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SPECIAL ISSUE ARTICLE

Autonomic biosignals, seizure detection, and forecasting

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Abstract

Wearable devices have attracted significant attention in epilepsy research in recent years for their potential to enhance patient care through improved seizure monitoring and forecasting. This narrative review presents a detailed overview of the current clinical state of the art while addressing how devices that assess autonomic nervous system (ANS) function reflect seizures and central nervous system (CNS) state changes. This includes a description of the interactions between the CNS and the ANS, including physiological and epilepsy-related changes affecting their dynamics. We first discuss technical aspects of measuring autonomic biosignals and considerations for using ANS sensors in clinical practice. We then review recent seizure detection and seizure forecasting studies, highlighting their performance and capability for seizure detection and forecasting using devices measuring ANS biomarkers. Finally, we address the field's challenges and provide an outlook for future developments.

KEYWORDS

autonomic nervous system, epilepsy, seizure detection, seizure forecasting, wearables

1 | INTERACTIONS OF THE CENTRAL AND AUTONOMOUS NERVOUS SYSTEMS IN EPILEPSY

Epilepsy is a central nervous system (CNS) disorder characterized by an enduring predisposition to generate epileptic seizures. A close relationship between the CNS and the autonomic nervous system (ANS) has long been established in persons with epilepsy (PwE) through the semiological study of autonomic manifestations of seizures, such as epigastric sensations, palpitations, syncope, pupillary dilatation, and facial flushing.[1] Moreover, autonomic symptoms in epilepsy not only are clinical markers for seizure localization but also present significant risks. For example, autonomic dysfunctions can lead to life-threatening cardiac arrhythmias and are potentially associated with sudden unexpected death in epilepsy (SUDEP), contributing to the increased mortality observed in PwE.[2] The central autonomic network (CAN), first described by Claude Bernard >150 years ago, plays a pivotal role in this interaction.[3] The CAN is highly interconnected and encompasses brain regions often recruited by the epileptic network, such as the insular cortex, anterior cingulate cortex, posterior orbitofrontal cortex, and amygdala. These regions are connected to other cortical and

subcortical areas within the hypothalamus, periaqueductal gray, parabrachial nucleus, nucleus of the solitary tract, ventrolateral reticular formation of the medulla, and medullary raphe. Thus, autonomic symptoms during preictal, ictal, or postictal phases are thought to result from either direct activation of CAN brain areas or systemic effects mediated by autonomic activation, such as the release of catecholamines affecting the sympathetic response. Chronic effects due to long-term autonomic dysregulation may be a contributing factor to ANS-related disease, most notably increased rates of cardiac comorbidity in PwE,[4,5] which in turn contribute to increased mortality in epilepsy.[6] Importantly, the close interaction between CNS and ANS suggests means to detect, characterize, and control epileptic seizures via the autonomic subsystems.

Key points

- ANS patterns of ictal and peri-ictal states are modulated by distinct influencing factors including age, medications, and stress.
- Multimodal wearables monitoring ANS function have demonstrated capability for tonic–clonic (phase 4) and focal (phase 2) seizure detection.
- Seizure forecasting uses ANS patterns and rhythms to provide multiday risk assessment and short-term predictions.
- AI explainability methods can help identify the factors influencing performance of detection and forecasting models.
- Considering influencing factors is crucial for improving approaches and identifying optimal target populations.

2 | IDENTIFYING RELEVANT AUTONOMIC BIOSIGNALS AND SENSORS FOR EPILEPSY MONITORING

The ideal autonomic biosignals should accurately represent the CNS dynamic state and afford long-term recording using nonstigmatizing and noninvasive sensors readily accepted by PwE. Within this framework, several subsystems of the ANS emerge as promising candidates for epilepsy monitoring, notably the cardiovascular and thermoregulatory systems (Figure 1). Across these autonomic subsystems, different biosignals have been shown to directly reflect changes in CNS in healthy people and PwE.

In the cardiac subsystem, variables related to heart rate (HR) represent a classical measure of autonomic function, mediating the heart–brain connection. These include HR and HR variability (HRV), which is a measure of the variation between heartbeats, measured in both the time and frequency domains, including power in different frequency bands, as well as nonlinear measures such as Poincaré plots, approximate entropy, and detrended fluctuation analysis, which quantify the nonstationarity and complexity of R-R interval series.[7] Additional cardiac markers are based on the electrocardiogram (ECG) and examine the morphology of QRS complexes, cardiac conduction abnormalities such as in QTc and PR intervals, or the interaction between respiration and HR.[8] Functional neuroimaging studies have established the direct CNS link to these HR features in healthy individuals, with large-scale meta-analyses associating HR and HRV to activity in the anterior cingulate, amygdala, insula, and prefrontal cortex, which are primary constituents of the CAN.[9,10] Intracranial electroencephalographic (EEG) stimulation and surgical studies have further demonstrated the influence of the CNS on cardiac function in PwE. The insula, for example, has been found to consistently mediate HR responses upon stimulation, with increased HR often triggered by more posterior stimulation. Other CAN-related brain regions, including the cingulate gyrus, temporal–mesial structures, and orbitofrontal cortex, have also shown significant mediating effects on HRV, often in parallel to evoking additional emotional or visceral sensations.[11,12]

In examining the thermoregulatory system, electrodermal activity (EDA), which reflects the modulation of sweat gland activity by measuring skin conductance, is often investigated. Unlike HR measures that are influenced by parasympathetic and sympathetic activity, EDA is predominantly modulated by the sympathetic nervous system. EDA's relationship to the CAN is evidenced from direct electrical stimulation or lesion studies of several cortical areas, including the orbitofrontal, ventromedial frontal, and anterior cingulate cortices.[13] Indirect transcranial magnetic stimulation of the CNS has also been shown to affect EDA, for example, decreased EDA associated with stimulation of the dorsolateral prefrontal cortex.[14] These areas exert both excitatory and inhibitory influences on EDA, highlighting the role of higher cortical areas in EDA regulation.

3 | ANS CHANGES IN RELATION TO SEIZURES

The field of seizure detection and forecasting builds on observations of ANS changes associated with seizures in

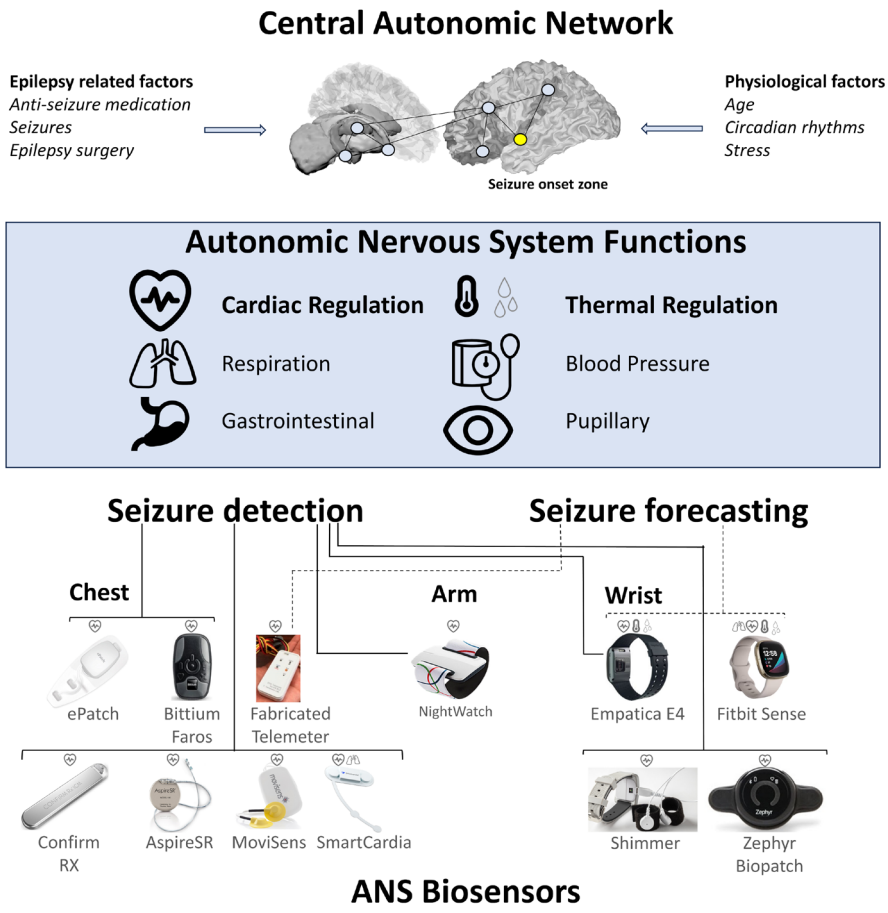

FIGURE 1 The central autonomic network (CAN), autonomic nervous system (ANS), and wearable technology used for seizure detection and forecasting. The CAN is composed of cortical and subcortical brain regions that are affected by physiological and epilepsy-related factors. These dynamics influence the activity of the ANS. Wearable biosensors are particularly useful in measuring biosignals reflecting changes in the cardiac and thermoregulatory subsystems of the ANS, providing clinically useful information for seizure detection and forecasting. Noninvasive, nonstigmatizing, and easy-to-use solutions have been developed, and can be worn on the chest, arm, and wrist. Brain structures visualized using BrainPainter.[106]

PwE, which can occur in the preictal, postictal, and ictal states. In the cardiac subsystem, ictal HR increase is the most common phenomenon, occurring in >80% of patients.[15] The increase in HR may happen in the preictal period or within the first 30 s of the seizure. Of note, although preictal HR changes occur before clinical symptoms or scalp EEG changes, they may reflect cardiac effects of ictal activity in deep-seated brain regions, as studies of simultaneous scalp and intracranial EEG have demonstrated.[16] Although it appears in both generalized and focal epilepsies, in focal epilepsy, it is most prevalent in temporal lobe epilepsy (TLE).[17,18] Bradycardia or asystole are rare events, reported only in focal onset seizures, and in the vast majority of cases occur in patients with drug-resistant TLE.[19] Cardiac conduction abnormalities are also commonly reported, particularly involving the QT segment. These abnormalities most often include prolongation during ictal or interictal phases but may also show ictal or postictal shortening, particularly after generalized seizures.[20,21] ST-segment changes have also been observed, with T-wave inversion and ST-segment depression occurring more often during generalized seizures and sleep and interictally as T-wave alternans. These changes may reflect long-term cardiac conduction abnormalities or cardiac damage or be secondary to medical treatment with depolarization-blocking antiseizure medications (ASMs).[22] Despite these findings, it is important to note that the prevalence of ECG changes in PwE remains relatively low, although higher than in healthy individuals.[23] Finally, HRV is often lower in PwE, particularly those with TLE and drug resistance, suggesting a shift toward sympathetic dominance in autonomic tone. Notably, in both the preictal and postictal phases, a further decrease in HRV measures was observed.[24]

In the thermoregulatory subsystem, increases in ictal temperature and EDA have been shown to occur both during and after seizures.[25] EDA changes have been documented in multiple seizure types, including generalized, focal aware, and impaired awareness seizures, as well as motor and nonmotor seizures. However, the most pronounced response is consistently seen with major motor seizures, particularly tonic–clonic seizures. Chronic changes in EDA, such as increased sympathetic response latencies, have also been documented in PwE compared to controls.[26] Importantly for seizure forecasting, autonomic changes are also observed during the times preceding seizures, as epileptic networks in the CNS have a strong connection to CAN brain networks. The relevance of autonomic changes during the preictal state was specifically examined in studies focused on PwE undergoing simultaneous ECoG, scalp EEG, and ECG recordings.[27,28] In one study, the authors examined how noninvasive ECG

measurements compared to scalp EEG and invasive ECoG measurements in terms of identifying biomarkers distinguishing the preictal and interictal states. Using a deep learning approach, this study found that extracting power spectral density features from a single ECG sensor provided preictal information comparable to a 21-electrode scalp EEG and a single ECoG channel, underscoring the efficacy of ANS biosignals in reflecting CNS cortical dynamics.[27]

4 | INFLUENCES ON AUTONOMIC FUNCTION: AGE, MEDICATION, AND OTHER FACTORS

Although seizures and peri-ictal periods may exhibit distinct ANS signatures relevant to epilepsy monitoring, it is important to carefully consider the interplay between autonomic function and various physiological and pathological factors to accurately utilize ANS changes for monitoring seizures. Systematic age-related autonomic changes, as evidenced by HR or HRV fluctuations, are well documented.[29] HRV increases until late adolescence and then declines progressively with age. One study quantified this trend as a reduction of approximately 3.6 ms per decade.[30] Notably, the HRV decline correlates with cortical thickness thinning, particularly in regions associated with autonomic control, such as the ventromedial prefrontal cortex and lateral orbitofrontal cortex.[31] Likewise, multiple EDA measures are effected by age, for example, with increased age smaller phasic responses are observed.[32] Additionally, distinct differences in autonomic function are observed across sexes and ethnic groups. For instance, female adults generally have higher HRV than males, and African Americans show greater HRV compared to European Americans.[33] Gender and ethnic differences with relation to EDA have also been reported; however, patterns of change have not been consistent across different studies.[32] These inherent differences are significant in study design and interpretation, emphasizing that diverse cohorts are critical for generalizable findings.

Circadian rhythms, centrally regulated by the suprachiasmatic nucleus, also play a significant role in the ANS. These diurnal measures have been reported, for example, in the cardiac subsystem, with HR slowing at night and lengthening of the QRS, PR, and QT intervals. Similar diurnal changes are observed in the thermal and vascular subsystems, evidenced by alterations in EDA and nightly blood pressure dips.[34–36] Although less widely described, longer term rhythms are also known, with multiday and seasonal effects on HR and blood pressure.[37–39] In epilepsy patients, recent works have shown that the use of ASMs further modulates these effects. Although findings vary, most studies report that ASM treatment reduces HRV overall, with higher ASM loads linked to lower HRV and ASM withdrawal leading to increased HRV.[40–42] In contrast, ASM loads have been found not to effect EDA activity.[40]

Finally, an intricate connection exists between emotional regulation, cognition, stress, and the ANS, as reviewed by Critchley et al.,[43] Thayer and Lane,[44] and Gianaros and Wager.[45] CAN regions mediate this interplay and can affect autonomic measurements. For instance, studies reported that cognitively demanding activities demonstrated simultaneous increased activation of the dorsal anterior cingulate or prefrontal medial cortex and higher low-frequency HRV power and EDA measurements, which reflect increased sympathetic cardiac influence. Likewise, emotional states and stress are closely related to CAN areas, notably the amygdala and the insula, and modulate the autonomic responses. Understanding these connections is essential, as emotional states, cognitive load, and stress can significantly impact seizure activity and overall autonomic function in PwE.

5 | CONSIDERATIONS IN THE USE OF ANS BIOSIGNALS IN CLINICAL PRACTICE

For PwE, the critical question is whether ANS biosignals reflect CNS changes related to seizure activity and how reliable they are for diagnosis and management. Traditional methods used by clinicians to assess disease activity, mainly self-reported seizure diaries, are recognized to be highly inaccurate, providing both over- and underestimations of actual seizure counts.[46–48] This aspect limits effective treatment response assessment and interpretation of clinical trials of drugs and other interventions, which often report outcomes in terms of seizure load reduction. In recent years, EEG solutions have been developed to address this issue, including long-term implantable intracranial, subscalp, subdermal, and auricular EEG recording devices. However, these may not be readily available, require invasive procedures, or be associated with stigma.[46,49–52]

Knowledge of changes in ANS features in epilepsy and technological advancements in the field of wearable biosensors have led to studies with two main aims: improved methods for seizure detection and seizure forecasting. Following these developments, the International League Against Epilepsy (ILAE) has established testing and validation standards for these technologies, outlining best practice study designs for artificial intelligence (AI) in this field.[53,54] These standards classify studies into five phases, ranging from initial exploratory studies (phase 0)

to large-scale in-field validation studies (phase 4), based on methodological robustness and generalizability. Key features determining the study phase are related to subject selection, recording method, analysis approach, and the reference standard used to determine the ground truth outcome. Based on these criteria, the ILAE issued a weak/conditional recommendation for the use of clinically validated wearable devices for the detection of tonic–clonic seizures. Additional work is needed to establish robust seizure detection in focal seizures.

6 | SEIZURE DETECTION USING ANS BIOSIGNALS

Developments in wearable device use for seizure detection have been described in several comprehensive reviews and a clinical practice guideline published by a joint working group of the International Federation of Clinical Neurophysiology and the ILAE.[54–64] Here, we focus on studies relevant to seizure detection based on autonomic biosignals, reviewed according to the study phase to better contextualize each approach's current clinical relevance (Table 1).

To date, two phase 4 studies have been reported, utilizing the Nightwatch system, an upper arm bracelet combining accelerometry and HR data to detect nocturnal motor seizures.[65,66] The first of these studies was conducted in the residential setting for adults with intellectual disabilities, whereas the second was conducted in homes of pediatric patients with motor seizures. The Nightwatch system showed good acceptability in adults, with a high median sensitivity of 86% and a low median false alarm rate (FAR) of .25 per night. However, FAR was >1 per night in several participants, suggesting further personalization is needed to improve overall performance. HR was the critical modality for both true and false positive detections. This study was followed by a phase 3 study aimed at testing whether the established detection algorithm developed for adults could be effectively applied for seizure detection in children.[67] Using the adult detection model for a pediatric cohort, a reduced median sensitivity of 75% was reported, with a notably high FAR level of .2 per hour that necessitated midtrial adjustments to the detection algorithm by modifying alarms to occur only when the child was in a horizontal position, eliminating out of bed detections. Subsequently, an additional stage 4 Nightwatch pediatric study, conducted in the in-home setting and using a pediatric specific detection model, reported a median sensitivity for detection of major motor seizures per participant of 100% (range = 49%–100%), with the best performance overall reported for tonic–clonic seizures. In this study, similarly to the adult Nightwatch trial, FAR per hour was low, with a median of .04 per participant. However, rather than HR, the accelerometry signal was more often responsible for triggering alarms, emphasizing differences in response to seizures between age groups.

An additional phase 3 multicenter prospective study assessed multimodal data using the Empatica wristwatch device, utilizing EDA and accelerometry for generalized tonic–clonic seizure detection among hospitalized adults and pediatric patients.[68] Using a previously US Food and Drug Administration-approved machine learning algorithm, the study reported high sensitivities for both groups (.92 for pediatric and .94 for adults) but noted a higher FAR in children (1.26 compared to .57 per 24 h). Similarly to the Nightwatch study,[66] the high FAR was affected by a few children having many false alarms. Seizure detection latency was approximately 37 s, reflecting a time period that is acceptable for interventions in life-threatening motor seizures to prevent aspirations or provide oxygen therapy.

Compared to phase 3 and 4 studies, phase 2 studies have been reported more frequently in recent years, providing valuable insights into initial experiences and novel methodologies. These studies, however, are generally not validated on large cohorts or in-field settings and often lack real-time, predetermined detection algorithms. One significant application involves the vagal nerve stimulation (VNS) device, a closed-loop stimulation system designed to detect seizures and provide treatment based on the detection of increased HR.[69,70] Two studies, including a combined 51 adult and pediatric patients, compared a foreground HR of 10 s against a background HR from the previous 5 min. Different thresholds of increase in HR were used to detect seizures and trigger VNS stimulation. Despite achieving sensitivity of >80% for multiple HR thresholds, a positive correlation between sensitivity and FAR was observed, ranging from .5 to 7.2 alarms per hour. Nevertheless, this approach successfully aborted 31% of seizures in the two studies combined and showed a positive 12-month benefit on seizure reduction. However, the broad applicability of this approach is limited by the requirement for an invasive implantation procedure.

Another focus of phase 2 studies has been on expanding seizure detection capabilities to encompass a broader range of focal impaired seizures, beyond major motor seizures. Two such studies using the Empatica wristwatch were conducted on a pediatric population hospitalized in epilepsy monitoring units.[71,72] Employing deep learning techniques, these studies sought to establish detection benchmarks across various seizure types. The first study, including 94 patients and 548 seizures across nine different seizure types, achieved an area under the receiver operating curve (AUC) of .75.[71] Subsequently, a larger study with 166 patients and 900 seizures reported improvement

TABLE 1 Review of evidence.

Study	Wearable device	ANS biosignals	Participants	Sensitiviy	FAR	Seizures	Study phase
Seizure detection							
Arends et al. (2018)[65]	NightWatch	ACC, HR	28 adults with intellectual disabilities	86% (median)	.25/night (median)	809 GTC, FBTC, GM, HK, other major motor	4
Van Westrhenen et al. (2023)[66]	NightWatch	ACC, HR	53 pediatric	89%	.07/h	552 GTC, FBTC, GM, HK, other major motor	4
Lazeron et al. (2022)[67]	NightWatch	ACC, HR	23 pediatric	79.4%	.08/h	384 GTC, FBTC, GM, HK, other major motor	3
Onorati et al. (2021)[68]	Empatica E4	EDA, ACC	85 pediatric 67 adults	92% 94%	1.26/24 h .57/24 h	35 GTC, FBTC 31 GTC, FBTC	3
Boon et al. (2015)[69]	AspireSR	HR	16 adults	>80% for multiple HR thresholds	.5–7.2/h	66 FBTC, FIA, FA	2
Fisher et al. (2016)[70]	AspireSR	HR	20 adults	>80% for multiple HR thresholds	Not reported	89 FBTC, FA, FIA	2
Tang et al. (2021)[71]	Empatica E4	EDA, BVP, ACC	94 mixed cohort	.752 AUC		548 multiple generalized & focal onset	2
Yu et al. (2023)[72]	Empatica E4	EDA, BVP, ACC	166 mixed cohort	83.9%	35.3% FPR	900 multiple generalized & focal onset	2
Jahanbekam et al. (2021)[74]	MoviSens	HRV	35 adults 97 adults 30 adults	66.9% 39% 31.4%	.7/24 h .4/24 h 1.2/24 h	33 GTC, FBTC, FIA, FA 255 GTC, GM, FBTC, FIA, FA 51 GTC, GM, FBTC, FIA, FA	2
Jeppesen et al. (2019)[76]	ePatch	HRV	43 adults (53.5% responders)	93.1%	1.0/24 h	126 GTC, FBTC, FIA, FA	2
Jeppesen et al. (2020)[77]	ePatch	HRV	11 adults	87%	.9/24 h	23 GTC, FBTC, FIA, FA	2
Jeppesen et al. (2023)[78]	ePatch	HRV	62 adults	78.2%	.62/24 h	174 GTC, FBTC, FIA, FA	2

TABLE 1 (Continued)

Study	Wearable device	ANS biosignals	Participants	Sensitiviy	FAR	Seizures	Study phase
Jeppesen et al. (2024)[79]	ePatch	HRV	22 adults	84.8%	.25/24 h	59 GTC, FBTC, FIA, FA	2
Jeppesen et al. (2023)[80]	Confirm Rx	HRV	6 adults	92.6%	2.7/24 h	54 FBTC, FIA, FA	1
Forooghifar et al. (2019)[81]	SmartCardia INYU	HRV, EDR	18 adults	88.66%	85.65% specificity	154 focal	2
Hegarty-Craver et al. (2021)[105]	Zephyr Biopatch Bittium Faros	HR, HRV, ACC	18 pediatric	72%	1.03/24 h	25 multiple generalized & focal onset	2
Vandecasteele et al. (2017)[83]	Empatica E4 eMotion Fraos	HR	11 adults	32% 70%	1.80/h 2.11/h	47 FIA	2
van Andel et al. (2017)[84]	Shimmer	HR, ACC	43	71–87%	2.3–5.7/night	86 GTC, GM, HK	2
Poh et al. 2012[85]	Custom-built	EDA, ACC	80	94%	.74/24 h	16 GTC	2
Onorati et al. (2017)[86]	Empatica E3, E4 iCalm	EDA, ACC	69	94.55%	.2/24 h	49 FBTC 6 FTC	2
Böttcher et al. (2021)[87]	Empatica E4	EDA, ACC	38	90.9%	.19/24 h	21 GTC, FBTC	2
Seizure forecasting and prediction							
Gregg et al. (2023)[99]	Empatica E4	EDA, HR, HRV, TEMP, ACC	10	Not reported	Not reported	Mean of 76 seizures	2
Meisel et al. (2020)[100]	Empatica E4	EDA, TEMP, BVP, ACC	69	75.6%	47.2% TiW	452 multiple generalized & focal onset	2
Nasseri et al. (2021)[101]	Empatica E4	EDA, HR, TEMP, BVP, ACC	6	66.4%	4.98/24 h	Not reported	2
Karoly et al. (2021)[102]	Fitbit	HR	46	Not reported	Not reported	Mean of 72.4 seizures	2
Yamakawa et al. (2020)[104]	Fabricated telemeter	HRV	7	85.7%	.62/h	14 FBTC, FIA, FA	1

Note: Studies using wearable devices for seizure detection and forecasting based on autonomic nervous system biosignals. Performance metrics are reported as means, unless otherwise noted. Study phase is determined according to Beniczky and Ryvlin.[53]

Abbreviations: ACC, accelerometry; ANS, autonomic nervous system; AUC, area under the receiver operating curve; BVP, blood volume pulse; EDA, electrodermal activity; EDR, electrocardiography-derived respiration; FA, focal aware; FAR, false alarm rate; FBTC, focal to bilateral tonic–clonic; FIA, focal impaired awareness; FPR, false positive rate; GM, generalized onset motor; GTC, generalized onset tonic–clonic; HK, hyperkinetic; HR, heart rate; HRV, heart rate variability; TEMP, temperature; TiW, time in warning.

with AUC > .8 for 19 of 28 seizure types, raising the overall detection AUC to .79. Although these studies show promise for wider application of seizure detection, some seizure types were characterized by low overall seizure numbers and high variability in false positives (range = 15%–46%). An additional retrospective study examining 76 pediatric patients further reported that poorly detected seizures were associated with shorter seizure durations, lower age, and higher ASM dose, pointing to additional factors that affect the performance of deep learning approaches.[73] These caveats may limit the use of the currently developed models for an alarm system. However, they may still have value as a seizure-monitoring and diary adjunct tool or as a basis for future development as larger patient datasets become available.[72]

Other phase 2 studies have investigated seizure detection by exploring a broader range of cardiac features. One such study included 162 adult PwE undergoing simultaneous recordings with chest- and wrist-based wearable devices in the video-EEG monitoring unit. It focused on 105 HR- and HRV-related metrics.[74] The authors developed and tested unique seizure detection models across three patient groups in distinct conditions (either mobile or mostly in bed). When comparing separate patient groups for validation, the outcomes illustrated a broad spectrum of detection sensitivities (4%–62.8%) and false detection rates (.08–5.1 per 24 h). These results underscore the cardiac variability related to seizure type, the influence of patient conditions on detection efficacy, and the need to rigorously test for generalizability in developing cardiac-based seizure detection devices. Two additional studies used a wearable patch to extract a modified cardiac sympathetic index determined from 100 successive R-R peaks, an approach the same study group developed for real-time HRV analysis.[75] These studies demonstrated that 83.3%–90.5% detection sensitivities were reached in a subset of patients with ictal HR increase, with an FAR of approximately 1 per 24 h.[76,77] Notably, ictal HR increase of >50 beats per minute was identified as a predictor of good performance. A subsequent study on the same dataset further reduced the FAR to approximately .6 per 24 h through a logistic regression machine learning approach aimed at adaptive patient-specific detection thresholding for seizure alarms.[78] The patient adaptive threshold method was recently also validated in a dataset consisting of different demography from Brazilian patients with reproducible sensitivity and even lower FAR of .25 per 24 h. However, these investigators collected data retrospectively, and therefore, discontinuous data were used from standard wired ECG recording during long-term monitoring.[79] To allow for longer term recordings and alleviate the need for changing ECG wearable patch adhesives, a phase 1 proof of concept study examined the use of a subcutaneously implantable cardiac monitor for seizure detection in six patients and up to 8 months of recording, reporting a high sensitivity of 92.6% and a 24-h FAR of 2.7.[80] HRV features were also explored in an additional study, including 18 patients and 211 h of recording using the chest-worn SmartCardia INYU sensor, which also took respiration in relation to the R-R interval into account. Although FARs are not reported, seizures were detected with a sensitivity of 88.7% and a specificity of 85.7% while employing a reduced energy consumption that allowed for a battery life of 137 days.[81]

Although these studies demonstrate the potential of cardiac features for seizure detection, they also underscore the challenges posed by data quality and artifacts from daily activities. One investigation into 28 patients with 62 focal seizures examined photoplethysmographic (PPG) measurements from the Empatica wristwatch, compared against ECG recordings, to assess the impact of seizures and spontaneous movements on signal quality.[82] This study reported that spontaneous and epileptic movements hinder the ability of the biosensor to obtain good-quality data. However, in 60% of motor seizures, ictal HR increase could still be identified, as it occurred before the motor symptoms. Furthermore, the PPG signal was well correlated temporally to both the ECG and EEG ictal recordings, making it a valuable biomarker, especially at rest. The issue of motion artifacts impairing HR detection, particularly with ictal HR increase, was highlighted in another study.[83] This study found that in a dataset of 11 patients and 47 temporal lobe seizures, PPG-based seizure detection provided a sensitivity of 32%, considerably lower than an additional wearable ECG device (70%) and a hospital ECG system (57%). This discrepancy underscores the influence of patient movement on the reliability of wearable device readings. Another multicenter prospective study used a different system for measuring accelerometry and HR, the Shimmer device, and also reported major recording issues, with data analysis only possible for 43 of 95 patients recruited. This study also reported high FARs (2.3–5.7 per night), resulting in low positive predictive values.[84] Together, these studies emphasize the need for improved methodologies to mitigate these issues in real-world settings.

In addition to the phase 3 study described above,[68] EDA has been employed in several phase 2 studies for seizure detection. The Empatica wristwatch, incorporating accelerometry and EDA signals, was used in a multicenter study including 45 adult and 24 pediatric patients with 55 tonic–clonic seizures. This study achieved a sensitivity of 94.5% with an FAR of .2, improving on a previously published algorithm that was trained on a smaller and less heterogeneous cohort.[85,86] These findings were reinforced in an additional relatively small two-center study with 10

patients using the same wearable device but with a different, openly available detection algorithm. In this study, 10 of 11 tonic–clonic seizures were detected with an FAR of .19 per day.[87] These outcomes indicate that employing various algorithms can yield consistent detection results. However, it is important to note that all detections in these phase 2 studies were conducted within hospital settings, potentially obscuring the FARs in everyday environments.

One potential of using autonomic markers is not only for detecting seizure occurrence but also to predict seizure severity and determine predictive biomarkers for an adverse seizure outcome, such as SUDEP. Biomarkers of seizure severity derived from wearables have been previously reviewed[64] and include cardiac markers such as ictal and postictal bradycardia and asystole, interictal HRV dysregulation (both increased and decreased HRV), and a postictal decrease in parasympathetic activity. Likewise, increased postictal EDA, reflecting abnormally heightened sympathetic activity, is particularly marked in postictal generalized EEG suppression cases and SUDEP.[88]

7 | SEIZURE FORECASTING USING ANS BIOSIGNALS

Whereas seizure detection aims to accurately quantify seizure counts and implement alarm systems to prevent injury, seizure prediction or forecasting may enable patients to take preventive measures during periods of increased risk, such as taking additional medication or avoiding dangerous settings. Unlike the deterministic nature of seizure detection, which confirms the presence or absence of seizures, forecasting adopts a more probabilistic approach, assessing the likelihood of a seizure within a specific time period. Clinical recognition of cyclical patterns in seizure occurrences—similar to other biological rhythms observed in immune, endocrine, and cardiovascular functions—has provided further opportunity for seizure forecasting.[38,89] More recently, studies leveraging long-term intracranial EEG recordings from people with drug-resistant epilepsy have indicated that both seizure risk and interictal epileptic activity fluctuate with circadian and multiday rhythms.[90–93] Based on these observations and novel theoretical insights into the dynamics of seizure onset mechanisms and precursors,[92,94] the seizure prediction and forecasting field has recently seen considerable attention, as evidenced by several comprehensive reviews published.[95–98] Including autonomic biosignals for forecasting offers a promising avenue for providing seizure prediction without invasive procedures, making it more widely applicable in clinical settings.

One study exploring the cyclical patterns in intracranial EEG and autonomous biosignals compared simultaneous recordings from both modalities in 10 PwE (seven subjects had an average of 76 seizures each) over an average recording duration of 232 days.[99] This study identified that, in parallel to multiday patterns of elevated seizure risk associated with intracranial EEG recordings, cyclical patterns were seen in temperature in five patients, in HR in six patients (after adjusting for the confounding effects of physical activity), and in the phasic component of EDA in four patients. Furthermore, there was a strong coherence between intracranial and autonomous circadian patterns, suggesting that the latter could be used as a surrogate measure. However, notably, no such significant association was found concerning multiday patterns. Importantly, this study reinforced prior works that focused exclusively on autonomic biosignals concerning patterns of increased seizure risk.[50,100–102] Another study included 31 PwE using wearable wristwatches and examining circadian and multiday cardiac patterns associated with increased seizure risk, as documented by seizure diaries.[102] In this study, the authors found that multiday HR cycles in most patients correlated to approximately weekly and monthly frequencies. In 10 of 19 patients who recorded seizures, an increased risk aligning with these patterns was found.

Several studies were aimed not only at examining heightened risk periodicities but also at establishing shorter term, clinically relevant prediction horizons. One phase 2 study used a deep learning approach to analyze HR, EDA, temperature, and accelerometry from wearable wristwatches in a cohort of 69 pediatric patients with 452 seizures during video-EEG monitoring.[100] Findings revealed that for 30 of the 69 patients, seizures could be predicted at better-than-chance level with an average improvement over chance of 28.5% and a 31-min prediction horizon on average. Prediction performance was highest when combining multiple autonomous biosignals. Although the study was constrained by a relatively brief average recording duration per patient, it did not require patient-specific fine-tuning of prediction models. It provided evidence that performance may improve with increased training data size. Other studies have focused solely on cardiac measures. One phase 2 study examining 15 patients during video-EEG monitoring reported a sensitivity of 89% for prediction of seizures within a horizon of 15 min. This study, however, required a model to be trained specifically for each patient and still had a high FAR of almost 10 per day.[103] Another study similarly reported a prediction horizon of 15 min, using a real-time wearable HRV measurement device, with a sensitivity of 85% and an FAR of 14 per day.[104]

Other studies have focused on examining in-field, long-term data to evaluate feasibility of seizure forecasting in home environments. A notable study included six PwE using the RNS implantable device as a seizure reference,

thus predicting electrophysiological rather than just clinical seizures.[101] This study analyzed multiple signals measured using the Empatica device, including temperature, EDA, HR, and accelerometry. In five of six PwE, seizure forecasts were significantly above chance level, with a mean AUC of .75. Alerts occurred on average 33 min before seizures. Another study in a retrospective and pseudoprospective setting with 11 patients also demonstrated that forecasting is feasible, achieving above chance hourly and daily predictions in all patients, compared to seizure diary self-reports.[50] Notably, in this latter study, models were retrained weekly on personalized data. Thus, this study does not provide an out-of-the-box solution that would be immediately available for a prospective new patient but highlights the utility of personalized retraining. Despite the small cohorts, both works are important to establish the clinical feasibility of long-term in-field seizure forecasting.

8 | CHALLENGES AND FUTURE DIRECTIONS

Although significant progress has been made in seizure detection and forecasting, several challenges remain. One primary concern is the relatively low number of patients and seizures included in studies, coupled with brief durations of data recording. Classification algorithms, particularly those based on deep learning, require substantial data to refine their accuracy and reliability.[100] Although computational techniques such as data augmentation are employed to expand datasets artificially, larger, more diverse data collections are critical to enhance these approaches' generalizability and practical applicability. Further compounding this challenge are the training conditions under which many models are developed. The majority of studies are currently conducted in the hospital setting, where PwE are often confined to bed and patterns of autonomic activity do not reflect those of daily life activities, as demonstrated by Jahanbekam and colleagues.[74] Training and testing conditions must be expanded to improve generalizability and robustness of models in out-of-hospital settings. Another complex issue involves the evaluation of prediction algorithms, which must account for a variety of factors, including a baseline chance level for meaningful comparison, the specific periods being assessed (e.g., interictal vs. preictal, sleep vs. wake states), definitions of seizures, and the decision to include or exclude clusters of seizures. The introduction of testing and reporting standards marks progress toward harmonizing the field,[53] yet a comprehensive benchmark dataset is essential for effectively comparing the performance of diverse methodologies. Ideally, such a dataset would facilitate cross-center comparisons, increase sample sizes, and enable out-of-sample validation, contributing to developing detection models that demonstrate enhanced performance across different patient demographics and clinical settings.

In addition to these methodological challenges, several critical clinical aspects must be considered. First, seizure detection and forecasting need to be further developed for multiple seizure types and vigilance states. So far, clinical applicability of seizure detection has only been demonstrated on major motor seizures, and although other seizure types have been investigated, these should be more rigorously studied. Likewise, many studies have reported high detection rates during sleep, with limited and clinically insufficient performance during wake. Age also significantly affects model efficacy, with younger PwE often showing decreased performance.[73] This highlights the need for further research into age-adaptive models, especially considering the mixed pediatric and adult cohorts in many studies. Methods from explainable AI will be crucial in further identifying these data constraints.[73] Third, ASM regimes have been shown to modulate autonomic biomarkers and affect detection performance, with decreased ASM load associated with improved sensitivities and decreased FAR.[73] The impact of nonepilepsy medications, such as beta-blockers and carbonic anhydrase inhibitors, on autonomic signals like HR and EDA remains unexplored. Fourth, algorithms have been trained on drug-resistant PwE. However, special populations, including those with epileptic encephalopathies or syndromic diseases, may require tailoring of devices. Moreover, in older populations, the presence of comorbidities—particularly cardiovascular conditions—may interfere with the accuracy of autonomic measures, necessitating models that can differentiate between epilepsy-related changes and those stemming from other health issues. Fifth, the influence of biological rhythms, including circadian and multiday patterns, on autonomic signals warrants further investigation. These natural fluctuations can impact the manifestation of seizures and the efficacy of forecasting models. Finally, conducting additional studies in patients' home environments is essential. The majority of current research has been conducted in controlled hospital settings, which do not fully replicate the home environment, where behavior is less restricted and different stressors may trigger seizures.

9 | CONCLUSIONS

We here provided a narrative review about the progress made and the challenges that remain in seizure detection and forecasting using autonomic biosignals. Although this

field is rapidly growing, the success of this endeavor will rely on the community's ability to expand datasets and establish robust testing and benchmarking methodologies, share knowledge and technology, and integrate patient-specific requirements. Future research needs to develop scientifically robust and practical methodologies, ensuring that technological advancements improve outcomes for individuals with epilepsy.

AUTHOR CONTRIBUTIONS

Gadi Miron: Writing–original draft; writing–review and editing; conceptualization of study. **Mustafa Halimeh, Jesper Jeppesen, Tobias Loddenkemper:** Writing–review and editing. **Christian Meisel:** Conceptualization of study; writing–review and editing.

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CONFLICT OF INTEREST STATEMENT

T.L. is part of patents and patent applications to detect and predict clinical outcomes, and to detect, manage, diagnose, and treat neurological conditions, epilepsy, and seizures, but none of these has been licensed. He has received device donations to Boston Children's Hospital for research purposes from various companies, including Empatica. In the past, he has received research support paid to Boston Children's Hospital from Empatica for research unrelated to this study. C.M. is part of patent applications to detect and predict clinical outcomes and to manage, diagnose, and treat neurological conditions. C.M. has received speaker and/or consultation fees from UNEEG and Bristol-Myers Squibb, all outside the submitted work. The remaining authors have no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article, as no new data were created or analyzed in this study.

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