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SUPPLEMENT ARTICLE

Noninvasive detection of focal seizures in ambulatory patients

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Abstract

Reliably detecting focal seizures without secondary generalization during daily life activities, chronically, using convenient portable or wearable devices, would offer patients with active epilepsy a number of potential benefits, such as providing more reliable seizure count to optimize treatment and seizure forecasting, and triggering alarms to promote safeguarding interventions. However, no generic solution is currently available to reach these objectives. A number of biosignals are sensitive to specific forms of focal seizures, in particular heart rate and its variability for seizures affecting the neurovegetative system, and accelerometry for those responsible for prominent motor activity. However, most studies demonstrate high rates of false detection or poor sensitivity, with only a minority of patients benefiting from acceptable levels of accuracy. To tackle this challenging issue, several lines of technological progress are envisioned, including multimodal biosensing with cross-modal analytics, a combination of embedded and distributed self-aware machine learning, and ultra–low-power design to enable appropriate autonomy of such sophisticated portable solutions.

KEYWORDS

focal seizure, seizure detection, wearable devices

1 | INTRODUCTION

Reliable seizure detection methods to be used chronically (ie, over periods of months or years), in ambulatory patients going about their daily activities, are generally considered an important objective for persons with active epilepsy.[1] A few US Food and Drug Administration–approved or CE-marked noninvasive devices are already available for the detection of generalized or bilateral tonic-clonic seizures (GTCSs),[2–10] but none yet for the detection of focal seizures without GTCSs (which will be referred to as FSs in this review). This reflects the greater complexity of detecting FSs due to their large variety and less dramatic ictal semiology as compared to the very stereotyped and prominent ictal features observed during GTCSs. However, GTCSs only affect a minority of patients with active epilepsy, and also account for a minority of seizures in most patients with focal epilepsy and focal to bilateral tonic-clonic seizures. In a meta-analysis of adjunctive antiepileptic drug (AED) randomized controlled trials in uncontrolled focal epilepsy, which collated 20 studies with information on the proportion of patients with GTCSs, only 36% of 6643 patients suffered at least one GTCS during baseline.[11] In a more recent population-based Swedish study, 51% of patients

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with seizures in the past year did not suffer GTCSs during that period.[12] Thus, moving from the detection of GTCSs to that of only FSs appears highly desirable. In this review, we will address the expected clinical benefits, current stage of development, and foreseeable future of specifically detecting FSs without secondary generalization during ultra-long noninvasive recordings using wearable devices in ambulatory patients, thus excluding the field of electroencephalography (EEG)-based FS detection during in-hospital or home-based short-term (ie, hours to weeks) EEG monitoring.

Key Points

- Detection of focal seizures in ambulatory patients with active epilepsy might provide a number of clinically relevant benefits
- However, no FDA-approved or CE-marked portable noninvasive devices have yet shown reliability for detecting focal seizures
- Effective detection of such seizures is likely to require the combination of neurovegetative and movement-based sensing
- Personalized algorithms will likely prove mandatory to achieve an acceptable level of detection accuracy

2 | POTENTIAL BENEFITS OF FS DETECTION

One of the strong rationales for detecting GTCSs is the possibility of triggering an alarm and allowing timely intervention from a family member or caregiver to reduce the risk of GTCS-induced morbidity and mortality, including sudden unexpected death in epilepsy patients (SUDEP). SUDEP most often occurs in the immediate aftermath of a GTCS, and appears likely to be prevented by early peri-ictal intervention.[13,14] It should be noted, however, that no controlled study has yet demonstrated that the use of GTCS detectors prevents the risk of SUDEP.

Risks entailed by FSs differ from those associated with GTCSs, with lower incidence of traumatizing falls and inhalation, and no available video-EEG evidence that FSs without GTCSs can lead to SUDEP. However, FSs can be responsible for severe trauma and burns, as well as drowning,[15] which might be partly prevented by an alarm-triggered timely intervention of a caregiver. Whether the magnitude of FS-related injuries and their preventability justify the development of FS detection remains uncertain. For instance, a Canadian study showed that the 12-month weighted prevalence of injuries was not different in persons with epilepsy (14.9%) than in the general population (13.3%).[16]

One of the main benefits expected from seizure detection devices is to provide reliable seizure count to guide adjustment of therapy.[17] According to video-EEG monitoring studies, more than half of patients with epilepsy fail to report all their seizures, with overall underreporting exceeding half of seizures.[18] How this issue impacts the quality and efficacy of treatment decision remains uncertain, however. One might argue that physicians should attempt to optimize therapy in patients suffering seizures, regardless of their true seizure frequency, and that unnoticed paucisymptomatic seizures, like interictal epileptiform discharges, do not necessarily require adjustment of AEDs. Here again, studies will be needed to demonstrate that detection of FSs leads to significantly improved patients' outcome. In any event, reliable FS detection would improve the quality, and possibly reduce the sample size, of randomized controlled trials of add-on antiseizure drugs in drug-resistant epilepsy.

Detection of FSs might have a greater role in empowering patients against the many consequences of seizure apparent unpredictability. A seizure-triggered alarm can reduce the burden of not being able to indicate the occurrence of a seizure to witnesses. It might help in self-controlling the propagation of the ictal discharge, aborting it, and reducing the risk of secondary generalization. FS detection could also automatically trigger a therapeutic intervention, although such a noninvasive closed-loop solution would risk adversarial attack. Finally, a reliable detection of FSs could leverage the possibility of identifying individual patients' cycle of seizure recurrence and lead to effective seizure forecasting.[19,20] All of the above could reduce the anxiety and overall handicap resulting from epilepsy, and lead to greater quality of life.

Overall, empirical evidence suggests that persons with FSs are likely to benefit from the development of reliable solutions for detecting their seizures, although such benefit cannot be considered guaranteed and will need to be firmly demonstrated in the future.

3 | CURRENT STAGE OF FS DETECTION

As previously mentioned, no currently available noninvasive device enables a reliable detection of FSs in general. However, a number of studies, summarized in this section, have evaluated the capacity to detect FSs using various measurements of neurovegetative functions (heart rate [HR], electrodermal activity [EDA], respiration), body movements, or ear-EEG.[21]

4 | HR-BASED FS DETECTION USING PHOTOPLETHYSMOGRAPHY OR ELECTROCARDIOGRAPHY

Among potential extracerebral indicators of FS-related autonomous changes, tachycardia is of primary interest due to its common co-occurrence with seizures, reflecting propagation of ictal discharges to central autonomic and limbic networks, and possibly, seizure-induced catecholamine release.[22,23] Tachycardia is related to increased sympathetic activity and has been reported in up to 80% of all seizures, occurring consistently in GTCSs but also in many FSs.[22,24–29] These studies monitored HR using either electrocardiography (ECG) or photoplethysmography (PPG) from wearable sensors.[30,31]

Although sensitive, tachycardia is not a specific marker, because of inevitable changes in HR with daily life activities like walking, climbing stairs, or emotional states. Another HR-related biomarker of interest is HR variability (HRV). HRV is controlled by reciprocal sympathetic and parasympathetic influences and serves to adapt cardiovascular function to external and internal demands.[32] Most of the studies analyzing HRV are retrospective and have used linear time and frequency domain signal processing for feature extraction, as well as nonlinear parameters to assess the changes and the dynamics of RR intervals.[30,33–37] Their sensitivities and false alarm rate (FAR), presented in Table 1, range respectively from 77% to 96.4% and from 0.5/h to 5.4/h.

In the context of vagus nerve stimulation with cardiac-based seizure detection, two epilepsy monitoring unit (EMU)-based series have established the prevalence of various levels of ictal tachycardia, and their respective rate of false detection.[38,39] For the most liberal threshold of 20% increase in HR, sensitivity ranged from 43% to 52.3%, with a false detection rate between 7.15/h and 9/h.[38,39] In contrast, for a more conservative threshold of 60% increase in HR, sensitivity ranged from 8% to 13%, with a false detection rate of 0.5/h and 0.49/h.[38,39]

Two phase 2 studies used a wearable ECG device and HRV measurements to detect FSs. In the first one, 53.5% of patients were considered responders based on the observation of prominent HR changes during seizures. In this subgroup, sensitivity was 90.5%, with an FAR of 1/24 hours.[40] In the second study, the performance of ECG- and PPG-based detection was compared, with the former providing 70% sensitivity and FAR = 2.11/h, whereas the latter only achieved 32% sensitivity with FAR = 1.8/h.[30]

A few commercially available systems based on the noninvasive monitoring of ECG have been developed for seizure detection, including the Proguardian from Livanova using a chest-worn patch, and the Neuronaute from Bioserenity, using a smart T-shirt with textile electrodes. To the best of our knowledge, no clinical study has been reported with these devices.

5 | FS DETECTION BASED ON OTHER NEUROVEGETATIVE BIOSIGNALS, INCLUDING EDA AND PERIPHERAL OXYGEN SATURATION

EDA refers to the dynamic of skin electrical conductance, including slow changes in basal conductance level and transient skin conductance responses. In contrast to cardiac regulation, EDA depends solely on sympathetic control of sweat gland function.[41,42] It is closely linked to emotional and mental arousal. Thus, EDA also offers the possibility of assessing the patient's stress level in general, and might be capable of detecting stress patterns that could trigger seizures and help in their forecasting. An increase in EDA has been reported in some FSs, although of much lower degree than in GTCSs.[42] Thus, although EDA has become one of the most reliable ways to detect GTCSs, it does not appear capable of reliably detecting other seizure types in isolation. Accordingly, there is no study testing EDA for FS detection.

Respiratory changes during seizures result from abnormal activation of the respiratory centers in the brain or brainstem and might result in tachypnea, bradypnea, apnea, hypoventilation, and hypercapnia.[43] These changes can occur during both GTCSs and FSs and are especially common in seizures originating from the mesial temporal structures.[44] Seizure-induced tachypnea appears to follow a specific pattern that differs from increased ventilation during activities of daily living.[26] Hypoxemia, more easily captured than the other respiratory abnormalities using pulse oximetry (to measure peripheral oxygen saturation [SpO_2]), has been the most studied peri-ictal respiratory biomarker. In several studies, hypoxemia < 90% was observed in about one-third of FSs.[45–49]

To perform an appropriate alarm setting for a continuous pulse oximeter, a study assessed cardiopulmonary measures of patients in the EMU. Through systematic evaluation, an optimal balance between true detection and false alarms was achieved with an SpO_2 threshold of 80%-86%, detecting 81%-94% of focal to bilateral tonic-clonic seizures, and 25%-36% of FSs without bilateral spread. FAR ranged from 0.41 to 2.43/h.[50]

6 | MOVEMENT-BASED FS DETECTION USING THREE-DIMENSIONAL ACCELEROMETRY, ELECTROMYOGRAPHY, VIDEO, AND BED SENSORS

A large variety of involuntary body movements can occur during seizures and be detected by three-dimensional (3D) accelerometry (ACC), electromyography (EMG), video, and bed sensors. Although these can vary between patients,

TABLE 1 Validity of extracerebral seizure detection methods for focal seizures

Seizure type	Biosignal	Publication	Device	Patients	Performance	Phase
Focal seizures	ECG	Boon et al (2015)[39]	Hospital ECG & VNS Aspire SR	16	For HR increase > 20%: sensitivity = 52.3%, FP = 7.2/h	2
Focal seizures	ECG	Fisher et al (2016)[38]	Hospital ECG & VNS Aspire SR	16	For HR increase > 20%: sensitivity = 43%, FP = 9/h	2
Focal seizures	ECG	Fujiwara et al (2016)[34]	Hospital ECG	8	Sensitivity = 91%, FP = 0.7/h	1
Focal seizures	ECG	Qaraqe et al (2016)[36]	Hospital ECG	10	Sensitivity = 96.4%, FP = 5.4/h	1
Focal seizures	ECG	Pavei et al (2017)[35]	Hospital ECG	12	Sensitivity = 94%, FP ≤ 0.5/h	1
Focal seizures	ECG	De Cooman et al (2018)[33]	Hospital ECG	19	sensitivity = 77%, FP = 1.24/h	1
Focal seizures	ECG	Jeppesen et al (2019)[40]	ePatch ECG	43	In the 53.5% of responders, sensitivity = 93%, FP = 1/24 h	2
Focal seizures	ECG PPG	Vandecasteele et al (2017)[30]	Hospital ECG, 180° eMotion, E4 Empatica	11	ECG: sensitivity = 57%, FP = 1.92/h; 180°: sensitivity = 70%, FP = 2.11/h; E4: sensitivity = 32%, FP = 1.8/h	2
Focal seizures	ECG EMG	Fürbass et al (2017)[28]	Hospital EMG, ECG	55	EMG: sensitivity = 25%, FP = 0.3/24 h; ECG: sensitivity = 40%; FP = 0.6/24 h	1
Tonic, tonic-clonic, hypermotor	ECG ACC	van Andel et al (2017)[70]	Shimmer	42	Sensitivity = 56%-71%, FP = 2.3-5.9/d, depending on type of signal	1
Tonic, myoclonic, complex partial	ACC	Nijsen et al (2005)[53]	ADXL202E	18	Sensitivity = 0%-100%, depending on patient	1
Myoclonic	ACC	Nijsen et al (2010)[54]	ADXL202E	36	Sensitivity = 34%-80%, PPV = 15%-16%, depending on algorithms	1
Hypermotor	ACC	Van de Vel et al (2013)[55]	Custom-made ACC wristbands	7	Sensitivity = 70%-100%, PPV = 48%-65%, depending on patient	1
Tonic, myoclonic, hypermotor, complex partial	ACC, pressure audio	Patterson et al (2015)[9]	Medpage MP5 Medpage ST-2 Smartwatch, Emfit	41	Sensitivity: 0%-37%, depending on seizure type and device	2
Seizures with motor component	Pressure	Poppel et al (2013)[6]	Emfit bed mattress	45	Sensitivity = 0%-100%, depending on seizure type	2
Seizures with motor component	Pressure audio	Fulton et al (2013)[58]	Medpage MP5 Medpage ST-2	15	Sensitivity = 0%-13%, depending on seizure type and device	2
Myoclonic	Video	Cuppens et al (2012)[57]	Near infrared	3	Sensitivity = 77%, PPV = 87%	1
Tonic	EMG	Larsen et al (2014)[52]	Hospital EMG	6	Sensitivity = 100%, FP = 0.08-7.9/h	1
Focal seizures	EEG	Gu et al (2017)[21]	Behind the ear EEG	12	Sensitivity = 94.5%, FP = 0.52/h	2

Abbreviations: ACC, accelerometer, ECG, electrocardiogram; EEG, electroencephalogram; EMG, electromyogram; FP, false positive; HR, heart rate; PPG, photoplethysmography; PPV, positive predictive value; VNS, vagal nerve stimulation.

detected events are often highly reproducible across seizure episodes within the same individual. Surface EMG proved to reliably detect GTCSs, in particular when placed over the biceps,[2,51] but was also found to be useful for detecting tonic seizures when positioned on the deltoid. Its sensitivity was 100% in four of six patients, but with a high FAR of 7.9/h.[52]

3D accelerometers have proved reliable to detect specific seizure-related movements during FSs. In an early study, accelerometers attached to both arms and legs detected 95% of simple motor seizures, such as myoclonic, clonic, and tonic types.[53] In a subsequent study, the authors could distinguish myoclonic from clonic and tonic seizures, with a success rate of 80%.[54] Using wrist- and ankle-worn accelerometers in a

pediatric population, hypermotor seizures could be detected with a sensitivity of 95.7% and a positive predictive value of 58%.[55] Subsequently, these authors used a subject-specific model in seven patients, achieving a classification rate of 95%, and a positive predictive value of 60%.[56] Movements such as myoclonic jerks can also be detected by appropriate algorithms using only video signal coupled with spatiotemporal interest points, achieving a sensitivity of >75% and a positive predicate value of >85%.[57]

In contrast, in a phase 2 study, the Smartwatch 3D accelerometer (Smartmonitor) was found to detect only 24% of hypermotor seizures and no myoclonic/myoclonic-tonic seizures.[9] Several phase 2 studies were performed using bed mattress sensors. In a series of 15 patients, the Medpage ST-2 was found to detect only one of 10 motor seizures, and none was detected by the Medpage MP5.[58] Using another bed mattress device (Emfit), a greater proportion of motor seizures could be detected, including 57% of simple motor seizures, 27% of tonic seizures, 25% of complex partial seizures with motor involvement, and 8.3% of myoclonic-tonic seizures.[6]

7 | MULTIMODAL DETECTION OF FSS

Combining the outputs of several sensors into one seizure detection method might optimize the sensitivity and reduce the FAR. Only very few studies have addressed this issue.[59,60] In a phase 1 study, detection of FSs was 27% with an FAR of 0.7/d when using ECG only, and 8% with an FAR of 0.4/d for EMG alone; the combination of both sensors raised sensitivity of 89% but also the FAR to 16.4/d.[28] To the best of our knowledge, no phase 2/3 study has yet tested a multimodal sensor device for the detection of FSs.

8 | TOWARD AMBULATORY VERY LONG-TERM EEG FOR DETECTING FSS

Until very recently, there was no available material enabling ambulatory scalp-EEG recordings over ultra-long periods of time (ie, months or years), and the stigmatizing appearance of a scalp-EEG cap had not been addressed. However, over the past few years, systems based on subcutaneous or intra-auricular electrodes have been developed, which might eventually provide reliable chronic EEG recordings.[61] However, the prevalence of movements and muscular artifacts in ambulatory patients is likely to represent a huge challenge for these technologies. Furthermore, although a large variety of algorithms developed for in-hospital EEG seizure detection have demonstrated a good sensitivity (75% and 90%), they have consistently suffered from FARs > 2/d,[62] well above what is acceptable for very long-term monitoring. Thus, it is the view of the authors that future solutions for ambulatory FS detection are unlikely to use EEG in isolation but rather to combine it with non-EEG biosignals.

9 | THE FUTURE OF FS DETECTION

As illustrated by the low accuracy of most previously tested solutions summarized above, the main challenge of FS detection lies both in the large variety of seizure types and in the limited impact on most available biosignals. These challenges translate into the following issues and related objectives for the foreseeable future of FS detection:

1. The most salient ictal phenomenology will effect different biosignals across patients, thus requiring different biosensors to be detected. Some FSs are primarily characterized by prominent movements (hypermotor seizures), which would be best captured by 3D ACC or video in the home environment. Others are not associated with significant movements, but lead to remarkable autonomic changes reflected in biomarkers extracted from HR, EDA, and/or respiratory functions. Finally, some seizures fail to translate into detectable body motion or vegetative changes, and are only captured by EEG.
2. In a significant proportion of FSs, a single biosignal is likely not to be sufficient to reliably distinguish seizures from physiological activities. There, the combination of multiple biosignals will be necessary to make such a distinction, as illustrated in the following example. A patient might present with seizures primarily characterized by centrally triggered tachycardia while not moving. The intensity and type of tachycardia might be comparable to that observed during physical exercise, and thus not able to distinguish seizure from such exercise. Conversely, the information provided by coupling HR and movement measurements will allow firmly ascribing the non–movement-related tachycardia to a seizure. With at least six raw biosignals currently available to assess brain and body outputs (movements, HR, other ECG features, SpO_2, EDA, EEG), the potential for enhancing cross-modality informativeness is huge. Thus, we need not only a multibiosignal solution, but also effective cross-talk between these biosignals.
3. All of the above developments will generate a very large number of options and parameters to adapt to individual patients and specific situations. The sentinel biosignal and sequence of secondarily activated sensors will likely differ as a function of ictal signs but might also vary within the same individual as a function of sleep-wake cycle. The same applies to the algorithmic features that will provide an optimal accuracy in seizure detection. Although some adjustments

might be preset, the potential for personalizing such settings is likely to strongly benefit from embedded machine learning applied at the individual level. FS detectors will thus progressively learn the very unique and stereotyped characteristics of each patient's seizure, as well as of nonepileptic activities leading to false alarms (eg, tooth brushing, a typical movement mimicking convulsive seizures, is likely to demonstrate person-specific characteristics).

4. Although seizure detection and forecasting are viewed as distinct objectives bringing complementary benefits to patients with epilepsy, their underlying solutions appear highly interdependent and synergistic. To achieve forecasting, one needs a reliable account of seizure events during a sufficiently long period of time (varying across patients as a function of their individual cycle of seizure recurrence), which is often missing in most patients. As a consequence, developing a reliable FS detection solution will be easier and will allow leveraging the potential of seizure forecasting. Reciprocally, once reliable seizure forecasting has been established in a given patient, the resulting statistical features can be used to optimize the classification of seizure versus nonseizure events and the overall performance of seizure detection. Thus, seizure detection and forecasting algorithms should ideally be integrated into the same system.
5. All of the above developments require significant improvement in several core aspects of wearable hardware and software technologies, including low power requirements. The energy consumption of high-frequency sampling processes can be reduced by novel event-triggered[63] and adapted compressed sensing paradigms.[64] Alternatively, emerging technologies might distribute the complex and energy-consuming machine-learning computations among distributed levels of machine learning, combining both smart wearables or edge artificial intelligence and intermediate server levels at home (ie, fog computing). Such technology might improve >10× the system lifetime with respect to data transmitted to the central cloud medical system, and reduce the system latency by up to 60%.[65,66] Recent findings also demonstrate that multimodal wearables with multiparametric machine-learning techniques can detect seizures by selectively performing cross-modality analyses (ie, self-aware learning) with different types of algorithms according to the classification confidence and target system devices.[67] Cutting edge self-learning algorithms, such as generative adversarial networks, which proved highly effective for image processing, might also carry significant progress in FS detection and forecasting.[68] Such approaches would benefit from the next generation of ultra–low-power multicore platforms with embedded machine-learning accelerators, which can offer many advantages in terms of parallelization capabilities to execute complex algorithms and process multimodal data inputs in complex real-life wearable setups.[69]

The ideal solution delineated above is not yet available and will require some years to be developed, tested, and validated. Intermediate suboptimal devices that could prove useful to a subgroup of patients (eg, hypermotor seizures) are welcome and shall bring important knowledge to the field. Another important key to the successful development of reliable FS detection lies in the capacity to collect and share much larger amount of data than currently done in the field, similar to what has been successfully achieved in the field of epilepsy and genetics. A similar level of international collaboration is thus advocated.

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CONFLICT OF INTEREST

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