



## Review

## Peripheral multimodal monitoring of ANS changes related to epilepsy

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## ABSTRACT

The goal of this study was to evaluate and summarize the current literature on multimodal changes of the autonomic nervous system (ANS) in people with epilepsy (PWE). We included studies reporting ANS measures of at least two modalities and with a minimum of one group of people with epilepsy. We screened two hundred eighty-three abstracts and sixty-six full texts, of which twenty-two met our inclusion criteria. Eleven studies reported ictal and interictal cardiac and respiratory changes. Three studies investigated the correlation between cardiac and respiratory markers, whereby two found no correlation and one showed a relation. Six studies evaluated electrodermal and cardiac parameters and showed effects on both ANS subsystems that jointly indicate a shift toward increased sympathetic activity for people with epilepsy during rest and during activity. Two studies assessed three modalities and reveal epilepsy-related alterations within the ANS. In summary, there is a growing interest in multimodal monitoring approaches, such as combining at least two ANS modalities, to describe epilepsy-related changes in ANS activity and to test for the potential to use ANS markers for seizure detection and prediction. Most studies report multiple unimodal analyses while only few studies analyzed multimodal patterns. Patterns of changes depend on the type of epilepsy and differ on an individual level; therefore, a multimodal approach might offer an approach to more individualized monitoring and, ultimately, management.

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## 1. Introduction

Epilepsy and seizures can be associated with dysfunction within several modalities of the autonomic nervous system (ANS). Furthermore, alterations in ANS activity, especially cardiac and respiratory complications, might also be associated with risk for sudden unexpected death in epilepsy (SUDEP) [1–4]. In this context, changes in ANS activity are of great interest as they may offer potential biomarkers that could contribute to seizure semiology, detection, and reporting, as well as prediction [3].

The main tasks of the ANS include maintenance of internal homeostasis and response to stressors, including seizures. The ANS thereby regulates several organ systems by a finely tuned centrally orchestrated neuronal network [5]. The central ANS network contains neocortical and subcortical regions, which innervate structures of several ANS subsystems, such as the cardiac, pulmonary, and temperature regulation systems [6–8]. Several studies have demonstrated alterations of ANS activity in patients with epilepsy (PWE) and in relation to seizures. In

the literature, the cardiac system represents the best-described ANS modality. Results comprise short-term and long-lasting changes of cardiac function in PWE, especially changes in heart rate (HR), such as ictal tachycardia, bradycardia, and heart rate variability (HRV) [9,10]. More recently, more specific markers of cardiac activity, such as T-wave alternans (TWA), relate to cardiac arrests and may provide a potential marker of the cardiac component of SUDEP [4,11]. This example highlights the potential to influence the progression of disease and the need to better understand the interplay within the ANS. Cardiac and respiratory changes often interrelate [2]. There is also an alteration of thermoregulation in animal models of epilepsy [12]. Epilepsy-related (ictal) cold and shivering occur in some patients [13] and indicate clinically significant activation of human thermoregulatory circuitry. Additionally, electrodermal activity (EDA) constitutes an ANS modality that reveals epilepsy-related changes. An increase in EDA can occur during and after convulsive seizures [14], and the detected EDA changes might contribute to improved seizure detection [15]. Collectively, these changes suggest a modulation of the ANS. In most severe presentations, ictal and postictal dysautonomia may even result in SUDEP [15]. Therefore, an assessment of ANS activity by means of several modalities may potentially offer significant benefit related to seizure detection and closed-loop warning systems. Considering the integrated control of ANS

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subsystems, changes in these ANS subsystems are likely linked across modalities. Consequently, studies combining measures of several ANS modalities – and studies that look into ANS modality interactions – might contribute to a better understanding of the modulation of central control mechanisms related to epilepsy and seizures.

One of the first multimodal investigations of seizure-related changes in the ANS studied 20 seizures from 13 patients with analog measurements and graphical methods. This study revealed a congruent pattern of rising blood pressure (BP), increasing HR, decreasing skin resistance and thereby rising skin conductance, as well as the appearance of expiration apnea [16]. Further studies utilizing analog recordings of ANS activity aimed at localizing pathophysiological processes and seizure localization and reported limited additional benefit of the combination of modalities at that time [17]. Based on improvements in technologies, such as digital recordings, data analysis, and sensor techniques [18], the recording of multimodal channels is now more frequently implemented in relation to seizures and interictal states, among other covariates and confounders. To capture the complexity of the effects of seizures on the ANS (and the effects of the ANS on seizures), multimodal approaches permit deeper insights into complex ANS activity patterns by extracting information from complementary modalities and combining results.

This manuscript aimed to provide an overview of studies that combine ANS measures of at least two modalities to assess the benefit of multimodal approaches in seizure detection and to describe possibilities to analyze autonomic signals and their interactions jointly in PWE.

## 2. Methods

We conducted the systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19]. We performed the literature search in PubMed, Web of Science, Embase, and Cinahl. We also expanded the search to the reference lists of the retrieved and reviewed articles. Modalities included in our search referred to the cardiac, respiratory, electrodermal, and thermal systems. Two of the authors (RE and SV) and a librarian developed the search strategy. We searched the full date range of indexed articles in each of the abovementioned databases until August 2018. We used a combination of search terms from the following categories: (1) multimodal wearable device, (2) epilepsy or seizure, (3) HR, electrocardiogram, or blood volume, (4) electrodermal or skin response, (5) body temperature, and (6) respiration or breathing. We excluded animal studies.

Subsequently, we matched the aforementioned inclusion criteria to studies (1) written in English, German, or French, (2) reporting randomized controlled trials, cohort studies, or cross-sectional studies, (3) including at least one group of PWE, and (4) reporting results of at least two of the mentioned ANS modalities. We excluded reviews, letters, editorials, conference proceedings, case reports and animal studies, or unpublished work and studies as well as studies using analog recording techniques. Screening for eligibility followed a two-stage process, first by screening the title and abstract, followed by a full-text review.

## 3. Results

Our initial search strategy yielded 348 records, and 283 articles remained after removal of duplicates (PubMed: 102, Web of science: 100, Embase: 80, Cinahl, 1). After browsing the titles and abstracts, 217 studies were excluded based on the abovementioned criteria. During full-text evaluation, we included studies utilizing digital recording methods (Fig. 1 & Table 1). No study published in French or German fulfilled the inclusion criteria. All 22 studies report measures of the cardiac system. Fourteen studies combined measures of the respiratory system with the cardiac system, and six studies incorporated measures of the electrodermal system with measures of the cardiac system. No study referred to the thermal system in a multimodal approach. Two studies specifically reported multimodal changes in the ANS.

### 3.1. ANS activity changes related to epilepsy combining cardiac and respiratory measures

Studies combining assessments of cardiac and respiratory systems addressed a variety of research questions yet reported similar measures. The most commonly reported measures for the cardiac system were HR, BP, mean arterial pressure (MAP), and HRV. The HRV is expressed either in the time domain mostly by root mean square error of successive differences (RMSSD), or in the frequency domain by high frequency (HF) power, or the ratio of low frequency (LF) and HF power as an indicator for sympathetic or parasympathetic dominances. The most commonly reported measures of the respiratory system were arterial oxygen saturation (SpO<sub>2</sub>) and respiratory rate (RR).

Most studies depicted cardiac and respiratory measures as two unconnected measures only without considering a common driver for changes within both modalities. Those studies described the alterations in the ANS in ictal and interictal states. More specifically, Chroni et al. [20] focused on parasympathetic cardiac markers in response to physiological perturbations at rest and during deep breathing. Patients with epilepsy had a significantly lower sural nerve action potential amplitudes and or R-R intervals, capturing the time intervals between consecutive heartbeats, compared with healthy controls. The R-R interval during breathing was particularly low when epilepsy duration exceeded 10 years or in patients on phenytoin. Heart rate was generally comparable between the two groups. These researchers also measured Valsalva and tilt ratios to assess for HR changes in relation to respiratory strain and shift in position, and found curtailed ratios in PWE. Results suggested that parasympathetic activity was suppressed in PWE.

Two studies compared interictal ANS parameters before and after temporal lobe surgery [21,22]. Hilz et al. [22] questioned whether the laterality of temporal lobe epilepsy (TLE) surgery can affect or can trigger changes in ANS parameters. They recorded and analyzed HR, systolic BP, and RR from patients months before and after surgery. Low frequency power and BP as well as baroreflex sensitivity decreased after surgery independent of laterality while HR, BP, HF power of HR, and BP, as well as RR, did not change. Authors interpreted those findings as postoperative reduction of sympathetic overflow. Dütsch et al. [21] showed similar changes related to the postoperative period, namely reduction of LF power and increase in cerebral blood flow velocity. Other parameters such as HR, BP, respiration, SpO<sub>2</sub>, and HF power remained unaffected. The authors concluded that through reducing sympathetic activation and improving cerebral and cardiovascular autoregulation, TLE surgery may contribute to improved autonomic balance in PWE and decrease their risk of SUDEP.

O'Regan & Brown [23] focused on ictal changes in cardiac and respiratory functioning in children and expected the effect of a seizure to be a sympathetic discharge. Based on this work, seizures may disrupt cardiac and respiratory functioning, however, this effect depended on seizure types: focal seizures were frequently associated with various changes in the respiratory system while generalized seizures led to an increase in RR only. There was no association between focal seizures and other respiratory markers, such as apnea or hypoxemia. Changes in cardiac parameters occurred more frequently in generalized seizures than focal seizures, with changes in 48% of generalized events versus 26% of focal seizures.

Moseley et al. [24] studied the relationship between autonomic dysfunction and postictal generalized Electroencephalogram (EEG) suppression (PGES). Postictal generalized EEG suppression is a phenomenon related to SUDEP based on the correlated inhibition of brain areas such as the brainstem and thus may relate to autonomic measures. In this study, the authors found that PGES correlated with peri-ictal hypoxemia and peri-ictal tachycardia and that children with PGES may have higher risk for SUDEP. Two other research studies questioned how seizures differ depending on onset either during wakefulness or during sleep. In this context, Lee et al. [25] compared HR and RR in patients with nocturnal and diurnal generalized convulsive seizures (GCS) and did not find significant differences, besides lower HR in preictal measures for nocturnal

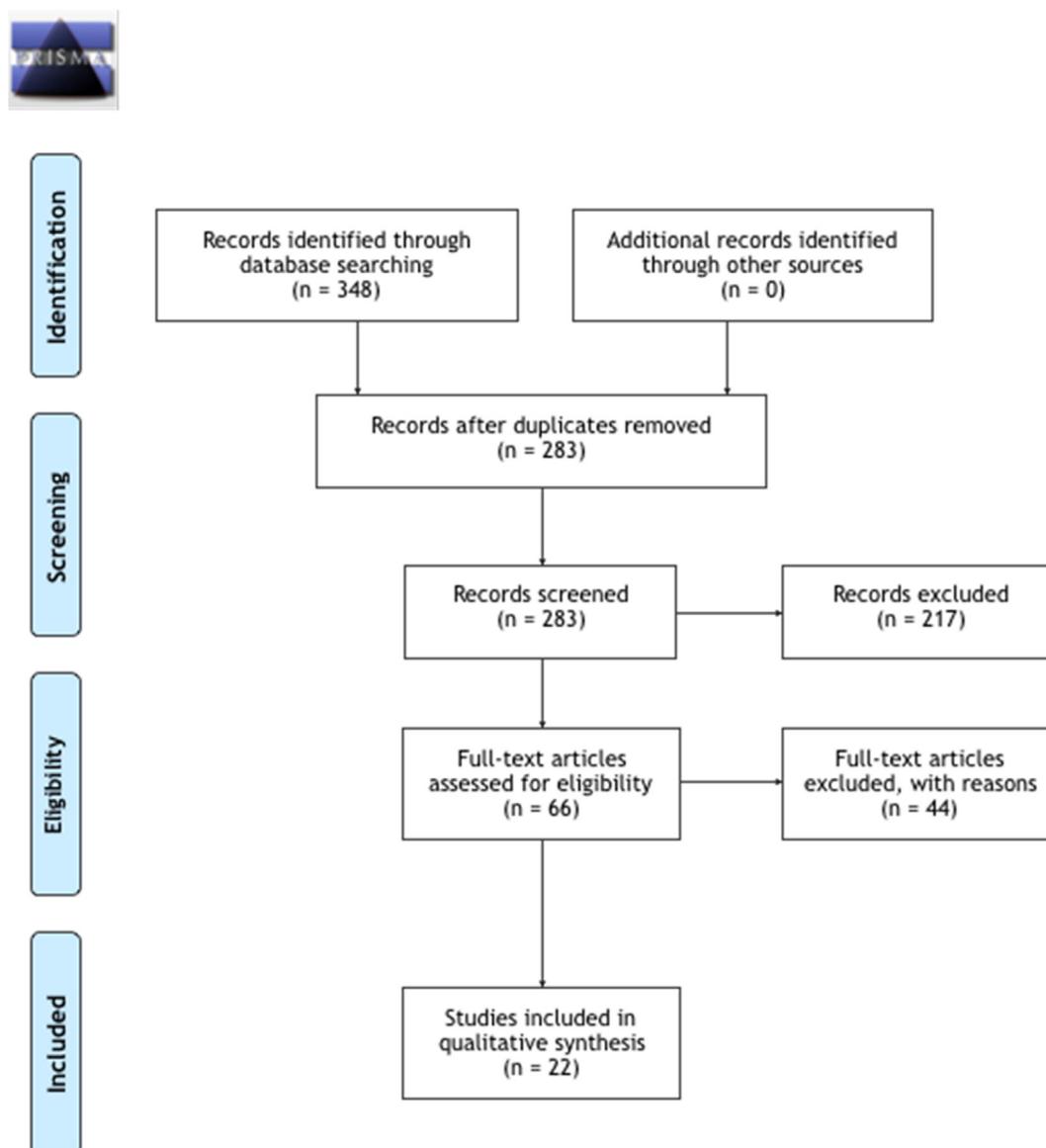


Fig. 1. PRISMA flow chart of literature search on multimodal ANS activity changes related to epilepsy [19].

compared with diurnal GCS. Similarly, Peng et al. [26] measured seizure-related changes in respiratory parameters and HR as well as PGES in patients with generalized tonic-clonic seizures (GTCS) and determined differences between seizures occurring during wakefulness and those that occur during sleep. Oxygen saturation did not differ significantly during sleep and wakefulness while HR changes were more prominent at the onset of seizures that occurred during sleep. Postictal generalized EEG suppression occurred more frequently during sleep, but this risk did not relate to respiratory changes. Similarly, a study by Lee et al. [25] showed no difference in RR between groups of patients with diurnal and nocturnal seizure onsets, but HR changes were more prevalent and frequent when seizure onset occurred during sleep. Also based on ictal measures, Goldenholz et al. [27] studied seizure profiles based on cardiopulmonary markers, especially SpO<sub>2</sub>, for seizure detection. In this study, most PWE had baseline dysfunction in the cardiac or respiratory systems, or both domains. A threshold for seizure detection with an acceptable rate of false alarms was also proposed.

Five studies investigated correlations of respiratory and cardiac parameters. Three described a correlation while two found none. Varon et al. [28] examined the interaction between respiration and HR, by means of a time series method based on information dynamics, i.e., entropy that represents the amount of information transferred

between respirations to HR on a signal level. Interactions differed between seizure types. For focal seizures, HR became more predictable during a seizure indicating alterations in cardiorespiratory interactions. Interestingly, this alteration starts as a transient change during the course of signal pattern changes prior to the seizure. Also, absence seizures are associated with cardiorespiratory changes. The same group of authors later focused on interictal cardiorespiratory interactions [29]. In line with their previous results, they found that patients with absence epilepsy have a lower complexity in their structure of variability classified by entropy measures in their HR signal, which implies that HR changes are more predictable and less adaptable. Further, less information was transmitted from respiration to HR in patients with absence epilepsy than in controls. In the third study, Tatum et al. [30] used ANS measures to describe differences and similarities between epileptic seizures and psychogenic nonepileptic seizures (PNES). Changes in ANS measures, including higher HR and BP and lower SpO<sub>2</sub> values, were more prominent in epileptic seizures than PNES. Patients with epileptic seizures experienced a greater increase in HR and reduction in SpO<sub>2</sub> during ictal phases. Additionally, this HR increase correlated inversely with SpO<sub>2</sub> decrease in PWE, but not in patients without epilepsy. Furthermore, for both disorders, seizure-dependent changes were highest for events with motor symptoms.

**Table 1**  
Overview of patient characteristics, methods and results of the included studies by modalities reported.

Study	n	Age	Gender	Number of seizures	Years of seizure	Epilepsy syndrome/ EEG locus	Seizure type	Measurement condition	Modalities	Devices	Preictal	Ictal	Postictal	Interictal	Multimodal implications
<i>Cardiac and respiratory</i>															
Chroni et al., 2008	71 Pt 71 Con	Pts: 37.8 age-matched	Pts: 38 F sex-matched		15.3		5 SPSs, 24 CPS, 26 SGTCS, 16 PGTCS	Pt vs con	Cardiac	Battery of neurophysiological tests				No difference in deep breathing and rest heart rate Rest and DP R-R interval variation was lower No difference Valsalva ratio lower Tilt ratio lower	Suppressed cardiovagal response in epilepsy pts
Dütsch et al., 2004	16 Pt	36.2	9 F		22.9	TLE	4 SPS and CPS, 7 CPS and GTC, 5 all 3 types	Preoperative and postoperative	Cardiac	Three lead ECG Colin Pilot™				HR, BP mean, CBFV mean and HF powers unchanged, LF powers of HR, BP, CBFV and LF transfer function gain had decreased Respiration, SpO <sub>2</sub> , pCO <sub>2</sub> unchanged	Reduced sympathetic modulation after surgery
Goldenholz et al., 2017	45 Pt	40	16 F	193	23			Continuous data	Cardiac	Radical-7 single-channel ECG		HR increases			Baseline dysfunction in either cardiac, pulmonary, or both domains, and that ictally there was dissociation
									Respiratory	Two-belt chest–abdomen inductance plethysmograph Respitrace Calibrator™		SpO <sub>2</sub> decreases			
Hampel et al., 2016	37 Pt	37	20 F	45	18	23 TLE 14 Extra-TLE	28 FS, 9 SGTCS		Cardiac	ccNexfin device		Elevated HR and MAP with FS	BP increases, but goes back to baseline within 5 min HR remains elevated for at least 10 min in SGTCS	No significant changes	Systemic BP and HR but not SpO <sub>2</sub> display distinct patterns depending on seizure type
Hilz et al., 2002	18 Pt	37	10 F		22.1	TLE	4 SPS and CPS, 7 CPS and GTCS, 7 all 3 types	Preoperative vs postoperative	Cardiac	Three-lead ECG noninvasive arterial tonometry		SpO <sub>2</sub> dropped in 2 pts with FS		HR, BPsys and HF power were unchanged, LF power of HR and BPsys decreased after surgery,	TLE surgery can lead to decreased sympathetic activation in pts and reduce the risk for SUDEP

									Respiratory	Two-belt chest-abdomen inductance plethysmograph	Cardiac	ECC (Nihon Kohden)	Increase in heart seen at or after EEG seizure onset. No ictal bradycardia seen with ictal central apnea	baroreflex sensitivity decreased No significant changes
Lacuey et al., 2018	126 Pt	40	77 F	213		156 temporal, 79 frontal, 11 parietal, 24 occipital, 2 insula, 30 generalized, 2 unknown	109 FS, 17 PGTCs	Comparing seizure types						
	Respiratory	Pulse oximetry		Ictal central apnea in FS					Ictal central apnea is a common feature in FS and may constitute potential warning for SUDEP	Cardiac				
Lee et al., 2013	46 Pt with nocturnal GCS	37 34	57 F 42 F	10 12		Generalized, temporal, frontal, parietal and occipital	GTCS	Nocturnal vs diurnal seizures	Cardiac	Single-channel ECG		HR lower for nocturnal than diurnal	No difference	SUDEP risk during sleep is not related to postictal autonomic dysregulation
									Respiratory	Visual and auditory analysis from video			No difference	
Moseley & Britton, 2014	29 Pt					39 CPS, 11 SGTCs, 6 PGTC, and 2 tonic seizures			Cardiac	Precordial single channel ECG			QT lengthening was more frequently observed than shortening (11 vs 3 times)	QTc lengthening and shortening were not associated with peri-ictal hypoxemia
									Respiratory	Pulse oximetry			Peri-ictal hypoxemia in 18/58 seizures	
Moseley et al., 2013	37 Pt	10.2	24 F	168	4.9	34 no syndrome, 2 JME, 1 Jeavons	25 FS, 5 GS, 4 FS and GS, 3 FS and spasms	Continuous recording	Cardiac	ECC			Tachycardia in 41.1% seizures	PGES in pediatric pt may imply a high risk for SUDEP
									Respiratory	Pulse oximetry			Peri-ictal hypoxemia was observed in 26% of seizures	
O'Regan & Brown, 2005	37 Pt	7.5	17 F			24 symptomatic cause, 3 PGE, 1 LKS, 2 LGS, 4 undefined		Continuous data and changes detected based on thresholds	Cardiac	BP: conventional Dynamap cuff ECG: Two electrodes			Heart rate variability, short-lived rise in heart rate in many seizures	Seizures can lead to cardiac and respiratory dysregulation.
									Respiratory	Impedance system using two skin electrodes			GS: frequent increase in respiratory rate FS: frequent respiratory abnormalities	

Table 1 (continued)

Study	n	Age	Gender	Number of seizures	Years of seizure	Epilepsy syndrome/ EEG locus	Seizure type	Measurement condition	Modalities	Devices	Preictal	Ictal	Postictal	Interictal	Multimodal implications
Peng et al., 2017	41 Pt with diurnal seizures 26 Pt with nocturnal seizures	35.5 36.77	22 F 13 F			Diurnal: 71 temporal, 8 extratemporal, 2 generalized, 22 undetermined Nocturnal: 43 temporal, 1 extratemporal, 2 generalized, 4 undetermined	Diurnal: 7 bilateral, 42 left, 43 right, 11 undetermined Nocturnal: 7 bilateral, 42 left, 43 right, 11 undetermined	Nocturnal vs diurnal seizures	Cardiac	Single channel ECG			HR changes higher for seizure onset during sleep No differences		PGES is not related to sleep-related respiratory compromise
Tatum et al., 2016	46 Pt with epilepsy 50 Pt with PNES	38 43	23 F 34 F			FS with impaired consciousness (FS w/ IC), FS without IC (FS w/o IC), or GTCS	Motor, hypomotor or nonmotor	Comparing ES to NES for baseline and measures during events	Cardiac	Real-time multi-parameter pt monitors			HR increased more for epilepsy pts; GTCS had greater increases than FS higher increases in hypermotor events SpO2 decreased, more for epilepsy pts FS: HR is higher and more predictable, especially when respiration intake into account		Inverse relationship between ictal HR and ictal SpO2 in epilepsy pts
Varon et al., 2014	37 Pt	9				28 frontal lobe, 20, temporal lobes and 39 generalized seizures		24 h recordings, analysis around seizures	Cardiac	Single-lead ECG			In AS, cross entropy is reduced during seizure, while GTCS showed no effect		Cardiorespiratory functions are significantly affected during seizures
Varon et al., 2015	10 AS, 10 TLE 10 Con	10 10.3 10.8			AS and TLE			Group comparison in seizure-free episodes	Cardiac Respiratory	Single-lead ECG Single-lead ECG			HR higher in pts with AS than in con Mean RR variability of RR higher in AS compared to con		Information transfer from respiration to HR expressed as cross-entropy is lower in AS group compared to con

*Cardiac and electrodermal*

Drake et al., 1998	50 Pt including 20 male with suggested SUDEP risk con	15-61 20-40			GTCS, CPS, SGTCS	Auditory and tactile stimuli and respiration	Cardiac  EDA	Nihon Kohden Neuropak EMG/EP at forearm  Nihon Kohden Neuropak EMG/EP at hand	Shorter R-R interval especially with risk for SUDEP Greater SSR latency and higher amplitude in pts with high SUDEP risk No significant results Left TLEs higher skin conductance than con at baseline and higher than con and right TLEs during negative pictures	ANS dysfunction is more pronounced in epilepsy pts after a stimulus.
Lee et al., 2002	13 left 7 right 10 Con	37.2/ 34.2 30.6	8 F 3 F 6 F			Reaction to positive and negative pictures from the International Affective Picture System	Cardiac  EDA	Sensor attached to the 4th fingers of left and right hand Ag/AgCl adhesive electrodes on 2nd and 3rd fingers of left and right hand		Lesion in left temporal lobe may lead to sympathetic activation
Poh et al., 2012	11 Pt (34 seizures)	3-20	3 F	34		Comparison of pre- and postictal	Cardiac  EDA	ECG  Wrist-worn sensor	HR increases, HRV decreases EDA increases	Sympathetic activation and parasympathetic activation provide autonomic correlation of EEG suppression Sympathetic activation and vagal suppression is more pronounced in pediatric pts.
Sarkis et al., 2015	20 Pt	13 adults: 19-67 7 pediatric: 11-17		30	SGTCS and PGTCs	Adult and pediatric group Data 30 min before and after seizure	Cardiac  EDA	ECG  Q-sensor affectiva	Drop in HF power More prominent in pediatric pts Pediatric pts have higher EDA amplitude	
Müngen et al., 2010	30 Pt with epilepsy 25 Pt with PNES 20 Con	31.6 30.2 31.1	16 F 19 F 10F		21 PGTCs and 9 SGTC	Interictal and postictal periods of NES and ES at rest with normal and deep breathing	DB-RRIV  EDA	Dantec Keypoint 4-channel EMG  Ag/AgCl disk and active electrodes on the palm and sole of the feet	DB-RRIV lower than con and PNES R-R interval lower and SSR prolonged in ES compared to con and different from PNES	Changes within the ANS might be specific to ES

(continued on next page)

Table 1 (continued)

Study	n	Age	Gender	Number of seizures	Years of seizure	Epilepsy syndrome/ EEG locus	Seizure type	Measurement condition	Modalities	Devices	Preictal	Ictal	Postictal	Interictal	Multimodal implications
Labuz-Roszak & Pierzchal, 2009	21 Pt	35.9			16.7				Cardiac EDA Symptoms	Cardiovascular reflex tests (Ewing's battery) Neurophysiological method ANS questionnaire				One test had an abnormal result in 3 pts and two tests in one pt. Abnormal sympathetic skin response was found in 33.3% of pts 57% of pts had an abnormal score indicating autonomic dysfunction	Changes in EDA and cardiovascular biomarkers were present but insignificant. The questionnaire needs a confirmatory tool.
Multimodal Cogan et al., 2016	10 Pt	41.8 (21–64)	4 F	26	18.1	3 left temporal, 4 right temporal, 1 right and left temporal, 1 frontal, 1 nonfocal	7 CPS, 2 SGTCS, 1 PGTCs	Continuous data	Cardiac Respiratory EDA	Affectiva Q-curve monitors Nonin WristOx2		HR increase SpO <sub>2</sub> decrease EDA increase			Consistent pattern of results aided in seizure detection with a high specificity
Berlingen et al., 2004	32 Pt 32 Con	22.4 22.1	12 F 14 F				23 pt with PGE 9 pt FS	RFTs, antiepileptic treatment:	Cardiac Respiratory EDA	EMG RFT Ag/AgCl electrodes on palm				In PGE: decreased RRIV RFT remained within normal limits In FS: prolonged SSR latency RFT improved after treatment	Sympathetic dysfunction was determined in pts with partial epilepsy and parasympathetic dysfunction in pts with generalized epilepsy

ANS: autonomic nervous system; AS: absence seizure; BP: blood pressure; CBFV: cerebral blood flow velocity; Con: control; CPS: complex partial seizure; DB-RRIV: cardiac during deep breath R-R interval variation; ECG: electrocardiogram; EDA: electrodermal activity; EMG: electromyogram; ES: epileptic seizure; FS: focal seizure; GCS: generalized convulsive seizures; GS: generalized seizure; GTCS: generalized tonic-clonic seizure; HF: high frequency; HR: heart rate; HRV: heart rate variability; JME: juvenile myoclonic epilepsy; LF: low frequency; LGS: Lennox–Gastaut syndrome; LKS: Landau–Kleffner syndrome; NES: nonepileptic seizure; pCO<sub>2</sub>: partial pressure of carbon dioxide; PGE: primary generalized epilepsy; PGES: postictal generalized EEG suppression; PGTCs: primary generalized tonic-clonic seizure; PNES: psychogenic nonepileptic seizures; Pt: patient; RFT: respiratory function Tests; RR: respiratory rate; SGTCS: secondarily generalized tonic-clonic seizure; SpO<sub>2</sub>: oxygen saturation; SPS: simple partial seizure; SSR: sympathetic skin response; SUDEP: sudden unexpected death in epilepsy; TLE: temporal lobe epilepsy.

In contrast to studies reporting epilepsy-induced correlations of cardiac and respiratory parameters, Hampel et al. [31] described that in focal seizures, MAP and HR increase during the ictal period, especially when seizures were accompanied by altered awareness, but SpO<sub>2</sub> remained unchanged in most patients. Oxygen saturation levels declined in less than 6% of these patients. For patients with secondarily generalized seizures, artifacts disrupted ictal measurements of these features, and increases in HR and MAP occurred in the postictal period. Similarly, those measures remained uncorrelated to SpO<sub>2</sub> levels. Moseley & Britton [32] explored the correlation between cardiac repolarization and low SpO<sub>2</sub> and hypoxemia and QT interval alteration presented during the peri-ictal period; however, the two features were unrelated. Therefore, other factors besides hypoxemia may prompt peri-ictal changes of cardiac conduction [32].

### 3.2. ANS activity changes related to epilepsy combining cardiac and electrodermal measures

Studies combining cardiac and electrodermal measures differentiated between sympathetic and parasympathetic activity. Electrodermal activity is solely sympathetically controlled. Assessment may include amplitude of activity by measuring mean values, calculating the area under the curve, or amplitude and latency of peak activity related to a stimulation or seizure. Two studies obtained interictal measures during resting conditions [33,34]. Labuz-Roszak and Pierzchala [33] showed that abnormal EDA values in autonomic measures occur in approximately one-third of patients during interictal states while cardiovascular alterations due to autonomic dysfunction were uncommon. A positive association between EDA and HR was noted when an abnormality occurred in both measures. Müngen et al. [34] showed altered sympathetic and parasympathetic functions in PWE compared with healthy controls in interictal and postictal states. Features of ANS function in patients with epileptic seizures differed, i.e., lower deep breathing interval and slower latency of sympathetic skin response, from those in patients with nonepileptic seizures, whose values were comparable with the control group. Therefore, changes in the ANS might be epilepsy-specific.

Drake et al. [35] and Lee et al. [36] attempted a comparison of EDA and cardiac activity in patients with epilepsy with healthy controls in relation to external stimuli. Specifically, Drake et al. [35] assessed peri-ictal EDA as a measure of sympathetic and R-R interval as a measure of parasympathetic activity in PWE and healthy controls. After stimulation, the increase in EDA was more prominent in PWE. The latter had a shorter R-R duration as well, especially in patients with possible risk for SUDEP. Lee et al. [36] tested skin conductance level and HR changes in patients with left and right TLE in comparison with healthy controls while seeing emotional pictures. They found selective skin conductance levels suggestive of hyperarousal in left TLEs and no difference in HR measures. The other two studies assessed ANS changes related to seizures. Poh et al. [15] studied the association between autonomic changes and PGES as a biomarker for SUDEP, by measuring EDA using a wrist-worn device and the HF power using electrocardiogram (ECG). Electrodermal activity and HR increased and the HF power decreased during the postictal period. This change corresponded to a longer PGES duration and may thus play a role in SUDEP. In a similar approach, Sarkis et al. [37] showed comparable results regarding the EDA and HF power during the postictal period, as well as the correlation with PGES. Interestingly, pediatric patients had more robust sympathetic activation and vagal suppression than adult patients.

### 3.3. ANS activity changes related to epilepsy combining cardiac, respiratory, and electrodermal measures

Two studies [38,39] combined findings from three modalities. Berilgen et al. [38] showed that patients with focal epilepsy compared with controls showed a sympathetic dysfunction evident by a more durable EDA response to supramaximal electric stimulation. Electrodermal activity

response decreased after treatment in this group while patients with generalized epilepsy showed a parasympathetic dysfunction, which was evident by the significant drop in the RR interval. Respiratory function tests remained within normal limits during the interictal period in patients with focal and generalized epilepsy. Cogan et al. [39] focused on the improvement of seizure detection algorithms based on biosignals from a wearable device, or in combination with a limited channel EEG in patients with mostly focal epilepsy presenting with complex partial seizure (CPS) and GTCS. Utilizing changes in HR, EDA, and SpO<sub>2</sub>, they detected 15 of 26 seizures from 7 of 10 patients with a pattern of HR and EDA increase and SpO<sub>2</sub> decrease. Personalizing threshold values and relative times between changes across modalities allowed for increasing accuracy and specificity increase in 6 of the 10 patients to 100%. Using the limited channel EEG, they detected seizures in two additional patients. Hence, multimodal monitoring may be a promising approach to improve seizure detection by informing caregivers and improving seizure logs in closed-loop warning systems.

## 4. Discussion

We provide a synthesis of studies that present a multimodal approach to describe ANS changes in relation to epilepsy. In parallel with improvements on sensor technology and analysis methods, the body of literature on this topic continues to grow. All studies reported cardiac measures in combination with either respiratory or electrodermal measures. Most studies report multiple unimodal analyses while only few reported multimodal patterns detected on a group or individual level. Epilepsy-related differences occurred in all modalities for interictal states as well as pre- and postictal and ictal periods. Some studies reported nonsignificant results on a group level, comparing patients with controls. Autonomic nervous system measures were recorded either during rest or in response to stimuli. These results jointly indicate that seizures evoke ANS changes but also that ANS changes may lead to permanent alterations in ANS functioning in PWE and occur in different facets for different seizure types.

Studies reporting significant epilepsy-related effects on ANS measures presented results for several modalities measured at the same time or the relations of ANS signals across modalities. For the cardiac system, several markers demonstrated alterations. Heart rate increases before [27]; and during seizure [28,30,39] and remains elevated in postictal states [40] for up to 10 min [31]. Heart rate was higher in interictal states [28,38]. Blood pressure rises [31] while HRV decreases [15] and LF power decreases [31]. Results jointly support the hypothesis of a shift to more sympathetic activation in PWE, and these changes were most prominent in patients with GTCS compared with those with other seizure types, in nighttime seizures [26] and in seizures with longer durations [33]. Moreover, less adaptability of the cardiac system in the interictal state, indicated by lower R-R interval variation in response to deep breathing [20,34] and lower complexity at rest [29] and during seizure [28], has been hypothesized in PWE compared with controls. Autonomic dysfunction seems to exacerbate as the duration of the disease increases [20]. For the respiratory system, SpO<sub>2</sub> decreases before [39] and during [27,30] a seizure, as well as a lower mean RR and higher variability of RR in absence epilepsy compared with controls [29]. Electrodermal activity levels increased with epileptic events, which are also described as EDA peaks [15,39]. Furthermore, patients with focal seizures show increased response latencies in the electrodermal system [34,38]. These results may indicate reduced adaptability to external stimuli as part of dysfunctional ANS regulations.

Combining modalities lead to the conclusion that PWE exhibit suppressed vagal control [20] and an autonomic imbalance toward an increased sympathetic activity [15,37,38]. As a confirmation, sympathetic activity was reduced after TLE surgery, contributing to an improved autonomic balance [21,22]. Tests for correlations between measures of modalities are scarce, and results differ between studies and modalities. Two found no correlation [31,32], and three showed

a relation between changes in cardiac and respiratory parameters [28–30], indicating less information transmission between modalities and an increase in HR that relates to a reduction in blood oxygen levels. Studies including more than two modalities describe sympathetic activation and parasympathetic suppression. Nevertheless, the pattern seems to vary between seizure types and individuals. In that sense, both studies including measures of three modalities attempted to describe the differences between effects, in relation to patient characteristics based either on seizure type [38] or for biosignal patterns, on individual patient level better [39]. The differences between patterns of changes seem to be robust for the individual person, which offers the potential to use individually determined patterns for seizure detection. Indeed, the latter study reported reduced false alarm rates when integrating multiple modalities. Consequently, the personalized multimodal approach bears a huge potential for personalized monitoring.

Multimodal ANS-based methods represent the potential to consider strengths and weaknesses of each method within the evaluation context and consider the complex nature of human physiology. Therefore, multimodal methods can account for the great interindividual variability [39] seen in PWE and the general population.

The observed epilepsy-related changes in ANS are rooted in the same alterations in central activity, both during seizures and over time, and therefore are presumably dependent and show across modalities. Two signals measuring two modalities from a joint source share redundant and additive information. Redundant information is especially helpful to cancel noise and improve reliability. Additive information provides support for further description, such as discriminating the reason for a specific reaction within the ANS to improve classification accuracy, which might be useful in clinical settings. Autonomic dysfunction occurs with focal and generalized seizures during the preictal interictal and postictal periods. Different seizures originate from the various areas in the autonomic network of the brain (Devinsky, 2004), which accounts for the wide array of different semiologies and presentations. Seizure-related autonomic dysfunction, especially cardiac and respiratory alterations, thus, plays a role in the pathogenesis of SUDEP [41,42]. Therefore, ANS changes may serve as potential biomarkers for SUDEP [15,22–26,32,35,37,43].

Autonomic nervous system dysfunction can occur in both focal and generalized seizures [23,34,43], especially when the seizure involves a hypermotor state [30]. However, ANS differences in various epilepsy syndromes require further elucidation, considering current work in largely heterogeneous and small groups with a variety of confounders within group measures.

Besides the variability between patients, studies differ in experimental design. Methods used vary within chosen ANS modalities, used sensors, and analyzed parameters. Sensor techniques are still in development. Devices in the different studies, and device application, often do not have a long track record. For example, the location of measurements is frequently not reported but might be relevant. Results reported by Mungen et al. [34] showed that upper extremity measures of EDA seem to be more sensitive than lower extremity measures, and therefore, the location of sensor placement on the body may play a role. Another difference among studies is the use of one or multiple systems in combination. Combinations might allow for the use of the best system for each modality; however, it may be challenging to synchronize signals. In addition, some methods are specifically targeted to measure a specific system while other studies also provide an indirect calculation from another signal reported, like RR from video recording [36], and therefore, the type of evaluation of a signal may be important. Furthermore, several of the used recording techniques are subject to technical limitations, such as movement, muscle and electrode artifacts, that reduce data quality especially in the not completely standardized recording settings.

Of note, the expression of differences depends on the comparator, which varies considerably between studies. Several studies report PWE in comparison with an age- and gender-matched healthy control

group while other studies compare between seizure types or syndromes, or the same group in different conditions, such as pre- and postoperation. It would be of great interest to combine those comparisons systematically within one dataset.

Within studies, there are also other confounders: Sarkis et al. [37] pointed out that ANS activity changes as a function of age and that this might require controls, as samples normally include large age spans. Lee et al. [36] mentioned that epilepsy could affect other functioning, such as emotional processing, that might also cause alterations in ANS functioning and therefore have a moderating effect. Consequently, potential confounders may need to be evaluated with regard to moderating or modulating effects as well, as this would alter the interpretation of ANS changes. Nevertheless, some studies have tested the specificity of epilepsy-related ANS changes compared with ANS responses related to epileptic and nonepileptic seizures [30,34]. These studies used different modalities to show that changes were greater for epileptic than for PNES.

## 5. Conclusion

Collectively, multimodal approaches that assess the ANS measures may offer a simple means to evaluate the alterations and risks induced by epilepsy and may potentially play a role in seizure detection and prediction. Further consensus on ANS parameters, acquisition, and reporting is needed to obtain more evidence based on meaningful clinical data.

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## Competing interests' statement

Tobias Loddenkemper serves on the Council (and as President) of the American Clinical Neurophysiology Society (active), on the American Board of Clinical Neurophysiology, served as an Associate Editor for *Seizure*, served on the Laboratory Accreditation Board for Long Term (Epilepsy and Intensive Care Unit) Monitoring, and serves as an Associate Editor for *Wyllie's Treatment of Epilepsy* 6th and 7th edition.

He is part of patent applications and license agreements to detect and predict clinical outcomes, and to manage, diagnose, and treat neurological conditions, epilepsy, and seizures, and future revenue from these scientific contributions cannot be ruled out. Dr. Loddenkemper is a co-inventor of the TriVox Health technology. Dr. Loddenkemper and Boston Children's Hospital might receive financial benefits in the form of license payments in the future.

He received research support from the NIH, Epilepsy Research Fund, the Epilepsy Foundation of America, the Epilepsy Therapy Project, the Pediatric Epilepsy Research Foundation, Lundbeck, Eisai, Upsher-Smith, Sunovion, Mallinckrodt, Empatica, Sage, and Pfizer, including past device donations from various companies, including SmartWatch, Empatica, and Neuro-electrics. He served as a consultant for Zogenix, Upsher Smith, Amzell, Sunovion, Engage, Elsevier, UCB, Advance Medical, and Grand Rounds.

He performs video-electroencephalogram long-term and ICU monitoring, electroencephalograms, and other electrophysiological studies at Boston Children's Hospital and affiliated hospitals and bills for these procedures and he evaluates pediatric neurology patients and bills for clinical care.

He has received speaker honorariums from national societies including the AAN, AES, and ACNS, and for grand rounds at various academic centers.

His wife, Dr. Karen Stannard, is a pediatric neurologist and she performs video-electroencephalogram long-term and ICU monitoring, electroencephalograms, and other electrophysiological studies and bills

for these procedures and she evaluates pediatric neurology patients and bills for clinical care.

Claus Reinsberger serves on the Council of the German Society of Sports Medicine and Prevention and the Westfalian Board of Sports Medicine. He receives research support from the Federal Institute of Sports Science in Germany and the Westphalian Foundation. He serves as a consultant for Sleepmed Inc. and Boston Children's Hospital and speaker honorariums from national societies including ACNS, DGSP, DOSB, and DFB, as well as for grand rounds at various academic centers.

All other authors declare to have no competing interests.

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