Portable noninvasive focal seizure detection in epilepsy: A systematic review

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***Abstract*—**
***Background*:** Detection of focal epileptic seizures during activities of daily living has potentially important benefits, from robust and objective seizure reporting, to life-saving precautionary measures by notifying the patients themselves, family members or caregivers in a timely manner.
***Objective*:** This systematic review aims to account for current research on portable focal seizure detection solutions and to give a scientific basis for future development of telemonitoring solutions.
***Methods*:** The PubMed database was systematically searched for original records validating the use of portable noninvasive devices and setups for focal seizure detection. Reviews and meta-analyses were screened for relevant references to identify original records not covered by the search in PubMed. Included records are summarised in terms of modality, seizure type, study phase, aim, description and result metrics.
***Results*:** A total of 17 out of 153 identified records were included in the qualitative synthesis. 11 records used ECG modality, out of which 8 were single-modality, and 3 were used in a multi-modal setup.
***Conclusion*:** Future focal seizure detection will likely rely on the fusion of multiple biosignals to reliably distinguish movement-related tachycardia and onset of focal seizures. One of the most promising single-modality methods for detecting focal seizures, is the use of ECG for heart rate variability analysis. Combining heart rate variability with movement data from e.g. accelerometer is an attractive direction for future research.

***Index Terms*—seizure detection, focal seizure, telemonitoring**

I. Introduction

A. Background

Epilepsy is one of the most common neurological disorders in the world, with a prevalence between 5.8 and 15.4 per 1000 citizens depending on the country [1]. WHO estimates around 50 million people worldwide are actively living with epilepsy, of which 70 % could live seizure-free, if properly diagnosed and treated [2]. This leaves an estimated 30 % of people with epilepsy untreatable, and obliged to live with unpredictable symptoms, such as seizures, which can be life-threatening, especially when unattended [3].

Detection of focal epileptic seizures (FS) is a growing research area, with many wearable devices used in recent papers. Today, several wearable devices for detecting seizures are commercially available [4], but these primarily focus on generalized tonic-clonic seizures (GTCS), or focal onset seizures (FOS) with motor features. Wearable devices for detecting focal seizures without convulsion are not yet available to patients.

Devices with this capability would help quantify the seizure burden to patients with focal epilepsy, as they would provide objective data on the number of seizures the patient has. This would provide caregivers with an insight into how well the patient responds to medication plans over time, and mitigate the well-known challenge of under-reporting epileptic seizures [5].

For the patient group living with FOS, an alarm in the early stages of a seizure could reduce the response time before caregivers or family members arrive to attend the patient during the tonic-clonic phase. Further, it could warn the patient about an impending seizure, and potentially dangerous activities such as driving or operating heavy machinery can be discontinued.

Current research points at multiple biomarkers for detecting focal seizures, such as electrocardiography (ECG) [6]–[13], behind-the-ear electroencephalography (EEG) [14], accelerometry (ACM) [15], [16] and more. Many of these biosignals can be recorded in wearable devices, which has the potential to help patients with focal epilepsy in their daily lives. Multiple studies have investigated the effect of combining the analysis of several biosignals to improve sensitivity and lower false alarm rates (FAR) in multimodal setups [17]–[21].

B. Objective

To support the current direction of research in wearable focal seizure detection, this systematic review aims to elucidate the current research in wearable devices for focal seizure detection. Ultimately this will provide researchers with an informed basis, on which telemonitoring solutions can be developed.

To the best of our knowledge, this is the first review to focus specifically on literature for wearable devices to detect focal seizures.

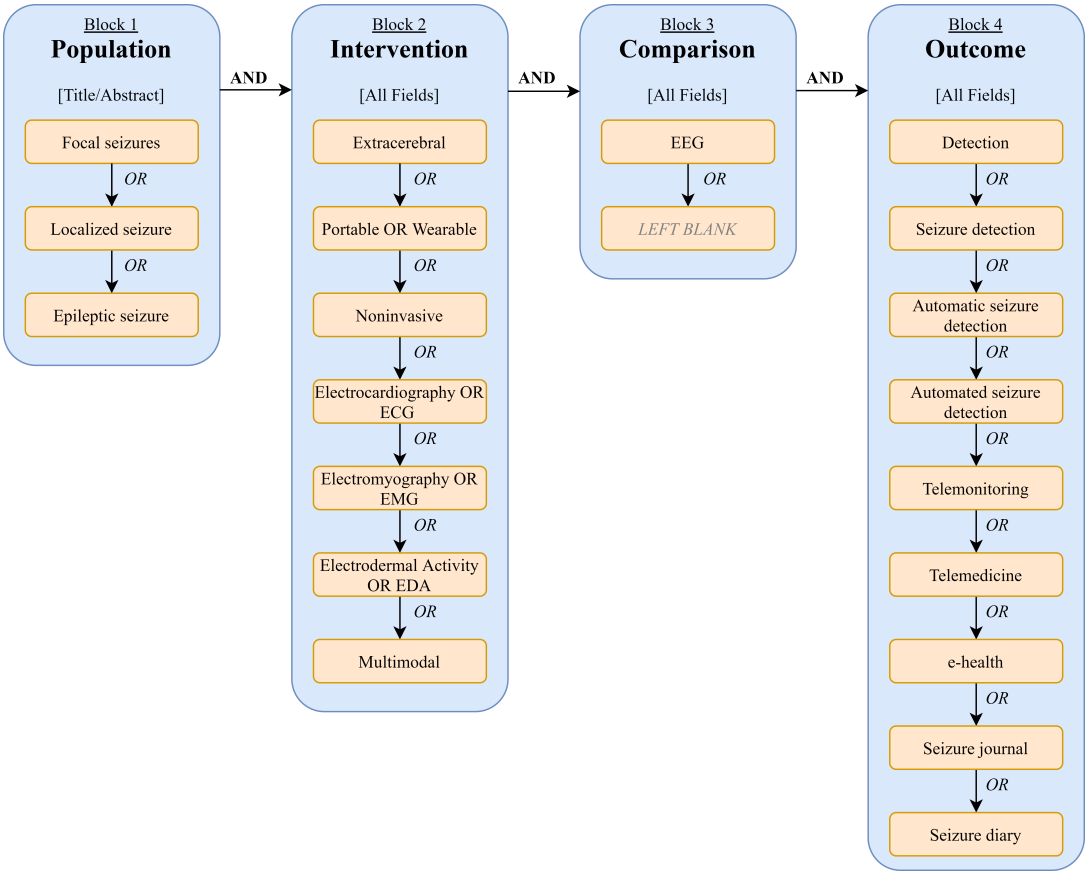

Figure 1. Structure of the block search

Table I
PICO MODEL

P	I	C	O
Population	**Intervention**	**Comparison**	**Outcome**
Patients with focal epileptic seizures	Portable noninvasive detection devices	EEG/video-EEG as the golden standard	Reliable detection of focal seizures without convulsion

II. METHODS

The recommended reporting items for systematic reviews, PRISMA-P, guidelines were adhered to for structuring the search protocol, and for setting up the flow diagram [22]. This was done to ensure the highest possible level of reproducibility.

The PubMed database was systematically searched in November 2020 for original records validating the use of portable noninvasive devices and setups for focal seizure detection.

A. Structuring research subject

The PICO process was used for focusing the search protocol, and building the search query [23]. The database search was carried out using block search with search terms as specified in figure 1.

B. Inclusion and exclusion criterias

Records were included if they met the following criteria: (1) English language, (2) Dates after 2010, (3) disease in question is epilepsy with focal seizures (4) record is either a clinical trial, validation study or comparative study, (5) focus is on wearable technology and (6) record is original research.

Records were excluded if there were no specification of which biomarker was used, or if the device in question was implantable, i.e. 'invasive'.

C. Selection process

For structuring the selection process, a PRISMA flow diagram was utilized, as seen in figure 2 [24]. All reviews and meta-analyses found in the selection process were excluded as "Not original research", however, all references contained were screened to assess whether they fit with the research subject of this systematic review. This was done to identify original studies not covered by the search in PubMed. The relevant records identified through references in the reviews and meta-analyses were marked as "Additional records identified through other sources" in the flow diagram.

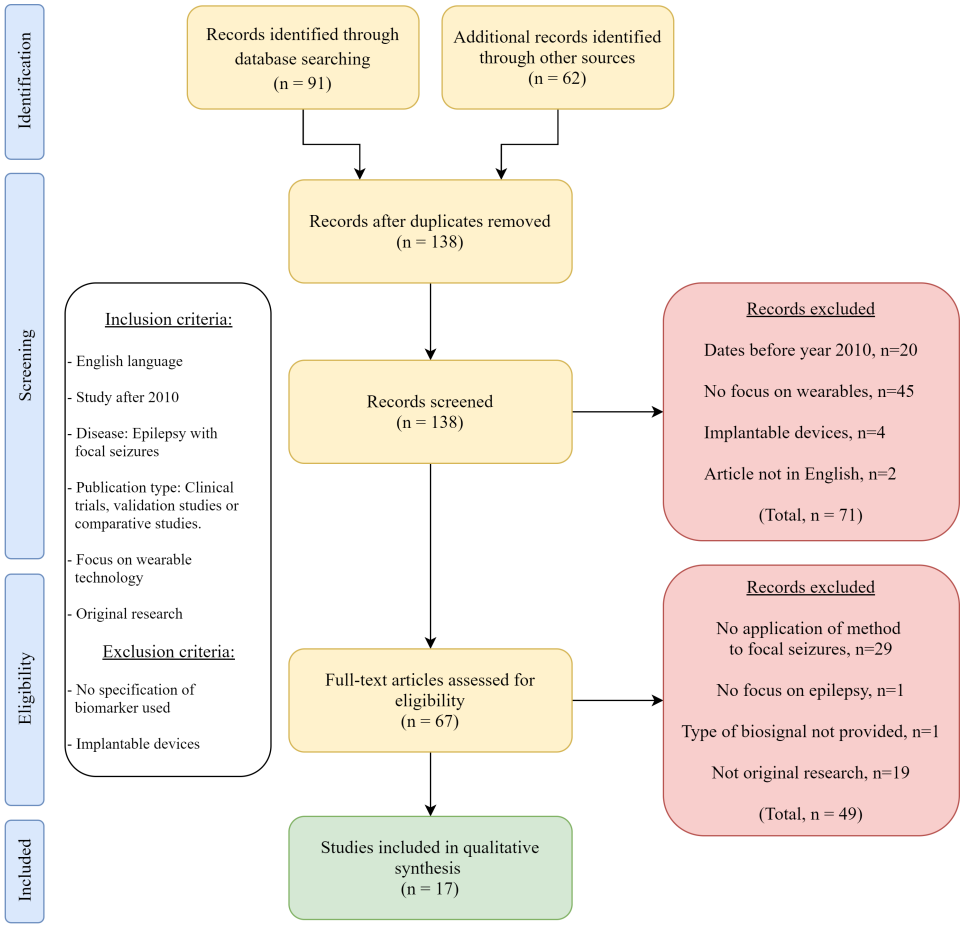

Figure 2. PRISMA Flow-diagram [24]

III. Results

When including all four search blocks, a total of 91 records are identified in the database search. A total of 62 studies were identified through other sources, which constitute chain searching the references in identified reviews and meta-analyses listed in table II. After title/abstract screening, 67 records were selected, and after full-text screening, a total of 17 articles were found eligible for qualitative synthesis. Most of the excluded records had no focus on wearables (n=45), and many others had no focus on focal seizures (n=29). Another group of excluded records are those dating back to before 2010 (n=20).

Table II
Reviews and meta analyses identified

Reference	Year	Review type	# records included
Ryvlin et al. [25]	2020	Narrative review	19
Kim et al. [26]	2020	Narrative review	34
Bruno et al. [4]	2020	Narrative review	22
Westrhenen et al. [27]	2019	Systematic review	21
Beniczky et al. [28]	2019	Narrative review	22
Amengual-Gual et al. [29]	2019	Narrative review	Unclear
Leijten [30]	2018	Narrative review	7
Behbahni [31]	2018	Narrative review	Unclear
Van de Vel et al. [32]	2016	Narrative review	29
Ulate-Campos et al. [33]	2016	Narrative review	Unclear
Shmuely et al. [34]	2016	Narrative review	Unclear
Jory et al. [35]	2016	Systematic review	43
Hemery et al. [36]	2014	Meta analysis	24

A. Types of acquisition methods identified

Table III shows the types of biosignals measured in the included records. Most of the studies focused on ECG (n=11) as the primary modality for detecting focal seizures.

1) Electrocardiography (ECG): The primary focus of the ECG in all included records was to isolate the heart rate variability, as seizures are related to an increase i sympathetic activity, leading to a rapid variation in heart rate. Another primary biomarker of interest, which can be derived from ECG, is tachycardia due to its common co-occurance with focal seizures. It reflects propagation of ictal discharges in the brain, leading to an increase in heart rate [37].

Alternative methods for detecting tachycardia, included photoplethysmography (PPG) in a wearable sensor (n=2) [17], [20]. These were only included as part of a multimodal setup. Vandecasteele et al (2017) [17], did a comparison

Table III
MODALITIES IN INCLUDED RECORDS

Modality investigated	# of records
Multimodal	5
Electrocardiography (ECG)	11
Heart rate (HR)	1
Electroencephalography (EEG)	1
Behind-the-ear EEG	1
Electrodermal activity (EDA)	3
Accelerometer (ACM)	4
Electromyography (EMG)	1
Photoplethysmography (PPG)	2
Near-infrared spectroscopy (NIRS)	1

between seizure detection based on wearable ECG, hospital ECG and wearable PPG. They found the algorithm only performed with a sensitivity of 32 % when solely relying on PPG for focal seizure detection.

2) Accelerometry (ACM): 2 records [15], [16] used ACM as the only modality, but these included focal seizure types with motor features, like focal onset tonic-clonic seizures. ACM alone cannot detect seizures without motor features, as it relies on movement. All records using ACM placed the device on the patient's wrist, as this would entail the largest oscillations during convulsive seizure.

3) Ear-EEG: A single record used behind-the-ear EEG in order to compare with conventional EEG for seizure detection [14]. This involved placing two electrodes behind each ear (four in total) to capture EEG activity. At the time of this study, this solution was not yet embedded in a wearable device, but wired to a clinical EEG amplifier. The results show a relatively higher sensitivity for behind-the-ear EEG (94.5 % as opposed to 100 % for conventional scalp EEG), as well as a relatively lower false alarm rate (0.52 / hour, as opposed to 1.14 / hour for scalp EEG). As these performance metrics are very much comparable to scalp EEG, this poses a viable modality in a future wearable system.

However, as pointed out by Yamakawa et al (2020) [6], using EEG in a wearable devices could cause practical challenges. EEG typically requires a sampling frequency of at least 500 Hz, producing a large amount of data for processing and transmitting, and thus a large amount of battery consumption.

4) Near-infrared spectroscopy (NIRS): A single record explored the use of NIRS to measure changes in oxygenated (HbO), deoxygenated (HbR), and total hemoglobin (HbT) at left and right side of the frontal lobe [38]. The authors found a sensitivity of 6-24 % suggesting NIRS is not a viable modality for a wearable seizure detection system.

5) Multimodal: 5 records used multimodal algorithms [17]–[21], including combinations of ECG (n=3), EDA (n=3), PPG (n=2), ACM (n=2) and EMG (n=1). None of the studies were based on EMG, EDA or PPG as the only modality.

A single record using a multimodal setup did not report any performance metrics [21].

B. Characteristics of included records

Based on the "Standards for testing and clinical validation of seizure detection devices" by Beniczky and Ryvlin [39], 11 of the 17 included records are classified as phase 2 studies. This implies the use of dedicated seizure detection devices, and typically on a somewhat larger number of patients (n≥10), and typically with a substantial amount of seizures (n≥15).

Based on the "Operational Classification of Seizure Types" of 2017 [40], all records investigated one or more focal seizure types. These include focal impaired awareness seizures (FIAS), focal awareness seizures (FAS), focal to bilateral tonic-clonic seizures (FBTCS) and focal onset tonic-clonic seizures (FOTCS). Some records (REF) include generalized onset seizures, while also covering focal seizure types.

All records, except one [21], reported the sensitivity of the proposed method, and 13 of the 17 records reported the false alarm rate.

Most of the records used offline recording and analysis of data, but some used Bluetooth to continuously send data or events (n=4) [6], [15], [16], [21]. No records used data collection in patient home, or anywhere outside a hospital setting.

The characteristics of the included records are summarised in tables IV and V.

Table IV
PART 1: SUMMARY OF INCLUDED RECORDS

Reference	Modality	Seizure type	Study phase	Aim and description of study	Results
Yamakawa et al. (2020) [6]	ECG	Focal	2	Evaluation of prototype telemeter. An originally developed telemeter for measuring ECG and deriving R-R intervals was developed. In this study, the authors evaluate the feasibility and reliability of this device on seven patients admitted to long-term video-EEG monitoring. The developed device streams Bluetooth to a custom made Android app.	Sensitivity: 85.7% FAR: 0.62 / hour
Jeppesen et al. (2020) [7]	ECG	FOTCS, GTCS, FIAS, FAS	2	Validation of predefined seizure detection algorithm based on heart rate variability (HRV) using patient-specific cutoff values. ECG was recorded using an offline wearable device (ePatch). 19 patients were admitted to long-term video-EEG monitoring, and 11 of these were classified as responders.	Sensitivity: 87.0% FAR: 0.9 / 24 hours (95% CI: 73.2%-100%) and 0.22 / night
Jeppesen et al. (2019) [8]	ECG	FOTCS, GTCS, FIAS, FAS	2	Assessing the feasibility and accuracy of seizure detection based on heart rate variability (HRV) using a wearable ECG device (ePatch). Comparison of 26 automated algorithms. Offline recording/analysis This study included 126 seizures (108 nonconvulsive, and 18 convulsive) from 43 patients.	Sensitivity: 93.1% for all seizures. 90.5 % for non-convulsive. FAR: 1.0 / 24 hours 0.11 / night
Forooghifar et al. (2019) [9]	ECG	Focal	1	Evaluation of machine learning algorithm, which can autonomously adjust performance/power trade-off. In this study, they use data from the SmartCardia INYU wearable sensor. 18 patients with 211 hours of data total.	Sensitivity: 88.7% or 85.54% to 79.33% when considering battery life
Gu et al. (2018) [14]	Ear-EEG	FIAS	1	Comparison of scalp EEG and wearable behind-the-ear EEG. Data from 12 patients, where both scalp and behind-the-ear EEG were recorded for comparison. Detection algorithm based on support vector machine (SVM). The recording was done using electrodes behind the ear, and not a dedicated device, however, the method can be implemented into a wearable behind-the-ear EEG device.	Scalp EEG Sensitivity: 100% FAR: 1.14 / hour Behind-ear-EEG Sensitivity: 94.5% FAR: 0.52 / hour
Cooman et al. (2018) [10]	ECG	Focal	1	Nocturnal heart rate based seizure detection algorithm that automatically adapts to the patient without requiring seizure labels. Evaluated on 28 pediatric patients with a total of 107 seizures, of which 77 were focal. Data recorded with stationary hospital ECG equipment, but the low complexity algorithm is suitable for implementation on wearable devices.	Sensitivity: 77,6 % FAR: 2.56 / night
Vandecasteele et al. (2017) [17]	Multimodal (ECG and PPG)	Focal	2	Comparison between wearable ECG and PPG to hospital ECG using existing seizure detection algorithm made in MATLAB. PPG device: Empatica E4. ECG device: eMotion Faros. Data was recorded and analyzed offline for this study, byt the Faros has Blutooth data streaming capabilities. Recruited 11 patients with a total of 47 seizures. Wearable ECG proved to have the same overall performance as conventional stationary hospital ECG.	Sensitivtiy Hosp. ECG: 57% Wear. ECG: 70% Wear. PPG: 32% FAR (pr. hour): Hosp. ECG: 1.92 Wear. ECG: 2.11 Wear. PPG: 1.80
Onorati et al. (2017) [18]	Multimodal (EDA and ACM)	FOTCS, FBTCS	2	Aims to quantify performance of new multimodal wrist-worn convulsive seizure detectors. Empatica E3 and E4, as well as iCalm from MIT Media Lab. 69 patients admitted to long-term video-EEG monitoring, of which 22 had seizures (6 FOTCS and 49 FBTCS). 5928 hours of data. Seizures were annotated and used to train three machine learning classifiers in MATLAB.	Sensitivity: 94.5% FAR: 0.2 / day
Jeppesen et al (2017) [11]	ECG	Focal, GTCS	2	Validation study of improved seizure detection algorithm based on ECG. 14 patients were admitted to long-term video-EEG monitoring. ECG was recorded using wearable ePatch for offline recording and analysis.	Sensitivity: 99.9% FAR: 1.08 / hour
Fürbass et al. (2017) [19]	Multimodal (EEG, EMG, ECG)	FBTCS, Focal	1	This study investigated sensitivity and false detection rate of a multimodal automatic seizure detection algorithm and the applicability to reduced electrode montages for long-term seizure documentation in epilepsy patients. Focus on wearable hardware setup for future research.	Sensitivity: 89% FAR: 12.8 / 24 h

FOTCS = Focal onset tonic-clonic seizure, GTCS = Generalised tonic-clonic seizure, FIAS = Focal impaired awareness seizure
FAS = Focal awareness seizure, FBTCS = Focal to bilateral tonic-clonic seizure, FAR = False alarm rate

Table V
PART 2: SUMMARY OF INCLUDED RECORDS

Reference	Modality	Seizure type	Study phase	Aim and description of study	Results
Cogan et al. (2017) [20]	Multimodal (HR, PPG, and EDA)	FIAS, FOTCS, GTCS	2	Evaluation of seizure detection algorithm implemented in MATLAB based on multiple biomarkers. Wrist-worn wearable devices placed on 10 patients admitted to long-term video-EEG. A total of 26 seizures were recorded to develop and evaluate the algorithm. In this study, the devices were divided into two seperate devices, but the recording of these biosignals can be combined into a single device in the future.	Sensitivity: 100% FAR: 0.015/h
Ahmed et al. (2017) [21]	Multimodal (ECG, EDA, ACM)	N/A	1	Continuous streaming of data via Bluetooth BLE to patient smartphone for real-time seizure detection. System is composed of two wearables, a wrist-worn with EDA and ACM, and an ECG device with three channels.	N/A
Velez et al. (2016) [16]	ACM	FOTCS, FIAS, GTCS	2	Prospective trial with a wristwatch ACM that transmit events via Bluetooth to a tablet next to the patient's bed. Device: SmartWatch, SmartMonitor 27 patients were admitted to long-term video-EEG, where 62 seizures (31 convulsive, 31 nonconvulsive) were recorded. The authors mention the problem of using ACM as a biomarker for nonconvulsive seizures.	Sensitivity: 92.3% (For GTCS)
Fujiwara et al. (2016) [12]	ECG	Focal	1	Validation of heart rate variation analysis algorithm. 14 patients were admitted to long-term video-EEG, where 11 seizures were recorded in 8 of the patients. The recorded ECG signal for this study has been performed with hospital equipment, but the authors mention the intention behind the method is to implement it into a wearable device.	Sensitivity: 91% FAR: 0.7 / hour
Jeppesen et al. (2015) [38]	NIRS	FIAS	2	Use of near infrared spectroscopy as a possible biomarker for focal epileptic seizures. 33 patients were admitted to long-term video-EEG, and 15 of those had 34 focal seizures. Two wireless NIRS spectroscopy devices (PortaLite, Artinis Medical Systems) were placed on the patient's forehead.	Sensitivity: 6-24%
Massé et al. (2013) [13]	ECG	FOTCS, GTCS	2	Describes development and evaluation of wireless wearable ECG monitor (single-lead). 3 patients admitted to long-term video monitoring with an Emfit pressure-sensitive bed mattress, who had a total of 19 seizures. ECG device is worn in a pocket strapped to the patient's upper arm, with wires connected to two electrodes on the torso. Signal is transferred to a computer via radio signal.	Sensitivity: 99.97% FAR: 0.06 / hour
Beniczky et al. (2013) [15]	ACM	FOTCS, GTCS	2	To assess the clinical reliability of a wrist-worn, wireless accelerometer sensor for detecting generalized tonic–clonic seizures (GTCS). 73 patients were admitted to long-term video-EEG monitoring, Data transmitted to a computer via Bluetooth. 149 seizures other than the GTCS were recorded, and none of them triggered an alarm.	GTCS Sensitivity: 91% FAR: 0.2 / day No response on focal seizures

IV. Discussion

The majority of the included records describe a setup in which the biosignal is recorded locally on either a wearable device or stationary hospital equipment. The signal is then transferred to a computer for offline analysis, thus the signal is not continuously processed for real-time seizure detection. Before a system is mature for real-world use, it is required to detect seizures as they occur [4], [39]. So while many of the proposed algorithms show promising results, a challenge still lies in the implementation of these in a real-time detection setup [27].

The next step for this research field is to start phase 3 studies, where the study is still carried out in a hospital setting, but with a complete system as it would function in a home-setting with dedicated seizure detection devices [39].

Common for all the included records, is the focus on algorithm performance in terms of metrics such as sensitivity and false alarm rates. In a phase 3 or 4 study, an additional set of parameters will need to be addressed, as the primary user of the system will shift from being the researchers and hospital staff to being the patients themselves, family members or caregivers [39]. This will require the research to address aspects related to usability of the system, power consumption and general changes in the patients' quality of life [4].

From the findings of this study, it is clear that accelerometers alone can only be used to detect seizures with motor features. However, when designing a multimodal system, accelerometers in combination with other modalities such as ECG could provide a more holistic impression of the context in which the seizures occur. For focal seizures without motor features, the inclusion of accelerometer data in detection algorithms to identify physical activity, could provide a more robust seizure detection with fewer false alarms.

Another promising modality is the use of behind-the-ear EEG, which has the potential to implement the sensitivity from conventional EEG in a portable form factor [14]. However, this modality is still to be implemented in a wearable device.

V. Conclusion

With today's research it is possible to detect changes in the preictal and early ictal phase of a focal epileptic seizure. Heart rate variability analysis by ECG is the most distinctive non-EEG based biomarker for these changes, but a challenge still lies in lowering the false alarm rates to an acceptable level for real-world use.

A future seizure detection system will likely be based on a multimodal approach to maximize sensitivity and minimize false alarm rates. Large prospective phase 3 or 4 studies in a home setting is the next step, to validate the use of multimodal detection systems, and to demonstrate the change in quality of life for the patients and relatives.

Conflicts of interest

There are no conflicts of interests to declare.

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