Twenty-four-hour patterns in electrodermal activity recordings of patients with and without epileptic seizures

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Abstract
Objective: Daytime and nighttime patterns affect the dynamic modulation of brain and body functions and influence the autonomic nervous system response to seizures. Therefore, we aimed to evaluate 24-hour patterns of electrodermal activity (EDA) in patients with and without seizures.

Methods: We included pediatric patients with (a) seizures (SZ), including focal impaired awareness seizures (FIAS) or generalized tonic-clonic seizures (GTCS), (b) no seizures and normal electroencephalography (NEEG), or (c) no seizures but epileptiform activity in the EEG (EA) during vEEG monitoring. Patients wore a device that continuously recorded EDA and temperature (TEMP). EDA levels, EDA spectral power, and TEMP levels were analyzed. To investigate 24-hour patterns, we performed a nonlinear mixed-effects model analysis. Relative mean pre-ictal (−30 min to seizure onset) and post-ictal (I: 30 min after seizure offset; II: 30 to 60 min after seizure offset) values were compared for SZ subgroups.

Results: We included 119 patients (40 SZ, 17 NEEG, 62 EA). EDA level and power group-specific models (SZ, NEEG, EA) (h = 1; P < .01) were superior to the all-patient cohort model. Fifty-nine seizures were analyzed. Pre-ictal EDA values were lower than respective 24-hour modulated SZ group values. Post hoc comparisons following the period-by-seizure type interaction (EDA level: χ² = 18.50; P < .001, and power: χ² = 6.73; P = .035) revealed that EDA levels were higher in the post-ictal period I for FIAS and GTCS and in post-ictal period II for GTCS only compared to the pre-ictal period.

Significance: Continuously monitored EDA shows a pattern of change over 24 hours. Curve amplitudes in patients with recorded seizures were lower as compared to patients who did not exhibit seizures during the recording period. Sympathetic skin responses were greater and more prolonged in GTCS compared to FIAS. EDA recordings from wearable devices offer a noninvasive tool to continuously monitor sympathetic activity with potential applications for seizure detection, prediction, and potentially sudden unexpected death in epilepsy (SUDEP) risk estimation.

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INTRODUCTION

A better understanding of underlying causes, potential seizure patterns, and clinical implications are essential to improved seizure management and treatment algorithms. With recent developments in wearable technologies, further insight into autonomic manifestations of seizures may now be more attainable.

People with epilepsy exhibit suppressed vagal control and an autonomic imbalance toward increased sympathetic activity. Electrodermal activity (EDA), an autonomic marker for sympathetic skin activity, exhibits unique properties in the setting of seizures and thus can be used for seizure monitoring, as well as for seizure detection and prediction. Biofeedback based on EDA for people with epilepsy (PWE) has decreased seizure likelihood in prior studies, and change may have been related to central regulatory effects and modulation of EDA levels.

Practical implementation of utilizing EDA to monitor seizures is often challenged by the low specificity of EDA changes. Potential factors contributing to the variability of EDA are environmental conditions, temperature, body position, and stress. In addition to these factors, diurnal rhythms are also likely an important source of variability within physiological signals. These 24-hour and circadian patterns are of relevance as they may contribute to rhythmic patterns of seizure occurrence and can thereby be related to the seizure-associated EDA response. Furthermore, time of seizure occurrence and type of seizure may also affect EDA peak height, which varies within and between patients, particularly when controlled for a pre-ictal baseline. Therefore, we took a three-pronged approach to elucidate the relationship of EDA, seizures, and diurnal patterns further.

The first aim of our study was to characterize 24-hour patterns in EDA and skin temperature (TEMP) recordings in patients with epilepsy, based on our central hypothesis that continuous EDA recordings show patterns of circadian rhythms beyond the effects of thermoregulation.

Second, we assessed if 24-hour patterns of EDA and TEMP differ between patients with and without seizures within the recording. In this setting, we hypothesized that the impact of seizures may have an effect on 24-hour modulation.

Third, we evaluated seizure-induced EDA response relative to the EDA level and power calculated from a 24-hour modulation pattern. Based on previous studies, we expected a seizure response within the EDA system that may demonstrate an increase in EDA level and power following the seizure.

MATERIALS AND METHODS

2.1 Standard protocol approval and patient consents

The study was approved by the Boston Children's Hospital Institutional Review Board. Written informed consent was obtained from all participants, or their guardians.

2.2 Patient selection

We included prospectively enrolled pediatric patients admitted to the Long-Term Monitoring Unit for video electroencephalography (vEEG) monitoring at Boston Children's Hospital, who wore an E4 biosensor (Empatica Inc., Milan, Italy) on either wrist or ankle. Two clinical epileptologists reviewed the vEEG recordings to determine clinical seizure type based on International League Against Epilepsy (ILAE) classification, including EEG localization and onset and offset times.

We selected patients who had at least 8 hours of E4 recording and qualified for one of the following three subgroups: (a) patients who had at least one seizure during vEEG (generalized tonic-clonic seizures [GTCS] or focal impaired awareness seizures [FIAS]) while wearing the E4 device (SZ), (b) patients with normal EEG (NEEG) during
vEEG (no seizures, interictal epileptiform activity, or encephalopathic patterns), and (c) patients with epileptiform activity but no seizures during vEEG (EA) (Supplement 1). For additional sub-analyses of seizure-related EDA response relative to the 24-hour modulated SZ group values, we selected seizures from patients of the initial cohort (Supplement 1) who had at least one seizure during vEEG (GTCS or FIAS) while wearing the E4 device, regardless of the total time recorded. For this analysis, we used more than one seizure per patient in some cases (patients with: 1 seizure = 23, 2 seizures = 6, 3 seizures = 5, 4 seizures = 1, 5 seizures = 1). We excluded patients with low quality signal in the pre- or post-ictal periods, no EEG or vEEG seizures = 1). We excluded patients with low quality, recordings with less than 8 hours of data, and patients who did not have at least a 2-hour seizure-free interval during the recording. To identify unreliable signals or biosensor removal, the remaining data were screened for low EDA activity (<0.001 for more than 15 minutes) and sudden temperature changes (>3 °C). In these cases, the recording was analyzed only from that point forward or until that point, and previous or subsequent samples were discarded to preserve signal quality. If there were multiple periods of concern for disconnection or artifact throughout the measurement, the patient was excluded from analysis. We also calculated the mean EDA amplitude of the sections that were included in the 24-hour period and compared the EDA levels recorded from the wrist (mean = 1.25 μS, SD = 1.53 μS) and ankle (mean = 1.03 μS, SD = 1.69 μS) recordings. As there was no difference (T = 0.73, P = .470), we combined patients. For the SZ group, we also screened signal quality for 30 minutes of pre-ictal and 60 minutes of post-ictal data. After data visualization, seizures were excluded when one or more of the following conditions were observed: low EDA activity (<0.001 μS) for more than 5 minutes, or repetitively (>5 times) for shorter times (less than 5 minutes), or when individual spikes (increase higher than 1 μS and back to previous level in 2 seconds or less) or drops (decrease of more than 1 μS and back to previous level in 2 seconds or less) occurred in the signal, as we considered these as indication of loss of contact between the sensor and the skin.

2.3 | Data recording and quality check

Patients wore an E4 biosensor on either their left or right wrist or ankle for long-term recording during their hospital admission. These sensors captured EDA with a sampling rate of 4 Hz. The recordings started between 9 am and 4 pm. We excluded patients with low signal quality, recordings with less than 8 hours of data, and patients who did not have at least a 2-hour seizure-free interval during the recording. To identify unreliable signals or biosensor removal, the remaining data were screened for low EDA activity (<0.001 for more than 15 minutes) and sudden temperature changes (>3 °C). In these cases, the recording was analyzed only from that point forward or until that point, and previous or subsequent samples were discarded to preserve signal quality. If there were multiple periods of concern for disconnection or artifact throughout the measurement, the patient was excluded from analysis. We also calculated the mean EDA amplitude of the sections that were included in the 24-hour period and compared the EDA levels recorded from the wrist (mean = 1.25 μS, SD = 1.53 μS) and ankle (mean = 1.03 μS, SD = 1.69 μS) recordings. As there was no difference (T = 0.73, P = .470), we combined patients. For the SZ group, we also screened signal quality for 30 minutes of pre-ictal and 60 minutes of post-ictal data. After data visualization, seizures were excluded when one or more of the following conditions were observed: low EDA activity (<0.001 μS) for more than 5 minutes, or repetitively (>5 times) for shorter times (less than 5 minutes), or when individual spikes (increase higher than 1 μS and back to previous level in 2 seconds or less) or drops (decrease of more than 1 μS and back to previous level in 2 seconds or less) occurred in the signal, as we considered these as indication of loss of contact between the sensor and the skin.

2.4 | Pre-processing

Data analysis was performed using Matlab (R2018a, The MathWorks Inc.). Raw EDA data were low-pass filtered (Butterworth filter of fourth order; cutoff frequency of 0.4 Hz), smoothed (factor 9), and had spikes eliminated using medfilt1 function. Data start was determined based on data quality and rounded up to the nearest complete hour. Data end was rounded down to the previous complete hour. In the time domain, EDA level was analyzed. In the frequency domain, a wavelet was calculated by the cwt function in Matlab with Morlet template and the power in the frequency range 0.01 to 0.3 Hz was determined. Although the EDA level is affected by a variety of influencing factors, activity in low frequencies (up to 0.25 Hz) has been shown to be responsive to sympathetic tone arousal with comparably low intra-individual variability.11,12 Because EDA relates to thermoregulation, we additionally analyzed surface body temperature recorded at wrist or ankle (TEMP) by the same device. Raw TEMP data were low-pass filtered (Butterworth filter of fourth order; cutoff frequency of 0.4 Hz), smoothed (factor 9), and the level was analyzed.

2.5 | Data analysis and statistics

Further analyses consisted of three different steps. For analysis steps 1 and 2, mean values of EDA level, EDA power, and TEMP level were analyzed over all consecutive 60-minute windows of the entire recording. For analysis step 3, EDA signals starting 30 minutes prior to the seizure until 60 minutes after the seizure were selected. We have excluded ictal data from our analysis, as signal quality is often impaired due to movements, especially during convulsive seizures. First, we described the circadian EDA patterns in the entire data set across all patients. We modeled the 24-hour pattern of (1) EDA level, (2) EDA power, and (3) TEMP level with nonlinear mixed-effects harmonic models and accounted for correlation between repeated measurements with a random intercept.15 Harmonic models refer to the statistical models in which the mean structure of the response variables is represented by a Fourier series with a finite number of sine and cosine terms. Random effects are imposed in such models to represent between-subject variation. Together, they form nonlinear mixed-effects harmonic models for characterizing circadian rhythms. The number k is the number of cosine functions and dominates the complexity of the models. We would like to select an optimal k to balance on goodness-of-fit. In a first step, we fit the model for the entire patient cohort with the number of harmonic terms ranging from 1 to 3 and then selected the best model based on the Bayesian information criterion (BIC). Bayesian information criterion (BIC), a criterion based in part upon likelihood for selection
among a finite set of models, is employed to select the optimal number $k$. We also analyzed TEMP recorded at the wrist or ankle, to support the evaluation of potential confounding by skin temperature.

Secondly, we examined differences in 24-hour circadian patterns of EDA recordings in patients with and without seizures. Therefore, we fit the model for each group separately, again with 1, 2, or 3 harmonic terms to identify the best model based on BIC values. To compare the groups among each other, we fit a nonlinear mixed-effects harmonic model that included group indicators and allowed each group to have a different circadian pattern. Then we conducted likelihood ratio tests between this complex model and the previous model that assumed a unified circadian pattern for all patients.

Third, we describe seizure-induced EDA responses relative to the EDA level and power expected from the 24-hour modulation. We subtracted the SZ group 24-hour modulated value at seizure time from the mean EDA level and power for the 30-minutes pre-ictal period (starting at 30 minutes prior to seizure onset and ending at the time of seizure onset), the 30-minute post-ictal period (post-ictal I, 30 minutes after seizure onset) and the 60-minute post-ictal period (post-ictal II, >30 to 60 minutes after seizure offset).

We ran generalized estimating equations (GEEs) with EDA level and EDA power as the dependent variables and seizure type (GTCS and FIAS), patient ID as subject variable, as well as period (pre-ictal, post-ictal I, and post-ictal II: within-subject-variable), and the seizure type-by-time interaction as independent variables. The interaction terms characterized whether a change in outcome over time differed between the seizure types. To account for repeated seizures within the same patients, the autoregressive covariance structure was chosen to adjust the estimator by number of patients and robust sandwich estimators were obtained for variance estimation. All statistical tests were two-tailed and had a significance level of $P < .05$. SPSS version 23 (IBM Corp., Armonk, New York, United States) was used for data analysis. Model effects are expressed as mean percent change with 95% confidence intervals.

3 | RESULTS

3.1 | Patient characteristics, recordings, and seizure descriptions

To analyze 24-hour patterns, we included 2306 hours of recordings from a pediatric population of 119 patients. The seizure group consisted of 40 patients (20 GTCS and 20 FIAS). The NEEG group had 17 patients, and the EA group consisted of 62 patients (see Supplement 1 for inclusion diagrams of the SZ group (A) and the non-seizure groups NEEG and EA (B)). Demographic and clinical characteristics are summarized for each subgroup in Table 1. The average length of recording per patient was 19.4 hours (SD: 3.0 hours; min 8 hours and max 24 hours). After data cleaning, we included 59 seizures from 40 patients. An example recording is displayed in Figure 1. Clinical and seizure characteristics based on seizure type are summarized in Table 2.

3.2 | Twenty-four-hour patterns of EDA recordings in patients with epilepsy

Mean and standard error values per hour of the day, excluding hours during which seizures occurred, are presented in Figure 2 for the overall patient group. In a first step, we tested the optimal $k$ for the nonlinear mixed-effects model for all patients together. Optimal $k$, indicated by lowest BIC for EDA level as well as EDA power, was 2. For TEMP level, lowest BIC was revealed for $k = 1$, indicating a less-complex sinusoidal pattern (Table 3 and Figure 2). Maxima for EDA and TEMP levels are located at night (EDA level at 11 pm and TEMP level 1 am) and minima at 11 am and 12 pm, respectively. EDA power maximum is located around 5 pm and the minimum around 5 am.

3.3 | Differences in 24-hour patterns of EDA recordings in patients with and without seizures

BIC values for harmonic models per group are presented in Table 3 and illustrated in Figure 2. For TEMP level, $k = 1$ revealed the best fit for all groups. For EDA level, optimal $k$ differed between groups, and for power, optimal $k$ was 2 for NEEG and EA groups and 1 for SZ group. For EDA power, models with $k = 1$ fit best for SZ and NEEG groups, while $k = 2$ revealed lowest BIC values for the EA group.

The comparison of $H_0$ (the small model not differentiating between groups), and $H_1$ (the larger model including terms per patient group), revealed that the model differentiating between groups ($H_1$) was superior for EDA level ($h = 1; P < .01$) and EDA power ($h = 1; P < .01$), whereas $H_0$ represents data better for TEMP level ($h = 0; P = 1$).

When $H_1$ was superior, we continued with pairwise group comparisons. Follow-up analysis for EDA level and EDA power compared restricted and unrestricted models per two groups. The comparison of the EDA level pattern of the SZ group to the patterns of NEEG or EA groups, respectively, showed that the groups differed ($h = 1; P < .01$), whereas patterns of NEEG and EA groups did not differ significantly ($h = 0; P = 1$). For EDA power, all pairwise group comparisons revealed that the larger model differentiating between groups was superior ($h = 1; P < .01$).
|                                | Normal EEG group (n = 17) | Epileptiform activity without seizures group (n = 62) | Seizure group (n = 40) |
|--------------------------------|---------------------------|--------------------------------------------------------|------------------------|
| **Sex**                        |                           |                                                        |                        |
| Male                           | 11 (65%)                  | 22 (35%)                                               | 25 (62%)               |
| Female                         | 6 (35%)                   | 40 (65%)                                               | 15 (38%)               |
| **Age**                        |                           |                                                        |                        |
| In years, median (p25–p75)     | 12.8 (4.4–15.5)           | 9.2 (6.1–13.0)                                         | 12.0 (9.2–14.4)        |
| **Epilepsy diagnosis**         |                           |                                                        |                        |
| Yes                            | 12 (71%)                  | 52 (84%)                                               | 40 (100%)              |
| No/unknown                     | 5 (29%)                   | 10 (16%)                                               | 0 (0%)                 |
| **Etiology of epilepsy/seizure**|                           |                                                        |                        |
| Unknown                        | 6 (35%)                   | 25 (40%)                                               | 14 (35%)               |
| Structural                     | 6 (35%)                   | 22 (36%)                                               | 22 (55%)               |
| Genetic                        | 0 (0%)                    | 5 (8%)                                                 | 1 (3%)                 |
| Metabolic                      | 0 (0%)                    | 0 (0%)                                                 | 0 (0%)                 |
| Others                         | 0 (0%)                    | 0 (0%)                                                 | 3 (7%)                 |
| Not applicable                 | 5 (30%)                   | 10 (16%)                                               | 0 (0%)                 |
| **Epileptiform activity on EEG**|                           |                                                        |                        |
| Frequent and more than focal   | NA                        | 25 (40%)                                               | 14 (35%)               |
| Frequent and focal             | 8 (13%)                   | 5 (12.5%)                                              |                        |
| Rare/occasional and more than focal | 13 (21%)             | 5 (12.5%)                                              |                        |
| Rare/occasional and focal      | 16 (26%)                  | 16 (40%)                                               |                        |
| **Background on EEG**          |                           |                                                        |                        |
| Normal                         | NA                        | 31 (50%)                                               | 13 (33%)               |
| Focal or intermittent slowing  | 17 (27%)                  | 25 (62%)                                               |                        |
| Generalized and continuous slowing | 14 (23%)              | 2 (5%)                                                 |                        |
| **History of neurosurgery**    |                           |                                                        |                        |
| Yes                            | 1 (6%)                    | 4 (6%)                                                 | 4 (10%)                |
| No                             | 16 (94%)                  | 58 (94%)                                               | 36 (90%)               |
| **ASM during EMU stay**        |                           |                                                        |                        |
| Levetiracetam                  | 5 (29%)                   | 23 (37%)                                               | 19 (48%)               |
| Oxcarbazepine                  | 5 (29%)                   | 15 (24%)                                               | 14 (35%)               |
| Carbamazepine                  | 0 (0%)                    | 3 (5%)                                                 | 2 (5%)                 |
| Eslicarbazepine acetate        | 0 (0%)                    | 1 (2%)                                                 | 1 (2%)                 |
| Perampanel                     | 0 (0%)                    | 1 (2%)                                                 | 0 (0%)                 |
| Clobazam                       | 3 (18%)                   | 13 (21%)                                               | 15 (37%)               |
| Valproic acid                  | 1 (6%)                    | 9 (15%)                                                | 6 (15%)                |
| Lamotrigine                    | 1 (6%)                    | 13 (21%)                                               | 5 (13%)                |
| Lacosamide                     | 2 (12%)                   | 9 (15%)                                                | 12 (30%)               |
| Clonazepam                     | 2 (12%)                   | 2 (3%)                                                 | 5 (12%)                |
| Topiramate                     | 1 (6%)                    | 3 (5%)                                                 | 1 (3%)                 |
| Vigabatrin                     | 0 (0%)                    | 4 (6%)                                                 | 0 (0%)                 |
| Rufinamide                     | 0 (0%)                    | 2 (3%)                                                 | 1 (3%)                 |
To evaluate the seizure-induced changes in EDA level and power, we subtracted the expected value based on the SZ group-specific modeled 24-hour pattern at seizure time from the pre- and post-ictal periods (see Figure 3). Results per seizure type are illustrated in Figure 3. EDA level of the pre-ictal period was lower than expected, that is, 40 of 59 pre-ictal segments were negative. During the post-ictal period I, values increased and then decreased in the post-ictal period II. EDA power remained lower than expected for all segments, but showed an increase during the post-ictal period I.

GEE analysis having EDA level as outcome revealed a significant main effect of period ($\chi^2 = 16.40; P < .001$), and seizure type-by-period interaction ($\chi^2 = 8.75; P = .004$). Main effect of seizure type was not significant ($\chi^2 = 0.11; P = .739$). Follow-up analysis of the interaction revealed that GTCS and FIAS did not differ for the pre-ictal ($P = .814$) or post-ictal period I ($P = .308$). For post-ictal period II, GTCS EDA levels were 8.44 times as high as FIAS’ levels (confidence interval [CI] 1.47, 48.54; $P = .017$). For GTCS, EDA level of the post-ictal period I was 11.93 times (CI 2.61, 54.58; $P = .001$) and of the post-ictal period II was 5.46 times (CI 1.19, 25.00; $P = .029$) higher than levels of the pre-ictal period. For FIAS, EDA level of post-ictal I was 30.23 times higher than the levels of the pre-ictal period (CI 2.65, 344.92; $P = .006$).

For EDA power, the main effect of seizure type ($\chi^2 = 0.02; P = .889$) and the seizure type-by-period interaction ($\chi^2 = 4.25; P = .120$) were not significant, but the
main effect of period ($\chi^2 = 14.96; P = .001$) was significant. Follow-up analysis showed that for the post-ictal period I, the EDA power was higher, that is, less negative, than the power during the post-ictal period II (1.01 times; CI 1.01, 1.02; $P < .001$).

Taken together, results indicated that EDA response represents a relative and not an absolute increase, as pre-ictal values are lower than the values expected from time-adjusted 24-hour modulation. The response was higher and longer lasting for GTCS seizures than for FIAS.
FIGURE 2  A shows mean and standard error for the whole patient group for electrodermal activity (EDA) level, EDA power, and TEMP level (from left to right) in the top part. Lower part shows the best fitting 24-hour pattern from nonlinear mixed-effects model analysis for EDA level, EDA power, and TEMP level (from left to right). B illustrates group-specific mean values (top part) and fitted 24-hour patterns (lower part) for EDA level, EDA power, and TEMP level (from left to right) for the seizure (SZ, red), the normal electroencephalography (NEEG, green), and the epileptiform activity (EA, bluegreen) groups.
4 | DISCUSSION

4.1 | Summary

Twenty-four-hour patterns are present in patients with epilepsy within EDA level and power with different peaks and troughs. In addition, 24-hour patterns of EDA recordings differed between the groups with and without seizures, suggesting longer-term effects representing flattening before and after seizures. Pre-ictal periods exhibited lower values than expected based on 24-hour modeling of the SZ group’s EDA pattern.

4.2 | EDA may represent an important measurement of sympathetic ANS activity

EDA reflects the sympathetic nervous system through activity on the sweat glands, and is linked to arousal and other physiologic stimuli. The peri-ictal periods in patients with epilepsy, including focal and generalized seizures, exhibit signs of altered autonomic nervous system (ANS) function, commonly from its seizure-activated sympathetic component. EDA has been studied in patients with epilepsy as a measure of sympathetic activation; it was shown that spontaneous epileptic seizures are followed by an EDA elevation, also referred to as EDA peak. As such, EDA activity may provide an approach to assess risk of sudden unexpected death in epilepsy (SUDEP) and provide an important marker of dysautonomia associated central nervous system shutdown in SUDEP.

4.3 | Circadian patterns are reflected in EDA recordings

The central regulation of circadian patterns plays a role in modulating the ANS, with the goal of maintaining homeostatic
constancy, efficiency of physiological processes, and the adaptation to internal and external changes and requirements. The circadian timing system is hierarchically organized and temporally controlled, and coordinates multiple physiological systems with a central pacemaker in the suprachiasmatic nucleus. Because ANS subsystems are interconnected, they are sensitive to control mechanisms within and across subsystems. Thermal changes have a strong influence on the sweat gland activity. Therefore, we analyzed temperature at wrist or ankle and saw a simpler pattern, based on the optimal k = 1. The pattern may be reflected in the EDA level and contribute to differences in timing of peaks of EDA level and EDA power. Our results suggest that EDA recordings reflect more than thermoregulation, and that non-thermal factors might be related to central modulations. Power might be more sensitive to central autonomic arousal based on the peak in the evening.

4.4 Epilepsy patients with and without seizures during vEEG presented with different EDA patterns

Specifically, and within our cohort, amplitudes of the 24-hour oscillation in EDA level and power is lower in patients with seizures than in patients without seizures. In turn, this may suggest that there is less variability in EDA patterns among patients with epileptic seizures, resulting in potentially reduced adaptability to internal and external stressors, such as seizures. However, because we do not have a healthy control group, we cannot elucidate the epilepsy-specific impacts on circadian patterns in EDA recordings. Nonetheless, studies demonstrate cardiac and respiratory ANS subsystems are altered in people with epilepsy. In our study, we were able to detect differences in patients with and without seizures on the recordings. Furthermore, differences between epilepsy patients during interictal periods and healthy controls have been described in EDA responses with heterogeneous results showing either longer latencies or higher amplitudes. Our findings are aligned with a previous study that reported marginally decreased EDA levels in patients with epilepsy compared to healthy controls. In this study, within the group of epilepsy patients, the EDA level inversely correlated with seizure frequency in 10-minute recordings in a relaxed state. Furthermore, modulation of the EDA level toward an increase was related to reduced seizure frequency. This suggests potential bidirectional interaction of central and peripheral ANS parts, and may open up further avenues for research and potential monitoring and intervention. Biological basis related to EDA regulatory effects and the changes throughout the daytime remain unclear, and suspected relationships include enhanced functional connectivity between brain regions activated during executive control and attention allocation, also involving structures relevant for autonomic control.

4.5 Opportunities for biomarker development

Based on the bidirectional interactions of the circadian rhythm and the autonomic network, not only seizure occurrence likelihood, but also seizure-induced alterations of the autonomic patterns are relevant. One indicator for this is the above-described flattening of the pattern that indicates more lasting seizure-related effects. The EDA level and power showed reduced levels in pre-ictal periods for many patients irrespective of the time of occurrence in relation to the time-adjusted SZ group-specific 24-hour modulated values. This finding might relate to studies describing the EDA peak when analyzing peri-ictal data, but as the increase is relative to a level lower than normal, the peak might not be a prominent feature when reviewing entire recordings. This might reduce the specificity of EDA changes for seizure detection and suggests looking into the pattern of change in peri-ictal periods instead of comparing the periods as each has its own dynamical properties. The negative values may indicate a suppression of sympathetic activity prior to seizure onset, especially because the EDA power extracted for a frequency band is most sensitive to central sympathetic control. Our results may improve specificity of seizure detection by utilizing modulated values as a baseline, and calculating relative changes and peaks. Furthermore, our results may provide the basis for a future marker for seizure prediction. Therefore, validation of our results in a longitudinal dataset is a crucial next step. Values staying very low throughout the peri-ictal period may indicate a disturbance of the central control of the EDA level throughout the seizure. If the reduction of central control can identify impeding seizure, EDA may serve as an interesting potential biomarker for seizure prediction.

4.6 EDA response was more prominent in GTCS than FIAS

In line with previous findings, we observed a sympathetic skin response in EDA level and power within the comparison of pre- and post-ictal periods. The response is higher and more long-lasting after GTCS than after FIAS, again confirming previous results. GTCS may therefore lead to greater perturbations of the ANS than FIAS. However, the pre-ictal levels do not differ between our two seizure groups.

4.7 Challenges

Findings need to be interpreted in the setting of data acquisition, including selection and information bias, lack of a
healthy control group, as well as relatively small sample size, not permitting adjustment for many potential confounders. Due to sample size, we were unable to control for confounders such as age, sex, epilepsy onset, location of the sensor, anxiety level, stress level, wakefulness and sleep, circadian rhythm, and room temperature, among others. Regarding room temperature, we only assessed temperature recorded at the wrist or ankle, and included these details in the analysis to adjust for temperature, and identify EDA changes beyond those related to thermoregulation. In the hospital setting, room temperature is comparably well controlled, and future studies may include room temperature assessment. Of note, assessment of the temperature at the point of care has the advantage of assessing temperature differences related to blanket coverings, and may therefore in this setting provide additional information. Furthermore, our study is limited by unequal group sizes. We cannot rule out that the smaller size of the control NEEG group might have impacted results by introducing large variances and finite sample bias. However, with the available data, we did our best to increase the overall sample size, while continuing to differentiate between both control groups, as patient with NEEG and interictal epileptiform activity on EEG may be ultimately also different, as also suggested based on the EDA power analysis. Although numbers of observations are relatively small and recordings were relatively short, we were able to corroborate seizures and seizure onset with vEEG monitoring, which allowed for standardized conditions that are comparable between patients, and therefore supports the group analysis. As this was a pilot study, we did not recruit healthy controls, but despite this we found differences between patients with and without seizures, in epilepsy patients, suggesting that differences compared to healthy control patients may tentatively be even larger. We only used patient data limited to a single admission. A longitudinal study with continuous data over prolonged periods would allow the investigation of individual patterns to determine if the flattening of the patterns and the suppression of activity are patient specific or truly seizure induced. In addition, starting times and length of recordings could be better controlled in an ambulatory longitudinal study. Besides reproducibility, longitudinal data would also allow us to analyze cycles with different durations, such as true circadian rhythms as determined by circadian markers other than temperature that might vary from 24-hour or multidien patterns. However, a 119-patient sample is a comparably large sample in the clinical context. Furthermore, we cannot rule out confounding by sleep patterns, as circadian patterns and sleep are interrelated, and as both may be disrupted by seizures or impact their occurrence. Of note, EDA may vary with different sleep stages, including and EDA peaks and EDA storms, which contribute to an increased EDA activity. Although our study only includes children, the age range is large within this sample and vEEG monitoring conditions and physiological characteristics differ in children of different age groups, as well as between pediatric and adult populations. However, pediatric patients show a more robust EDA response, so the expected impact is larger. Another limitation is the data quality of recordings from wearables. Screening signals and excluding artifacts resulted in the exclusion of peri-ictal recordings. Nevertheless, wearables interfere less with children’s movement and baseline behavior than other recording techniques, such as multi-channel EEG.

Taking these limitations into account, our study contributes to a better understanding of how seizures impact the autonomic regulation of EDA. Clinically, this study highlights the importance and potential for long-term monitoring by wearable devices in the inpatient and outpatient settings. These recordings would allow for individualized monitoring aimed at detecting systematic seizure-induced changes. The reduced EDA on days with seizures and in pre-ictal periods may contribute to seizure detection and prediction. The existence of a 24-hour pattern suggests including time of day in further detection and prediction approaches, so that EDA can be quantified according to 24-hour modulated values. The altered autonomic control of circadian rhythms, especially in GTCS, might also relate to SUDEP risk, as the reestablishment of the bidirectional interactions of peripheral and central structures after seizures seems crucial to regain homeostasis.

5 | CONCLUSION

EDA recordings from wearable devices offer a noninvasive tool to continuously monitor sympathetic activity. In patients with epilepsy, EDA level and power are affected by daytime and nighttime. EDA patterns differ from the TEMP pattern. We confirmed post-ictal EDA responses that last longer in GTCS compared to FIAS, and described a relationship between seizures and EDA patterns, as well as potential interactions between seizure patterns and 24-hour EDA patterns. Seizures occur in relation to EDA patterns, and even affect the pattern, that is, flatten the amplitude of oscillation. Seizure-related responses start from reduced EDA levels in the pre-ictal period and evolve into relatively high EDA responses in post-ictal periods. These seizure-related changes surrounding the possible rhythmic nature of EDA bear the potential of a relevant biomarker for seizure detection and prediction.

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CONFLICT OF INTEREST
SV, MA, BZ, CU, REA, MJ, SS, and CR report no disclosures related to this study. Tobias Loddenkemper serves on the Council of the American Clinical Neurophysiology Society, on the American Board of Clinical Neurophysiology, as founder and consortium PI of the pediatric status epilepticus research group (pSERG), as an Associate Editor for “Wyllie’s Treatment of Epilepsy” 6th edition and 7th edition, and as a member of the New Onset Refractory Status Epilepticus Institute, PACS1 Foundation, and CCEMRC. He served as Associate Editor of Seizure and served on the Laboratory Accreditation Board for Long Term (Epilepsy and Intensive Care Unit) Monitoring in the past. He is part of patent applications to detect and predict clinical outcomes, and to manage, diagnose, and treat neurological conditions, epilepsy, and seizures. Dr. Loddenkemper is co-inventor of the TriVox Health technology, and Dr. Loddenkemper and Boston Children’s Hospital might receive financial benefits from this technology in the form of compensation in the future. He received research support from the Epilepsy Research Fund, the National Institutes of Health (NIH), the Epilepsy Foundation of America, the Epilepsy Therapy Project, and the Pediatric Epilepsy Research Foundation; and he received research grants from Lundbeck, Eisai, Upsher-Smith, Mallinckrodt, Sunovion, Sage, Empatica, and Pfizer, including past device donations from various companies, including Empatica, SmartWatch, and Neuro-electrics. In the past, he served as a consultant for Zogenix, Upsher Smith, Amzell, Engage, Elsevier, UCB, Grand Rounds, Advance Medical, and Sunovion. He performs video electroencephalography long-term and ICU monitoring, electroencephalography, 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 electroencephalography long-term and ICU monitoring, electroencephalography, and other electrophysiological studies and bills for these procedures, and she evaluates pediatric neurology patients and bills for clinical care.

ETHICAL APPROVAL
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.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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