each; blue bars indicate asystole and yellow bars the duration of loss of consciousness (LOC). In one case syncope end could not be determined using video and the EEG recording was not available (yellow triangle). (A) All 38 IA events sorted according to their duration in seconds and aligned to the end of asystole. Note that syncope was rare in seizures with short asystole (lower bars) but occurred in all those with an asystole duration ≥10 s. (B) All 22 syncopal events sorted by their time difference in onset of asystole and syncope, and aligned to the beginning of LOC. The vertical line identifies the threshold of 3 s before syncope. The horizontal dotted line separates seizures in which asystole started ≤3 s before syncope (Group B) and >3 s before syncope (Group C).
*Two cases with an asystole <10 s and syncope in group A, one in group B and one in group C.

onset (Group C). Finally, syncope occurred more often in those patients who were seated compared to those who were lying down at the start of IA (11/14, 79% vs. 11/24, 46%; p = .049). The latter supports the view that in people with IA, the threshold for syncope is impacted by posture-related effects on BP.
22 subjects experiencing IA with syncope had a median follow-up period of 5.3 years [range: 2 months–11.5 years], with two lost to follow-up. Sixteen out of

nineteen subjects (84%) with asystole starting >3 s before syncope (Group C) received a pacemaker during follow-up. Of the remaining three, one subject was seizure- free after epilepsy surgery, another experienced only seizures without syncope after epilepsy surgery, and the last one was lost to follow-up. Only one subject from Group C experienced syncope recurrence after pacemaker implantation (6%).

DISCUSSION

Main Findings

This study provides three main findings. First, we found that in most IA cases the onset of asystole occurred early enough before syncope onset that cardioinhibition may have been the dominant syncope mechanism. Conversely, only in a minority of cases did IA start too close to the onset of syncope (≤3 s) to have been the primary cause. In this smaller group of individuals, pacemaker implantation may not prevent syncope as vasodepressor hypotension may have already progressed sufficiently to result in syncope. Second, syncope often lasted longer than did the asystole, suggesting that another factor may have become operational in sustaining LOC. The latter factor may have been later onset or slower evolution of a vasodepression component during the event. Although the numbers are small, within one person multiple IA events exhibited the same presumptive dominant syncope triggering mechanism (i.e., cardioinhibition or vasodepression). This observation tends to lend support to the expected pacemaker utility in patients with cardioinhibition detected. Finally, our long-term follow-up results show that pacemaker treatment was effective to prevent or reduce syncope recurrence in all cases in which syncope started >3 s after IA onset (Group C).

Pacemaker Therapy in IA

IA is most commonly associated with seizures arising in the temporal lobe or nearby insula region. Stimulation of the latter has, in particular, been associated with triggering spells similar to vasovagal syncope.[6] In any case, the primary treatment of IA is optimizing seizure control by antiseizure medication or epilepsy surgery.[5,7-9] In terms of drugs, a number of agents are readily available and are generally well tolerated.[18] Additionally temporal lobe resection surgery has proved generally effective. However, if seizure freedom cannot be obtained, pacemaker implantation may be considered, but guidelines are lacking.[8,9] Case series suggest that pacemakers may reduce falls and injuries, but these

observations are based on potentially unreliable diary data; large follow-up studies are lacking.[12,19,20] Furthermore, if pacemaker treatment is considered, careful pacemaker programming is important as one recent case report has highlighted the possibility that excessive pacing may unintentionally delay seizure termination, by maintaining cerebral perfusion and prolonging IA.[21]

Syncopal LOC Mechanism

Cardiac standstill causes syncope when the duration of circulatory arrest exceeds the cerebral ischemic anoxia reserve time.[14] The anoxia reserve time may vary among individuals from 4 to 15s with an average duration of 5-6s.[14] Consequently, it is reasonable to expect that an isolated cardiac standstill of less than 3 s cannot lead to syncope.[10,16,19] Using the 3s threshold, we concluded that cardioinhibition was the dominant pathomechanism for syncope in the majority of our cohort. However, whether vasodepression ensued later or more slowly during the episode in some patients, thereby representing a differential effect of asystole on syncope onset and end, or an additional process, remains an unknown in need of future study.

Impact of Posture on Syncope

Upright body position appeared to contribute to syncope susceptibility in our IA patients. This finding suggests a role played by gravity; presumably, upright position accelerated cerebral hypoperfusion whether due to cardioinhibition or vasodepression. Unfortunately, we did not have access to BP data in our cases, but other reports tend to support this contention.[10,16] Continuous BP recordings in two people with temporal lobe epilepsy and ictal bradycardia in the supine position illustrated a progressive BP decrease before bradycardia in one and a BP decrease with concomitant bradycardia in the other.[20] Another case report on temporal lobe epilepsy and recurrent ictal syncope after pacemaker implantation for IA, demonstrated symptomatic hypotension during a focal seizure in the supine position, despite pacemaker activation.[12] The latter finding suggests that seizure-induced vasodepression can cause syncope on its own. A study on asystole and LOC timing in tilt-induced reflex syncope revealed a lower mean arterial pressure (MAP) in syncope occurring ≤3s after asystole than in later onset syncope[10]; this suggested a major role of vasodepression causing syncope in these cases. Low MAP, however, was also observed in some asystole events occurring >3 s before syncope,[9] raising the possibility that the contribution of vasodepression to the occurrence of syncope may be

underestimated using this approach. Perhaps vasodepression takes longer to evolve and acts less to start the event than to prolong it as suggested earlier.

Limitations

Interpretation of our findings is limited by a number of factors. First, the ability to detect syncope within 3 s of onset of asystole may be questioned. In this regard, we set up a method in which groups of experienced yet independent observers determined the timings and differences were adjudicated. Second, inferences regarding the possibility that vasodepression may extend the syncope period beyond the duration of asystole cannot be substantiated by direct BP measures, and remains to be reassessed in future studies. Finally, while the overall number of patients was relatively large in terms of published IA studies, the number of cases with multiple episodes was small. These numbers only in- clude those seizures that are recorded on video-EEG during a short clinical stay, thus only reflecting a snapshot. Therefore, conclusions regarding the consistency of pathophysiology within an individual warrant further study.

CONCLUSION

Cardionihibition appears to play an important role in syncope associated with seizure-induced IA; in only a few cases is vasodepression the dominant triggering mechanism. Consequently, in most IA cases, when conventional therapy has not adequately prevented syncope due to seizure recurrences, cardiac pacemaker therapy is likely to prove helpful.

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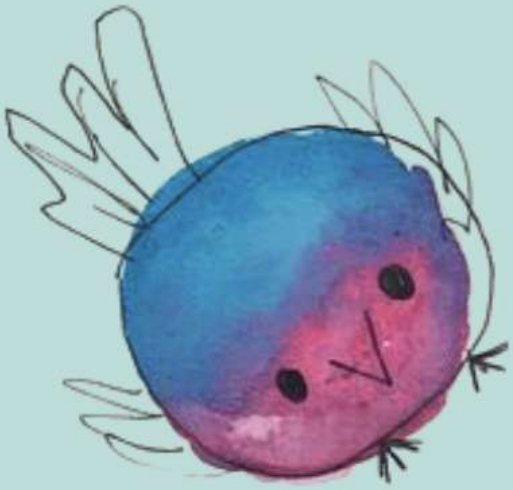

CHAPTER 5

Multimodal nocturnal seizure detection in children with epilepsy: a prospective, multicenter, long-term, in-home trial

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on behalf of the Dutch TeleEpilepsy Consortium

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ABSTRACT

Introduction

There is a pressing need for reliable automated seizure detection in epilepsy care. Performance evidence on ambulatory non-electroencephalographybased seizure detection devices is low, and evidence on their effect on stress, sleep, and quality of life (QoL) is still lacking. We aimed to determine the performance of NightWatch, a wearable nocturnal seizure detection device, in children with epilepsy in the family home setting and to assess its impact on caregiver burden.

Methods

We conducted a phase 4, multicenter, prospective, video-controlled, in-home NightWatch implementation study (NCT03909984). We included children aged 4-16 years, with ≥1 weekly nocturnal major motor seizure, living at home. We compared a 2-month baseline period with a 2-month NightWatch intervention. The primary outcome was the detection performance of NightWatch for major motor seizures (focal to bilateral or generalized tonic-clonic [TC] seizures, focal to bilateral or generalized tonic seizures lasting >30 s, hyperkinetic seizures, and a remainder category of focal to bilateral or generalized clonic seizures and "TC-like" seizures). Secondary outcomes included caregivers' stress (Caregiver Strain Index [CSI]), sleep (Pittsburgh Quality of Sleep Index), and QoL (EuroQol five-dimension five-level scale).

Results

We included 53 children (55% male, mean age=9.7±3.6 years, 68% learning disability) and analyzed 2310 nights (28173h), including 552 major motor seizures. Nineteen participants did not experience any episode of interest during the trial. The median detection sensitivity per participant was 100% (range=46%-100%), and the median individual false alarm rate was .04 per hour (range=0–.53). Caregiver's stress decreased significantly (mean total CSI score=8.0 vs. 7.1, p=.032), whereas caregiver's sleep and QoL did not change significantly during the trial.

Conclusions

The NightWatch system demonstrated high sensitivity for detecting nocturnal major motor seizures in children in a family home setting and reduced caregiver stress.

INTRODUCTION

There is a pressing need for reliable automated seizure detection in epilepsy care.[1,2] Seizures are unpredictable and may cause life-threatening situations through injury, status epilepticus, and sudden unexpected death in epilepsy.[3] Convulsive seizures (i.e., focal to bilateral or generalized tonic-clonic seizures) have the highest mortality risk, particularly among those with nocturnal convulsions sleeping alone.[4-6] This suggests that having someone providing essential support following a convulsion can be lifesaving. Seizure detection devices (SDDs) are developed to alert caregivers in case of potentially dangerous seizures. This enables timely intervention, which may help reduce seizure-related risks.[3,5,7] Accurate detection may also empower people with epilepsy, by allowing them to sleep alone and relieving the burden of seizure vigilance for their caregivers.[4,8,9] Evidence on the effect of an SDD on caregiver's stress, sleep, and quality of life (QoL), however, is still lacking.[8] SDDs also have the potential to improve seizure documentation, as seizure diaries are known to be unreliable.[10] Various ambulatory non-electroencephalography (EEG)-based SDDs are available, but their performance evidence is low.[1,11] Many devices lack external validation. Almost all SDD studies were performed in a clinical setting with short follow-ups and lacking essential user feedback.[11-13] Long-term, home-based trials addressing aspects related to usability (classified as phase 4 by recent guidelines) are therefore mandatory to guide SDD implementation.[12] In a prospective phase 4 study, we demonstrated the good performance of a wearable multimodal device (NightWatch) for the detection of nocturnal major motor seizures (median sensitivity of 86% per person and median false alarm rate [FAR] of .25 per night).[14] Subsequent validation of NightWatch in a pediatric cohort revealed higher FARs, with rates amounting to .2 per hour.[15] To improve performance, we adapted the algorithm and found that it could reduce FAR to levels close to that of adults while maintaining high sensitivity.[15] We, therefore, set up a long-term, home-based phase 4 study to prospectively validate the performance of the adjusted NightWatch algorithm in children with severe epilepsy while monitoring the effect on caregiver's stress, sleep, and QoL.

METHODS

Protocol Approvals, Registrations, and Patient Consents

We conducted a multicenter, prospective, long-term, inhome implementation study (the PROMISE trial, short for Promoting the Implementation of SDDs in Epilepsy Care). We collected data between August 2018 and August 2020. The trial was registered at Clinicaltrials.gov (identifier: NCT03909984) and approved by the research ethics committee of University Medical Center Utrecht in the Netherlands (NL62995.041.17). The child's legal representatives provided written informed consent (in most cases, both biological parents) as did participants ≥12 years old when capable.

Participants

We recruited children with epilepsy aged 4-16 years from three tertiary epilepsy centers in the Netherlands, namely, Stichting Epilepsie Instellingen Nederland (SEIN), University Medical Center Utrecht (UMCU), and Academic Center for Epileptology Kempenhaeghe (KH), with at least one weekly nocturnal major motor seizure event, and living at home. Seizure frequency was based on clinical history and checked with the caregivers before signing informed consent and again before the start of the intervention. We excluded children with comorbid conditions that could lead to high false alarm rates, such as movement disorders, cardiac arrhythmias, or wearing a pacemaker. We originally defined skin pigmentation as an exclusion criterion, as we assumed that the light-based plethysmography (PPG) signal would be less reliable through pigmented skin. After validating NightWatch on pigmented skin, we discovered that the PPG method worked reliably on all types of skin pigmentation, so we abandoned this criterion after 42 inclusions.

Seizure detection algorithm

The multimodal algorithm of NightWatch, based on photoplethysmography and accelerometry (ACC) data, is described in more detail in previous publications.[14,15] Heart rate (HR) values are determined and updated every second based on a 5-min average of past individual peak-to-peak intervals. The accelerometry sensor measures motion and position, where position represents the angle of the sensor with respect to the gravity vector. Rhythmic movements are identified by counting the number of zero crossings for each axis per second. The plethysmographic waveform is evaluated to estimate the signal

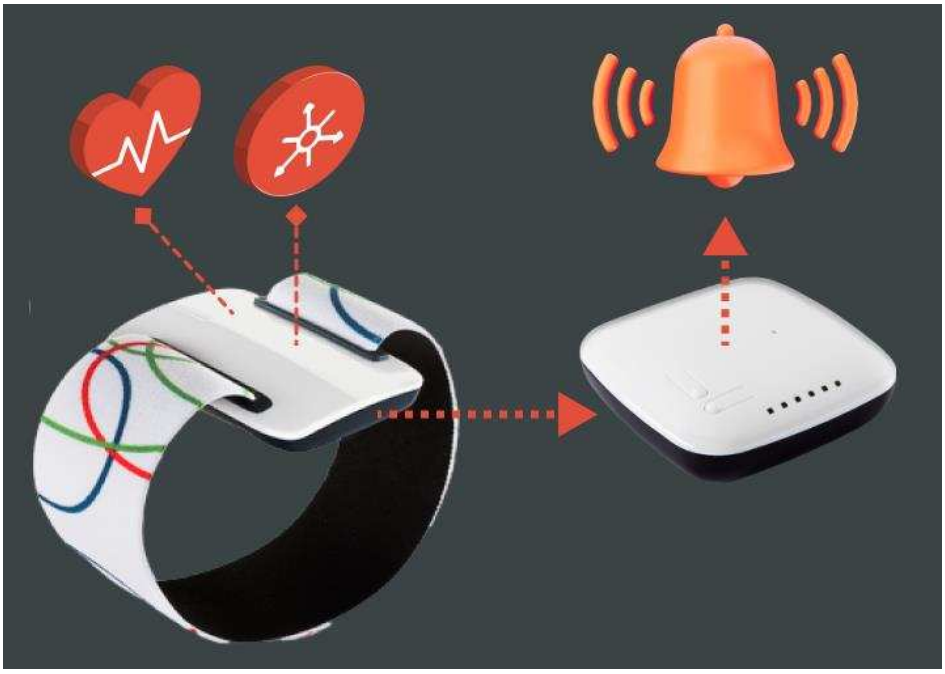

Figure 1 The **NightWatch** bracelet contains a photoplethysmographic heart rate module and a three-dimensional accelerometer. When a specific heart rate or movement threshold or pattern is detected, the algorithm triggers an alarm so caregivers can intervene. The signals or alarms are transmitted by Digital Enhanced Cordless Telecommunications Ultra Low Energy (DECT ULE) directly to the base, which may be connected to a local area network for further transmission of the data and alarms. DECT ULE is a wireless communication standard with greater range, reliability, and safety than Bluetooth or Wifi. *Figure published with permission from LivAssured.*

quality, and the multimodal algorithm is applied if the signal quality is adequate (>80%). If HR is unreliable, then only the ACC algorithm is used for detection. When both modalities are active, they work in parallel. Several situations may trigger an alarm: increasing HR slope when it exceeds an absolute or relative threshold (compared to baseline), and sustained rhythmic movements. We applied the adjusted algorithm developed in the previous pediatric trial.[15]

Intervention

The intervention consisted of a 2-month baseline period without any SDD (usual care) followed by 2months of NightWatch usage at home (intervention; Figure 1). The NightWatch base station (generating alarms) was installed in the participant's home, with a video camera and audio sensor attached to a pole

and directed to the child's bed. Data were generated only during the time NightWatch was worn. We asked participants to wear the NightWatch every night during the intervention period. All data were transmitted to a laptop in the child's room and stored for analysis. We asked the caregivers to keep a seizure diary during the intervention. After the intervention, caregivers, if they wanted to continue using the device, could purchase NightWatch for €750 (half of the regular price).

Study outcomes

The primary outcome measure was the individual performance of NightWatch to detect major motor seizures, including sensitivity, positive predictive value (PPV), F1 performance score, and FAR per hour. Secondary outcomes included the quality of the signal data, the impact of NightWatch on caregivers' stress, sleep, and QoL, and their expectations and experiences with NightWatch.

Questionnaires

We used validated questionnaires to examine caregivers' stress (Caregiver Strain Index [CSI]), sleep (Pittsburgh Quality of Sleep Index [PQSI]), and QoL (EuroQol five-dimension five-level scale [EQ-5D-5L]) during the baseline period and following the intervention. We asked one caregiver per participant to complete the online questionnaires at the start of the study (T0), after the baseline period (T1), and after NightWatch usage (T2; Figure 2). The CSI includes 13 items assessing the burden of care/stress, each carrying 1 point, with a score of 7 indicating a high-stress level. The PQSI consists of seven components, each with a range of 0-3 points, to assess sleep quality, with a global PSQI score varying from 0 (no difficulty sleeping) to 21 (severe difficulties sleeping). The first part of the EQ-5D-5L combines five dimensions: mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be scored on five levels ranging from "no problems" to "extreme problems." In the second part, respondents must indicate how good or bad their health is at the given moment on a scale from 0 (the worst health you can imagine) to 100 (the best health you can imagine). Additionally, we developed a questionnaire with eight items assessing caregiver's expectations and 11 items on experiences with NightWatch using a 5-point Likert scale.

Sample size

We estimated a sample size of 384 major motor seizures to obtain acceptable confidence limits (precision=4%) assuming a conservative sensitivity of 80%.[15]

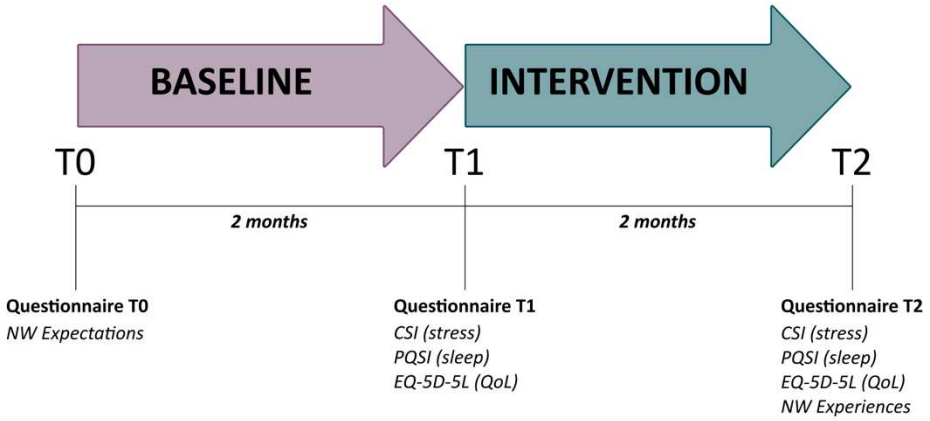

Figure 2 Study flow including a 2-month baseline period with usual care followed by a 2-month intervention period with NightWatch at home, and the different questionnaires at study points T0, T1 and T2.
CSI caregiver strain index*, EQ-5D-5L* quality of life questionnaire*, NW* NightWatch*, PQSI* Pittsburgh Quality of Sleep Index*.*

We aimed to include 60 participants with ≥1 major nocturnal motor seizure per week. We expected a 2-month intervention period (9weeks) with a dropout rate <25% to yield at least 405 significant seizures.

Data analysis

Data selection

Only full night recordings with complete and sufficient video data were included to analyze the sensor performance. Records were excluded when >75% of data transmission from NightWatch to the base station was lost, when computer storage issues had appeared, or when the nightly average signal quality of the HR measurements was <75%. The first two situations impeded the analysis of trial data but did not impact NightWatch performance at home. Poor quality of the HR data (e.g., if the sensor is not worn correctly) could potentially affect performance. The device itself constantly monitors the quality of the HR signal. If the HR data quality is insufficient for seizure detection, the NightWatch generates a distinct “technical” alarm to alert the caregiver to reposition the sensor.

Annotation process

Although video-EEG monitoring is considered the gold standard for diagnosing epileptic seizures, implementing continuous EEG was not feasible in this long-term homebased trial. We therefore made a pragmatic choice to apply video

recordings without EEG as our reference standard, focusing on motor signs for epilepsy classification. Video images were annotated with a specifically developed computer program. Trained trial nurses screened the video of 5% ofall nights for missed seizures; every video was screened by one nurse. We also retrospectively analyzed video tracings with a previously validated automated video-based seizure detection algorithm.[16-18] Trial nurses annotated all events (generated NightWatch alarms, video alarms, and caregivers' seizure diary) using the video recordings while blinded for alarm type and NightWatch sensor data (HR and movement). We considered the following seizure types as clinically urgent and classified them as "major motor seizures": (1) generalized or focal to bilateral onset tonic-clonic seizures (TCs); (2) focal to bilateral or generalized onset tonic seizures lasting >30s (T>30); (3) focal onset hyperkinetic (HK) seizures; and (4) a remainder category of other major (OM) motor seizures. Category 4 includes focal onset clonic, generalized onset, and "TC-like" seizures, the latter defined as bilateral movements without classical TC pattern (i.e., no tonic phase, pronounced asymmetry, short duration, or quick recovery). All other seizures that did not meet these criteria were classified as "non-major motor seizures" and, if detected, as false positives. In case of discrepancies (when the recorded night was annotated by one nurse, but screened by another) or doubt, the trial nurses consulted one of the principal investigators (R.D.T., R.H.C.L.) for a final decision. The principal investigators double-checked a random sample of 5% of the annotations. An event was considered true positive when an alarm was generated within 3min before or 3min after the annotated start of a seizure of interest. Other detections within a 3-min interval were scored as one event; this rule was applied for true and false positives.

Performance

We estimated performance (sensitivity, PPV, FAR, F1) per subject and the median individual performance on the population level. We excluded participants who did not have seizures of interest during the intervention period from the sensitivity, F1, and PPV analysis, but included these cases in the FAR analysis. The following formula estimated the F1 score for detection performance accuracy: F1 score=2 * (PPV×sensitivity) / (PPV+sensitivity). We performed post hoc analyses to identify clinical determinants of NightWatch performance, including age, sex, presence of learning disability, and distribution of seizure types (% TCs of the total amount of major motor seizures).

Statistics

Data are presented as mean±SD or median and range where appropriate. We used paired t-tests to analyze differences between secondary study outcomes at T1 and T2, and Mann-Whitney U-tests (sex, presence of learning disability),and Spearman rank correlation (age, % TCs) to identify clinical determinants of NightWatch performance.

RESULTS

We identified 85 eligible children, and 60 caregivers consented to participate in the trial. Seven withdrew before the intervention started due to personal situations (n=4) or seizure freedom (n=3). Of the remaining 53 participants (38 from SEIN, 10 from UMCU, and five from KH) who completed the intervention,two were excluded from the performance analysis due to lack of video recordings or recordings of insufficient video quality (e.g., wrong position

Table 1 Summary of participants' demographics

Demographic data (n=53)	No.	Mean	Range
Sex			
Male	29 (55%)		
Female	24 (45%)		
Age (years)		9.7 ± 3.6	4-16
Learning disability			
Yes	36 (68%)		
No	17 (32%)		
Epilepsy etiology			
Structural	13 (25%)		
Genetic	20 (38%)		
Infectious	1 (1%)		
Metabolic	0 (0%)		
Immune	0 (0%)		
Unknown	19 (36%)		
Epilepsy treatment			
ASMs, *n*		2.5 ± 1.2	0-6
Ketogenic diet	6		
VNS	2		

ASM Anti-seizure medication, *VNS* vagal nerve stimulation.

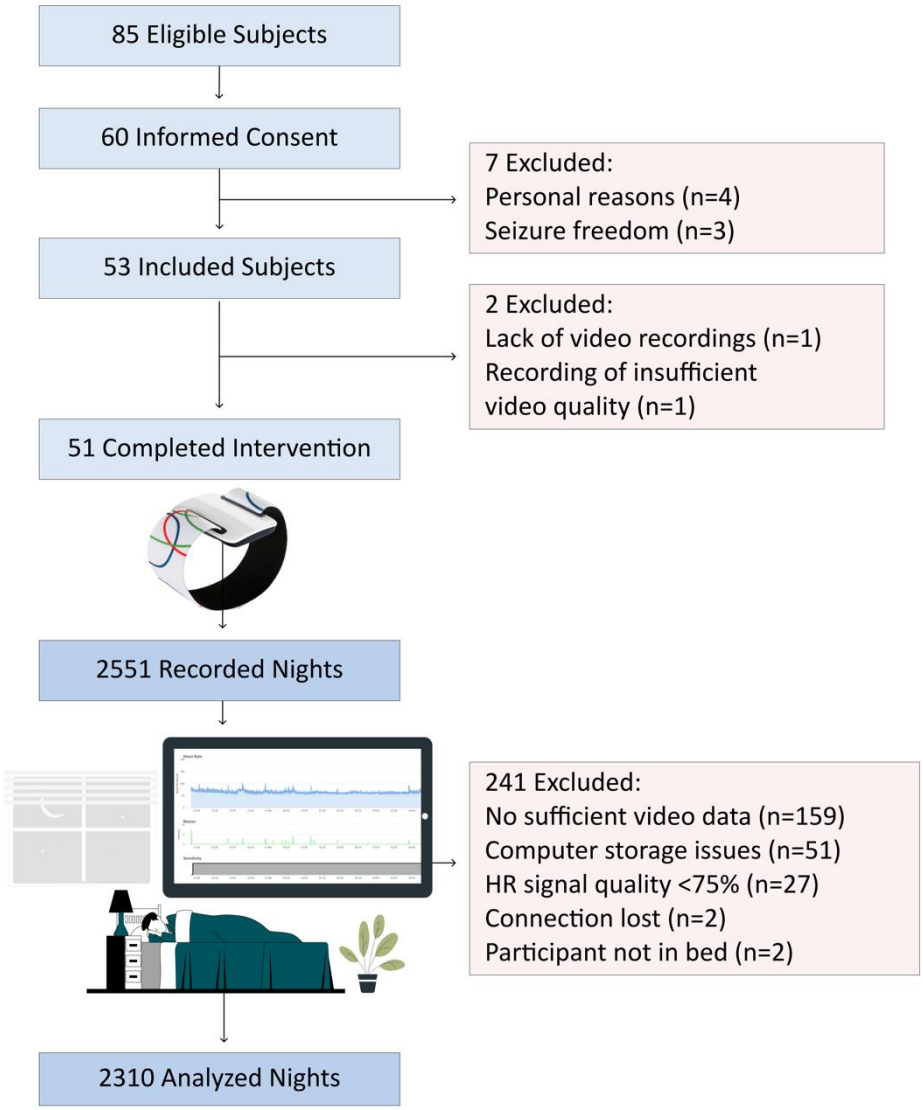

Figure 3 Study and data flow diagram. Overview of eligible subjects, included and excluded participants and selected data with reasons for exclusion.
HR heart rate.

of the camera; Figure 3). Table 1 presents the demographics of the 53 children (55% male, mean age=9.7±3.6 years, 68% learning disability). The questionnaires were completed by 51 biological parents and two legal representatives. We analyzed 2310 nights (28 173h of data, median=611h per participant [range=26-1298h]), including 552 major motor seizures (median

number of seizures per participant=2 [range=0-147]). In total, 1402h (5%) of all recorded nights were screened, ranging from half a night to four full nights per participant. All participants had a history of at least one nocturnal major motor seizure per week upon inclusion, but 19 did not have such a seizure during the intervention period. We noted medication adjustments in 18 children, resulting in higher doses of antiseizure medication in 15 children and lower doses in three.

Primary outcome: NightWatch performance

Four hundred ninety-two of 552 major motor seizures were correctly detected by NightWatch (overall seizure sensitivity=89%). Median sensitivity per participant for the detection of major motor seizures was 100% (range=46%-100%, mean=90% [95% confidence interval (CI) =84%-95%]; Table 2). We found 204 TC (37%), 30T>30 (5%), 48 HK (9%), and 270 OM (49%) seizures during the intervention. NightWatch performance for these different major motor seizure types was (median sensitivity per participant [range], overall seizure sensitivity): TC (100% [71%-100%], 94%), T>30 (100% [0%-100%], 53%), HK (75% [0%-100%], 83%), OM (100% [0%-100%], 91%; Figure 4). The median false negative alarm rate for NightWatch per participant per hour, representing the seizures missed, was 0 (range = .00-.04, mean = .002 [95% CI = .0001-.005]). NightWatch missed 60 episodes (25 OM, 14T>30, 13 TC, eight HK). These seizures were identified by the video algorithm (n=40, 67%), screening (n=13, 22%), or the caregiver (n=10, 17%). The video algorithm and the caregivers detected three missed seizures together. We identified 1642 false alarms, including 469 nonmajor motor seizures (29%). Median FAR per subject per hour amounted to .04 (range = .00-.53, mean = .07 [95% CI = .04-.10]). Median PPV per participant was 24% (range=3%-94%, mean=31% [95% CI=23%-40%]). The overall F1 score amounted to .47, with a median score of .38 per participant (range = .05-.97). We analyzed the determinants for true positive and false positive alarms. Because multiple causes can trigger one alarm, the sum of the individual numbers and percentages is more than the total amount. Of the 492 true positive alarms, 424 (86%) were triggered by accelerometry, 114 (23%) by rapid HR increase, and 90 (18%) by tachycardia. The false positive alarms were also mainly triggered by accelerometry (n=1086, 66%), followed by rapid HR increase (n=592, 36%) and tachycardia (n=103, 6%). A minority of alarms (27% of true positive and 8% of false positive alarms) were triggered by more than one signal.

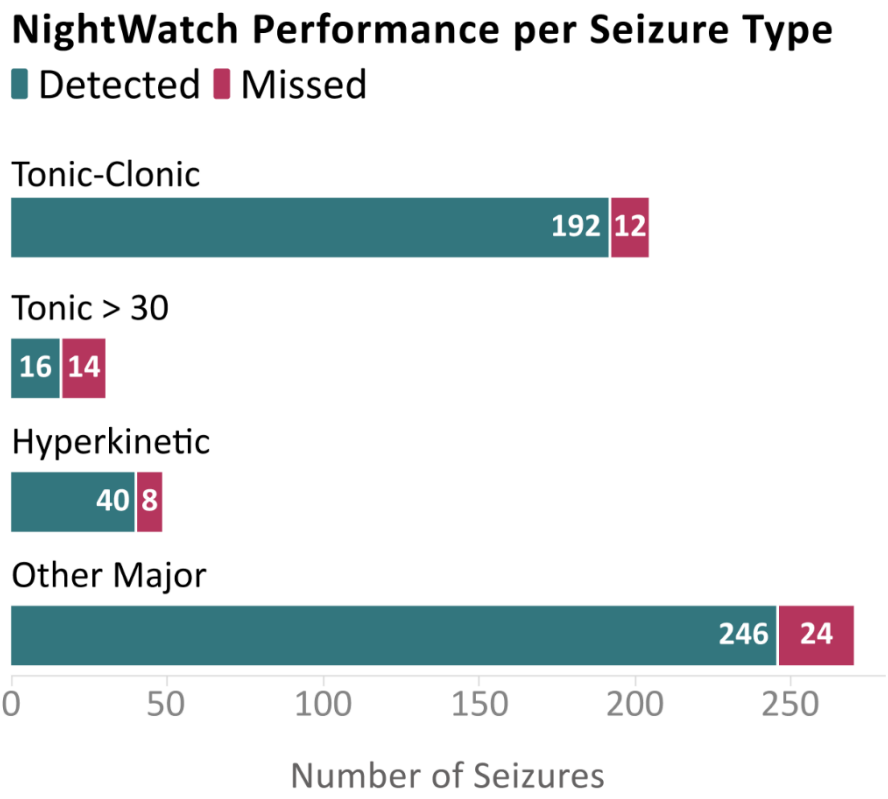

Figure 4 NightWatch performance per seizure type. Overview of number of seizures correctly detected (green bars) and number of seizures missed (red bars) by NightWatch for the different seizure types.

Post hoc analyses

Our post hoc analyses revealed that children with learning disabilities were more like to exhibit higher FAR (.05/h) than those without (.02/h, p=.001), whereas we found no contrasts in sensitivity between both groups. The other factors (age, sex, proportion of TCs) did not impact NightWatch performance.

Secondary outcomes

Quality of signal data

Two hundred forty-one of 2551 recorded nights were excluded from analysis due to insufficient video data (n=159), computer storage issues (n=51), inadequate HR signal quality (n=27), lost connection with the base station (n=2), or because the child was no longer in bed (n=2; Figure 3). In the 27 excluded

nights because of poor HR data, caregivers did not respond to the technical alarm to reposition the sensor. No data loss due to insufficient HR data was seen in cases in which NightWatch was used correctly. The accelerometry sensor provided sufficient quality signal throughout the entire study.

Adverse effects

Eight children developed mild, reversible skin irritation during the first trial period from the NightWatch device. We advised alternating recording sites (e.g., left and right arm), and in three cases we advised wearing the NightWatch around the lower leg because of skin irritation on both arms. The manufacturer developed a laser-cut kinesiology tape to stick on the inner side of NightWatch to soften skin contact. With the use of the tape, no further skin irritation was reported.

Video detection algorithm

The video detection algorithm was initially designed to detect convulsive seizures and showed a median sensitivity of 44% (range=0%-100%, mean=42% [95% CI=25%-59%]) for this type of seizure. For the detection of all major motor seizures, the median sensitivity per participant was 30% (range=0%-100%, mean=29% [95% CI=19%-39%]), with a median FAR per hour of .05 (range = .00-1.44, mean = .13 [95% CI = .06-.20]). We performed a post hoc investigation to understand why scores were lower than previously reported[16,17] and noticed that the video recordings had an unstable frame rate, which may hinder the performance of the detection algorithm. In a prospective setting this problem would never emerge, but during retrospective analysis we discovered that it is very important that the video recordings are stored with a fixed frame rate, because the algorithm has to detect specific frequencies in movement. An unstable frame rate disrupts these frequencies and thereby influences the algorithm's performance.

Questionnaires

The online questionnaires on caregiver's stress, sleep quality, and QoL were fully completed by 25 (47%) and partly completed by 17 (32%) caregivers, and the questionnaires on caregiver's expectations and experiences were fully completed by respectively 25 (47%) and 22 (42%) caregivers.

Caregiver's stress, sleep, and QoL

The mean CSI score was >7 points throughout the study, indicating high levels of caregiver stress. During the intervention period there was a small but significant decrease in caregiver stress (mean total CSI score=8.0 vs. 7.1, p=.032). The median difference in stress score was −1, and nine caregivers

Table 2 Characteristics of included subjects and individual results

Sub-ject	Characteristics Child					Recorded data			Primary outcome: Night-Watch Performance[a]			Secondary outcomes: Parental stress, sleep and QoL					
	Sex	Age (yrs)	Epilepsy Etiology	Learning disabilities (Yes/No)	No. of ASMs	No. of recorded nights	No. of major seizures	Type of seizures	Sens (%)	PPV (%)	FAR/ hour	CSI score T1	CSI score T2	PSQI score T1	PSQI score T2	QoL score T1	QoL score T2
1	F	8	Genetic	No	3	63	9	HK	100	69	0.01	11	9	9	3	0.74	0.80
2	M	7	Structural	No	3	43	0	-	-	-	0.01	4	2	4	2	1	1
3	F	14	Unknown	No	2	62	0	-	-	-	0.02	4	4	6	6	1	1
4	M	15	Unknown	Yes	3	38	4	TC	100	21	0.03	11	10	10	13	0.86	0.77
5	F	8	Structural	Yes	3	61	4	TC, T>30	100	11	0.04	4	na	8	na	0.90	na
6	F	6	Unknown	No	2	65	0	-	-	-	0.02	5	2	7	8	0.82	0.91
7	M	16	Genetic	Yes	2	51	2	HK, OM	50	17	0.01	1	1	2	3	1	1
8	M	9	Structural	Yes	3	30	0	-	-	-	0.17	9	7	5	8	1	1
9	M	14	Unknown	Yes	5	14	13	TC, T>30, OM	46	35	0.06	12	12	11	6	0.87	0.87
10	M	14	Genetic	Yes	2	56	147	TC, T>30, HK, OM	80	75	0.05	10	8	14	12	0.84	0.86
11	F	15	Genetic	Yes	2	14	5	HK, OM	80	29	0.06	na	na	na	na	na	na
12	M	6	Genetic	Yes	4	60	22	TC, T>30, OM	100	37	0.05	12	12	8	8	0.89	0.89
13	F	13	Structural	Yes	3	70	0	-	-	-	0	na	na	na	na	na	na
14	F	10	Structural	Yes	1	56	24	TC, T>30, OM	100	49	0.03	8	7	8	4	0.61	0.92
15	M	5	Unknown	Yes	1	Excl[b]	-	-	-	-	-	12	11	9	10	1	0.93
16	F	12	Genetic	Yes	3	25	0	-	-	-	0.19	5	7	10	11	0.91	0.93
17	M	11	Structural	No	2	32	7	OM	86	15	0.11	7	9	8	7	na	na
18	F	16	Genetic	Yes	1	18	0	-	-	-	0.53	4	6	6	4	1	1
19	M	10	Genetic	No	3	59	0	-	-	-	0.05	na	na	na	na	na	na
20	F	5	Genetic	Yes	2	81	3	OM	100	4	0.06	na	na	na	na	na	na
21	F	12	Unknown	Yes	2	20	0	-	-	-	0	na	na	na	na	na	na

Table 2 (Continued)

Subject	Characteristics Child					Recorded data			Primary outcome: Night-Watch Performance[a]			Secondary outcomes: Parental stress, sleep and QoL					
	Sex	Age (yrs)	Epilepsy Etiology	Learning disabilities (Yes/No)	No. of ASMs	No. of recorded nights	No. of major seizures	Type of seizures	Sens (%)	PPV (%)	FAR/ hour	CSI score T1	CSI score T2	PSQI score T1	PSQI score T2	QoL score T1	QoL score T2
22	F	15	Genetic	Yes	4	56	6	TC, T>30, OM	100	13	0.06	5	5	8	9	0.83	0.96
23	F	13	Unknown	Yes	3	45	17	TC, HK, OM	94	17	0.14	12	9	11	13	0.75	0.65
24	F	15	Unknown	No	2	31	17	HK	100	94	0	na	na	na	na	na	na
25	F	10	Genetic	Yes	2	41	10	TC, OM	100	36	0.03	10	na	4	na	0.85	na
26	M	4	Genetic	No	2	30	1	OM	100	9	0.02	9	8	0	4	na	na
27	M	8	Genetic	Yes	6	16	0	-	-	-	0.25	na	na	na	na	na	na
28	M	9	Genetic	Yes	4	57	86	OM	99	26	0.34	8	9	8	8	1	1
29	M	12	Structural	Yes	3	54	70	TC, T>30, HK, OM	87	75	0.03	9	11	7	6	0.9	0.83
30	M	4	Genetic	Yes	3	80	0	-	-	-	0.18	11	na	10	na	1	na
31	F	7	Genetic	Yes	1	54	1	TC	100	3	0.05	9	9	10	7	0.93	0.83
32	M	14	Unknown	Yes	0	16	6	TC, T>30	83	10	0.24	10	9	10	4	1	1
33	M	10	Unknown	No	2	30	4	TC, OM	100	24	0.02	na	na	na	na	na	na
34	F	8	Genetic	Yes	2	27	12	TC, T>30, OM	100	23	0.11	na	na	11	na	na	na
35	M	13	Unknown	No	2	18	0	-	-	-	0.01	na	na	na	na	na	na
36	M	8	Structural	No	2	2	2	TC	100	67	0.04	8	na	5	na	1	na
37	M	14	Unknown	Yes	3	59	35	TC, OM	100	51	0.04	9	5	4	5	1	1
38	M	5	Infectious	Yes	2	Excl.[b]	-	-	-	-	-	na	na	na	na	na	na
39	F	5	Structural	Yes	5	59	0	-	-	-	0.02	10	9	7	2	0.93	0.93
40	F	12	Unknown	No	3	57	2	T>30, OM	50	25	0	0	1	6	4	1	1
41	M	4	Unknown	No	3	53	0	-	-	-	0	12	na	12	na	0.47	na
42	F	9	Structural	Yes	2	17	0	-	-	-	0.05	0	na	4	na	0.93	na

Table 2 (Continued)

Sub-ject	Characteristics Child					Recorded data			Primary outcome: Night-Watch Performance[a]			Secondary outcomes: Parental stress, sleep and QoL					
	Sex	Age (yrs)	Epilepsy Etiology	Learning disabilities (Yes/No)	No. of ASMs	No. of recorded nights	No. of major seizures	Type of seizures	Sens (%)	PPV (%)	FAR/ hour	CSI score T1	CSI score T2	PSQI score T1	PSQI score T2	QoL score T1	QoL score T2
43	F	8	Structural	Yes	3	42	0	-	-	-	0.01	6	3	4	2	1	1
44	M	7	Unknown	Yes	2	55	0	-	-	-	0.05	7	3	2	2	0.86	0.86
45	M	4	Genetic	Yes	1	58	4	OM	75	5	0.05	10	na	10	na	1	na
46	M	12	Genetic	Yes	5	95	1	OM	100	3	0.05	11	na	18	na	0.61	na
47	M	10	Structural	No	1	60	0	-	-	-	0.01	6	na	8	na	1	na
48	F	6	Structural	Yes	1	47	0	-	-	-	0.24	na	na	na	na	na	na
49	M	12	Unknown	Yes	2	4	2	TC, T>30	100	33	0.01	11	na	14	na	0.93	na
50	F	7	Unknown	No	3	27	9	TC, OM	78	54	0.01	10	na	na	na	0.90	na
51	M	9	Genetic	Yes	4	38	10	TC, OM	100	22	0.06	9	na	12	na	0.91	na
52	F	10	Unknown	No	1	60	2	TC	100	6	0.03	7	na	7	na	0.89	na
53	M	5	Unknown	No	4	108	15	OM	67	37	0.02	11	11	15	na	0.83	0.45

ASM anti-seizure medication, *CSI* Caregiver stress index, *F* female, *FAR* false alarm rate, *HK* hyperkinetic, *M* male, *na* not available, *OM* other major, *PPV* positive predictive value, *PSQI* Pittsburgh sleep quality index, *TC* tonic-clonic, *T>30* tonic >30 seconds, *QoL* quality of life., *yrs* years.

[a] *Overall seizure sensitivity for all seizure types combined.*

[b] *All recorded data of this participant was excluded due to insufficient video data.*

indicated that ≥2 items (of 13) on the CSI were no longer difficult for them to handle. Caregiver sleep quality and QoL did not significantly change following NightWatch usage (mean total PSQI score=7.9 vs. 6.7, p=.117; mean total EQ-5D-5L score = .9 vs. .9).

Caregiver's expectations and experiences

Table 3 summarizes the results of the online questionnaires on caregivers' expectations and experiences with NightWatch. Trial participants had high expectations of the NightWatch before the start of the trial. Nearly all users reported that NightWatch was easy to use. Postintervention, caregivers were asked if they decided to keep using NightWatch (which meant they needed to buy it); 32% of caregivers (n=7) (strongly) agreed, 18% (n=4) were neutral, and

Table 3 Caregiver's expectations of and experiences with NightWatch

Evaluated item	Mean [SD] on the 5-point Likert scale
Expectations (n=25)	
I expect NightWatch to be a reliable device	3.83 [0.38]
I expect NightWatch to be useful	4.25 [0.53]
I expect NightWatch to provide a safe night	3.79 [0.42]
I expect NightWatch to be our last resort	3.17 [0.82]
I don't expect that much, I'll wait and see	2.92 [1.06]
I expect that NightWatch must prove itself	3.54 [0.78]
I need a seizure detection device (other than the ones I might have used before)	4.13 [0.85]
I expect to keep using the device after the trial	3.71 [0.69]
Experiences (n=22)	
I am overall satisfied with using NightWatch as a device	3.05 [1.09]
I am satisfied about the fixation of NightWatch on the upper arm	3.36 [0.95]
I am satisfied about the way NightWatch alerts during a seizure	2.77 [1.15]
NightWatch met my expectations	2.55 [0.96]
NightWatch is simple to use	4.41 [0.73]
For me, the NightWatch is a reliable device	3.18 [0.96]
I could better let go of the care of my child during the night, because I trusted the NightWatch	2.86 [1.04]
My child was not bothered by NightWatch	3.77 [1.02]
Other members of our family were not bothered by the device	3.32 [1.13]
I believe that I'm better able to report the number of seizures of my child to our neurologist	3.14 [1.28]
I will keep using the NightWatch after the trial	2.77 [1.23]

50% (n=11) disagreed. Reasons to differ included a decrease in seizure frequency during the trial (n=5); high FAR (n=3), too expensive to purchase (n=2), and skin irritation (n=1).

DISCUSSION

This phase 4 SDD trial provides class II evidence that NightWatch accurately detects nocturnal major motor seizures in children (median sensitivity=100%). Besides high sensitivity for the detection of convulsive seizures, NightWatch also showed good performance in detecting HK and OM motor seizures in children. NightWatch was well tolerated and easy to use. Caregivers reported a positive effect on their experienced stress during NightWatch use, whereas their quality of sleep and QoL did not change significantly.

Strengths and limitations

Strengths of the PROMISE trial include the prospective, home-based, video-controlled design, long-term follow-up, and many recorded nights and seizures. The long-term follow-up helped to estimate the performance reliably. Contextual conditions may significantly impact the seizure detection algorithm's performance. For instance, electrocardiography-based algorithms yielded poorer results in freely moving people than in those lying in bed.[19] The home environment allowed us to examine a realistic setting, but we could also evaluate user satisfaction. One of the challenges with a home-based approach is the risk of missing seizures due to the lack of continuous EEG supervision, which may inflate sensitivity. To reduce this bias, we applied different screening methods. First, we asked the caregivers to record all seizures. Second, trial nurses screened 5% of all video recordings. Third, we retrospectively ran an automated, previously validated video detection algorithm on all tracings.[16,17] During this process, we found that the frame rate of the video recordings was not constant, hampering performance of the method compared to previous work.[16,17] Nonetheless, the video algorithm accounted for 67% of all false negative detections. In the randomly selected 5% of all data that we visually reviewed, we found 25 seizures in total (NightWatch detections+detected false negatives). If this number is representative for the complete dataset, we would expect 25×20=500 seizures in total. However, we found 552 seizures with our approach, suggesting that our method probably detected most of the seizures. Another challenge of our home- and video-based approach concerns the observer reliability. We expect that the reliability depends on the seizure type,

with likely high accuracy for the identification of TCs and longer tonic seizures, whereas other seizure types (e.g., certain types of HK seizures and the seizures that we classified as "OM") can be more challenging to distinguish from normal or sleep-related behavior. Nevertheless, in our previous NightWatch trial in adults we found a substantial interobserver agreement for the different seizure types used in this study.[14] A significant advantage of our approach over conventional phase 4 studies includes the video-controlled design that allowed us to verify user feedback. Users may recognize nonepileptic events as seizures or label seizure-related alarms false if the caregiver arrives late and the seizure is shortlasting. Another strength includes the detection of a broad range of motor seizures. A limited number of caregivers completed the online questionnaires, which may have biased results. This bias could work both ways; people who are either satisfied or unsatisfied may doubt the usefulness of the questionnaires, which reflects a realistic scenario of adherence in practice. Children of caregivers who did not complete the full questionnaire had on average fewer recorded nights during the intervention period compared to children of caregivers who did. This difference was not statistically significant but may have caused bias. The questionnaires provide some indicators but fall short of understanding the experienced value of NightWatch given the many interfering contextual factors (e.g., fluctuating disease course and parental coping). We addressed this limitation by conducting qualitative, in-depth interviews with 23 parents of 19 children, including dropout cases. We found that the experienced value of NightWatch resulted from an interplay of contrasting factors: on the one hand, the amount of assurance it could offer to reduce their fear of losing their child and the associated protective behavior, and conversely, their resilience to handle the potential extra burden of care (e.g., false alarms).[8]

Related research

Unlike other commercially available SDDs, NightWatch demonstrated relatively high sensitivity and a slightly lower FAR.[1,11,20] A recent meta-analysis on the performance of wearable SDDs yielded a mean sensitivity of 91% for detecting convulsive seizures and an overall FAR of .08/h.[21] However, it is hard to compare our results with other devices, because almost none provides phase 4 studies or focuses on children or people with learning disabilities. Other devices usually include only small datasets with short-term follow-ups and recordings in a hospital or epilepsy monitoring unit. Another critical contrast with previous

SDD trials consists of the seizure types; most trials focused on convulsive seizures only, whereas we included a broader range of significant motor seizure types. Previous surveys indicated that incorporating a broader range of seizures other than TCs may better meet the users' needs.[22-24] Unlike our previous video-controlled trial in adults, NightWatch sensitivity in this pediatric cohort is slightly higher, but so is the FAR.[14] The FAR is partly explained by a high seizure burden, as almost one third of false alarms are related to seizures that did not meet our criteria for clinically urgent. The remainder is related to arousals or nonepileptic rhythmic movements. NightWatch algorithm corrects for individual baseline HR, but HR fluctuations and nonepileptic rhythmic movements may trigger false alarms. HR profiles of children differ from adults and are characterized by higher resting values and more significant variability.[25,26] Children, particularly those with developmental disorders, may also present with challenging behavior and sleep-related rhythmic movements.[27] Children with comorbid movement disorders were excluded from the trial, yet we did encounter some children with excessive or restless movements and body rocking. Accordingly, our post hoc analysis indicated that children with learning disabilities had higher FARs. We expect lower FAR in older cohorts and cohorts with less challenging behavior. Approximately one third of the participants did not experience a significant seizure during the intervention period. In parallel to this trial, children were treated by their neurologist and in 15 cases higher doses of antiseizure medications were given during the intervention compared to baseline, which might explain the lower seizure frequency. Possible other reasons for this include the reflection of a natural course of seizure frequency, or perhaps even a protective effect of SDD usage providing reassurance. Clinical trial simulations with time running forward and in reverse revealed that the placebo response is almost entirely attributable to the natural variability of epilepsy.[28] Prospective, real-time, video-controlled performance studies in a home environment are scarce. Only two other phase 4 SDD studies have been performed, including the previous NightWatch study assessing its performance in adults living in a residential care facility.[1,14,29] NightWatch scored high on user-friendliness, and caregivers indicated that implementation facilitated a timelier response and more freedom. In contrast, the burden of care remained unchanged.[14] This is in line with our results of lower stress scores following NightWatch usage. The second in-field study examined the applicability and usability of a wearable accelerometer device (Epi-Care) for detecting focal to bilateral convulsive seizures.[29] Most users were overall satisfied with the device,

many indicated that the use of the device had resulted in fewer seizure-related injuries, and only a small group stopped using the device due to reasons related to it (e.g., high FAR, irritation or discomfort, low effectiveness). The study included a large population and longterm follow-up, but device performance data were based only on seizure diaries. Nearly all people with epilepsy included in these phase 4 studies lived in residential care facilities, reflecting a different ambulatory setting and possibly different user needs than in our study.[14,29] A pilot study on 10 adolescents with epilepsy and their families showed an insignificant increase in QoL (Quality of Life in Epilepsy Inventory for Adolescents 48) while using a wearable SDD (SmartWatch) for 6 months.[30] A larger survey study found that most SDD users experienced reduced anxiety from device usage. At the same time, there was no significant difference in overall HR-QoL between SDD users and nonusers.[31] In a second large survey study, the majority of SDD users (including one third of users of NightWatch) agreed that using the device improved their QoL (median=6 on a 7-point Likert scale).[32] Another large study followed families of children with newly diagnosed epilepsy. Those who wanted to use an SDD (approximately half of the families) were randomly allocated to the Epi-Care or an audio baby monitor.[33] QoL improved significantly over time in all parents, suggesting that QoL increases independently of SDD usage. We recently performed an economic assessment of NightWatch. We found no significant changes in quality-adjusted life years after NightWatch intervention. Nonetheless, we demonstrated a decrease in societal costs (€775 reduction during the 2-month intervention period), suggesting that NightWatch might be a cost-effective addition to usual care for children with severe epilepsy living at home.[34] We found a small but significant reduction in caregiver stress, possibly partly explained by the short intervention period. The latter might also explain why we could not find a considerable change in caregivers' quality of sleep and life. Caregivers were optimistic about the practical use of NightWatch. Nonetheless, not all wanted to continue NightWatch, mainly due to cost (NightWatch is not yet reimbursable in the Netherlands), FAR, or seizure remission, thus emphasizing that SDD implementation is a multifactorial process. Acceptance of a device into a family home depends on device performance and even more on contextual factors like the burden of care8 and taking time to trust the device.[35,36] Future SDD studies should focus on ways to reduce FAR, which could facilitate implementation. Possible avenues include validating multiple algorithms that improve performance in specific subgroups (e.g., by focusing more on HR parameters

than movement) and applying machine learning techniques to create individual-specific algorithms.[37,38] These approaches also have the potential of addressing the varying needs among users regarding the trade-off between true positives and FAR.[21]

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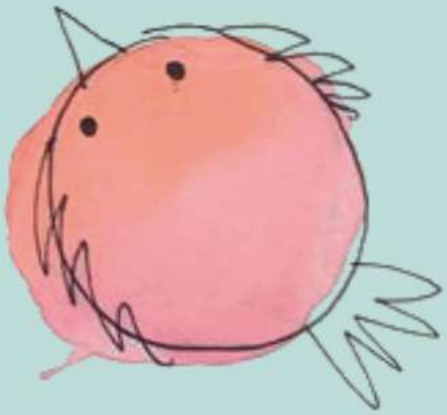

CHAPTER 6

Automated video-based detection of nocturnal motor seizures in children

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ABSTRACT

Introduction

Seizure detection devices (SDDs) can improve epilepsy care, but wearables are not always tolerated. We previously demonstrated good performance of a real-time video-based algorithm for detection of nocturnal convulsive seizures in adults with learning disabilities.

Methods

The algorithm calculates the relative frequency content based on the group velocity reconstruction from video-sequence optical flow. We aim to validate the video algorithm on nocturnal motor seizures in a paediatric population.

Results

We retrospectively analysed the algorithm performance on a database including 1661 full recorded nights of 22 children (age 3-17 years) with refractory epilepsy at home or in a residential care setting. The algorithm detected 54 of 69 convulsions (median sensitivity per participant 54%; overall sensitivity 78%, 95% CI 57.5-100%) and identified 117 of 161 hyperkinetic seizures (overall sensitivity 73%). Most children had no false alarms; 87 false alarms occurred in seven children (median false alarm rate (FAR) per participant per night 0 [range 0-0.53]; overall FAR 0.05 per night). Most false alarms (58%) were behaviour-related (e.g., awake and playing in bed).

Conclusions

Our noncontact detection algorithm reliably detects nocturnal epileptic events with only a limited number of false alarms and is suitable for real-time use.

INTRODUCTION

Nocturnal convulsive seizures, particularly if unwitnessed, pose the highest risk of sudden unexpected death in epilepsy (SUDEP).[1,2] Nocturnal supervision seems to have a protective effect on SUDEP, likely by permitting an intervention, but the exact protective mechanism is unknown.[3,4] Seizure detection devices (SDDs) can be used to alert for nocturnal seizures and allow others to intervene. Wearable devices are not always tolerated, especially not by children or those with intellectual disabilities, and may require charging. We previously demonstrated good performance of a remote real-time video-based seizure detection in adults living in a residential care setting.[5] The algorithm was able to detect all 50 nocturnal convulsive seizures (sensitivity 100%) with a median false alarm rate (FAR) of 0.78 per night and a latency of ≤10 seconds in 78% of detections. We aimed to validate the video detection algorithm in a paediatric population.

METHODS

Algorithm adjustment

The methodology used was previously published.[6] Detection thresholds were recently determined in a training set and the detection performance was validated in a test set of nocturnal video recordings of adults with refractory epilepsy.[5] The algorithm is composed of different steps to identify specific movement patterns of convulsions in the video image sequence. The first step is to reconstruct spatial movements by creating a vector field of velocities from changes in luminance (optical flow). Secondly, these velocities are grouped into six rates of spatial transformation (translation (horizontal & vertical), rotation, dilatation, and shear rates (horizontal & vertical)). Subsequently, time-frequency spectra of these group velocities are calculated using Gabor aperture functions with central frequencies ranging from 0.5-12.5Hz. The final step is to derive the power in the 2-6Hz frequency range (which is assumed to be the spectrum of convulsive seizures) relative to the total Gabor power.[6] The relative 2-6 Hz power is expressed as a value between zero and one, thus reflecting the probability of registering a convulsion. If the output signal exceeds the previously determined threshold of 0.51 for more than 4 seconds, an alarm is set.[5] We made the following adjustments to the original algorithm: (1) the optical flow calculation was extended to the multi-channel (colour) level to avoid potential information loss due to the image interpolation to the greyscale[7] (2) a

novel algorithm (Global Optical Flow Reconstruction Iterative Algorithm (GLORIA)) was applied to bypass the time-consuming task of first reconstructing the local vector field and subsequently fitting the group transformation templates.[8] The GLORIA algorithm improves calculation speed by directly reconstructing relevant global group transformation velocities from the image sequences.

Validation in a paediatric population

For validation we used a dataset of all children in the LICSENSE trial (NTR4115). This prospective multicentre study validated a wearable multimodal SDD (NightWatch) combining heart rate and accelerometry. Children with refractory epilepsy were included if they were ≥3 years of age and had at least one monthly nocturnal motor seizure (i.e., tonic-clonic (TC), generalized tonic >30 seconds, focal hyperkinetic and a 'remaining' category, consisting of TC-like seizures with atypical semiology and clusters of minor seizures lasting >30 minutes). Exclusion criteria comprised frequent non-epileptic movement patterns (e.g., choreatiform movements, sleep walking) and only minor motor seizures. They were monitored for a period of two to three months in their home or in a residential care setting. All recorded sequences of digital images had an H.264 (MPEG-4) format with a resolution of 640(H) x 480(V) pixels, 24-bit RGB colour encoding and a constant frame rate of 32 frames per second.
Experienced epilepsy nurses analysed all alarms generated by the wearable device together with caregiver's seizure diaries and screened 10% of all recorded nights for possibly missed seizures. Events were annotated as 'seizure' or 'no seizure' and seizure type was specified (e.g., convulsive, hyperkinetic). Isolated minor seizures were annotated as 'no seizure' and classified as false alarms. In case of doubt, annotations were discussed with a neurologist.
We retrospectively analysed the detection performance of the algorithm on the annotated LICSENSE video database. All timestamps of the video alarms were compared with the annotations of the LICSENSE database. If the algorithm detected a clinical event also reported by the caregiver or coincided with a NightWatch alarm, the video detection was labelled with the same annotation. All other video alarms were designated as 'new alarms' and annotated by experienced epilepsy nurses, and in case of doubt discussed with a neurologist. Detection performance was evaluated as sensitivity for the detection of convulsive seizures per participant and FAR per participant and as overall sensitivity for the detection of all seizures of a specific seizure type (i.e., TC,

generalized tonic >30 seconds, focal hyperkinetic and 'remaining') and overall FAR (i.e., total number of false alarms divided by total number of recorded nights). We restricted sensitivity analysis to those who had motor seizures during the trial period, false alarm rate was calculated for the entire dataset. False alarms were categorized as (1) Awake and playing or moving in the bed; (2) Rhythmic movement disorder (e.g., body rocking); (3) Rhythmically moving object in the room; (4) Another person in the room. For the generalizability of the results, we also calculated the F_1-score for the detection of convulsive seizures.[9]

The study protocol of LICSENSE was approved by a regional ethics committee and written consent was provided by participants or their guardians provided ascent were applicable. Data were handled anonymously.

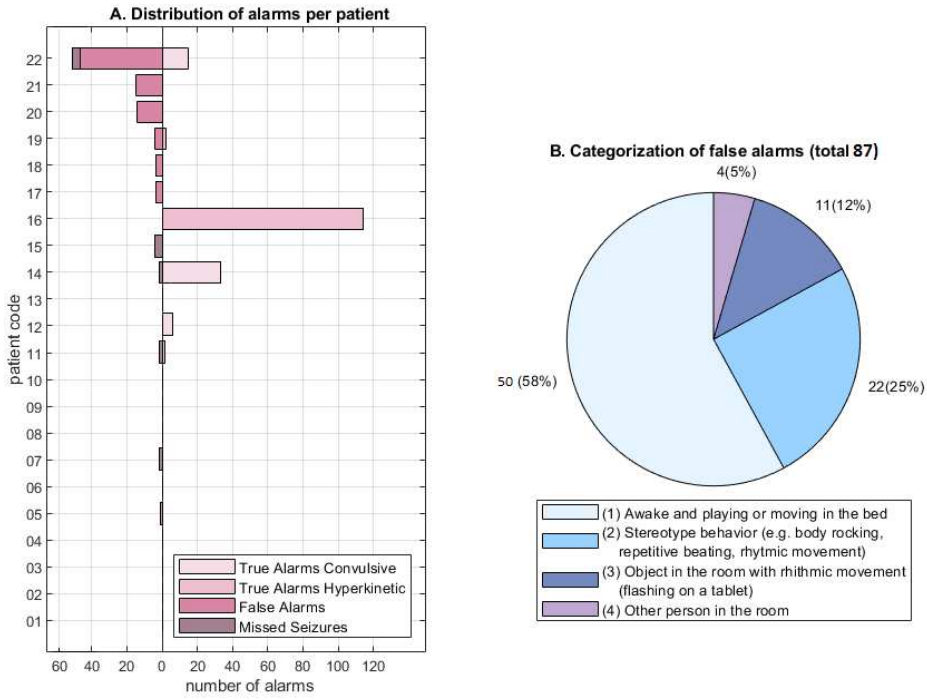

Figure 1 (A) Distribution of video alarms (true and false) and missed seizures among all 22 participants. True alarms are defined as convulsive and hyperkinetic seizures. **(B)** Categorization of false alarms.

RESULTS

The dataset included 1661 full recorded nights of 22 children (13 male) with a median age of 9 years [range 3-17 years]. Sixteen children were monitored in a residential care setting, three at home and three between home and in a residential care setting. We analysed 69 convulsive seizures in six children. The video detection algorithm was able to detect 54 out of 69 convulsive seizures (median sensitivity per participant 54% [range 0-100%]; overall sensitivity 78% [95% CI 57.5-100%]; F_1-score = 0.51; Figure 1A). The algorithm also detected 117 of 161 hyperkinetic seizures (mean sensitivity 86% SD 19.6; overall sensitivity 73%) occurring in two children. The overall sensitivity of the algorithm for the detection of generalized tonic seizures >30 seconds was 9.8% and 1.0% for the detection of the 'remaining' major seizures. Median FAR was 0 per participant per night [range 0-0.53] (overall FAR 0.05/night). All 87 false alarms were clustered in seven children (Figure 1A). Most false alarms (58%) were behaviour-related (awake and playing in bed; Figure 1B).

The calculation speed of the algorithm was improved; a video epoch of 366 seconds took 263 seconds to analyse using the old algorithm and 194 seconds with the new GLORIA algorithm (with MatLab 2019b, Windows 10pro, Processor Intel I Core i7 7700 3.5Ghz 32Gb RAM).

DISCUSSION

This phase 2 study (according to the recent SDD guidelines)[10] validated our seizure detection algorithm in children and it showed good performance for the detection of nocturnal convulsions and hyperkinetic seizures. False alarms were mostly behaviour-related during wakefulness. Our adjustments in the processing speed makes the algorithm more suitable for real-time use and ready for clinical implementation.

A limitation of this study is the evaluation of possibly missed seizures since we did not screen all recorded nights. This is almost inevitable for such a long-term follow-up study but may have induced an overestimation of the sensitivity.

Several small phase 1 and phase 2 studies have been performed with various methods for automated video-based seizure detection, including motion tracking, periodicity estimation and optical flow[11,12] All had acceptable detection rates (overall sensitivity 75-100%), but algorithms were tested and trained using the same dataset, thus posing a risk of overfitting.[13-16] All studies used retrospectively collected video epochs of infants and children with various

motor seizure types and short selections of other non-epileptic movements but lacked prospective or continuous data. These studies thus demonstrated the feasibility of these techniques but overall performance is uncertain as reliable false alarm rates could not be derived.

Multiple phase 2, 3 and 4 studies on non-EEG based wearable SDDs have demonstrated good performance for the detection of convulsive seizures, with overall sensitivities over 90% and overall FARs ranging from 0.2/day to 1.44/day.[12] Best performance was achieved by multimodal devices combining various sensors including accelerometry, electrodermal activity, surface electromyography and heart rate. Most devices were validated in an epilepsy monitoring unit with relatively short monitoring periods. Our dataset includes long-term (2-3 months) home-based video recordings, which not only resulted in a large number of seizures, but also allowed for a reliable estimate of the FAR. The absence of false alarms in the majority of children despite the long-term follow-up makes our detection algorithm an attractive alternative to wearable SDDs. Most false alarms occurred during wakefulness in the early evening or morning, thus minimizing false alarm impact. Our algorithm detected all hyperkinetic seizures. Other modalities (EMG, accelerometry combined with heart rate) are likely more sensitive to detect a broader range of motor seizures.[17,18] A further advantage of our method is that it operates remotely without sensors attached to the individual. A survey on first-hand experiences of people with epilepsy using wearable devices during a clinical stay indicated that most participants found the devices convenient.[19] The presence of wires, bulky size discomfort and need for support did, however, moderate experience. Visibility and accuracy were important determinants about wearing them in everyday life. Video systems may raise privacy concerns, but our system generates real-time alarms without requiring video storage or monitoring. Our analysis was restricted to bedtime period. Daytime monitoring is possible but requires multiple cameras or portable video technology (drones, robots) likely to increase false alarm rate due to the more diverse movement patterns and thus require other algorithms. Compared to other remote SDDs using bed sensors, our video algorithm had a lower sensitivity for the detection of convulsive seizures (overall sensitivity 78% vs. 89%), but fewer false alarms (overall FAR 0.05/night vs 0.13/24h).[17]

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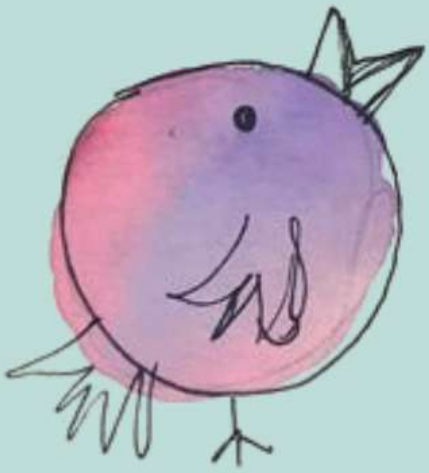

CHAPTER 7

An economic evaluation of the NightWatch for children with refractory epilepsy: insight into the cost-effectiveness and cost-utility

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ABSTRACT

Introduction

We performed an economic evaluation, from a societal perspective, to examine the cost-utility and cost-effectiveness of a wearable multimodal seizure detection device: NightWatch.

Methods

We collected data between November 2018 and June 2020 from the PROMISE trial (NCT03909984), including children aged 4-16 years with refractory epilepsy living at home. Caregivers completed questionnaires on stress, quality of life, health care consumption and productivity costs after two-month baseline and two-month intervention with NightWatch. We used costs, stress levels and quality-adjusted life years (QALYs) to calculate incremental cost-effectiveness ratios (ICERs). Missing items were handled by mean imputation. Sensitivity analyses were performed to examine the robustness of the results including bootstrap sampling.

Results

We included 41 children (44% female; mean age 9.8 years, standard deviation (SD) 3.7 years). Total societal costs of the baseline period (T1) were on average €3,238 per patient, whereas after intervention (T2) this reduced to 2,463 (saving €775). The QALYs were similar between both periods (mean QALY 0.90 per participant, SD at T1 0.10, SD at T2 0.13). At a ceiling ratio of €50,000, NightWatch showed a 72% cost-effective probability. Univariate sensitivity analyses, on the perspective and imputation method, demonstrated result robustness.

Conclusions

Our study suggests that NightWatch might be a cost-effective addition to current standard care for children with refractory epilepsy living at home. Further research with an additional target group for a large timeframe may support the findings of this research.

INTRODUCTION

Epilepsy is a significant health problem that imposes a substantial burden on individuals, their caregivers and health systems.[1] Seizures are unpredictable and may cause serious complications, including sudden unexpected death in epilepsy (SUDEP).[1] Having (generalised or focal to bilateral) tonic-clonic seizures, particularly if nocturnal and unattended, constitutes the most significant SUDEP risk factor.[2-4] This poses an opportunity for seizure detection devices (SDDs), which might lower the morbidity and mortality risk in epilepsy and potentially reduce the burden.[5] NightWatch is a multimodal wearable combining photoplethysmography and accelerometry to alert for nocturnal major motor seizures.[6] A previous prospective multicenter, video-controlled cohort study demonstrated good performance of NightWatch in adults, with 86% sensitivity and a median false alarm rate of 0.25 per person per night.[6] Yet economic studies addressing the cost-effectiveness of NightWatch and other SDDs are still lacking. Since no studies were found on this subject, this study aims to fill in that gap. As resources are scarce, evidence-based decisions on costs and effects are increasingly important in current health care decision-making.[7] particularly in the field of epilepsy, compromising 0.3% of the European total healthcare budget.[8] This is a pressing question as SDDs rapidly emerged in epilepsy care while costs of these devices are substantial and often not reimbursed, thus causing health inequality. We, therefore, aimed to perform an economic evaluation from a societal perspective to examine whether implementation of NightWatch is preferable over usual care in terms of costs, effects and utilities.

METHODS

This study followed Dutch guidelines for economic evaluations[9] and the CHEERS reporting guidelines for economic evaluations.[10]

Data collection

Target population and setting

We used data from a prospective multicenter home-based implementation study, the Promoting implementation of seizure detection devices in epilepsy care (PROMISE) trial; NCT03909984. PROMISE included 60 children aged 4-16 years with at least one major nocturnal motor seizure per week, living at home and treated at a tertiary epilepsy center in the Netherlands (SEIN,

Kempenhaeghe or University Medical Center Utrecht). Background information from the children and caregivers participating in the PROMISE study was extracted from the PROMISE database (Table 1).

Table 1 Demographic characteristics of study particpants

Baseline characteristics (N=41)	**N**	**%**
Characteristics of children		
Female	18	44
Mean age	9.8 (SD 3.7)	-
Mean age at seizure onset	2.8 (SD 3.3)	-
Epilepsy etiology		
Genetic	15	37
Structural	11	27
Unknown	15	37
Learning disability	29	71
Number of ASMs at start study		
None	1	3
One	7	17
Two	11	27
Three	14	34
Four	5	12
Five	3	7
Characteristics of caregivers		
Female	33	81
Mean age	40.9 (SD 6.2)	-
Marital status (living together)	28	68
Paid work	31	76
Mean no. of working hours/week	28.3 (SD 8.3)	-

N number, *SD* standard deviation, *ASMs* antiseizure medications.

Study perspective and time horizon

The economic evaluation was executed from a societal perspective. This perspective accounts for both directs costs (i.e., health care costs) and indirect costs (i.e., lost productivity costs). The PROMISE study consisted of a two-month baseline period without any SDD used (comparator), followed by a two-month period with NightWatch use at home (intervention). Data for our analysis was collected between November 2018 and June 2020. The Research Ethics Committee of University Medical Center Utrecht approved the study (PROMISE: NL62995.041.17). The study devices and equipment were provided free of

charge by the company that developed NightWatch (LivAssured). LivAssured had no role in the study design, analysis, or decision to submit for publication.

Outcomes

Caregivers from the PROMISE study were asked to complete online questionnaires before the baseline period (T0), at the end of the baseline period (T1) and the end of the intervention period (T2). T0 included questions on baseline characteristics of the child and the caregiver. We used validated questionnaires to measure caregiver's stress (Caregiver Strain Index [CSI]), quality of life (EQ-5D-5L), medical consumption (Institute for Medical Technology Assessment Medical Consumption Questionnaire [iMTA MCQ]) and productivity (Institute for Medical Technology Assessment Productivity Costs Questionnaire [iMTA PCQ]) at T1 and T2. The iMTA MCQ and iMTA PCQ were specifically adjusted to the care situation of a child with epilepsy; the iMTA MCQ covered questions about the medical consumption of the child and the caregiver, while the other questionnaires focused only on the caregiver. We asked the caregiver that took primary care of the child to complete all questionnaires.

Data analyses

Missing data

Missing items at T1 or T2 were handled by mean imputation, consisting of the mean score of the non-missing data.[11] At T1 data of two participants was missing (5% of the total study population). At T2 data of fifteen participants was missing (37% of the total study population).

Effectiveness

The effectiveness of the intervention, compared to the baseline period, was measured by the CSI questionnaire on caregiver's stress. Individual CSI scores were calculated by adding up all questions answered with 'yes' (1 point per question).

Utility

The EQ-5D-5L questionnaire on caregiver's quality of life (QoL)[7] was used to measure the utility of the intervention, compared to the baseline period. The five dimensions of the EQ-5D-5L questionnaire were summed into a health state, with the help of the Dutch EQ-5D-5L utility values.[12]

Societal costs

The iMTA MCQ and the iMTA PCQ were included to measure the societal costs. A bottom-up approach was used to estimate the health care costs;

information on each element of used service was multiplied by an appropriate unit cost (reference cost) and summed to provide overall costs.[7]

Table 2 Treatment costs per service and costs productivity losses in the Netherlands indexed for 2021

	Costs in €
Treatment	
GP (per consultation)	
Occupational therapist	178.54
Usual consult	35.73
Home visit	54.13
Paramedical care (per session)	
Dietician	35.73
Physiotherapy	35.73
Speech therapist	32.28
Alternative cure (per session)	
Homeopath	67.50
Home care (per hour)	
Help in the household (i.e., domestic chores)	21.65
Home care (i.e., personal care)	54.13
Home nursing (i.e., hospital-based home care)	79.03
Mental health care (per session)	
Psychologist	69.29
Mental health care (GGZ)	18.41
Social worker	70.38
Hospital care	
Ambulance emergency transport	663.69
First aid	557.59
Night Hospital (weighted average)	515.36
Nursing day hospital (weighted average)	515.36
Outpatient clinic (weighted average)	98.53
Respite care (per hour)	
Respite care children	14.10
Respite care children learning disability	11.46
Respite care children night (24 hours)	174.51
Costs productivity loss	
Hourly wage (average)[a]	37.62
Hourly wage informal care	15.16

[a]For irregular working days, an average working day of 8 hours is assumed.
GP General practitioner, *GGZ* Geestelijke gezondheidszorg [mental healthcare].

The health care costs were extracted from national databases in line with the Dutch costing guidelines.[9] For a homeopathic consultation, the cost price stated by the Society of Homeopathy [Vereniging Homeopathie] was used.[13] The cost prices of respite care were calculated by comparing the cost prices of different respite care providers, and taking the average cost price.[14] Informal care costs were calculated by using shadow pricing, applying the general hourly minimum wages (Table 2).[9] Productivity losses were estimated using the friction cost method, based on a mean added value of the Dutch working population.[9] Cost prices are expressed in euros in the year 2021. Existing cost prices were indexed to 2021 using the consumer price index (Table 2).[9, 15]

Statistics

Statistical analyses were performed using SPSS V.27. We used nonparametric bootstrapping (1000 replications) to test for statistical differences in costs between the intervention and the baseline period. Microsoft Excel 2016 was used to quantify the uncertainty around the incremental cost-effectiveness ratio (ICER; 5000 bootstrap replications). The ICER represents the costs of an additional quality-adjusted life year (QALY) gained and was used to estimate the cost-utility of the intervention compared to usual care. ICERs were estimated by dividing the incremental costs by the incremental quality-adjusted life-year (QALY). The bootstrapped cost-effectiveness ratios were presented in a cost-effectiveness plane. The choice to implement the intervention depended on the maximum amount of money society is prepared to pay for a gain in QALYs (willingness-to-pay), determined as the 'threshold'. As previously estimated in a Swedish study, we used a threshold (ceiling ratio) of €50,000 for refractory epilepsy per QALY gained.[16, 17] We constructed a cost-effectiveness acceptability curve (CEAC) and calculated the incremental costs per responder to show the probability of a cost-effective intervention at different thresholds.

Sensitivity analysis

We performed three one-way sensitivity analyses to check the potential influence of base-case assumptions on the study findings. (1) To analyze the influence of our choice of perspective on the costs, we performed the data analysis from a health care perspective instead of a societal perspective.[7] (2) We tested a different imputation method (i.e., individual mean imputation), which replaces missing data by the individual mean score of a complete answered questionnaire at an earlier or later moment. (3) To test whether the

mean imputation method was an appropriate way to handle missing data, all missing data (n = 17) were excluded from the analysis.

RESULTS

We collected data from the PROMISE trial, including 60 participants, between November 2018 and June 2020, data from 41 participants was available for analysis. There were no statistically significant differences in characteristics (mean age, mean age at seizure onset, epilepsy etiology, learning disability (yes/no), number of anti-seizure medications at start study) between the dropped-out (N = 19) and included participants (N = 41), so no baseline corrections were performed.

Total resource use and total societal costs

Total societal costs of the baseline period were on average €3238 per patient (Table 3), whereas after intervention this reduced to €2463. During baseline, the health care costs (child and caregiver) accounted for 90% (€2910) of the total costs, compared to 91% (€2250) during the intervention. The productivity costs were respectively 10% (€328) and 9% (€212) (Table 3).

ICERs

Cost-utility

Figure 1A illustrates the cost-utility analysis' cost-effectiveness (CE) plane from a societal perspective, representing the uncertainty surrounding the costs per QALY ratio. Based on the cost-utility analysis, the NightWatch was a cost-effective treatment compared to usual care alone (95% CI €19,387 - €28,182). The NightWatch is less expensive than usual care alone and equally effective in terms of QALYs (Table 3).

Cost-effectiveness

The incremental costs divided by the incremental effect (score on the CSI) resulted in an ICER of €846 per patient. The uncertainty analysis of this ICER is presented in a CE plane in Figure 1C. Most ICERs lie in the dominant southeast quadrant (82%), indicating that the NightWatch is less expensive and more effective compared to usual care (95% CI €376-€7946).

Sensitivity analyses

Results from the sensitivity analyses are provided in Table 3. Looking at the costs per QALY from a health care perspective, instead of a societal perspective, the probability of NightWatch being cost-effective decreased by

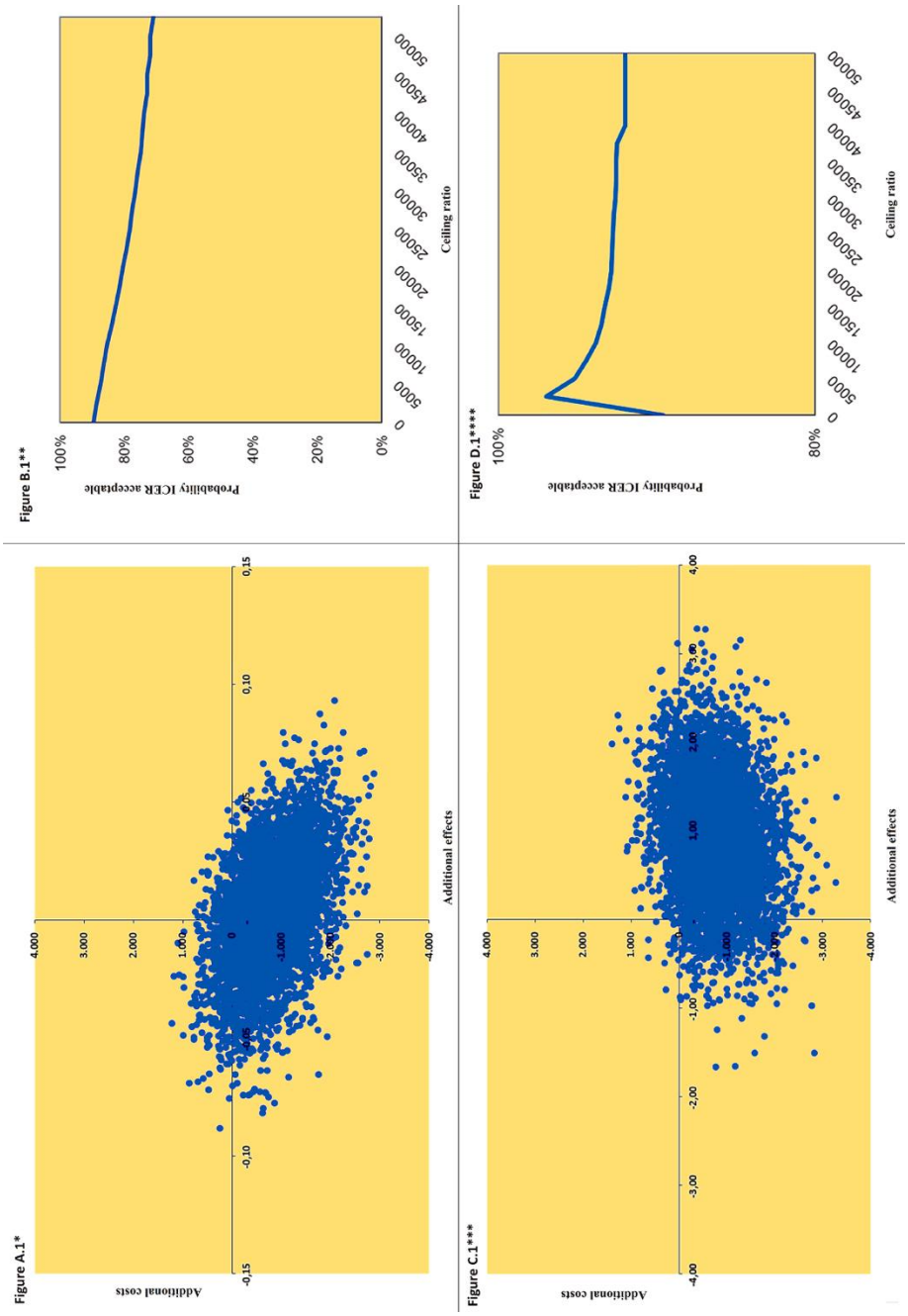

Figure 1 Cost-effectiveness planes and cost-effectiveness acceptability curves for the NightWatch intervention.

Legend figure 1

*__A.1 Cost-effectiveness plane, costs per QALY.__ The horizontal axis represents the additional effects in Quality Adjusted Life Years [QALY] of the intervention (NightWatch) compared to baseline (usual care) (0); The vertical axis represents the additional costs of the intervention compared to baseline (€ -775,49); The blue dots represent the bootstrapped Incremental Cost-effectiveness Ratios [ICERs].

**__B.1 Cost-effectiveness acceptability curve, costs per QALY__. The horizontal axis represents the ceiling ratio/threshold (for refractory epilepsy this is € 50.000); The vertical axis represents the threshold/willingness to pay; The blue line represents the probability of NightWatch being cost-effective (72% at a ceiling ratio of € 50.000).

***__C.1 Cost-effectiveness plane, costs per stress score.__ The horizontal axis represents the additional effects in stress of the intervention compared to baseline (-0,91); The vertical axis represents the additional costs of the intervention compared to baseline (€ -775,49); The blue dots represent the bootstrapped Incremental.

****__D.1 Cost-effectiveness acceptability curve, costs per stress score__. The horizontal axis represents the ceiling ratio/threshold; The vertical axis represents the threshold/willingness to pay; The definition of the clinical outcomes, in this case stress levels, differs per study, we could not determine the ceiling ratio (threshold) for NightWatch. Therefore, it is not possible to interpret the probabilities of NightWatch being cost- effective in terms of costs and stress.

Table 3 Bootstrapped mean of the QALY, stress, and costs (€) per participant during the baseline period and the intervention

	Bootstrap (N=41)			**Sensitivity analysis**					
				Healthcare perspective		Individual mean imputation		Only complete cases	
	Normal	Intervention	Difference	Normal	Intervention	Normal	Intervention	Normal	Intervention
Outcomes									
Caregivers' QALY[a]	0.9 (SD 0.12)	0,9 (SD 0.10)	0	0.9	0.9	0.9	0.89	0.92	0.9
Caregivers' Stress level	8.02 (SD 3.29)	7.11 (SD 2.74)	-0.91	8.02	7.11	7.51	8.02	7	7.96
Health care costs									
Intervention costs	0	49.67	49.67	0	-	-	-	-	-
Health care costs	2,910.13 (SD 3601.24)	2,200.9 (SD 1603.03)	-709.23	2,910.61	-	-	-	-	-
Costs in other sectors									
Lost productivity costs[b]	328.39 (SD 800.67)	212.46 (SD 391.53)	-115.93	-	-	-	-	-	-
Total costs	3,238.52	2,463.03	-775.49	2,910.61	2,235.51	3,307.39	3,223.48	2,504.47	2,325.94

[a] *QALY* Quality Adjusted Life Year.

[b] Also includes costs for informal care (part of the patient and family costs).

2%. Using the individual mean imputation method, the cost-effectiveness probabilities of NightWatch decreased to 46%. This method resulted in higher caregivers' stress levels (8.02 vs. 7.11) and higher costs (3223 vs. 2463) during the intervention period, compared to the mean imputation method. By removing incomplete cases cost-effectiveness probabilities of NightWatch decreased to 33%. This method resulted in lower caregivers' stress levels (7.00 vs. 8.02) during the baseline period and higher stress levels (8.02 vs. 7.11) during the intervention period, compared to the mean imputation method. Also, costs decreased (2504 vs. 3238) during the baseline period using this method. From both a societal perspective and a healthcare perspective, most of the savings occur in healthcare costs (i.e., €659).

DISCUSSION

Study findings

Our cost-utility and cost-effectiveness analysis suggests that a two-months intervention with NightWatch saves costs, reduces stress, and is equally effective in terms of QALYs, compared to usual care without an SDD.

Generalisability

We could not compare our results directly to others, as comparable studies are lacking. Some reports of the impact of wearables on caregivers' HR-QoL are available.[18, 19] The caregiver burden scores from our study (mean QALY 0.90) were similar to the previously reported EQ-5D-5L scores of 86 caregivers of children with epilepsy (mean QALY 0.88).[18] Another cross-sectional survey study examined the relation between SDD use and HR-QoL in 371 people with epilepsy and their caregivers.[19] Compared with non-users, SDD users were significantly more likely to have been impacted by epilepsy in multiple HR-QoL domains. 80% of caregivers using an SDD (20% of total) reported a reduction in anxiety following SDD deployment. Of note, the SDD usage tended to be skewed toward younger age, and caregivers with higher income, reflecting health care inequality. In-depth interviews with caregivers from the PROMISE study revealed that the amount of assurance NightWatch could offer, strongly depended on the ability to reduce their protective behavior as well as their resilience to handle the potential extra burden of care (e.g., due to false alarms or technical problems).[20] The total price of NightWatch (€1500) is on the higher end of the spectrum compared to other SDDs. Yet, according to recently published standards, NightWatch' level of performance evidence is relatively

high, and validation in adults support accurate detection of major nocturnal motor seizures.[5] Due to the wide variation in study designs, it is, however, hard to compare performances and estimate cost-effectiveness of other devices.[3]

Limitations

The high probability of NightWatch being cost-effective (72%) found in our study might encourage NightWatch implementation. These results should, however, be interpreted with caution due to the small sample size and short time period. The cost-effectiveness of NightWatch was mainly due to the decrease in costs during the intervention, while effects on stress and QoL were less pronounced. Alternatively, the NightWatch is already manifesting its potential positive impact within this time frame but may be outweighed by alarm fatigue, thus resulting in unaltered levels of parental stress and QALY's. Although the EQ-5D5L is an extensively validated questionnaire often used for the assessment of QoL in health technology assessment studies, it might not be discriminative enough to measure an effect in our study. The relatively small sample size might be another explanation for the lack of gain in QoL found in this study. Also, within this short time horizon it is uncertain whether the potential costs associated with the seizures are accurately captured. Another important unknown is the long-term retention rate (due to alarm fatigue) and the impact of NightWatch on SUDEP prevention, as this could significantly affect the cost-effectiveness. We speculate that alarm fatigue may vary over time particularly in periods with high parental care burden.[20] We lack prospective long-term data to monitor the impact of NightWatch or any other SDD on survival. A retrospective analysis in two residential units demonstrated that the center with the lowest grade of supervision had the highest incidence of SUDEP.[3] The significant contrast between sites was due to a central acoustic system, with only a minority of participants using additional SDDs. More economic evaluations on different SDDs could be helpful to get more insight in probabilities to improve the financial accessibility to SDDs. The overall burden for caregivers of children with epilepsy cannot be fully alleviated, but the use of SDDs such as NightWatch could decrease the burden. Another limitation of our short-term evaluation is that we could not study how much medication up titration NightWatch may create. NightWatch implementation may unveil a higher than previously reported seizure frequency and, in turn, impact epilepsy management. Despite these limitations, we found an evident effect in cost-effectiveness during the short time horizon and sensitivity analyses demonstrated result robustness. For further research we suggest to expand the

time horizon and sample size to identify the long-term effects of SDD intervention, like SUDEP, visits the emergency room and alarm fatigue.

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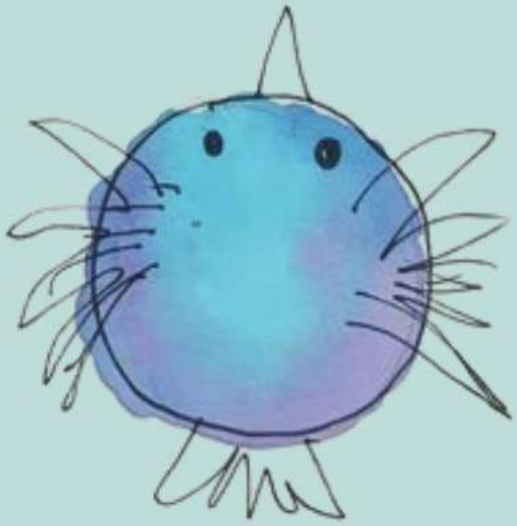

CHAPTER 8

Parental experiences and perspectives on the value of seizure detection while caring for a child with epilepsy: a qualitative study

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ABSTRACT

Introduction

Caring for a child with epilepsy has a significant impact on parental quality of life. Seizure unpredictability and complications, including sudden unexpected death in epilepsy (SUDEP), may cause high parental stress and increased anxiety. Nocturnal supervision with seizure detection devices may lower SUDEP risk and decrease parental burden of seizure monitoring, but little is known about their added value in family homes.

Methods

We conducted semi-structured in-depth interviews with parents of children with refractory epilepsy participating in the PROMISE trial (NCT03909984) to explore the value of seizure detection in the daily care of their child. Children were aged 4-16 years, treated at a tertiary epilepsy center, had at least one nocturnal major motor seizure per week, and used a wearable seizure detection device (NightWatch) for two months at home. Data were analyzed using inductive thematic analysis.

Results

Twenty-three parents of nineteen children with refractory epilepsy were interviewed. All parents expressed their fear of missing a large seizure and the possible consequences of not intervening in time. Some parents felt the threat of child loss during every seizure, while others thought about it from time to time. The fear could fluctuate over time, mainly associated with fluctuations of seizure frequency. Most parents described how they developed a protective behavior, driven by this fear. The way parents handled the care of their child and experienced the burden of care influenced their perceptions on the added value of NightWatch. The experienced value of NightWatch depended on the amount of assurance it could offer to reduce their fear and the associated protective behavior as well as their resilience to handle the potential extra burden of care, due to false alarms or technical problems.

Conclusions

Healthcare professionals and device companies should be aware of parental protective behavior and the high parental burden of care and develop tailored strategies to optimize seizure detection device care.

INTRODUCTION

Parents* of children with epilepsy are confronted with many complex and demanding caregiving situations. They have to cope with the unpredictability of seizure occurrence, potential complications including hospitalizations, and uncertain long-term outcome. Additionally, their children may experience developmental delays caused by seizures or the underlying brain disorder.[1] Varying degrees of cognitive and physical impairment may coincide with epilepsy, ranging from mild behavioral problems to complete dependency on parental caregiving. Caring for a child with epilepsy is associated with higher rates of parental stress, anxiety, and depression.[2, 3] Parents of children with epilepsy experience compromised quality of life (QoL), influenced mainly by psychological variables (i.e., parental stress response to the child's epilepsy) rather than disease-related ones.[4, 5]

Epileptic seizures may present danger as the result of traumatic falls, injuries and status epilepticus. Yet, the greatest fear of parents caring for a child with epilepsy is the fear of losing their child. Sudden unexpected death in epilepsy (SUDEP) has an estimated incidence of around 1 per 1000 person-years for children < 16 years.[6] Convulsive seizures, especially if nocturnal and unwitnessed, pose the highest SUDEP risk.[7-9] Conversely, SUDEP risk can be decreased by measures to prevent convulsive seizures (e.g., optimizing treatments and encouraging adherence) and also possibly by intensifying nocturnal supervision in those who experience seizures arising from sleep.[7, 10] It is suggested that nocturnal supervision helps to prevent SUDEP by enabling caregivers to intervene.[7, 11] In addition to parental surveillance, seizure detection devices (SDDs) may lead to the recognition of otherwise unwitnessed events and help to improve treatment and reduce SUDEP risk.[12] NightWatch is a wearable SDD assessing heart rate and movement to alarm for nocturnal major motor seizures.[13] Prospective validation of this device in 28 adults living in a residential care setting showed a median sensitivity of 86% and a median false alarm rate of 0.25 per night.[13] Devices like NightWatch may enhance parental QoL by decreasing the burden of seizure monitoring.[14] Little is known about the overall burden for parents and how SDDs impact family life. We aimed to explore parent experiences caring for a child with epilepsy and their perspectives on the value of seizure detection in daily care.

* 'Parents' does not only refer to biological parents, but any informal caregiver or legal representative structurally involved in caring for the child with epilepsy.

METHODS

We conducted a qualitative study exploring parent experiences and perspectives on the value of seizure detection while caring for a child with epilepsy in semi-structured interviews, analyzed using inductive thematic analysis.[15] We used the Consolidated Criteria for Reporting Qualitative Studies (COREQ) for our methods and reporting.[16]

Sample

This study was part of a more extensive prospective multicenter home-based implementation study: the PROMISE trial (NCT03909984). The PROMISE trial included 60 children with refractory epilepsy for a two-month intervention with nocturnal NightWatch usage in the home environment. LivAssured, the company developing the NightWatch device, provided the devices and equipment used in the study. The company had no role in the study design, analysis, or decision to submit for publication.

Children aged 4-16 years with epilepsy were evaluated for eligibility by their treating pediatric neurologist at three tertiary epilepsy centers in the Netherlands (SEIN, University Medical Center Utrecht and Kempenhaeghe). The children had to live at home and had at least one weekly nocturnal motor seizure. We excluded those with conditions that may generate false alarms such as intense nonepileptic movement patterns, minor motor seizures only (i.e., non-generalized or <10 s), or a pacemaker or cardiac arrhythmias. The Research Ethics Committee of University Medical Center Utrecht approved the study (NL62995.041.17). Between November 2018 and June 2020, we consecutively sampled Dutch-speaking parents who participated in the PROMISE trial and gave informed consent for an interview. We aimed for maximum variation in gender and to include both parents.

Data collection

The semi-structured, in-depth interviews were conducted by two qualified researchers (AvW and WdL). AvW also coordinated the home-based measurements in the PROMISE trial. Neither researcher was involved in the child's treatment.

We extracted background information on children and parents from the PROMISE database. We planned to conduct five pre-intervention interviews focusing on parent expectations of NightWatch and fifteen post-intervention interviews focusing on parent experiences. The interviews were held just before

or immediately after the intervention period to warrant an optimal recall. We conducted the interviews at the parents' home, to create a comfortable environment. During the COVID-19 pandemic, the PROMISE study continued with extra precautions and limited visits. We therefore switched to online interviews for safety reasons. The first interviews were guided by a topic list based on literature and expert knowledge, including the following feasibility items: implementation (i.e., the 'fit' of the device into the care situation of the child), demand (i.e., actual device usage and parental needs for a device), acceptability (i.e., satisfaction about the device), practicality (i.e., the value of the device in caring for the child), and integration (i.e., integration in their family and medical situation).[17] The list was further adjusted throughout the course, guided by the results from the preliminary analysis. The following topics were additionally supplemented: the burden of care, changes in burden and needs over time, and the added value of NightWatch. The exact number of interviews depended on code saturation (i.e., additional interviews do not further change conclusions).[18, 19]

Data analysis

Interviews were audiotaped with permission, transcribed verbatim, and analyzed using the software program NVivo (QSR International Pty Ltd. Version 12 Pro, 2018). We used an inductive thematic analysis with methods to ensure reliability and validity.[14, 15, 17-19] The data analysis was supervised by a senior researcher (MK), who read several transcripts to validate the results and guided the coding process. MK is an experienced qualitative researcher at UMCU with expertise in researching parents caring for a child with a life-limiting condition. We analyzed the data in batches of about five interviews. Two researchers (WdL and AvW) read the transcripts thoroughly to get familiar with the data. Subsequently, they identified and coded relevant parts of the data independently, drawing conclusions from what they observed in the complete interview. During joint meetings, all codes were compared, some initial interpretations were reconsidered, and some similar codes were merged, to reach consensus on drawn conclusions, and establish researcher triangulation. Using the constant comparative method, the coded data were continuously compared with newly collected data and grouped to form categories on a more abstract and conceptual level.[15] These categories were checked against new raw data. Code saturation was reached when no new categories or themes emerged from the new raw data. The final themes were used to describe the parent experiences

Table 1A Characteristics of participants: children

Case	Type of caregiver/ sex	Child						
		Age/ Sex	Age of epilepsy onset	Years with epilepsy	Intellectual disability	Epilepsy etiology	Type of seizures	Course of epilepsy[a]
1	Parent/ F	5/F	7 months	4.5	Yes	Structural	FOIA: FBTC, tonic, atonic and epileptic spasms	Stable[b]
2	Parent/ F	10/M	1 year	9	Yes	Structural genetic	(multi)FOIA: FBTC, tonic, myoclonic	Erratic
3	Legal representative/ F	9/M	Neonatal	9	Yes	Structural, traumatic	FOIA: Tonic-clonic, tonic, atonic and myoclonic	Stable
4	Parent/ F	16/M	Neonatal	16	Yes	Genetic	Generalized tonic-clonic	Stable
5	Parent/ F	7/M	8 months	6.5	Mild	Structural	FOIA: tonic	Stable
6	Legal representative/ F	10/F	2 years	8	Yes	Unknown	Tonic-clonic, tonic, absences	Stable
7	Parents/ F + M	14/M	2 years	12	Yes	Genetic	Generalized tonic-clonic, tonic, atonic, absences	Erratic
8	Parent/ F	13/F	5 years	8	No	Structural	FOIA: Tonic	Stable
9	Parents/ F + M	6/M	2 years	4	Mild	Unknown	Tonic-clonic, atonic	Erratic with cognitive decline
10	Parent/ F	7/F	5 years	2	Yes	Genetic	Generalized tonic-clonic	Stable
11	Parent/ F	12/F	Neonatal	12	Yes	Genetic	Generalized tonic, atonic	Erratic
12	Parent/ M	14/M	4 Years	10	Yes	Unknown	FOIA: FBTC	Erratic
13	Parents/ F + M	12/M	1 year	11	Yes	Genetic	Generalized tonic	Stable
14	Parent/ F	6/F	4 years	2	No	Unknown	Generalized tonic-clonic, tonic, absences	Stable
15	Parents/ F + M	11/M	3 months	11	Mild	Structural genetic	FOIA: tonic	Erratic with cognitive decline
16	Parent/ F	10/M	3 years	7	Mild	Unknown	FOIA: FBTC	Stable
17	Parent/ F	10/F	4 years	6	No	Unknown	Tonic-clonic, absences	Erratic
18	Parent/ F	16/F	14 years	2	Yes	Genetic	Generalized tonic-clonic	Erratic
19	Parent/ M	5/F	3 years	2	Yes	Genetic	FOIA: FBTC, tonic, atonic	Stable

F female, *FBTC* focal to bilateral tonic-clonic, *FOIA* focal onset with impaired awareness, *M* male.

[a]As experienced by the caregiver at the moment of the interview.

[b]A stable course of epilepsy is defined as a course with a stable seizure frequency, either high or low.

Table 1B Characteristics of participants: caregivers

Case	Respondent		Family composition	Siblings	Educational level respondent 1	Work situation respondent 1
	1: Age/sex	2: Age/sex				
1	36/F		Biological parents	0	Secondary vocational education	Part-time, irregular shifts
2	41/F		Biological parents	2	Secondary vocational education	Unemployed, caring for child
3	40/F		Legal representatives	2	Secondary vocational education	Part-time
4	45/F		Biological parents	3	Secondary vocational education	Part-time
5	40/F		Biological parents	3	Secondary vocational education	Part-time
6	35/F		Single legal representative	1	Secondary vocational education	Part-time
7	57/M	53/F	Biological parents	1	Secondary vocational education	Unemployed, housewife
8	39/F		Biological parents	3	Primary education	Unemployed, housewife
9	47/F	46/M	Biological parents	1	Secondary vocational education	Full-time
10	32/F		Combined family	1	Secondary vocational education	Part-time
11	40/F		Combined family	4	Secondary vocational education	Part-time
12	52/F		Biological parents	2	Secondary vocational education	Both unemployed, parents choose to take care of their children
13	37/F	41/M	Biological parents	1	Secondary vocational education	Part-time
14	34/F		Combined family	2	Secondary vocational education	Part-time
15	42/F	47/M	Biological parents	3	Secondary vocational education	Part-time
16	50/F		Biological parents	2	Secondary vocational education	Part-time
17	41/F		Biological parents	2	Secondary vocational education	Part-time
18	49/F		Single biological parent	1	Secondary vocational education	Part-time
19	44/M		Biological parents	2	Secondary vocational education	Part-time

F female, *M*: male.

and perspectives on the value of seizure detection while caring for a child with epilepsy.

RESULTS

The parents of 42 of 60 PROMISE participants consented to the semi-structured in-depth interviews. We included 23 respondents: fifteen mothers, six fathers, and two female legal representatives (mean age 43.0 ± 6.4 years) of nineteen cases (Table 1). 21 Interviews were completed, five before and sixteen after the NightWatch intervention, including two repeated interviews and four interviews with both biological parents. The first fourteen interviews took place in the home environment, and the last seven via video calls, due to the COVID-19 pandemic. The children with epilepsy had a mean age of 10.2 ± 3.5 years, had an average epilepsy duration of 7.7 ± 4.2 years, and 63% had severe intellectual disability (Table 1A). In some children the seizure frequency was stable during the intervention (n = 11), while others experienced an erratic course (n = 8), with increased seizure frequency, and some had a cognitive decline (n = 2). For most the two biological parents were present, with an average of two siblings. Some combined families and legal representatives were included. The majority of parents worked part-time. Many had adjusted their work hours to take care of their child, and some had stopped working completely (Table 1B).
The interviews indicated that the fear of losing a child encouraged parents to develop a particular protective behavior. We learned that this behavior helped them reduce fears, yet it could also increase their burden of care. The way parents handled their child's care influenced their perception of the care burden, affecting their fears and protective behavior. The experienced value of NightWatch was dependent on the amount of assurance it could add to their existing protective behavior, and their resilience to handle the potential extra burden of care, due to false alarms or technical problems (Fig. 1).

Fearing child loss

All parents expressed fears of missing a ''big", potentially dangerous seizure and the possible consequences if they could not intervene in time (Table 2, quote 1A). The fear of losing their child was presented to varying degrees; some parents felt the threat at every seizure (Table 2, quote 1B), while others thought about it from time to time (Table 2, quote 1C). Parents also emphasized their anxieties of not being present to help when their child needed them (Table 2, quote 1D). The fear of child loss varies over time and often seemed

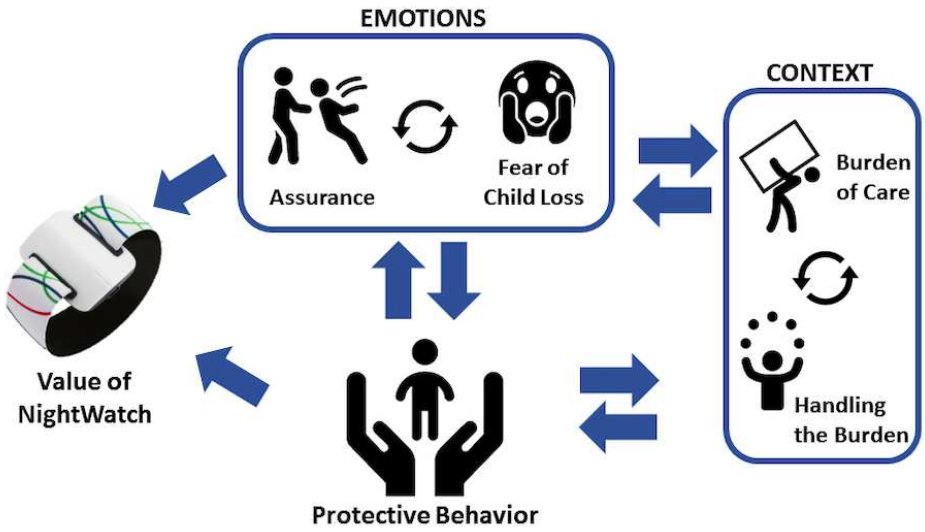

Figure 1 Schematic overview of most important themes describing parental experiences and perspectives on the value of seizure detection while caring for a child with epilepsy.

associated with fluctuations of seizure frequency. A decrease in seizure frequency could ensure that things would get better and lower the level of anxiety. In some cases, this was the other way around; the longer period without a seizure, the more watchful parents got, scared of a seizure soon to happen (Table 2, quote 1E). Some parents, however, were continually aware of potentially risky situations due to the unpredictability of seizures (Table 2, quote 1F). Even a silent night could frighten some parents because it could soon get too quiet (Table 2, quote 1G).

Protecting your child

From the parent stories, it became clear that all parents felt a strong need to protect their child. Most parents emphasized that this need was more significant than toward other siblings (Table 3, quote 2A). Presumably driven by the anxiety of child loss, parents developed specific strategies to protect their child. The goal of this ‘‘protective behavior” was to prevent any harm to the child. Almost all parents indicated that they had to keep an eye on their child constantly during the day due to seizures’ unpredictability (Table 3, quote 2B). At night, various measures were taken, from sleeping in the same room as their child, or even in the same bed (Table 3, quote 2C), to sleeping on the couch with a camera (Table 3, quote 2D) and staying awake all night (Table 3,

Table 2 Illustrative quotes for the theme: Fearing child loss + **Table 3** Illustrative quotes for the theme: Protecting your child

Quote	
1A	Case 1: Girl, 5 years, ID. Mother: *Well, you see, she usually recovers spontaneously from those small seizures. But I am terrified that one day she will get a big seizure, that gives her breathing problems and that I miss it. That I don't hear her. And then she dies.*
1B	Case 15: Boy, 11 years, MID. Mother: *The most intensive part is to see my child having a seizure […] every time I see it, I have a feeling as if I am going to lose him. And that feeling never passes.*
1C	Case 3: Boy, 9 years, ID. Legal representative: *The risk that you will miss something and it really goes wrong, is of course, out there. And it is not something you reflect on daily, but you think about it from time to time: what if you really miss a seizure and he does not recover spontaneously? I mean, two children died that way at his school….*
1D	Case 13: Boy, 12 years, ID. Father: *[…] but the last time, it took at least a few hours Before he recovered in the hospital. So, imagine that this would have happened at night and we would have missed it. […] that would have been very difficult.*
1E	Case 17: Girl, 10 years, NID. Mother: *It remains frightening […] Especially when she didn't have a seizure for several days, you know it's going to happen soon…*
1F	Case 17: Girl, 10 years, NID. Mother: *All the time it's in your head: oh girl, where are you? [..] two months ago, she fell backwards from the stairs […] she just has to pull that pan off the heat… […] she only has to hit her head on the bathtub …*
1G	Case 18: Girl, 16 years, ID. Mother: *And when I thought: now she lies very quiet, then I Will have a look to see: do I still hear her breathing?*
2A	Case 5: Boy, 7 years, MID. Mother: *With Tom we are extra attentive. Because he is just a bit different, so we are extra alert. Especially me, being a mother… We are more alert with him, with everything.*
2B	Case 17: Girl, 10 years, NID. Mother: *The past three months in lockdown were very intense for me. All the time I was listening: "What are you doing? Do I still hear something?"*
2C	Case 19: Girl, 5 years, ID. Father: *The moment we go to bed, she comes to lie between us and then we put one of our hands on her body, so in case we fall asleep and she has a seizure, we can feel it.*
2D	Case 10: Girl, 7 years, ID. Mother: *When she has many seizures, I usually don't sleep in my bed. Sophie sleeps downstairs, so I will go lay on the couch with the baby monitor with camera.*
2E	Case 8: Girl, 13 years, NID. Mother: *I couldn't sleep when she had many seizures, so I stayed here, awake in the living room until 5 am and I slept during the day.*
2F	Case 17: Girl, 10 years, NID. Mother: *She is sleeping in another room, but since she has the big seizures, we keep the doors open, so we can hear her. I often lie awake in bed to listen: is she still there?*
2G	Case 6: Girl, 10 years, ID. Legal representative: *I have a video camera on my baby monitor. This is connected to an app on my mobile phone, so I can watch her. When a babysitter is watching her and she has a seizure, and the babysitter is insecure, I can watch from a distance. That gives me a safe feeling.*
2H	Case 18: Girl, 16 years, ID. Mother: *She constantly needs someone around, not because of her seizures, but because she can't recognise dangerous situations.*

ID Intellectual Disability, *MID* Mild Intellectual Disability, *NID* No Intellectual Disability.
Some quotes are slightly modified to improve readability. Names are fictitious.

Table 4 Illustrative quotes for the theme: Handling the burden of care

Quote	
3A	Case 10: Girl, 7 years, ID. Mother: *It is hard to find a moment for yourself, to reboot, to do fun stuff. That is easily postponed, because you only have time to do the things you must do.*
3B	Case 2: Boy, 10 years, ID. Mother: *Most of the time I take care of him. I had no night's rest. Sometimes, he had a seizure in the morning, and it didn't feel good to go to work, so eventually I decided to quit my job.*
3C	Case 7: Boy, 14 years, ID. Mother: *Caring for him is a heavy burden. Everybody asks me: Is it not too heavy? And I answer: If I bring him to daycare five days a week, I will even get worse nights with him, because he can't handle all the commotion over there.*
3D	Case 14: Girl, 6 years old, NID. Mother: *[…] All sorts of things, personal budget, transportation. Because I take Anne to school myself, this causes a bizarre administrative load as well.*
3E	Case 15: Boy, 11 years, MID. Mother: *I think the psychological burden is heavier than a disrupted night's rest.*
3F	Case 15: Boy, 11 years, MID. Mother: *You might think that the feeling wears out if you have seen so many seizures from which he always recovers, but every time it gives me the sense that it is not right […] And also the uncertainty: what will this mean for his future?*
3G	Case 9: Boy, 6 years, MID. Mother: *The worst part is of course, that he is cognitively behind. Very slowly, we see him decline, and that is painful to watch.*
3H	Case 7: Boy, 14 years, ID. Father: *We notice that the care is getting heavier. So, it will not be possible to keep him at home for a long period. We are both convinced of that.* Mother: *And we are planning to set up our own house of care. […] Because John doesn't fit into a home with six to eight children, he will get way to overstimulated. […] He needs one-on-one care, that is really needed.*
3I	Case 9: Boy, 6 years, MID. Father: *I would like to know everything that is happing during the night. Even if it is exhausting and a burden, I would still like to know what is happening.*
3J	Case 17: Girl, 10 years, NID. Mother: *There are two sides to the coin: on the one hand, we must continue looking for something that might help her. On the other hand, I should not let it drive me crazy. I cannot let myself go down with it because I am certainly of no use for her.*
3K	Case 3: Boy, 9 years, ID. Legal representative: *Eventually, you sort of get used to it. If others see or hear what we experience, they think: … so many seizures. And we think, well… for us this is our reality, so to say.*
3L	Case 1: Girl, 5 years, ID. Mother: *He (husband) sleeps better than me and I think, as a man, you may experience it differently. He is less bothered by nightly fears, of course he is also scared, but we experience it differently.*

ID Intellectual Disability, *MID* Mild Intellectual Disability, *NID* No Intellectual Disability.
Some quotes are slightly modified to improve readability. Names are fictitious.

quote 2E). Some parents kept the bedroom doors open (Table 3, quote 2F), or installed monitoring devices (e.g., baby monitors with audio and/or camera facilities) in their child's bedroom. Sometimes parents used monitoring devices to watch from a distance when someone else watched their child (Table 3, quote 2G). Parents of children with intellectual disability mentioned that their child's behavior often led to unsafe situations, which demanded extra alertness (Table 3, quote 2H). All these strategies often had a significant impact on the parent night's rest and their whole life.

Handling the care of their child

Parents experienced a significant burden of care, caused by their child's specific needs and amplified by their fear of child loss and their developed protective behavior. This protective behavior often reduced parental anxiety, but it increased their burden of care in many cases. Their protective behavior resulted in constant alertness and broken nights, which significantly impacted their lives. Parents made many adjustments to provide optimal care, from downsizing their social life (Table 4, quote 3A) to quitting their job (Table 4, quote 3B). Some parents stated that they were the only ones that could deliver good care for their child and that it was hard to outsource care (Table 4, quote 3C). Additionally, many parents emphasized the extra burden of organizing all the care regulations (e.g., transportation, special adjustments in the house; Table 4, quote 3D). From the most recent interviews, it became clear that the COVID-19 pandemic aggravated the burden of care as day-care and daily structure for the child were suddenly lost.

Apart from the burden caused by their protective behavior, the anxiety of child loss also strongly affected the parental burden of care. The psychological burden seemed heavier for many parents than the physical one (Table 4, quote 3E). This psychological component also concerned parental struggle with the unpredictability of seizures and the uncertainty about their child's wellbeing in the future (Table 4, quote 3F). Parents of children without intellectual disability were worried about how epilepsy would affect their child's development. Some described that it was painful to watch their child's cognitive decline (Table 4, quote 3G). Conversely, parents of children with severe intellectual disability from a young age were mainly worried about the question of where their child would live if they could no longer keep care at home (Table 4, quote 3H). The way parents handled the care of their child varied greatly and seemed independent of the course of epilepsy (i.e., stable or erratic). In two cases of cognitive decline, however, there was a strong urge for parents to control the

situation. One family tried to regain control by monitoring every aspect of their child's life, even though this increased their burden (Table 4, quote 3I). Other parents stated that they were constantly trying to balance ''being there to protect the child" and ''keeping yourself standing" because if they let themselves fall, they would be of no use for their child (Table 4, quote 3 J). Some parents seemed to be used to the situation on the other end of the spectrum and explained that they had adapted to a ''new reality" (Table 4, quote 3K). Handling the care of their child could also differ between the mother and father (Table 4, quote 3L).

Valuing NightWatch

NightWatch was valued differently, depending on parental anxiety and their own developed protective behavior. Pre-intervention interviews suggested that parents were interested in using NightWatch, and several felt that the NightWatch would show promising results (Table 5, quote 4A). For many parents, NightWatch provided an extra backup, so they could let go and get their sleep back (Table 5, quote 4B). In some cases, NightWatch immediately provided relief (Table 5, quote 4C). In contrast, others emphasized that NightWatch could add extra support but would not suddenly relieve their anxiety or relax the domestic scenario (Table 5, quote 4D). It appeared that the value of NightWatch was not only linked to its detection performance but more associated with parents' flexibility in their routine to adjust to a new device. One mother described that she could not exchange her old device for NightWatch, even though it had better performance for seizure detection as she was so used to the old, and changing would be too much of a hassle (Table 5, quote 4E). Parents often experienced such a high burden of care that there was no or only a little flexibility in adjusting their daily routine, including their protective behavior.

As a fluctuating course often characterizes epilepsy, parental needs for an SDD could also change over time (Table 5, quote 4F). Parents expressed their possible future need for NightWatch if seizure type would change (Table 5, quote 4G) or the seizure-related shout that always woke them up would disappear (Table 5, quote 4H). Some parents mentioned that it would be nice to use NightWatch only during changes in anti-seizure medication so that leasing options could be convenient (Table 5, quote 4I). The investment for continuous NightWatch usage, financially and personally (i.e., the burden of changing daily routine and possible false alarms) was too high for some parents (Table 5,

Table 5 Illustrative quotes for the theme: Valuing NightWatch

Quote	
4A	Case 3: Boy, 9 years, ID. Legal representative: *Well, I read different things about NightWatch, and they were all positive. So, I expect a positive result.*
4B	Case 10: Girl, 7 years, ID. Mother: *What NightWatch adds? For me, that piece of backup, that I'm not alone watching her. What if I do fall asleep, it is okay.*
4C	Case 17: Girl, 10 years, NID. Mother: *The device immediately gave me peace, although I didn't have the confirmation, yet that NightWatch would alert for her convulsions.*
4D	Case 13: Boy, 12 years, ID. Father: *For us it's an extra support. But that doesn't mean that we are suddenly relaxed and our sleep is improved. That is just not possible.*
4E	Case 16: Boy, 10 years, MID. Mother: *It's quite a nice device, but for us it didn't have any added value. We already have another device, and we are used to that, it is quite a hassle to change to a new system.*
3F	Case 8: Girl, 13 years, NID. Mother: *At the moment she doesn't have any seizures, so we don't need the NightWatch. Maybe in the future. Back in the days, I really needed this device.*
4G	Case 19: Girl, 5 years, ID. Father: *In the current situation NightWatch is not adding value. But she just changed her anti-seizure medication, so maybe the seizures will change too and then we are going to need the device badly.*
4H	Case 15: Boy, 11 years, MID. Mother: *No, we don't want to keep using NightWatch, because he always screams, so we respond faster to the sound from the baby monitor. […] If his seizures would change, NightWatch would definitely be a good option.*
4I	Case 18: Girl, 16 years, ID. Mother: *Yes, I think renting the system could provide a nice solution for parents in times their child has to adjust to medication changes.*
4J	Case 11: Girl, 12 years, ID. Mother: *I also have all the regular house costs and I don't have a money tree in the backyard. It is quite an amount for a device, something I must consider at least three times: is it really worth it?*
4K	Case 15: Boy, 11 years, MID. Mother: *It would be helpful for us if NightWatch could be extended with a sensor for sound. Because it's way nicer to wake up by the sound of an alarm than the scream of your child.*
4L	Case 14: Girl, 6 years, NID. Mother: *The short power cord limits the range of the system, yes, that was the biggest problem. It would be nice to have a detection system which enables me to sit outside in the summer, while monitoring my child.*
4M	Case 7: Boy, 14 years, ID. Mother: *All those "technical alarms", it would be better if they could be turned off, because they drove me crazy.*
4N	Case 9: Boy, 6 years, MID. Father: *Those heart rate graphs really give us a nice insight and overview of what's happening during the night. I immediately took a picture of it and sent it to his neurologist to show: look, it's not going well.*
4O	Case 19: Girl, 5 years, ID. Father: *I would say: rather 20 times too much than one seizure missed.*
4P	Case 8: Girl, 13 years, NID. Mother: *You trust the device will give an alarm during a seizure, so any false alarm is no problem for me.*
4Q	Case 12: Boy, 14 years, ID. Father: *Okay, if there was one false alarm per week, that would have been acceptable. […] But there were too many if it starts beeping for nothing, for me that's worse than alerting too late or not at all.*

ID Intellectual Disability, *MID* Mild Intellectual Disability, *NID* No Intellectual Disability.
Some quotes are slightly modified to improve readability. Names are fictitious.

quote 4J). Especially in periods with low seizure frequency, this investment did not outweigh the low risk of missing a seizure; thus the course of epilepsy impacted parental needs.

Other parents emphasized the importance to adjust the device to their situation, e.g., by adding an audio sensor (Table 5, quote 4K), extend the range of the base station (Table 5, quote 4L), or turn off the sound of the ‘‘technical notifications” (Table 5, quote 4M). Providing insight and an overview of the night to share with the neurologist was stated by some parents as motivation to use NightWatch (Table 5, quote 4N).

There was significant variation in the acceptance of false alarms; most parents preferred false alarms over missed seizures (Table 5, quote 4O), but the number of false alarms outweighing missed seizure varied. This seemed to be mainly dependent on how parents handled care and experienced their care burden. Some parents were not concerned by false alarms, as long as the device would also alert them for a seizure (Table 5, quote 4P), while others stated that a high number of false alarms turned out to be worse than missing a seizure (Table 5, quote 4Q).

DISCUSSION

Driven by the fear of child loss, parents of children with epilepsy developed a personal protective behavior toward their child. This behavior could help parents to feel in control of their circumstances and decrease their fear. Conversely, monitoring every aspect of their child’s life could also increase the burden of care, with feelings of losing control, which leads to a vicious circle. Parents felt a great responsibility to protect their child and often had difficulties handing over the care due to their child’s specific needs. This responsibility further increased their burden of care, which may complicate the use of NightWatch. The extent to which NightWatch could support the family’s home circumstances depended mainly on the flexibility in the parents’ existing protective behavior. The way parents handled the care of their child and experienced the burden of care influenced their perceptions of the added value of NightWatch.

Symptoms of anxiety in parents of children with epilepsy were previously reported.[3, 20] Still, our results complement these findings by illustrating what parents are afraid of and how this influences their behavior. We established that parental anxiety fluctuates over time alongside the changing seizure frequency, but it was not always related to changes in seizure frequency. Some parents

experienced a constant fear. A recent study assessing parents of children with epilepsy also suggested that parental anxiety and depression were not only correlated to epilepsy-related factors but also to parental resources (i.e., available tools to handle stressful situations) and the child's degree of behavioral difficulties.[21]

Our results show that parents felt a strong responsibility to protect their child, which was influenced by their child's behavior and specific needs. This protective behavior is also seen in other qualitative studies on parents of children with different chronic or life-limiting conditions.[22-24] Parents described their caregiving role as the 'protector', encompassing holding all knowledge of the child's unique needs and the complete responsibility of caring for the child,[22] and the 'guard' to watch over and protect their child.[23] Parents of children receiving palliative care at home explained how they decided to protect their child maximally and how this protective behavior increased their workload.[24] Taking control as the protector requires extra effort and relieves parental stress as care will be arranged the way they prefer it.[25] Our study has also shown how protective behavior can influence the parental burden of care in both directions and confirms that this burden could be divided into a physical (i.e., constant alertness, organizing the care) and a psychological component (i.e., worries about the future). The parenting and childhood chronicity (PACC) model, based on interviews with parents, describes several features of the work required to raise a child with a chronic health condition.[26] Many of these components were also recognized in our study, including ''parenting plus" (i.e., compensating for the child's delayed skills), ''working the systems" (i.e., working with the health, social service, and education systems for their child) and ''keeping yourself going". The latter describes how parents often felt they had no choice but to keep on going, driven by their commitment to do everything they could to help their child.[26] This specific drive was also reflected in our interviews. Still, we observed significant variation in how parents handled their child care, from keeping absolute control to balancing the care for their child and themselves and adjusting to reality. These different strategies might reflect different coping styles of parents, which are related to variations in parental QoL.[27]

In many families, NightWatch added value by providing a backup and relieving the burden of seizure monitoring. NightWatch could not, however, take away the fear of child loss. There is limited evidence available on the effect of SDDs on parental fear and their perceived burden of care. The majority of SDD

studies focus on detection performance and do not examine the impact of SDD use on the family. In a cross-sectional survey study on SDDs and health-related QoL, including people with epilepsy and caregivers, most users reported moderate or more significant anxiety reduction after using an SDD.[28] This study, however, did not take into account what other strategies caregivers had developed to handle their anxiety and how this influenced the effect of SDD usage. For the successful use of SDDs it is essential to understand parental needs and flexibility to adjust their routine to a new SDD, and which SDD features can improve their anxiety and QoL. A qualitative study on caregivers' preferences for SDDs, using the context mapping approach, revealed several critical elements for SDD implementation, including the importance of gaining trust in a device and the possibility of personally adjusting device settings for different users.[29] Our results confirm these differences in parental needs for an SDD and add that parental needs can also fluctuate over time. For SDD developers, these inter-and intrapersonal differences in requirements may be challenging when designing a generic device. Another long-term prospective study evaluated the effect of nocturnal monitoring on QoL and sleep of parents of children with newly diagnosed epilepsy with validated questionnaires.[30] Families decided whether or not to use a device at the start of the study, and the ones who choose to do so, were randomly assigned to a mattress movement sensor or an audio baby monitor. No significant differences were reported in anxiety levels between groups, while QoL and sleep improved in all parents after 5-7 months, irrespective of whether they used a device and which one.[30] This may implicate that newly diagnosed epilepsy has a negative impact on parental QoL and sleep, which gradually stabilizes over time. In our cohort of children with refractory epilepsy, we found that epilepsy still significantly impacted parental QoL and sleep, even years after the diagnosis. Over time, stabilization was influenced mainly by how parents experienced and handled the burden of care and if an SDD could support their circumstances.

Limitations

We included parents of children with refractory epilepsy treated in tertiary centers, participating in the PROMISE study. This may have led to selection bias as most children had severe epilepsy. Additionally, only children with nocturnal major motor seizures were included because NightWatch is designed to detect those seizures only, so the results might not be generalizable to parents of children with other, or less severe, seizure types (e.g., only absences). The informed consent for an interview was given before the intervention period and

was therefore not influenced by the device's detection performance and parent experiences. Most parents agreed to participate in an interview. The sample mainly consisted of native Dutch-speaking parents from all over the country. We aimed to include a balanced number of mothers and fathers, but most responders were mothers, probably because they were the child's primary caregiver. One of the authors who analyzed the data (AvW) was also coordinating the PROMISE trial, which might have induced an interpretation bias.

The COVID-19 pandemic impacted the Netherlands around the beginning of 2020 and caused significant changes in the family's context and interview settings. The burden of care was significantly increased, as children were bound to their homes due to the lockdown, and their familiar daily structure and outsourcing of care was mostly lost. These changes may have impacted the way parents valued NightWatch. Additionally, we were forced to conduct part of the interviews online instead of in the home environment, which could have influenced the parents' responses. Yet, the majority of interviews (14/21) were conducted in the home environment and outside the COVID-19 pandemic.

Implications for practice

We learned that the need for an SDD could fluctuate over time, depending on changes in seizure type or frequency. Additionally, we observed the need to make personalized changes to the device (i.e., changing alarm thresholds). We recommend SDD developers and companies to offer leasing options and the possibility to personalize the device settings, provided that usability and support is warranted. Every person with epilepsy is different and so are their parents. It is an unrealistic expectation to find a device that will fit all, and developers cannot take every specific need into account. It is essential to appreciate these differences and keep an open mind for adjustments to improve implementability.

All parents from our study developed specific strategies to protect their child, which influenced the extent to which NightWatch was beneficial. We recommend that healthcare professionals take full account of the burden of care and the personal protective behavior when discussing SDD implementation.

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CHAPTER 9

Seizure detection devices: Exploring caregivers' needs and wishes

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ABSTRACT

Introduction

User preferences for seizure detection devices (SDDs) have been previously assessed using surveys and interviews, but these have not addressed the latent needs and wishes. Context mapping is an approach in which designers explore users' dreams and fears to anticipate potential future experiences and optimize the product design.

Methods

A generative group session was held using the context mapping approach. Two types of nocturnal SDD users were included: three professional caregivers at a residential care facility and two informal caregivers of children with refractory epilepsy and learning disabilities. Participants were invited to share their personal SDD experiences and briefed to make their needs and wishes explicit. The audiotaped session was transcribed and analyzed together with the collected material using inductive content analysis. The qualitative data was classified by coding the content, grouping codes into categories and themes, and combining those into general statements (abstraction).

Results

‘‘Trust" emerged as the most important theme, entangling various emotional and practical factors that influence caregiver's trust in a device. Caregivers expressed several factors that could help to gain their trust in an SDD, including integration of different modalities, insight on all parameters overnight, personal adjustment of the algorithm, recommendation by a neurologist, and a set-up period. Needs regarding alerting seemed to differ between the two types of caregivers in our study: professional caregivers preferred to be alerted only for potentially dangerous seizures, whereas informal caregivers emphasized the urge to be alerted for every event, thus indicating the need for personal adjustment of SDD settings.

Conclusions

In this explorative study, we identified several key elements for nocturnal SDD implementation including the importance of gaining trust and the possibility to adjust SDD settings for different types of caregivers.

INTRODUCTION

Epilepsy has a major impact on the lives of people and the risks involved pose a heavy burden on people with epilepsy and their caregivers.[1] Epileptic seizures are unpredictable, cause loss of control, and may lead to serious complications, including sudden unexpected death in epilepsy (SUDEP). The most important risk factor for SUDEP is the presence and frequency of convulsive seizures.[2] Sudden unexpected death in epilepsy is predominantly a sleep-related and unwitnessed event.[3-5] Nocturnal supervision may lower the risk of SUDEP.[5, 6] Timely alerts by nocturnal seizure detection devices (SDDs) can prevent such complications and, if accurate, may improve a night's rest. Seizure detection devices develop at a fast pace and designing novel medical products demands critical choices that are partly shaped by personal values.[7, 8] Values from designers and physicians may, however, differ from user's preferences. It is therefore important to avoid fixation on pre-set assumptions about the user or the product.

Previous assessments on users' preferences for SDDs indicated preferences for high accuracy, comfortable, wearable, and non-stigmatizing devices.[9-16] These assessments were predominantly based on surveys and interviews, yet these methods often do not allow for a deeper understanding of user values.[8] Context mapping is a qualitative research method, frequently applied in industrial design, to explore the end user's needs and wishes for a product.[8, 17] User's experiences and examples of interactions with the product are shared in a creative group session to clarify the context of the product. These generative sessions can expose latent wishes and enable designers to fit their product into the lives of the users (Fig. 1).[8] Context mapping has not yet been applied in the development of SDDs but may help to optimize implementability. This study focused on nocturnal SDDs and defined the end-user as the person who receives the device's alarms and responds to them: caregivers of people with epilepsy. We explored their latent needs and wishes using a context mapping approach.

METHODS

To better understand the reasoning behind caregivers' preferences for certain nocturnal SDD features, we used a qualitative research method. A context mapping session creates the ideal setting to elicit emotional responses from the participants. Users' memories, experiences, concerns, and feelings surrounding

the use of a nocturnal SDD were explored with the aim to create context awareness. The study was reviewed by the Medical Research Ethics Committee Utrecht with a waiver of informed consent.

Preliminary mapping

To make pre-set assumptions of the authors explicit, three authors (AW, MB, and RT) were invited to make an individual ‘‘mind-map” based on the following themes: ‘‘nocturnal seizures,” ‘‘seizure detection,” and ‘‘trust.” They were asked to list all associations with these three words which came to their mind, based on their experiences as a neurologist (RT), researcher (AW), and mother of a child with epilepsy (MB). These words and connections of words from different perspectives were used to create a framework for result analysis.

Recruitment

We selected two types of caregivers as end users of nocturnal SDDs: (1) professional caregivers, working with people with epilepsy in a residential care facility, institution, or hospital, and (2) informal caregivers, taking care of a person with epilepsy at home. Participants were selected from a residential care facility (professional caregivers) and through patient groups (informal caregivers). We aimed to select four to six participants, with a balanced number of professional and informal caregivers, to create a group large enough to have

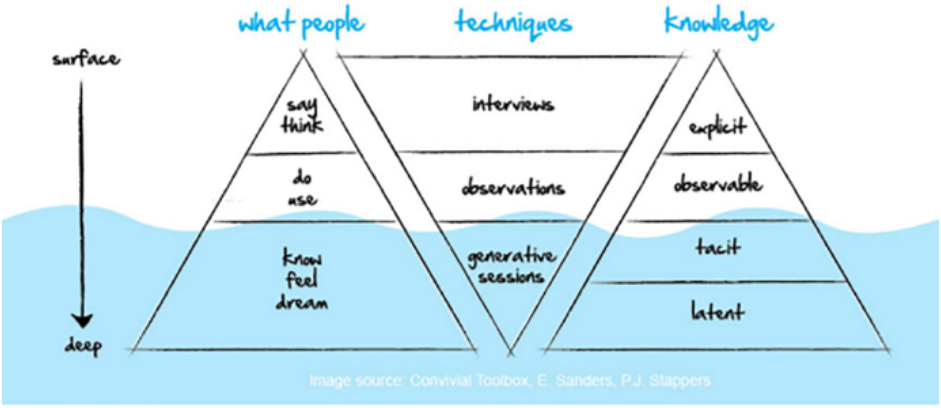

Figure 1 The **latent needs model** represents a schematic overview of different layers of user’s experiences and emotions, and research methods to gain information from these layers*. Image source: Sleeswijk Visser F, Stappers PJ, van der Lugt R, Sanders EBN. Context mapping: Experiences from practice. CoDesign: International Journal of CoCreation in Design and Arts. 2005;1(2):119-149. Reprinted with permission.*

a broad discussion and small enough to maintain a secured atmosphere for participants to share their thoughts and emotions.[8]

Sensitization

A week prior to the generative session participants received a briefing package, aimed to let their minds wonder on the theme ''nocturnal seizure detection." Six different tasks were bundled in a booklet (estimated completion time: two hours) to relive experiences and emotions relating to the monitoring of nocturnal seizures (any type). The following exercises were included:

1) Describe a typical night when using your SDD on the depicted timeline below. What are you doing and what is happening to your child or client? Express positive and negative feelings you experience during these events.
2) Please finish the following sentences: ''This is how I feel when... (1). ...I missed a seizure; (2). ...I am awakened by a seizure; (3). ...I am awakened by a false alarm; (4). ...there is no seizure overnight."
3) ''I am alerted for a nocturnal seizure by means of: ..." Please place a picture or drawing of the devices or methods you use to detect a seizure during the night.
4) How do these devices or methods help you during the night? Please describe positive and negative aspects.
5) Please finish the following sentences: ''I trust a detection method if..." and ''I don't trust a method if..."
6) ''My dream device in 2030 will look like this:..." Please describe different aspects of your ideal device and feel free to draw the device.

Session with caregivers

The participants were invited for a group session to share their experiences and to map their insights and feelings. The session consisted of three parts and was guided by one designer (TS) with considerable experience in context mapping sessions, who stimulated expression of feelings and group discussion, while another author (AW) took notes for the analysis. The total session was also audiotaped. Participants were first asked to present one exercise from the sensitizing package to the whole group. The second part consisted of context mapping. Participants received a large paper with four timelines of different nights: (1) with a seizure; (2) without a seizure; (3) with a false alarm; and (4) with a missed seizure. Different colorful tools were available, together with stimulating words and pictures associated with nocturnal seizures and seizure

detection in its broadest sense, to express experiences and emotions. In the last exercise, participants were asked to express their needs and dreams by crafting their ideal SDD from creative tools for future use in 2030 (Fig. 2).

Analysis

The full audiotaped session was transcribed and analyzed using inductive content analysis.[8, 18] Two authors (AW and TS) reviewed the whole content for interesting quotes and insights. These annotations (highlighted quotes and insights) were openly coded to describe all aspects of the content. The generated codes were clustered using constant comparison and organized to find specific patterns.[18] Lastly, clustered codes were grouped into different themes to create a structured overview of the content. Themes and related quotations described in Results section were selected by the first author (AW), verified by the second author (TS), and checked for relevance by all authors. Each quotation was coded referring to the different caregivers: P1-3 for the professional caregivers and I1-2 for the informal caregivers. The final thematic overview was compared to the thematic structure assembled from the author's preliminary mapping to see if both structures overlapped. In case of great differences, the authors would go back to the raw material to see if important insights had been overlooked.

RESULTS

Participants

We selected five participants for the generative session, including three professional caregivers and two informal caregivers. Professional caregivers worked at ''Stichting Epilepsie Instellingen Nederland," a large residential care facility for people (children and adults) with epilepsy and learning disabilities. They had five to 37 years of work experience in night shifts and all of them had broad experience with different types of nocturnal SDDs. One informal caregiver was mother of a five-year-old child with refractory epilepsy and learning disabilities living at home and had experience with a multimodal nocturnal SDD and a baby monitor with audio and camera facilities. The other informal caregiver was mother of a seven-year-old child with refractory epilepsy and learning disabilities. She had no experience with nocturnal SDDs, her child slept in a bed next to hers, and she used a listening device with camera before she went to bed herself.

Generative session

The generative session lasted 3h and 45m, and the transcript included 73 pages with 35.055 words. After data analysis, different major themes emerged, based on the number of actual quotations of the theme and associated quotes. Table 1 represents an overview of the most quoted themes in the database. The most quoted major themes and related quotations are described in more detail below. The major themes could be grouped into different needs for design and usage of an SDD and wishes related to emotions and purpose of a device. Table 2 represents an overview of these needs and wishes and distinctive examples of caregiver's preferences. The thematic overview generated from the inductive content analysis had great overlap with the structure created from preliminary mapping by the authors, indicating that the most important themes were included.

Table 1 Overview of most quoted needs and wishes

Needs and wishes		No. of quotes
Needs	Alarm	68
	- including false alarm	*20*
	Camera/video/screen	49
Wishes		
Emotions	Trust	51
	Fear	15
	Worry	9
	Sense of control	6
Purpose of device	Night's rest	15
	Safety	9

Trust

''Trust'' emerged as the most coded theme and the most quoted wish from the caregivers. There was overall agreement that ''technology can fail'' and the best monitoring system would be continuous observation by a person. Participants realized that this would not be feasible in practice, as parents need to sleep and professional caregivers have multiple clients to look after. Handing over the care of your child to a device has everything to do with trust. During the session, different factors were mentioned on how to gain trust in an SDD. First, participants stressed the importance of integrating different modalities into one device to increase the trustworthiness. Secondly, the better the insight on all these parameters overnight, the more they would trust it. Participants expressed

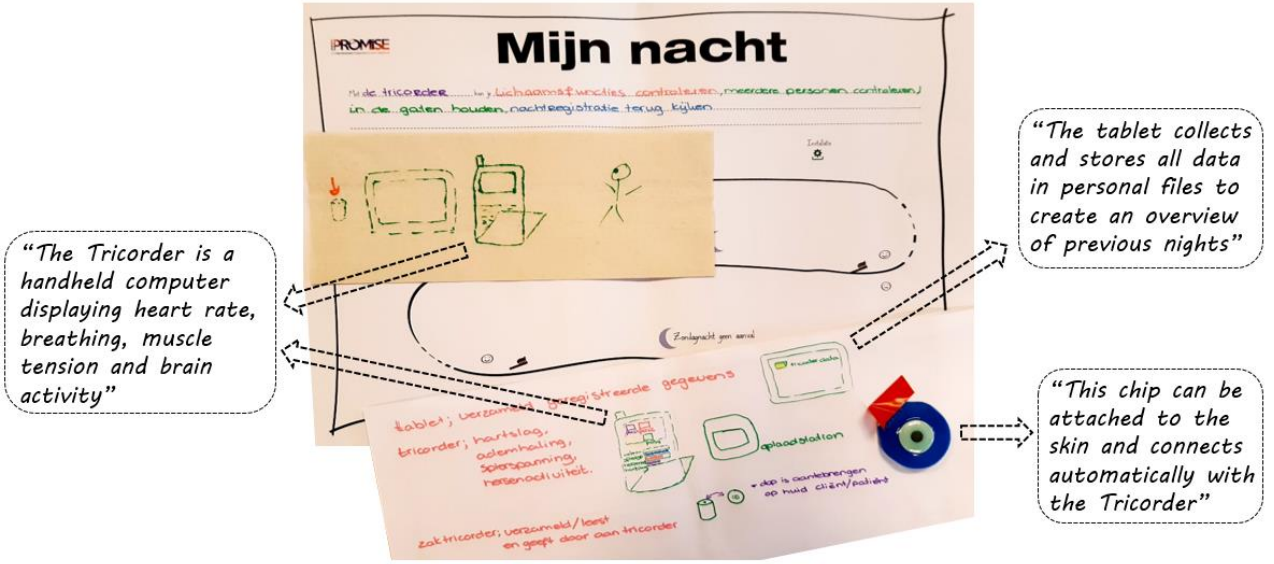

Figure 2 Example dream device in 2030 as drafted by one of the informal caregivers. Explanation during the interview: "The 'Tricorder' is inspired by the movie Star Trek, where the characters walk around with handheld computers. They are able to scan and read your whole body. In future, it would be ideal if you can walk around with one small computer in your hand, your pocket or attached to your trousers. You stick a chip like this (blue patch in the picture) on the person with epilepsy and the Tricorder automatically connects. The Tricorder shows heart rate, breathing, muscle tension, and brain activity, for multiple people at the same time. The data is clustered per person and you can easily switch between different people. All data is collected and stored on one tablet, so you can easily get an overview of the previous nights and weeks per person, to recognize patterns over time. The Tricorder also generates alarms. These can be personalized on the specific features you want to be alerted for. Every person has his/her own alarm melody, so you can recognize who you are alerted for."

their preferences for personal adjustment of the device's algorithm. A recommendation of a professional (e.g., neurologist) would also make it easier to trust a device. Participants preferred a set-up period over ''plug-and-play," as feedback of SDD performance following such period in a hospital/institution or at home could increase trust. The informal caregivers agreed that hospitalization of their child, even for a longer period, would outweigh the trust gained by this test period.

> *''[...] and when I see that he has found his peace again and falls asleep, I sometimes return to my own bed reluctantly, because I just want to stay with him sometimes to give him the feeling that there's someone around for him, but also for my own sense of security. As long as you're with me, I won't miss a thing. But on the other hand, when I lay there, he will have a good night's rest, but I won't."* (I1)
>
> *''And the next best thing was. . . I would take a woollen thread, put one end around my pink and the other end around the client's because then you are always there. But that's not reality."* (P3)
>
> *''For adults I would opt for an automatic system for emergency medication, but when I think about such system for my own child, I would say: ''no, that's too risky." I would prefer to control the situation myself [. . .] especially with children, they are much more vulnerable than adults. I would like to have some human control."* (I2)
>
> *''[. . .] Yes, that's how it currently works with EEGs and MRI scans, we now fully trust the information generated from these systems. The same applies for detection devices, we have to learn to trust them. If a device, for example, measures low muscle tension and you see for yourself that the muscle tension is low, you will feel that the device works. This way we learn to trust a device."* (I2)

Alerting

The most quoted need by the participants was ''alarm." During the session, there was no clear consensus on what the caregivers wanted to be alerted for. From the professional caregivers' perspective, it is crucial to be timely alerted for potentially dangerous seizures. As these caregivers must care for multiple people with epilepsy at the same time, it is inconvenient to be alerted for every minor seizure. Conversely, one of the professionals gave an example of a client who experienced mainly minor seizures but could not fall asleep afterward without someone comforting him. One of the informal caregivers indicated that she wanted to be informed about every seizure including the minor ones. She wanted to be alerted even for the minor seizures as she noted that they have a great impact on the child's behavior the next day especially if these events cluster. During the group discussion, it was suggested that different types of

alarms for different seizure types could address these different needs for alerting. For example, major seizures could set off loud buzzers, while minor seizures could be alerted by more quiet notifications. Personal adjustment of the alarm settings may provide a solution to meet the differences in caregiver's needs. All participants preferred having false alarms rather than missing potentially dangerous seizures. At the same time, they also expressed that the number of false alarms should be limited and this limit seemed to vary between caregivers. The tolerability of false alarms in professional caregivers seemed to be higher than the tolerability in parents who are alerted during their sleep. The informal caregivers emphasized the importance of a good night's rest to provide good care the next day, while the professional caregivers did not mind the false alarms keeping them busy at night, as long as it did not jeopardize the care for the other clients.

> *''A quiet notification will provide enough information. [. . .] Because when I receive three messages in one hour about minor seizures, I already know what is going to happen. I know my child. I don't have to call anyone. I immediately rush to the place where my child is, to get her, because this means trouble."* (I2)
>
> *''Silent seizures are the most tricky ones, the ones we do not notice and provoke respiratory arrest. Those are the seizures you want to be alerted for at all times. That would make work a little less stressful. [. . .] A silent seizure, and that I will find my client dead in bed, I hope that's something I will never have to experience. [...] So, I don't mind running for nothing."* (P1)

Video feedback

The third most quoted theme was the need for video feedback; both professional and informal caregivers emphasized the importance of live video tracings. Video footage would allow monitoring from a distance without having to disturb the person with epilepsy at every false alarm. Invasion of privacy was also discussed, but all caregivers agreed that the benefits of video monitoring outweigh these adverse effects. One professional caregiver mentioned the risk of missing a seizure when one has to review multiple video tracings.

> *''[. . .] Sense of urgency or I check the camera first and then I run. It is actually so, when I check the video, I immediately see that he has a convulsive seizure and if this is the case, I will start running. Sometimes I think: 'just run'."* (I1)
>
> *''For me, the disadvantage of video monitoring (we have 18 videos in building 9) is that you miss events because of the large amount of videos. Because you have to watch the screen with all the videos and the screen with the acoustic detection system at the same time. So that's a lot to focus on at once."* (P2)

Table 2 Overview of major themes in needs and wishes

	Themes	Examples of caregiver's preferences
Needs		
Design	Materialization	- Portable alarm station, not audible to the child - Comfortable device with freedom of movement
	Algorithm	- Automatic categorization of different types of seizures - Personalization of device algorithm (by caregiver's feedback or automatically)
	User Interface	- Different types of alarms for minor or major seizures - Clear overview of the past nights
Usage	Practice	- Facilitates to check upon the child/client without disturbing him/her
	Purchase	- Recommended by the attending physician/neurologist
	Settings	- A monitored set-up period supervised by a physician - Options for personalization of settings
Wishes		
Emotions	Trust	- Multimodal devices are believed to be more trustworthy - Insight in different parameters overnight may increase trust - Personalisation of the device's algorithm can help to gain trust - Recommendation by a neurologist may increase trust - Confirmation of accurate alerting during a set-up period may build trust
	Fear	- A reliable SDD may decrease the fear of losing your child
	Worry	- More information may also provoke worrying thoughts
	Control	- Feeling in control by anticipating the possible effects of one or multiple seizures
Purpose of device	Good care	- Providing a restful night for people with epilepsy and their caregivers
	Insight	- Providing an overview of seizure activity, so one can anticipate to certain changes in behaviour.
	Safety	- Too many false alarms can cause 'alarm fatigue'; one can become less alert
	Independence	- A reliable SDD may facilitate transition from dependence to independence

DISCUSSION

Throughout the design process of medical devices, it is important to appreciate the users' perspective. The context mapping approach enabled us to explore caregivers' latent needs and wishes for nocturnal SDD design. In comparison with quantitative research (e.g., questionnaires), this method allows for deeper understanding of values, by providing experiences and examples to clarify the context and expose latent desires. Context mapping thereby complements other qualitative research (e.g., interviews) by truly revealing deeper emotions and believes.

We identified ‘‘trust" as a fundamental wish from caregivers and discovered several factors helping to gain their trust in a device, including integration of different modalities, insight on all parameters overnight, personal adjustment of the algorithm, recommendation by a neurologist and a set-up period. Needs for alerting seemed to contrast between professional and informal caregivers, thus underscoring the importance of the possibility to adjust device settings.

Our study is limited by the small number of participants. Small sample sizes are inevitable using context mapping methods, as larger groups will prevent to create the secured atmosphere that is needed to explore deeper thoughts and emotions.[8] Our study was particularly targeted to professional and informal caregivers of people with refractory epilepsy and learning disabilities and did not include other professionals (neurologists, epileptologists) or people with epilepsy, thus limiting the generalizability of our results to other user groups. Specific experiences of caregivers (age of the person with epilepsy, seizure type and frequency, severity of learning disabilities, and SDD usage) may have biased the results.

We identified three other qualitative studies on user preferences for SDDs.[9, 10, 19] In accordance with our findings, a value-sensitive design study identified trust as one of the most relevant values for caregivers and professionals .[9] Our data complement these results by providing several approaches on how to gain trust in an SDD. A recent qualitative interview study indicated the readiness of people with epilepsy to use wearable SDDs on the assumption that they would provide an existential and comforting experience.[19] This underscores the importance to engage users in the designing process in order to ensure an optimal level of acceptability and usability. Semi-structured interviews of people with epilepsy following a short trial with wearables in the hospital revealed preferences for wireless, small size, comfortable devices that can be used without support.[10]

Another quantitative study focusing on self-managing a wrist worn device identified differences in coping with new technologies among participants.[20] These digital inequalities are strongly related to illness-perception-related factors (e.g., perceived disease timeline and personal control) and should be considered during implementation.[20]

We identified five large-scale quantitative studies using questionnaires to explore user's preferences.[11-15] In one survey, most people with epilepsy favored non-stigmatizing, multimodal devices but expressed varying needs for SDD usage, varying from ''keeping track of seizures" to ''alerting relatives".[11] This is line with our results that needs for alerting contrast between different caregivers. In another survey, most participants expressed their favor for wearable devices and willingness to care for the device (e.g., charging) or attend extra appointments scheduled.[12] It is, however, unclear what the participants expected from these interventions as the performance of these hypothetical devices was not specified in the questionnaire. Two short multiple-choice questionnaires identified 'the ability to detect all seizures', ''continuous SDD use" and ''alerting within one minute after seizure onset" as important user's preferences.[13, 14] A questionnaire that addressed elements of SDD performance (sensitivity or false alarm rate) independently indicated that the majority of participants favored 100% correct detections and no false alarms.[15] In accordance with our findings, the tolerance for false alarms appeared varied between users: Those with higher seizure frequencies are more willing to accept frequent alarms compared to those with lower seizure frequencies.[15] Only two out of five survey studies specified the actual number of SDD users, which was 2-6%.[11, 14] Additionally, the questionnaires did not combine different details related to a specific SDD design, to create a realistic device used in daily practice. The closed question format can pose bias and the reported preferences are not complemented by underlying considerations and possible solutions. Our context mapping session provides such complementary data but is limited by a small sample size. We aim to conduct a large-scale discrete choice experiment that incorporates the values of the current study. This design has the advantage that it may unveil how respondents value selected SDD features by asking them to state their preferences on different hypothetical SDDs.

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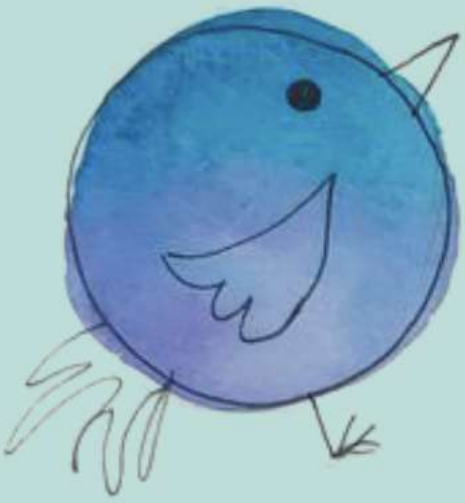

CHAPTER 10

Parental preferences for seizure detection devices: results from a discrete choice experiment

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ABSTRACT

Introduction

Previous studies identified essential user preferences for seizure detection devices (SDDs), without addressing their relative strength. We performed a discrete choice experiment (DCE) to quantify attributes' strength, and to identify the determinants of user SDD preferences.

Methods

We designed an online questionnaire targeting parents of children with epilepsy to define the optimal balance between SDD sensitivity and positive predictive value (PPV) while accounting for individual seizure frequency. We selected five DCE attributes from a recent study. Using a Bayesian design, we constructed eleven unique choice tasks and analyzed these using a mixed multinomial logit model.

Results

One hundred parents responded to the online questionnaire link; 49 completed all tasks, whereas 28 completed the questions, but not the DCE. Most parents preferred a relatively high sensitivity (80%-90%) over a high PPV (>50%). The preferred sensitivity-to-PPV ratio correlated with seizure frequency ($r = -.32$), with a preference for relative high sensitivity and low PPV among those with relative low seizure frequency ($p = .04$). All DCE attributes significantly impacted parental choices. Parents expressed preferences for consulting a neurologist before device use, personally training the device's algorithm, interaction with their child via audio and video, alarms for all seizure types, and an interface detailing measurements during an alarm. Preferences varied between subgroups (learning disability or not, SDD experience, relative low vs. high seizure frequency based on the population median).

Conclusions

Various attributes impact parental SDD preferences and may explain why preferences vary among users. Tailored approaches may help to meet the contrasting needs among SDD users.

INTRODUCTION

Seizure detection has rapidly advanced in epilepsy care as various new devices have been launched.[1-5] Meaningful implementation of these devices requires a good fit with the end users. Seizure detection devices (SDDs) are used mainly by people caring for an individual with epilepsy in an institution or at home. Caregivers' rapid response to SDD alarms might help prevent dangerous complications of seizures, including injury, status epilepticus, and sudden unexpected death in epilepsy (SUDEP).[6-9] SDDs may also help reduce the burden of seizure monitoring and promote independence.[4] These beneficial effects, however, can only be gained when the device meets the user's needs and is successfully implemented in the care setting.[5] Most SDD studies have focused on technological aspects and placed less emphasis on the user's role in coshaping SDDs.[10] People with epilepsy and caregivers have expressed the importance of an accurate device,[5, 11, 12] but little is known about how they evaluate the balance between sensitivity and positive predictive value (PPV) while accounting for individual seizure frequency. Previous research among potential users showed that design aspects also matter.[5, 11, 12] Several studies stressed the importance of attractive, nonintrusive, nonstigmatizing, comfortable devices, preferably wearable and removable, but securely fitted.[13-18] A recent qualitative context mapping study[19] explored caregivers' dreams and fears, and identified several key attributes influencing their trust in a device (e.g., ability to view all parameters overnight, personal adjustment of the algorithm, recommendation by a neurologist, and a setup period).[19]

Previous studies did not examine the relative strength of the attributes determining the user's choice of an SDD. A discrete choice experiment (DCE) is a method to quantify the strength of different aspects influencing users' preferences.[20] The scope of DCE applications is expanding, including the design of complex interventions.[21] Few DCE studies have evaluated preferences for diagnostic and treatment options in epilepsy care.[22-24]

This study builds on our context mapping study[19] by extracting the most important themes regarding SDD needs as attributes. We aimed to examine to what extent these attributes affect users' preferences for an SDD, using a DCE, and assess whether user characteristics influence SDD preferences. We also explored the optimal balance between sensitivity and PPV, while accounting for the seizure frequency of the individual.

METHODS

We designed an online questionnaire to explore the preferences of parents of children with epilepsy. The questionnaire consisted of three components: (1) background information about the parents and the child with epilepsy; (2) questions on motives for using an SDD, and the optimal balance between SDD sensitivity and PPV; and (3) a DCE.

Background information

We recorded family composition, parental educational level, the child's age and presence or absence of learning and/or physical disability, seizure frequency and types, and parental experience with SDD use. In the DCE, for the sake of ease, we referred to seizure types as "major" or "minor." We requested parents to describe the seizures of their child in the questionnaire and to indicate how they would label them (i.e., major or minor).

Questioning motives for using an SDD and the optimal SDD performance

Parents were asked to indicate their agreement on a 5-point Likert scale with the following motives for using an SDD: (1) to enable timely intervention in potentially dangerous seizures, (2) to be alerted for every seizure type of my child, and (3) to get a better overview of my child's epilepsy. The scale varied from 1 point (totally disagree) to 5 points (totally agree). We calculated the mean total score for each motive. The higher the score, the more parents agreed with the motive.

Optimal SDD performance was presented on a 6-point scale, varying from an optimal PPV with relatively low sensitivity, to an optimal sensitivity with relatively low PPV. The questionnaire included the following sensitivity (%)/PPV (%) balances: 50/100, 60/83, 70/67, 80/50, 90/33, 100/17. The chosen values reflect the overall discriminative power of current SDDs,[3, 8] with different set points for the tradeoff between sensitivity and specificity. SDD performance was expressed as numbers of missed seizures and false alarms while considering the individual seizure frequency. The data were presented as number of events per day, week, month, or year depending on the child's seizure frequency. For example, if a child experienced one seizure per day, one of the answer options would include four missed seizures per week and no false alarms (ratio sensitivity vs. PPV: 50%/100%), whereas the 60%/83% ratio would be presented as three missed seizures and one false alarm per week.

Discrete choice experiment

A DCE is often applied in health economics to evaluate preferences for health care products or programs.[25, 26] The product, in our case an SDD, is described by several attributes, and the assumption is made that variation within these attributes (levels) affects SDD preferences.[25] Each exercise presents two hypothetical scenarios constructed by assembling random levels for each attribute. Respondents were asked to indicate their preference for one of the two scenarios. Next, the exercises were repeated with different scenarios, thus helping to identify the relative importance of each attribute and corresponding levels.

Identifying attributes and levels

We extracted the key themes regarding SDD needs from the context mapping study,[19] and converted them into five attributes to minimize study burden. Attribute levels were based on different preferences that emerged from the group discussion in this study. The list was finalized in a consensus meeting with clinicians, experts, a parent, and a patient representative, and included (1) introduction to use (three levels), (2) alert (three levels), (3) interface (three levels), (4) interaction (four levels), and (5) personalization (three levels). The attribute "interface" refers to a display of the device's measurements. All attributes and their different levels are shown in Figure 1A.

Designing choice sets

The four attributes with three levels and one attribute with four levels used in this study could create 34 × 41 = 324 hypothetical scenarios. We used a subset of these scenarios for practical reasons, applying an algorithm to generate a Bayesian optimal design.[27] This method allows for a statistically efficient design that maximizes D-efficiency (i.e., the precision of estimated parameters). The choice set was constructed using Stata version 16 (module DCREATE).[28] The Bayesian design assumes a prior distribution of likely
parameter values (e.g., the beta coefficients in the regression analysis) for some or all parameters. We assumed that all coefficients had a positive sign (i.e., higher levels were assumed to be more preferred). To minimize participant burden, the number of choice tasks was limited to eleven.
The final version consisted of eleven unique choice tasks and one repeated task to examine the test-retest reliability. There was no opt-out option, so respondents were forced to choose between two hypothetical, unlabeled

1A

	Introduction to use	Alert	Interface	Interaction	Personalisation
Level 1	 Directly	 Alarms for major seizures only	 None	 None	 Fixed settings
Level 2	 After consulting a neurologist	 Alarms for major and minor seizures	 Ability to view measurements at the time of alarm	 Video image during an alarm	 Personal feedback on right and wrong alarms trains the device
Level 3	 After a 2-week test period in a clinical setting	 Alarms for major seizures, silent notifications for minor seizures	 Continuous ability to view measurements with option to look back in time	 Continuous video images with sound	 The device trains itself, without personal interference
Level 4				 Level 3 with option to talk back	

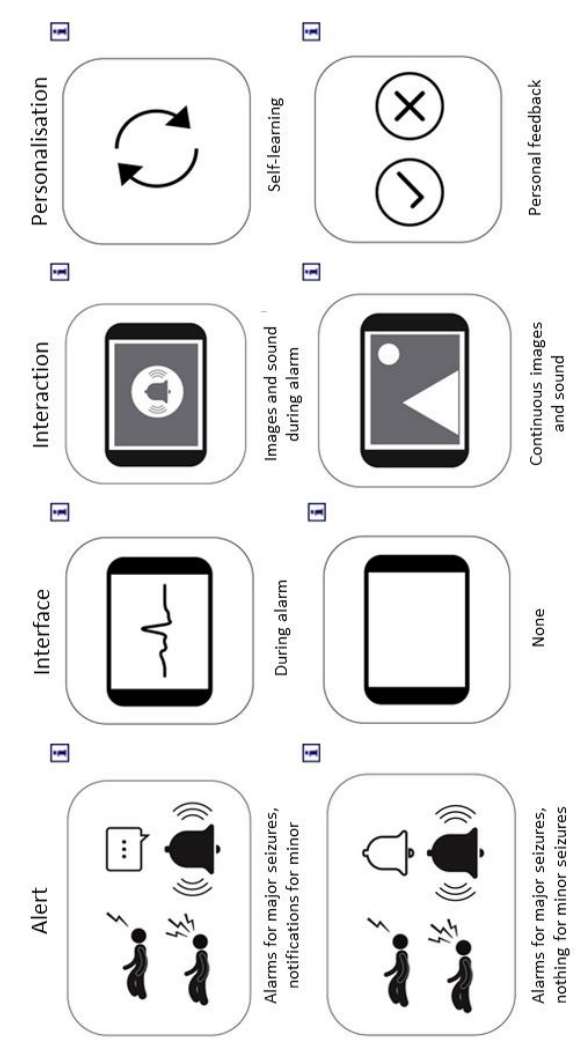

Figure 1 Illustrations and pictograms used in the questionnaire. **(A)** Illustrations for all attributes' levels. **(B)** Example of discrete choice task with pictograms of different levels. Parents could click on the "i" displayed in the upper right corner of each pictogram to open additional illustrations and textual explanation of each level, as shown in A.

scenarios. A designer specializing in health care was asked to provide illustrations for each level, which were presented at the start of the DCE, together with an explanation of the five attributes and their levels (Figure 1A). To simplify the exercise, we provided the choice tasks with pictograms (Figure 1B). Parents could click on the pictogram for additional textual explanation.

Testing the full questionnaire

Before distributing the questionnaire, we performed a pilot study with five parents of children with epilepsy admitted to our epilepsy center, to optimize question format, pictograms, and language. The full Dutch version of the questionnaire is available from the authors on request.

Data collection

A link to the online questionnaire was distributed via multiple social media used by three large epilepsy centers in the Netherlands (Epilepsy Institutes of the Netherlands Foundation, Academic Center for Epileptology Kempenhaeghe, and University Medical Center Utrecht), EpilepsieNL, the Dutch Epilepsy Foundation, and Facebook groups of representatives of people with epilepsy in the Netherlands and Belgium. We aimed to include a population that was as diverse as possible to represent a wide range of preferences. Any Dutch-speaking parent of a child with epilepsy, with or without SDD experience, was invited to participate. The questionnaire completion time was about 45 min. The study was evaluated by the Medical Research Ethics Committee Utrecht. An official approval was not required under the Medical Research Involving Human Subjects Act. All parents participated voluntarily and anonymously. Data were collected between March 2020 and March 2021.

Statistics and data analysis

Data on background information, motivation for using an SDD, and the optimal sensitivity/PPV balance are presented using descriptive statistics. We used $\chi 2$ statistics to analyze differences between groups for categorical data. To analyze the correlation between seizure frequency and preferences for SDD sensitivity-to-PPV ratio, we performed a 10-log transformation to create a normally distributed dataset and then used an analysis of variance test to estimate differences. Categories with a small number of responders ($n < 5$) were clustered together.

DCE data were analyzed using the statistics software package R (v4.0.4). We used a mixed multinomial logit (MMNL) model to determine the relative strength for each attribute on parents' preferences, using the following steps:

1) Defining the regression model: The regression function was constructed with the attributes as independent variable and the choice of the parents (i.e., either a “0” or “1” depending on which of the two alternatives was chosen for each question) as dependent variable. No constant term was included in the final model, as this was deemed irrelevant (i.e., it would be the mean of the unobserved effects for each of the alternatives). All attributes consisted of categorical variables and were included in the model as dummies using effect coding. We normalized the first level of each attribute to zero, and calculated preference weights relative to the effect of this first attribute's level.
2) Assigning distributions to each independent variable: All parameters included in the MMNL model were treated as random parameters (assuming a normal distribution), estimated using 2000 Halton draws.
3) Performing primary analysis: Data from all parents who completed the DCE were used to perform the primary analysis to test the attributes for significance.
4) Performing subgroup analyses: We tested interactions between responders' characteristics and attributes for three subgroups: learning disability of the child with epilepsy (yes/no), experience with SDD use (yes/no), and seizure frequency (relatively low/high). Seizure frequency was categorized as either relatively high or low using the median seizure frequency of all participants as a cutoff. A p-value < .05 was considered to be statistically significant.

MMNL was chosen to allow for possible preference heterogeneity across respondents and to account for the panel nature of the data (i.e., repeated measures within individuals and hence correlated observations).[29] A positive output for a level illustrates a positive effect on parental preferences with the first attribute's level as a reference.
The resulting regression coefficients show the relative importance of the attribute. Relative importance weights to ease interpretation were calculated using the method described by Malhotra et al.[30]

Table 1 Respondents' characteristics

Characteristics		Subgroup full data (n=49)	Subgroup incomplete data (n=51)
Family			
Family composition	Parents/caregivers	41 (84%)	25 (81%)
	Single parent/caregiver	3 (6%)	6 (19%)
	Composed family	5 (10%)	0 (0%)
	Missing		20[b]
Parental educational level	No school finished	0 (0%)	1 (3%)
	Primary education	0 (0%)	1 (3%)
	Secondary education	5 (10%)	11 (36%)
	Secondary vocational education	36 (74%)	16 (52%)
	Higher education	8 (16%)	2 (6%)
	Missing		20[b]
Child			
Age child	Median (range)	10 y (2-39)	15 y (1-43)
Learning disability	Yes	19 (39%)	20 (65%)
	No	30 (61%)	11 (35%)
	Missing		20[b]
Physical disability	Yes	11 (22%)	8 (26%)
	No	38 (78%)	23 (74%)
	Missing		20[b]
Seizure frequency	Daily	12 (25%)	8 (29%)
	Weekly	15 (31%)	4 (14%)
	Monthly	11 (22%)	6 (21%)
	Yearly	11 (22%)	10 (36%)
	Missing		23[b]
Type of seizures[a]	Mainly major	19 (39%)	11 (38%)
	Mainly minor	9 (18%)	5 (17%)
	Major and minor	21 (43%)	13 (45%)
	Missing		22[b]
SDD usage	Yes	21 (43%)	9 (32%)
	No	28 (57%)	19 (68%)
	Missing		23[b]
Type of SDD used	NightWatch	15	4
	Pulse oximeter	4	1
	Empatica Embrace	1	2
	Epicare Free	1	1
	Emfit		2
	Seizure alert dog		1

Table 1 (Continued)
Subgroup “full data” includes discrete choice experiment.
SDD seizure detection device, *y* years.
[a]Parents were asked to indicate whether their child suffered from major or minor seizures and to detail the seizure types they were referring to (see results section).
[b]Not calculated.

RESULTS

Respondent characteristics

In total, 100 parents responded to the link to the online questionnaire, and 49 responders completed the full questionnaire, including all DCE choice tasks, whereas 28 responders completed part of the questionnaires but did not start the DCE. Everyone who started the DCE, completed it.
Table 1 shows characteristics of the participants per subgroup; those who completed all tasks including DCE, and the subgroup who answered only some of the questions. A slightly higher parental educational level and a lower frequency of learning disabilities in the child were found among those who completed the DCE, but no other differences were noted between groups. Most responders lived as a family of two parents/caregivers with one or more children and had finished secondary vocational education or higher. The median age of the child with epilepsy was 11.5 years. Approximately half had a learning disability, and one quarter of the children experienced physical disabilities. Seizure frequency varied from one per year to several per day (median seizure frequency = one per week). Most parents reported major seizures (with or without minor seizures). Their descriptions of major seizures included "tonic-clonic," "loss of consciousness with intense jerks and salivation," "stiffen/overstretching and turning blue," "lots of movements and screaming," and "status epilepticus." Minor seizures were described as "absences/staring/freezing," "small jerks/myoclonias," "vibrations/jerks on one side of the face or body," and "loss of muscle tone or falls." Approximately 40% of responders had ever used an SDD.

Motives for using an SDD and the optimal SDD performance

The parents strongly agreed with all three motives for using an SDD: "to enable timely intervention in potentially dangerous seizures" (4.74), "to be alerted for

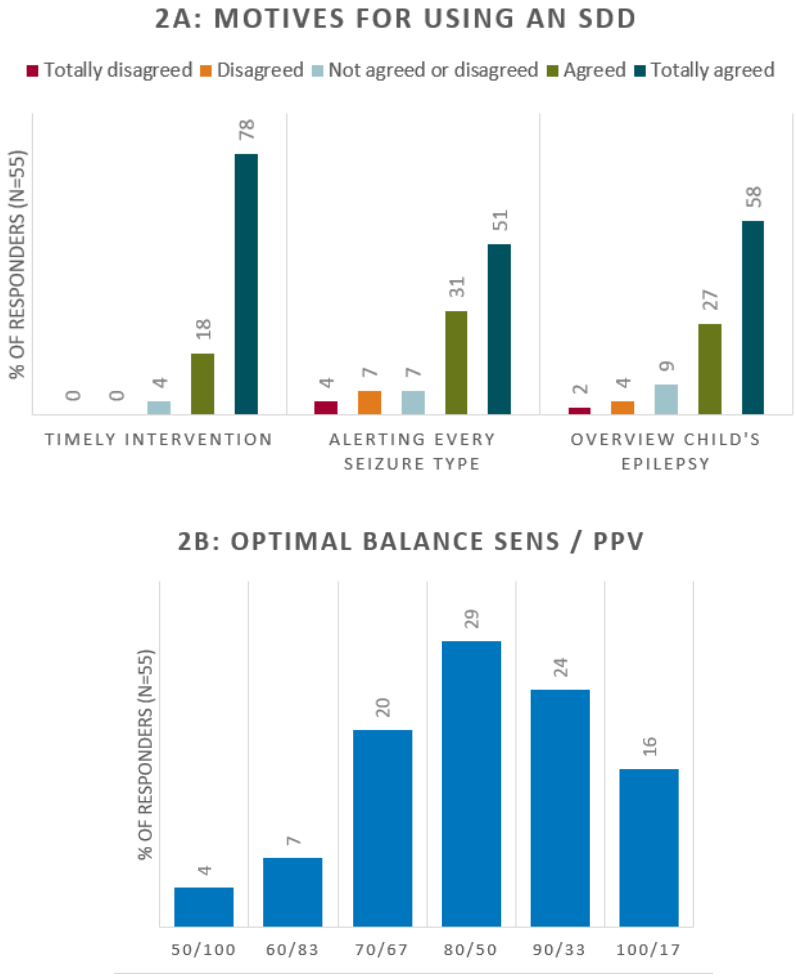

Figure 2 Responders' preferred motives for using a seizure detection device (SDD) and balance between sensitivity and positive predictive value (PPV). **(A)** Parental motives for using an SDD: (1) to enable timely intervention in potentially dangerous seizures (timely intervention: 4.74), (2) to be alerted for every seizure type of my child (alerting every seizure type: 4.18), and (3) to get a better overview of my child's epilepsy (overview child's epilepsy: 4.35). **(B)** Parental choices for the optimal balance between the sensitivity (SENS) and positive predictive value of an SDD. The bars show the percentage of parents (n = 55) who chose the corresponding answer.

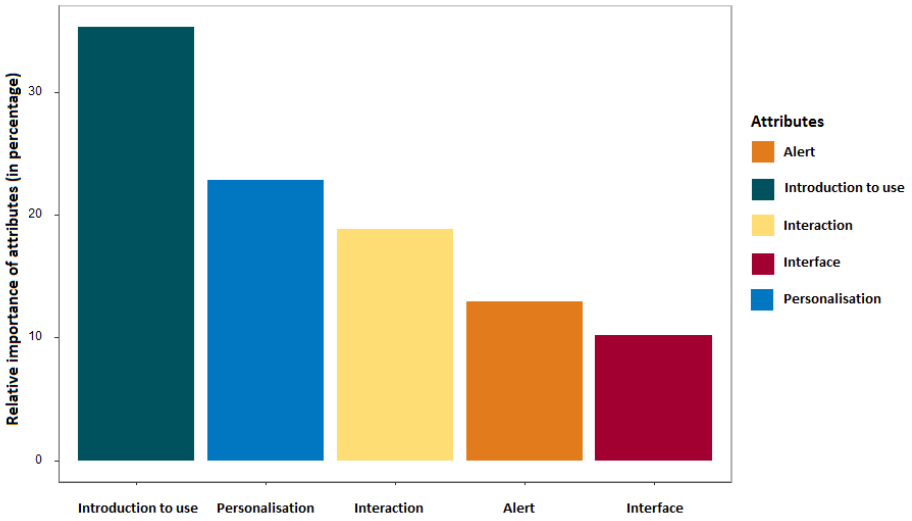

Figure 3 Relative importance of the five attributes used in the discrete choice experiment expressed as a percentage per attribute.

every seizure type" (4.35), and "to get a better overview of their child's epilepsy" (4.18; Figure 2A).

The most frequently chosen category of SSD performance included 80% sensitivity and 50% PPV (29% of responders), followed by 90%/33% (24% of responders; Figure 2B). The SDD preference depended on the individual seizure frequency: the higher the seizure frequency, the lower the sensitivity to PPV ratio ($r = -.32$; $p = .04$). Whether the parent had used an SDD before did not impact parental tradeoff choice.

Discrete choice experiment

Forty-five of 49 responders (92%) successfully completed the test-retest exercise (by providing the same answer), indicating a high reliability of the DCE. All attributes of the DCE were statistically significant, showing that they all had an important influence on parental preferences for an SDD. The relative importance of each attribute was expressed as a percentage, illustrating which attributes had the largest influence on parental choices (Figure 3). The relative effects of the attributes' levels by representing the output from the MMNL model expressed in log-odds are shown in Table 2. The attribute "introduction to use" had the largest impact on parental preferences. Parents expressed a high preference for consulting a neurologist before putting the SDD into use,

whereas a 2-week test period in a clinical setting had a strong negative effect on parental preferences. Personalization was the second most important attribute; parents preferred the option of personalizing the device's algorithm, favoring giving personal feedback on right or wrong alarms over automatic personalization. For the attribute "interaction," parental response was: the more interaction, the better. Parents preferred to be alerted for major and minor seizures, and an alarm for both types was mostly favored. The attribute "interface" appeared to be less important; parents indicated a preference for an interface option, with no large differences in whether this option was given during an alarm or continuously with the ability to look back in time.

DCE subgroup analyses

Users' preferences differed among subgroups (Table 3). Parents of a child with a learning disability, compared to those without, were more likely to prefer consultation with a neurologist before SDD use, device interface options during an alarm, and the option to adjust the device's algorithm by giving personal feedback (Table 3). Parents who already used an SDD had a stronger preference to be alerted for both major and minor seizures and a device that could tailor its algorithms for the individual to personalize, compared to the ones without any SDD experience. Parents with SDD experience and those of a child with a relatively high seizure frequency expressed a higher preference for continuous video and audio, and the option to talk back through the device, whereas they were less likely to choose the ability to view alarms and measurements at the time of an alarm, compared to parents without SDD experience and parents of a child with relatively low seizure frequency.

DISCUSSION

We explored parental preferences regarding usage motives, the tradeoff between sensitivity and PPV, and the attributes influencing SDD choice. We found that parents would rather have more false alarms than missed seizures. All DCE attributes had a high impact on parental choices, in the following order of importance: “introduction to use,” “personalization,” “interaction,” “alert,” and “interface.” Users' preferences varied between subgroups (learning disability or not, SDD experience, low vs. high seizure frequency based on the population median).

Table 2 Results from the mixed multinominal logit regression model illustrating the strength of different attributes on parental preferences for SDDs

		SDD preferences		
Attributes	**Levels**	**Log-Odds**	**CI**	**p**
Introduction to use	Directly	Reference	NA	NA
	After consulting a neurologist	1.75	1.38 to 2.12	<0.001[a]
	After a 2-week test periodin a clinical setting	-1.80	-2.17 to -1.43	<0.001[a]
Alert	Alarms for major seizures only	Reference	NA	NA
	Alarms for major and minor seizures	1.31	.97 to 1.65	<0.001[a]
	Alarms for major seizures, silent notifications for minor seizures	.86	.49 to 1.23	<0.001[a]
Interface	None	Reference	NA	NA
	Ability to view measure-ments at the time of alarm	1.03	.68 to 1.37	<0.001[a]
	Continuous ability to view measurements with op-tion to look back in time	.81	.52 to 1.10	<0.001[a]
Interaction	None	Reference	NA	NA
	Video image during an alarm	.75	.40 to 1.10	<0.001[a]
	Continuous video images with sound	1.90	1.43 to 2.36	<0.001[a]
	Continuous video images with sound and the option to talk back via the device	1.97	1.56 to 2.39	<0.001[a]
Personalisation	Fixed settings	Reference	NA	NA
	Personal feedback on right and wrong alarms to adjust the algorithm	.80	.46 to 1.14	<0.001[a]
	The device trains itself, without personal interference	.32	.02 to .62	.037

The table shows the output from the mixed multinominal logit regression model. The log-odds represent the effect of the attributes' levels relative to the mean effect of the different levels of the attribute in the respondent sample. A positive output for a level illustrates a positive effect on parental preferences, compared to the first attribute's level.

Table 2 (Continued)
The *p*-value represents the statistical significance of the attribute's level effect (either positive or negative) relative to the reference level. To obtain the relative likelihood of choosing for a hypothetical scenario, one needs to sum the log-odds of the levels of interest and take the exponential ($e^{\text{log odds}}$ = odds ratio).
CI confidence interval, *NA* not applicable, *SDD* seizure detection device.
[a]Statistically significant.

Strengths and limitations

Our study has its limitations. First, despite our efforts to draw attention to our online questionnaire among parents of children with epilepsy, we received a limited response. Additionally, only about half of the responders completed the DCE. The limited response might be explained by the complexity and length of the questionnaire. We tried to minimize the DCE complexity by providing pictograms and illustrations, and limiting the number of choice tasks, but the question format remains challenging. A recent review on DCEs in health economics indicated that the majority of DCEs have more than five attributes (our study uses five) and 54% use 9-16 choice tasks (we used 11).[31] A simpler, less onerous questionnaire would therefore need another question format. These studies have been performed previously but lack information on the relative strength of different attributes that determine the user's choice of an SDD.

Estimates regarding the minimal required sample size for DCEs vary. For example, previous literature suggested various “rules of thumb,” ranging from equations such as $n = 500c / (t \times a)$ (in which c = equal to the largest product of levels of any two attributes, t = number of choice tasks, and a = number of alternatives, resulting in 273 participants for this study), to studies stating that 20 respondents per questionnaire version is sufficient to estimate reliable models, based on empirical experience.[32]

Other studies have mentioned a minimal sample size of 30 for an adequate level of accuracy, based on econometric criteria.[33] The sample size of our study is on the lower end of this range and thus underpowered our subgroup analyses. These results should therefore be interpreted with caution. Despite our small sample size, we found large DCE effects. Hence, we believe that the sample size was sufficient to indicate the direction (i.e., which level has a positive or negative impact) and the importance (i.e., which attribute matters most) of participants' preferences. We found a slightly higher parental educational level in the subgroup that completed the DCE, which may have caused selection bias

Table 3 Contrasts between parental preferences for seizure detection devices among three subgroups of respondents: parents of a child with learning disability (n = 19), parents with previous SDD use (n = 21), parents of a child with a relative high seizure frequency (n = 25)[a]

Attributes	Levels	Learning Disability	SDD Usage	High seizure Frequency[a]
Introduction to use	After consulting a neurologist	++	++	=
	After a 2-week test period in a clinical setting		--	=
Alert	Alarms for major and minor seizures	-	++	=
	Alarms for major seizures, silent notifications for minor seizures	=	=	=
Interface	Ability to view measure-ments at the time of alarm	++	--	--
	Continuous ability to view measurements with option to look back in time	=	=	=
Interaction	Video image during an alarm	=	=	=
	Continuous video images with sound	=	+	-
	Continuous video images with sound and the Option to talk back via the device	=	++	++
Personalisation	Personal feedback on right and wrong alarms to adjust the algorithm	++	=	=
	The device trains itself, without personal interference	=	++	=

−/−− negative effect on parental preferences with $p < .05$/$p < .01$, +/++ positive effect on parental preferences with $p < .05$/$p < .01$, = no effect on parental preferences, *SDD* seizure detection device. [a]Seizure frequency was labeled as high if the frequency exceeded the median seizure frequency among participants (one seizure/week).

and thereby impacted the generalizability of our results. We had no signs to suggest that the task itself was too complex, as all responders who started the DCE also completed it. We speculate that the lower response rate relates to the required time to complete the study, which may have been too long for those parents with a high burden of care. The DCE design of this study is also one of its strengths; the method allows for a better understanding of how parents make choices for an SDD and quantifies the strength of their preferences. We carefully selected DCE attributes from a context mapping study,[19] and the results show that all selected attributes had a significant impact. Another strength is the way we investigated the preferred tradeoff between sensitivity and specificity. Previous survey studies including people with epilepsy and caregivers examined the preferred sensitivity and false alarm rate (FAR) independently, thus reflecting an unrealistic scenario.[12, 14] One study found that "detecting all seizures" was the most important device feature, but an accompanying FAR was not mentioned.[14] Most responders from another study required 100% sensitivity and allowed one false alarm per seizure, and one false alarm per week in those with seizure freedom.[12] We expressed the performance by calculating the absolute number of missed seizures and false alarms, taking into account the individual seizure frequency, to represent a realistic and recognizable scenario for the parents. Our results also showed a preferred FAR of one per seizure (PPV = 50%). We complement these findings with a preferred balanced sensitivity of 80%, and a tendency to favor more false alarms over a lower sensitivity. Finally, we included both parents who had experience with SDDs as well as those who did not, to include different perspectives. The question on SDD experience did not allow us to distinguish between current SDD users and parents who had used an SDD in the past. We therefore cannot examine whether the current or past use of a specific SDD influenced parental preferences. This might be an interesting topic for further research.

Main findings and related research

Previous surveys stressed the importance of design (attractive appearance, low visibility, low intrusiveness), comfort of use, confidentiality of recorded data, and timely support from both technical and clinical ends.[5] The attribute "introduction to use" had the most influence on parental preferences in our DCE, which might be explained by the strong positive (consulting a neurologist) and strong negative (clinical test period) effect of the different attribute's levels. A value-sensitive design study among different stakeholders, including parents, highlighted that the values "health," "reliability," and "trust" were most relevant

for SDD design.[11] We assume that a neurologist's advice helps to build trust in a device and optimizes implementation. Although a 2-week test period in a clinical setting could provide meaningful information on device accuracy, it is presumably outweighed by the time and effort it costs.

Parental descriptions of major and minor seizures matched our earlier criteria quite accurately,[34] where we labeled seizures as "major" due to risk of SUDEP (tonic-clonic seizures), respiratory distress (generalized tonic seizures of >30 s), injury (hyperkinetic seizures), or status epilepticus (cluster of minor seizures). Most available SDDs offer high sensitivity/PPV ratios, meeting parental preferences, but predominantly target focal to bilateral (FBTCS) or generalized tonic-clonic seizures (GTCS). In accordance with previous surveys, we found that caregivers prefer to be alerted for a broader range of seizure types.[3, 5] Incorporating a broader range of seizures will likely result in a lower sensitivity/PPV ratio, as minor seizures are often more subtle. The recent International League Against Epilepsy (ILAE) and International Federation of Clinical Neurophysiology (IFCN) guidelines on automated seizure detection recommend the clinical use of wearable devices for automated detection of GTCS and FBTCS, especially in unsupervised people with epilepsy, where alarms may promote rapid intervention.[34] Our survey confirms the expressed need for the detection of seizures other than GTCS or FBTCS. The ILAE/IFCN working group does not recommend the clinical use of the currently available devices for these seizure types in view of the low-quality evidence and the lower sensitivities. Our framework provides guidance on how to evaluate the tradeoff between sensitivity and FARs. It also highlights the need to take individual seizure frequencies into account. In this respect, it is important to stress that the SDD studies so far[3, 35] are skewed toward populations with a high seizure burden, thus impacting user evaluations.

Other important features to consider with SDD development are the parental preference for an interface allowing them to interact with their child through the device and to view the device's measurements.

Our study population favored personalization of the algorithms of their device over fixed settings. This requires considerable interaction with the device, which contrasts with previous results that showed preference for a limited number of interactions.[5, 16, 17] The same studies emphasize that device design, especially its appearance, visibility, and intrusiveness, is an important factor influencing user acceptance and that users desired a minimal number of alerts.[5, 16, 17] Following a previous survey of people with epilepsy and caregivers,[14] most parents in our

study choose to be alerted for every seizure type (e.g., major and minor). This contrasts with the findings of other studies addressing only people with epilepsy predominantly expressing their preference for detecting major seizures, thus underscoring heterogeneity among user groups.

Our results also show varying needs between different user groups. We found that preferences for a higher sensitivity and lower PPV (more false alarms) were associated with lower seizure frequencies. We speculate that sensitivity is critically important for those with low seizure frequencies, and a higher FAR, even at lower PPV, is still acceptable. This may differ for parents of children with relatively high seizure frequency, as even with relatively high PPV the alarm rate may still be a substantial burden.

CONCLUSION

We identified variation in SDD preferences between different user groups, both within our study and compared to other studies. People with epilepsy who live independently might consider the device's appearance and visibility more important, whereas parents caring for a child with epilepsy and severe learning disabilities might prefer to provide personal feedback on alarms, because they know their child best. We therefore expect that a generic device will not meet all users' needs and thus encourage the development of user-centered and tailored approaches to foster SDD implementation.

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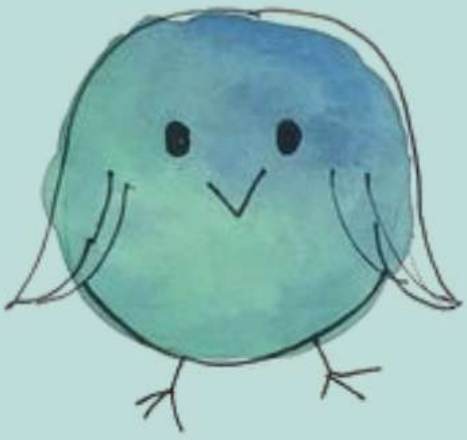

CHAPTER 11

GENERAL DISCUSSION

SUMMARY AND GENERAL DISCUSSION

We started our journey by exploring the value of various autonomic parameters for seizure detection. Following our review on hidden autonomic signs of epilepsy, we continued by studying the management of ictal asystole. We later focused on the home-based validation of a wearable autonomic and a remote non-autonomic seizure detection device in children with epilepsy and assessed the value of these devices for families and society. We extended our journey with qualitative user-evaluation studies aiming to explore needs of parents of children with epilepsy.

Uncovering autonomic signs in epilepsy

Autonomic manifestations in epilepsy can cause serious complications. Post-ictal arrhythmias are often associated with sudden unexpected death in epilepsy (SUDEP),[1, 2] and ictal asystole (IA) can cause dangerous, traumatic falls. Conversely, ictal autonomic phenomena may help in the development of interventions to prevent epilepsy complications.

In **Chapter 2** we explored the potential of changes in autonomic functions as a tool for timely seizure detection. We systematically reviewed the literature and evaluated the quality of studies using QUADAS-2[3] and recently reported quality standards on reporting seizure detection algorithms.[4] We found that the overall quality of studies on seizure detection using autonomic parameters was low. Heart rate (HR) and heart rate variability (HRV) were most frequently integrated into available detection algorithms. Overall, these algorithms yielded high sensitivity (mostly >80%)[5-18] and, especially for HRV, a short detection latency (varying from eight minutes prior to seizure onset to nineteen seconds after).[5-7, 9, 10, 13] False alarm rates (FARs), when mentioned, were high. These rates did not drop below one false alarm per three hours for an individual specific algorithm.[7] Generic algorithms resulted in up to five false alarms per hour.[13] We found evidence that the combination of multiple modalities may lower FAR. Another solution may be personalized tailoring of the detection algorithm to improve the FAR.[7, 8, 19] Long-term and real-time ambulatory validation studies are needed to obtain more reliable data, and to test the proposed strategies to optimize FAR.

In **Chapter 3** we discussed the complexity of IA management. IA is often misdiagnosed as a primary cardiac condition and treated with pacemaker implantation. While pacemaker therapy might help to prevent syncope in some

patients with IA, it will not prevent seizures. Pacemaker implantation should therefore only be considered in those in whom treatment failed to prevent seizures with syncope. The benefit of cardiac pacing may be limited when vasodepression dominates as the syncope triggering mechanism.[20-22] Cardioinhibition, vasodepression or a combination of both can cause syncope in IA.[23-26] In **Chapter 4** we examined a novel, indirect method of unravelling the dominant mechanism, considering the relative timing of IA onset and syncope onset. We retrospectively analysed video-electroencephalographic (EEG) recordings of 38 focal seizures in 29 individuals and found that in only two cases IA started too close to the onset of syncope (≤3 sec) to have been the primary cause. Awareness among physicians of the different pathophysiological mechanisms of syncope in IA might help to prevent unnecessary pacemaker implantation.

Validating the performance of seizure detection devices

The seizure detection device (SDD) market is booming, yet the level of performance evidence is low.[27] According to the standards for testing and clinical validation of seizure detection devices published in 2018,[4] only three available devices have been validated in phase 3 studies and two of them were also validated in a phase 4 study.[27] This shows that the majority of studies applied seizure detection algorithms that were trained and tested on the same dataset and also often lacked continuous real-time data, thus questioning the generalizability of the results.[4, 27] The two phase 4 studies demonstrated the feasibility and usability of wearables for the detection of convulsive seizures in the home environment, but included many people living in a residential care setting.[28, 29]

The PROMISE trial was the first prospective phase 4 multicentre implementation study in the home environment to combine long-term video-controlled performance data from NightWatch in a paediatric cohort with data from questionnaires on the effect of NightWatch on caregivers' stress, sleep, and quality of life (QoL). In **Chapter 5** we presented the results of the PROMISE trial. Based on 2310 recorded nights (28,173 hours), including 552 major seizures, NightWatch showed a median sensitivity of 100% (range 46 - 100%), with a median FAR of 0.04 (range 0.00 - 0.53) per participant per hour. Compared to previous results of NightWatch in adults, the sensitivity in this paediatric cohort was slightly higher and so was the frequency of false alarms.[29] One third of false alarms related to minor seizures, and the remainder to arousals or non-epileptic

rhythmic movements. Children present with different heart rate profiles than adults (i.e., higher resting values and greater HR variability)[30, 31] and with challenging behaviour and sleep-related rhythmic movements, particularly in those with developmental disorders.[32] Caregivers reported a positive effect on their experienced stress during NightWatch use, while their quality of sleep and QoL did not change significantly. A possible explanation for this minimal effect could be the duration of the intervention period, which might have been too short for parents to learn to trust the device and let go of their own alertness at night. Another explanation is that an SDD, at least in the short term, does not take away the overall burden of caring for a child with epilepsy and all its accompanying stressors.

The usability of two wearables has been shown in phase 4 studies,[28, 29] but not every person with epilepsy will tolerate a wearable device; some prefer remote solutions. We therefore retrospectively analysed the performance of a real-time video-based detection algorithm on 1661 recorded nights of 22 children (**Chapter 6**). The video algorithm had an overall sensitivity of 78% for the detection of convulsive seizures and 73% for the detection of hyperkinetic seizures. False alarms (n=87) occurred in only a minority of children (overall FAR 0.05/night) and were mainly behaviour related. Compared to the previous study in adults[33], we found a lower sensitivity for the detection of convulsive seizures as well as lower FARs. This was the first video-based seizure detection method that was tested on a large dataset (different from the training dataset) with continuous video recordings. Compared to other remote SDDs using bed sensors this method showed slightly lower sensitivity, but also lower FAR. It therefore provides an attractive alternative to wearable SDDs.[29]

The value of seizure detection devices for families and society

According to recent clinical practice guidelines, wearable devices are effective for accurate detection of convulsive seizures, but whether these detections result in meaningful outcomes remains unknown.[27] The value of SDDs can be measured on different levels; from clinical outcomes in the person with epilepsy, to the impact on a family, to even bigger effects from a societal perspective. All these contexts are important to establish the added value of SDDs.

In **Chapter 7** the first economic evaluation of an SDD from a societal perspective was described. Based on data from 41 children from the PROMISE study, we assessed the cost-utility and cost-effectiveness of NightWatch implementation. A decrease in mean costs of €775 during the two-month intervention period with NightWatch use was observed, compared to a two-month baseline period without any SDD. At a ceiling ratio of €50,000 per quality adjusted life year (QALY), NightWatch showed a 72% probability of being cost-effective. This effect was mainly due to changes in health care costs, including hospitalization, medication, and physiotherapy. Parental stress and QALYs did not, however, contribute to the cost-effectiveness, with similar scores between the baseline and intervention period. This may be explained by the short intervention period, as building trust in NightWatch might need more time. Alternatively, the NightWatch may already be manifesting its potential positive impact within this time frame, but the benefits may be outweighed by alarm fatigue thus resulting in unaltered levels of parental stress and QALYs.

In **Chapter 8** we explored the added value of seizure detection for parents caring for a child with epilepsy. In-depth interviews with 21 parents from the PROMISE study showed that the value of NightWatch was mainly influenced by the way parents handled the care of their child and experienced their burden of care. The detection performance of NightWatch seemed less important. Driven by the fear of child loss, parents developed a personal protective behaviour towards their child with epilepsy. This behaviour is also seen in parents of children with other chronic health conditions.[34-36] While it may be of help to feel in control of the situation and to decrease anxiety, this may also conversely increase the burden of care. Parental flexibility in the existing protective behaviour appeared to determine the extent to which NightWatch could support the family. In many families, NightWatch added value by providing an extra back-up and relieving the burden of seizure monitoring. NightWatch could not, however, take away the fear of child loss. Health care professionals and device companies should be aware of parental protective behaviour and the high parental burden of care. It is essential to appreciate differences in parental needs, and to keep an open mind for personalised adjustments to improve implementability.

User needs for seizure detection

During the development of SDDs crucial choices are made by device companies, often in collaboration with health care professionals. Their values,

however, may not be representative of all stakeholders. Successful SDD implementation requires a good fit with the end-user. It is therefore important to understand user preferences for SDDs.

In **Chapter 9**, we explored the deeper needs and wishes regarding SDDs of professional and informal caregivers of children with epilepsy, using a new qualitative research method in epilepsy: context mapping. Trust emerged as the most important theme; multiple elements were identified that could help caregivers gain trust in a device. The elements included integration of different modalities, ability to view all parameters overnight, personal adjustment of the algorithm, recommendation by a neurologist, and a set-up period. The most important elements were integrated into a discrete choice experiment (DCE) to quantify their relative strength influencing user preferences. **Chapter 10** shows the results from this online questionnaire, including the DCE, fully completed by 49 parents. All DCE attributes had a high impact on parental choices, in the following order of importance: “Introduction to use”, “personalisation”, “interaction”, “alert” and “interface”. Parents preferred to be alerted to both major and minor seizures, and to personalise the detection algorithm. This contrasts with results from previous studies in which preferences for limited and automated alerts and interactions with the device were expressed by users.[37] The online questionnaire also explored parental preferences regarding the trade-off between sensitivity and positive predictive value, while accounting for individual seizure frequency. Relatively more false alarms were favoured over missed seizures, particularly among those with a low seizure frequency. We identified considerable variation in SDD preferences between different user groups, both within our study and compared to other studies. For example, parents of children with a learning disability, compared to those without, were more likely to prefer consultation with a neurologist before SDD use, device interface options during an alarm, and the option to adjust the device’s algorithm by giving personal feedback. These findings underscore the heterogeneity among user groups and emphasises the importance of user-centred and tailored approaches of SDD development to meet the contrasting needs and to optimise implementation.

Future directions

Clinicians,[27] people with epilepsy and their caregivers[37-42] have expressed a need for reliable seizure detection at home. SDDs are being developed rapidly to meet this need, but device implementation does not always follow this pace.

The major delay in SDD implementation concerns the clinical validation process. This step is crucial in reliably estimating device performance and improving counselling, and reimbursement. Quality validations are, however, very time and cost consuming. There is a trend of SDDs becoming commercially available without any performance data published. The big advantage of this development is that these devices are instantly ready for use in practice. Yet, this overly ready availability may expose users to unknown risks without reimbursement of costs. The latter may create health care inequality if some people cannot buy a device. Another obstacle for successful SDD implementation is strict governmental regulations for medical devices. Recent adjustments in European Union legislations for medical devices (Medical Device Regulation; MDR) make it more difficult for devices to enter the market but are needed to guarantee quality.[43]

Decreasing seizure-related mortality is one of the main goals of SDDs.[27] Ideally, mortality may be chosen as a study endpoint, but this is not realistic. While SUDEP is the most common cause of epilepsy-related mortality,[44] it is still a relatively rare event with estimated incidence 1 in 1000 adults with epilepsy per year.[45-47] It is therefore impractical to use SUDEP as a primary study endpoint in the validation of SDDs. Instead, retrospective, long term cohort studies comparing SUDEP rates between SDD and non-SDD users could provide alternative evidence. These cohorts should, however, be large enough to account for the various factors affecting SUDEP risk.

Detecting different seizure types

Most available SDDs target potentially dangerous seizures only (focal to bilateral or generalized tonic-clonic seizures).[48] This thesis emphasises the need for devices that warn of all seizure types. Focal seizures without bilateral spread do not pose a SUDEP risk, but they do carry risks of other complications.[49] These risks include death by injury, drowning or traffic accidents, with important psychosocial consequences.[50] Focal seizures without bilateral spread are more difficult to detect, because they do not always show pronounced changes in autonomic function or motor signs.[51] Additionally their semiology is often less stereotyped and the variability between individuals may be high, which makes it hard for a generic device to detect them.[50, 52] The currently available evidence for the detection of seizure types other than convulsive seizures is derived exclusively from phase 2 validation studies.[4, 53] HRV algorithms seem to have the best performance (overall sensitivity 83%[54] and 91%[55]; FAR 0.11[55] and

0.22[54]/night), but only after a preselection of responders (i.e., >66% of seizures detected[55] or >50 bpm ictal HR increase[54]). A study on photoplethysmography (PPG) data from a wearable device, found significant changes during the ictal period of focal seizures.[56] A multimodal device combining electrodermal activity (EDA) and accelerometery was retrospectively tested on data from 22 individuals, which included six focal tonic-clonic seizures.[57] With optimal thresholds, the algorithm was able to detect half the focal seizures (sensitivity 50%).[57] Another study on bio-signals in focal seizures from twelve individuals confirmed the potential advantage of multimodal devices.[50] Common time-evolving patterns were recognised in HR, EDA and movement, especially in focal motor seizures with impaired awareness.[50] Prospective validation of these methods is needed to obtain reliable performance data for the detection of focal seizures.

Approaching big data

Commonly used bio-signals integrated in validated devices can also be used to monitor seizure severity.[27] Active monitoring of convulsive seizure frequency with markers of seizure severity can be used to further improve SUDEP prediction.[49] To expand the scope beyond convulsive seizures, new bio-signals and long-term ambulatory data is needed to recognise natural fluctuations and specific seizure-related patterns. Recently, the protocol was published for a long-term observational study on people with epilepsy using non-invasive SDDs at home (EEG@HOME study).[58] This study will collect EEG data from a portable EEG device twice a day, and continuous non-EEG bio-signals (HR, sleep quality index, steps) from a wrist-worn device (Fitbit Inc.). The person with epilepsy or the caregiver will register data related to seizure occurrence, medication taken, sleep quality, stress and mood using a smartphone application. This personal record represents the biggest challenge of collecting reliable long-term ambulatory recordings. Seizures are often underreported, which may result in unreliable seizure diaries.[59] Without an accurate reference standard, it is very difficult to identify the appropriate bio-signals and patterns in the data. Unfortunately, there is no simple solution to this problem. The optimal reference standard would consist of continuous video-EEG recordings. Scalp-EEG is very uncomfortable and obtrusive, and sufficient quality measurements require well-glued electrodes; this is impractical for ambulatory use. Smaller, less obtrusive EEG devices based on single-channel or multiple behind-the-ear channels are limited by their location, and have not yet provided high accuracy.[60, 61]

Intracranial EEG recording devices are highly accurate, though chronic implantation carries other disadvantages: cost and risk issues, and limitations in spatial sampling.[62] These devices may also detect subclinical seizure patterns, which may be valuable for seizure forecasting, but would not necessitate an alarm.[61, 63] To distinguish clinically relevant seizures from subclinical ones, EEG recordings are therefore often combined with video. Video monitoring is, however, limited to one place, unless multiple cameras or portable camera systems (e.g., drones) are used.

Another challenge is the interpretation of long-term SDD and reference data. Expert human analysis of this growing amount of data is very time consuming and will require automated approaches by artificial intelligence (AI) in the future.[64] As shown in chapter 2, machine learning (ML) techniques can help us to automate processes (e.g., algorithm feature selection) to improve SDD detection performances.[65, 66] ML algorithms have also shown good results for automated detection of ictal and interictal epileptiform discharges on scalp-EEG.[67] Recently, interest has grown in the application of deep learning (DL) in epilepsy care.[68] DL frameworks automatically and repeatedly optimise their parameters, so they presumably require less prior expert knowledge about the dataset for good performance.[68] Especially for large datasets, these methods can therefore have an advantage. Less control over the process is a huge disadvantage, and when bad quality data goes into the model, results will probably be of poor quality.

Seizure forecasting

Apart from seizure detection, ML and DL techniques can also be used for seizure forecasting. Seizure unpredictability is one of the major factors influencing the psychological burden of epilepsy and has great impact on QoL.[69] People with epilepsy and caregivers have emphasised the need for seizure forecasting to improve safety and independence.[70] A survey study using best-worst scaling on 346 people with epilepsy and 147 caregivers accentuated the importance of short forecasting range and notification of a high chance of a seizure.[70] As mentioned before, subclinical seizure patterns in the EEG signal can be used to forecast seizures.[63, 71] The Neurovista study was the first to collect long-term (six months - two years) intracranial EEG data from fifteen people with refractory epilepsy in an ambulatory setting.[71] The seizure-likelihood was predicted by pre-ictal electrical activity. Based on correlated clinical seizures in eleven subjects, the sensitivities to indicate ‘high seizure likelihood’

ranged from 65-100%. This dataset has been instrumental in unveiling circadian and multidien patterns in seizure occurrence and in improving forecasting algorithms.[72, 73] The methods described are, however, based on highly invasive devices and personalised algorithms, which makes them less generally applicable. Recently, seizure forecasting based on non-EEG wearables was examined, but these methods have not yet reached high accuracy.[74, 75] A feasibility study using wearable smartwatches found that circadian and multiday heart rate cycles showed the best predictive value for seizure forcasting.[76] Apart from bio-signal monitoring, SDDs and smartphones are able to detect more complex behavioural changes.[75] Activity and sleep patterns, and indicators of concentration and mood might provide an interesting tool for seizure forecasting in the future.

Personalized seizure detection

Multiple chapters of this thesis have discussed the potential advantages of tailored SDD approaches including personalised algorithms. The implementation of these strategies poses significant challenges. Manual adjustment by clinical experts is very time-consuming and can only be applied when a sufficient number of seizures is recorded. Real-time user feedback and automatic personalisation are more practical approaches.[7, 8] Personal feedback gives users control over their device and has the potential to optimise the device to the user's needs. Conversely, there is a high risk of incorrect feedback, especially in people with seizures with impaired awareness or post-ictal confusion. This might negatively influence device accuracy, and consequently may influence SDD certification and reimbursement. Automated personalisation methods using AI have more potential to become accurate. All performance claims, however, are based on the original, fixed algorithm, so they pose the same certification and reimbursement problems. A possible solution might be to develop a device with multiple certified and validated algorithms tailored to specific user groups and user needs. During ambulatory use, the device would recognise individual seizure characteristics and thus be able to select the best suitable algorithm in response to user feedback.

OVERALL CONCLUSIONS

In conclusion, while current wearable SDDs may accurately detect convulsive seizures, future long-term home-based trials are needed to improve performance for other seizure types, to offer tailored solutions for specific user groups and to explore their potential in monitoring individual treatments and seizure forecasting.

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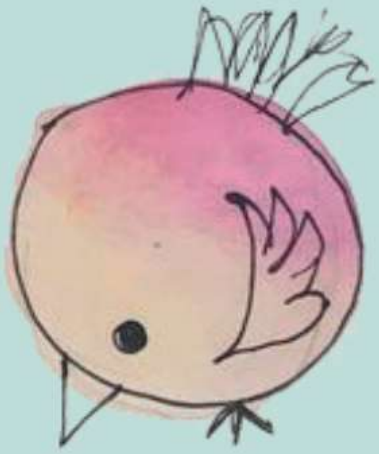

APPENDICES

NEDERLANDSE SAMENVATTING (Dutch Summary)

Onze wetenschappelijke reis begon met het verkennen van autonome uitingen van epilepsie. Deze kunnen ernstige complicaties van epilepsie veroorzaken, maar ook gebruikt worden om epileptische aanvallen te detecteren en zo complicaties te voorkomen. We valideerden aanvalsdetectiehulpmiddelen bij kinderen met epilepsie in hun thuissituatie en beoordeelden hierbij de waarde van deze apparaten voor families en de samenleving. Onze reis zette zich voort met kwalitatief gebruikersonderzoek om behoeften van ouders van kinderen met epilepsie te ontdekken.

Autonome symptomen van epilepsie onthuld

Autonome manifestaties van epilepsie kunnen ernstige complicaties veroorzaken. Postictale aritmieën zijn vaak geassocieerd met plotselinge dood in epilepsie (sudden unexpected death in epilepsy, SUDEP)[1,2] en ictale asystolie (IA), wanneer het leidt tot syncope, kan gevaarlijk traumatisch vallen veroorzaken. Omgekeerd kunnen ictale autonome fenomenen ook helpen bij de ontwikkeling van interventies om complicaties van epilepsie te voorkomen.

In **Hoofdstuk 2** bestudeerden we de potentie van veranderingen in autonome functie als hulpmiddel om tijdig epileptische aanvallen te detecteren. We doorzochten de literatuur op systematische wijze en beoordeelden de kwaliteit van de onderzoeken met een gevalideerde vragenlijst (QUADAS-2)[3] en recent gepubliceerde kwaliteitsnormen voor het rapporteren van aanvalsdetectiealgoritmes.[4] De kwaliteit van de gevonden artikelen over aanvalsdetectie op basis van autonome parameters was over het algemeen laag. In bestaande detectiealgoritmes werden hartslag en hartslagvariabiliteit het meest gebruikt. Over het geheel genomen leverden deze algoritmes een hoge sensitiviteit op, meestal >80%.[5-18] Ook toonden ze een korte detectie latentietijd, in het bijzonder voor hartslagvariabiliteit, variërend van acht minuten voor tot negentien seconden na het begin van de aanval.[5-7, 9, 10, 13] De frequentie van valse alarmen, als het genoemd werd, was hoog. Deze viel niet lager uit dan één vals alarm per drie uur voor een geïndividualiseerd algoritme[7] en kon oplopen tot vijf valse alarmen per uur voor een generiek algoritme.[13] We vonden onderbouwingen dat de combinatie van verschillende modaliteiten in één apparaat het aantal valse alarmen kan verlagen en dus een voordeel heeft ten

opzichte van unimodale apparaten. Een andere oplossing om de frequentie van valse alarmen te verlagen, zou gepersonaliseerd maatwerk van het algoritme kunnen zijn.[7, 8, 19] Wij concludeerden dat langdurige en 'real-time' monitoring in de thuissituatie nodig is om meer betrouwbare data te verkrijgen en om de voorgestelde strategieën voor het verminderen van valse alarmen uit te testen.

In **Hoofdstuk 3** bespraken we de complexiteit van de behandeling van IA, een periode van een afwezig hartritme tijdens een epileptische aanval. IA wordt vaak verkeerd gediagnosticeerd als primaire cardiale aandoening en behandeld met het implanteren van een pacemaker. Behandeling met een pacemaker kan in sommige patiënten met IA helpen om syncope te voorkomen, maar het zal geen epileptische aanvallen tegenhouden. Het implanteren van een pacemaker moet daarom alleen worden overwogen in die gevallen waar eerdere behandeling er niet in is geslaagd om epileptische aanvallen met syncope te voorkomen. Cardioinhibitie, vasodepressie of een combinatie van beide kan syncope in IA veroorzaken.[23-26] Het voordeel van een pacemaker kan beperkt zijn als vasodepressie domineert als het uitlokkende mechanisme achter de syncope.[20-22] In **Hoofdstuk 4** onderzochten we een nieuwe, indirecte methode om te ontcijferen welk mechanisme dominant is, waarbij de relatieve timing van het begin van de IA en het begin van de syncope worden vergeleken. We hebben video-elektro-encefalografie opnames van 38 focale epileptische aanvallen van 29 individuen retrospectief geanalyseerd. We ontdekten dat in slechts twee gevallen het begin van IA te kort op het begin van de syncope was (≤3 sec.), waardoor vasodepressie en niet cardioinhibitie de dominante oorzaak van de syncope moest zijn geweest. Bewustwording onder artsen van deze verschillende pathofysiologische mechanismen van syncope bij IA kan helpen om onnodige pacemaker plaatsing te voorkomen.

Validatie van prestaties van epilepsie aanvalsdetectoren

De aanvalsdetectiemarkt groeit enorm, maar het bewijs voor de prestaties van detectiehulpmiddelen is van lage kwaliteit.[27] Volgens de normen voor het testen en klinisch valideren van aanvalsdetectoren voor epilepsie, gepubliceerd in 2018,[4] zijn er maar drie beschikbare hulpmiddelen die gevalideerd zijn in fase 3 onderzoeken en zijn twee hiervan ook in fase 4 onderzoeken getest.[27] De overige onderzoeken worden geclassificeerd als fase 0, 1 of 2 en gebruiken vaak geen continue 'real-time' data en aanvalsdetectiealgoritmes die getraind en getest zijn op dezelfde dataset, wat vraagtekens plaatst bij de generaliseerbaarheid van deze resultaten.[4, 27] De twee fase 4 onderzoeken laten

de geschiktheid en bruikbaarheid van draagbare hulpmiddelen zien voor de detectie van convulsieve aanvallen in de thuissituatie, maar includeerden veel mensen die in een zorginstelling woonden.[28, 29] Deze onderzoeken zijn daarom niet helemaal representatief voor de thuissituatie.

PROMISE is het eerste prospectieve fase 4 multicenter implementatieonderzoek in de thuissituatie dat langdurige video-gecontroleerde prestatiedata van NightWatch in een kindercohort combineert met vragenlijstdata over het effect van NightWatch op stress, slaap en kwaliteit van leven van hun verzorgers. In **Hoofdstuk 5** presenteren we de resultaten van het PROMISE-onderzoek. Gebaseerd op 2310 opgenomen nachten (28.173 uur) met 552 grote aanvallen, toonde NightWatch een mediane sensitiviteit van 100% (spreiding 46-100%), met een mediane frequentie van valse alarmen van 0,04 (spreiding 0,00-0,53) per deelnemer per uur. Vergeleken met eerdere resultaten van NightWatch bij volwassenen is de sensitiviteit in dit cohort van kinderen iets hoger en dat geldt ook voor de frequentie van valse alarmen.[29] Eén derde van de valse alarmen was gerelateerd aan kleine aanvallen en de overige aan momenten van wakker worden in de nacht en niet-epileptisch ritmische bewegingen. Kinderen hebben andere hartslagprofielen dan volwassenen (hogere rustwaarden en grotere hartslagvariabiliteit)[30, 31] en vooral degenen met ontwikkelingsproblemen laten uitdagend gedrag en slaap-gerelateerde ritmische bewegingen zien.[32] Een baseline periode van twee maanden werd vergeleken met twee maanden interventie met NightWatch. Verzorgers rapporteerden een positief effect op hun ervaarde stress tijdens het gebruik van NightWatch, terwijl hun kwaliteit van slaap en leven niet significant veranderde. Een mogelijke verklaring voor dit minimale effect is de duur van de interventieperiode; het was wellicht te kort voor verzorgers om het apparaat volledig te vertrouwen en hun eigen alertheid in de nacht los te laten. Een andere verklaring kan zijn dat een aanvalsdetectiehulpmiddel, zeker op korte termijn, niet de algehele last en bijkomende stressoren van het zorgen voor een kind met epilepsie kan wegnemen.

Hoewel de bruikbaarheid van draagbare aanvalsdetectoren is aangetoond in twee fase 4 studies,[28, 29] zal niet iedere persoon met epilepsie een draagbaar apparaat verdragen en geven sommigen de voorkeur aan een hulpmiddel op afstand. Daarom hebben we retrospectief de prestaties geanalyseerd van een ‘real-time’ video detectiealgoritme gebaseerd op 1661 nachtelijke opnames van

22 kinderen (**Hoofdstuk 6**). Het videoalgoritme toonde over alle convulsieve aanvallen een sensitiviteit van 78% en voor de detectie van hypermotore aanvallen was dit 73%. Valse alarmen (n=87) kwamen alleen in een kleine groep kinderen voor (frequentie van valse alarmen 0,05/nacht) en waren vooral gerelateerd aan gedrag. In vergelijking met een eerder onderzoek bij volwassenen[33], vonden we een lagere sensitiviteit, maar ook minder valse alarmen. Dit is de eerste aanvalsdetectiemethode gebaseerd op video die getest is op een grote dataset (anders dan de training dataset) met continue video-opnames. Vergeleken met andere aanvalsdetectoren op afstand, die gebruik maken van bedsensoren, laat deze methode een iets lagere sensitiviteit zien, maar ook een lagere frequentie aan valse alarmen, waardoor het een mooi alternatief vormt voor draagbare aanvalsdetectoren.[29]

De waarde van epilepsie aanvalsdetectoren voor families en de maatschappij

Recente richtlijnen voor de klinische praktijk geven aan dat draagbare aanvalsdetectoren effectief zijn voor accurate detectie van convulsieve aanvallen, maar het blijft onbekend of deze detecties resulteren in betekenisvolle uitkomsten.[27] De waarde van een aanvalsdetector kan op verschillende niveaus worden gemeten; van klinische uitkomsten in een persoon met epilepsie tot de impact op een familie en zelfs tot grotere effecten vanuit een maatschappelijk perspectief. Al deze verschillende contexten zijn belangrijk om de toegevoegde waarde van aanvalsdetectoren vast te stellen.

In **Hoofdstuk 7** wordt de eerste economische evaluatie van een aanvalsdetector vanuit een maatschappelijk perspectief omschreven. Gebaseerd op 41 kinderen uit het PROMISE-onderzoek onderzochten wij de kostenutiliteit en kosteneffectiviteit van de implementatie van NightWatch. We observeerden een daling in gemiddelde kosten van €775 tijdens de twee maanden interventie met NightWatch ten opzichte van een periode van twee maanden zonder aanvalsdetector (baseline). Op een plafond verhouding van €50.000 per ‘quality adjusted life year’ (QALY) toonde NightWatch een kans van 72% om kosteneffectief te zijn. Dit effect kwam voornamelijk door veranderingen in gezondheidszorgkosten, inclusief ziekenhuisopnames, medicatie en fysiotherapie. Stress van ouders en QALY’s droegen niet bij aan de kosteneffectiviteit; beide toonden gelijke scores gedurende de interventie en baseline periode. Mogelijke verklaringen zijn de korte interventieduur of het

netto effect van enerzijds een positieve impact van NightWatch en anderzijds het nadelige effect van ‘alarmmoeheid’.

In **Hoofdstuk 8** onderzochten we de toegevoegde waarde van aanvalsdetectie op verzorgers van een kind met epilepsie. Diepte-interviews met 21 ouders van het PROMISE-onderzoek toonden dat de waarde van NightWatch voornamelijk beïnvloed werd door de manier waarop ouders omgingen met de zorg voor hun kind en hoe zij hun zorglast ervaarden. De prestaties van NightWatch-detecties leken hierbij minder belangrijk. Gedreven door de angst om hun kind te verliezen, ontwikkelden ouders een persoonlijk beschermingsgedrag naar hun kind met epilepsie. Dit gedrag wordt ook gezien in ouders van kinderen met andere chronische aandoeningen.[34-36] Het kan ouders helpen om het gevoel van controle te geven en angst te verminderen, maar het kan juist ook de zorglast vergroten. De flexibiliteit van ouders in dit beschermingsgedrag bleek doorslaggevend in hoeverre NightWatch de familie kon ondersteunen. NightWatch had in veel families een toegevoegde waarde door als extra back-up te fungeren en de last van aanvalsmonitoring te verminderen. Echter, NightWatch kon niet de angst om je kind te verliezen wegnemen. Zorgprofessionals en aanvalsdetectiebedrijven moeten zich daarom bewust zijn van dit ouderlijk beschermingsgedrag en de hoge zorglast die ouders ervaren. Het is noodzakelijk om verschillende behoeftes van ouders hierin te erkennen en open te staan voor gepersonaliseerde aanpassingen om de implementatie te verbeteren.

Gebruikersvoorkeuren voor aanvalsdetectie

Tijdens de ontwikkeling van epilepsie aanvalsdetectoren worden er cruciale beslissingen gemaakt door aanvalsdetectiebedrijven, vaak in combinatie met zorgprofessionals. Hun waarden zijn echter niet representatief voor alle betrokkenen. Succesvolle implementatie van aanvalsdetectoren vereist een goede aansluiting met de eindgebruiker. Het is daarom belangrijk om gebruikersvoorkeuren voor epilepsie aanvalsdetectoren te begrijpen.

In **Hoofdstuk 9** ontdekten we de diepere behoeftes en wensen voor aanvalsdetectie van professionele en informele verzorgers van kinderen met epilepsie. Hiervoor gebruikten we een nieuwe onderzoeksmethode in de epilepsie: ‘context mapping’. Vertrouwen kwam als meest belangrijke thema naar voren en we vonden verschillende elementen die verzorgers konden helpen om meer vertrouwen in een apparaat te krijgen. Dit betrof het integreren

van verschillende modaliteiten, de mogelijkheid om alle parameters inzichtelijk te maken, personalisatie van het algoritme, aanbeveling door een neuroloog en een testperiode. De belangrijkste elementen werden geïntegreerd in een 'discrete choice experiment' (DCE) om hun relatieve invloed op gebruikersvoorkeuren te kunnen kwantificeren. **Hoofdstuk 10** toont de resultaten van een online vragenlijst, inclusief het DCE, die volledig is ingevuld door 49 verzorgers. Alle DCE-attributen hadden een hoge invloed op de keuze van ouders in de volgende volgorde van belangrijkheid: 'in gebruik nemen', 'personalisatie', 'interactie', 'alarm' en 'interface'. Ouders gaven de voorkeur aan een alarm voor zowel grote als kleine aanvallen en om het detectiealgoritme te personaliseren. Dit staat in contrast met resultaten uit eerdere onderzoeken waar voorkeuren voor beperkte en geautomatiseerde alarmen en interacties met het apparaat werden geuit door gebruikers.[37] De online vragenlijst keek ook naar de voorkeur van ouders voor de balans tussen sensitiviteit en positief voorspellende waarde terwijl er rekening gehouden werd met individuele aanvalsfrequentie. Relatief meer valse alarmen had de voorkeur boven gemiste aanvallen, vooral bij diegenen met een lage aanvalsfrequentie. We ontdekten een brede variatie in voorkeuren voor aanvalsdetectie tussen verschillende groepen gebruikers, zowel binnen ons onderzoek als in vergelijking met andere onderzoeken. Zo gaven ouders van kinderen met ontwikkelingsproblemen eerder de voorkeur aan overleg met een neuroloog voor het gebruik van een aanvalsdetector, opties om meetwaarden in te zien tijdens een alarm en de mogelijkheid om het detectie algoritme aan te passen door middel van persoonlijke feedback. Deze bevindingen accentueren heterogeniteit onder gebruikersgroepen en benadrukken het belang van een aanpak op maat waarbij de gebruiker centraal staat tijdens de ontwikkeling van aanvalsdetectoren om zo tegemoet te komen aan de verschillende behoeftes en om implementatie te optimaliseren.

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אהוב שלי, מאיפה אני מתחילה להודות לך?
תודה שנכנסת לחיים שלי ,תודה על החיוך שלך, תודה על כל החיבוקים שלך, תודה על התמיכה האינסופית שלך ,תודה לך ההבנה ,תודה שתמיד היית שם בשבילי ,תודה על היותך מדהים ,אני פשוט לא יודעת מה הייתי עושה בלעדיך.

BIOGRAPHY Anouk van Westrhenen