Received: 12 January 2023 | Revised: 3 April 2023 | Accepted: 3 April 2023

DOI: 10.1111/epi.17607

Epilepsia®

RESEARCH ARTICLE

Seizure occurrence is linked to multiday cycles in diverse physiological signals

Nicholas M. Gregg[1] | **Tal Pal Attia**[1] | **Mona Nasseri**[2] | **Boney Joseph**[1] | **Philippa Karoly**[3] | **Jie Cui**[1] | **Rachel E. Stirling**[4,5] | **Pedro F. Viana**[6,7] | **Thomas J. Richner**[1] | **Ewan S. Nurse**[4,8] | **Andreas Schulze-Bonhage**[9] | **Mark J. Cook**[8] | **Gregory A. Worrell**[1] | **Mark P. Richardson**[6] | **Dean R. Freestone**[4] | **Benjamin H. Brinkmann**[1]

[1]Department of Neurology, Bioelectronics Neurophysiology and Engineering Laboratory, Mayo Clinic, Minnesota, Rochester, USA

[2]School of Engineering, University of North Florida, Florida, Jacksonville, USA

[3]Graeme Clark Institute for Biomedical Engineering, University of Melbourne, Victoria, Parkville, Australia

[4]Seer Medical, Victoria, Melbourne, Australia

[5]Department of Biomedical Engineering, University of Melbourne, Victoria, Melbourne, Australia

[6]School of Neuroscience, King's College London, London, UK

[7]Faculty of Medicine, University of Lisbon, Lisbon, Portugal

[8]Department of Medicine, St. Vincent's Hospital Melbourne, University of Melbourne, Victoria, Fitzroy, Australia

[9]Epilepsy Center, University Medical Center, University of Freiburg, Freiburg, Germany

Correspondence
Nicholas M. Gregg, Department of Neurology, Bioelectronics Neurophysiology and Engineering Laboratory, Mayo Clinic, Rochester, Minnesota, USA.
Email: gregg.nicholas@mayo.edu

Funding information
American Epilepsy Society, Grant/Award Number: Research & Training Fellowship for Clinicians; Epilepsy Foundation; National Institutes of Health, Grant/Award Number: R01-NS09288203 and UH3-NS95495; National Science Foundation, Grant/Award Number: CBET-2138378

Abstract

Objective: The factors that influence seizure timing are poorly understood, and seizure unpredictability remains a major cause of disability. Work in chronobiology has shown that cyclical physiological phenomena are ubiquitous, with daily and multiday cycles evident in immune, endocrine, metabolic, neurological, and cardiovascular function. Additionally, work with chronic brain recordings has identified that seizure risk is linked to daily and multiday cycles in brain activity. Here, we provide the first characterization of the relationships between the cyclical modulation of a diverse set of physiological signals, brain activity, and seizure timing.

Methods: In this cohort study, 14 subjects underwent chronic ambulatory monitoring with a multimodal wrist-worn sensor (recording heart rate, accelerometry, electrodermal activity, and temperature) and an implanted responsive neurostimulation system (recording interictal epileptiform abnormalities and electrographic seizures). Wavelet and filter–Hilbert spectral analyses characterized circadian and multiday cycles in brain and wearable recordings. Circular statistics assessed electrographic seizure timing and cycles in physiology.

Results: Ten subjects met inclusion criteria. The mean recording duration was 232 days. Seven subjects had reliable electroencephalographic seizure detections (mean = 76 seizures). Multiday cycles were present in all wearable device signals across all subjects. Seizure timing was phase locked to multiday cycles in five (temperature), four (heart rate, phasic electrodermal activity), and three (accelerometry, heart rate variability, tonic electrodermal activity) subjects. Notably, after regression of behavioral covariates from heart rate, six of seven subjects had seizure phase locking to the residual heart rate signal.

Significance: Seizure timing is associated with daily and multiday cycles in multiple physiological processes. Chronic multimodal wearable device recordings can situate rare paroxysmal events, like seizures, within a broader chronobiology context of the individual. Wearable devices may advance the understanding of factors that influence seizure risk and enable personalized time-varying approaches to epilepsy care.

KEYWORDS

biomarkers, chronobiology, seizure forecasting, wearable devices

1 | INTRODUCTION

Chronic brain recordings, spanning months to years, from humans,[1–4] dogs,[5,6] and mice,[7] have established that seizure risk fluctuates over daily (circadian) and multiday (multidien) cycles for most individuals with epilepsy. Pioneering work from the early 20th century identified circadian and multiday[8–10] periodicities in seizure occurrences based on clinical records and seizure diaries at supervised care facilities. More recently, chronic intracranial recordings from clinical[4,11–14] and investigational[1,2,5,6,15] devices have revealed that interictal epileptiform activity (IEA) is modulated over circadian and multiday cycles, and that seizures occur at preferred phases of these cycles.[3] These cycles in IEA and seizure risk may reflect changing brain excitability,[16–18] with implications for seizure risk forecasting.[13]

Research in chronobiology has established the importance of the cyclical modulation of human physiology in normal health and disease.[19–24] Multiday cycles, including circaseptan[25] (weekly) and circamonthly[26] cycles, have been identified in the regulation of immune,[19] endocrine,[21] metabolic,[27] and cardiovascular[28] systems, in human behavior,[25] and in brain excitability[16,18] and seizure risk.[2–6,12] Recent work using a wearable fitness device[29] provides exciting evidence that long timescale changes in physiology (heart rate [HR]) are also linked to seizure risk. The mechanisms connecting seizure risk and HR cycles are unclear, but may include interaction between brain excitability and autonomic regulation,[29–31] in addition to behavioral and homeostatic mechanisms.

Key Points

- Multimodal wearable recordings can assess the chronobiology of diverse physiological processes and provide context for seizure timing
- Seizure timing is associated with daily and multiday cycles in multiple physiological processes in some individuals with focal epilepsy
- Prospective studies of cycle-based seizure forecasting are needed

Wearable devices that provide multimodal physiology recordings are available in popular commercial smartwatch systems, and medical grade wearable sensors have gained US Food and Drug Administration approval for a variety of indications, including seizure detection.[32] There have been novel applications of commercial wearable devices, including identification of atrial fibrillation,[33] and presymptomatic COVID-19 detection.[34] Chronic ambulatory monitoring has the potential to facilitate chronotherapy, in which interventions are provided or behaviors adjusted to personalized time-varying models of disease.

Here, we tested the hypotheses that daily and multiday cycles regulate a diverse set of physiological processes in people with epilepsy, that these long timescale dynamics can be measured by a multimodal wrist-worn device, and that electroencephalographically (EEG)-confirmed seizures occur preferentially at a particular phase of physiological cycles. All participants were monitored

simultaneously with a multimodal wearable device measuring HR, beat-to-beat HR variability (HRV), accelerometry (ACC), temperature (TEMP), and tonic and phasic components of electrodermal activity (EDAt and EDAp) and an intracranial responsive neurostimulation (RNS) device that provides objective EEG measures of IEA and electrographic seizure activity (Figures 1 and S1).

2 | MATERIALS AND METHODS

2.1 | Subjects

Subjects undergoing clinical treatment with an implanted RNS device (NeuroPace RNS)[35] were considered for enrollment in this observational cohort study. The RNS device was managed per routine clinical practice. Prescreening attempted to identify individuals with reliable RNS electrographic seizure records. Fourteen individuals provided written informed consent and were enrolled in the study, and underwent concurrent monitoring with the RNS device and a research-grade multimodal wrist-worn sensor device (E4, Empatica). Participants were provided with two wrist-worn devices that were exchanged daily for nearly continuous recording with recharging and data transmission. Inclusion criteria required at least 100 days of monitoring. Subjects were recruited between November 2019 and February 2021, with monitoring lasting up to 12 months. Subjects received their care at Mayo Clinic. The study was approved by the Mayo Clinic Institutional Review Board (IRB 18–008357) and listed on ClinicalTrials.gov (NCT03745118). 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.

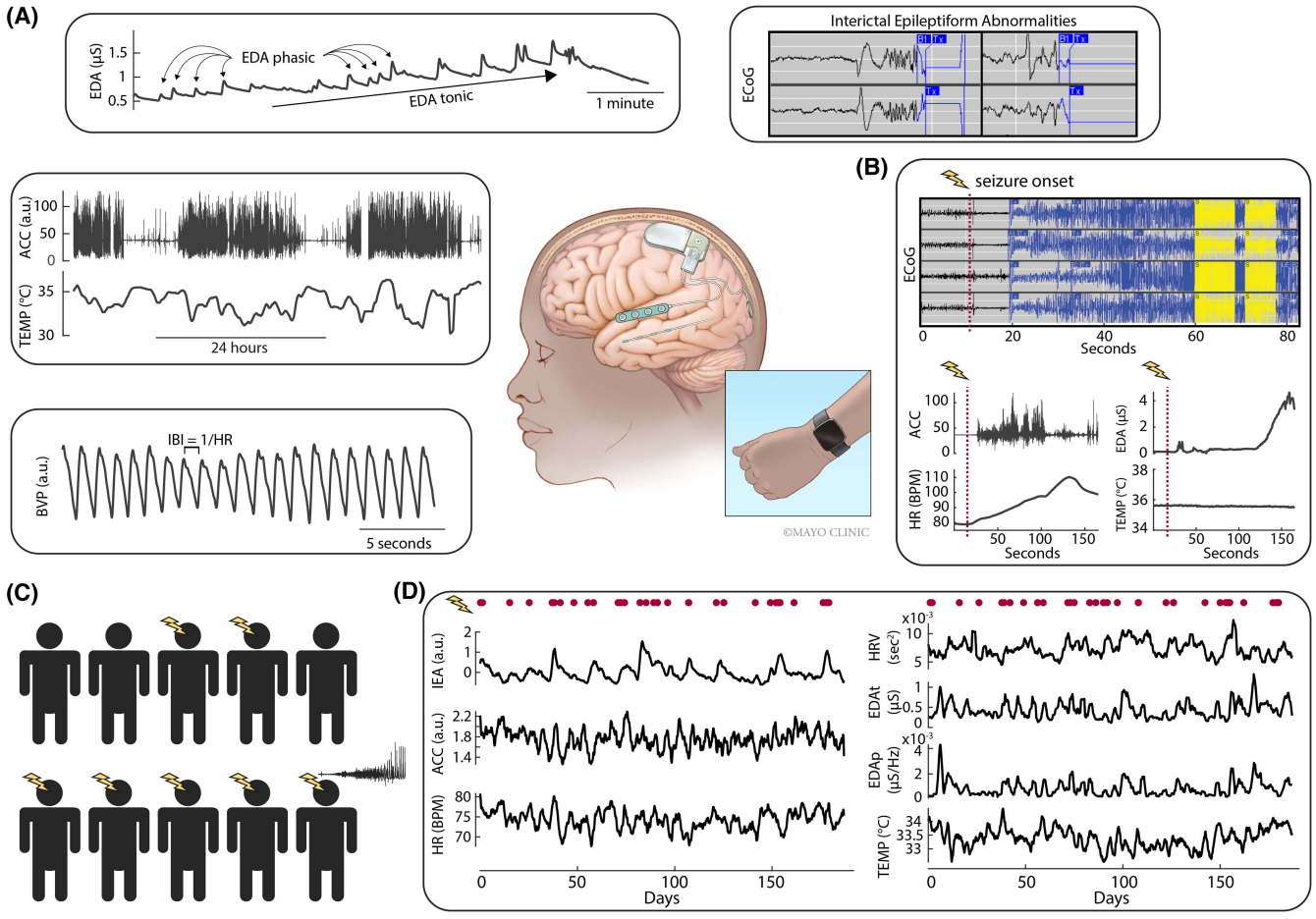

FIGURE 1 Chronic brain and wearable recordings. Unprocessed chronic brain and wearable device recordings are shown. (A) Brain and wearable recording device illustration, and representative interictal recordings. (B) Concurrent brain and wearable ictal recordings (Subject 3). (C) Data from 10 subjects were analyzed, seven of whom had reliable electrographic seizure detections (marked by lightning bolts). (D) Concurrent chronic ambulatory brain and wearable recordings; 2-day moving average values are shown; red dots mark seizure onset times. Interictal and chronic recordings are from Subject 4. ACC, accelerometry; BVP, blood volume pulse; ECoG, electrocorticogram; EDA, electrodermal activity; EDAp, phasic component of EDA; EDAt, tonic component of EDA; HR, heart rate; HRV, HR variability; IBI, interbeat interval; IEA, interictal epileptiform activity; TEMP, temperature.

2.2 | Wearable sensor recordings

The wrist-worn Empatica E4 device provides measures of blood volume pulse (BVP) from which HR and HRV were calculated, three-axis ACC, TEMP, and EDA from which tonic and phasic components were calculated. EDA, a measure of skin conductance, measures sympathetic arousal through autonomic innervation of sweat glands.[36,37]

2.2.1 | Preprocessing wearable sensor recordings

Chronic ambulatory wrist-worn sensor recordings are susceptible to artifacts, and noisy and nonrecording epochs were removed using validated signal quality measures.[38] Briefly, HR and HRV signal quality was assessed by the variance in the peak-to-trough amplitude of the raw BVP signal assessed in 5-s nonoverlapping blocks, after removing minor peaks (i.e., dicrotic notch). The peak-to-trough variance rejection threshold was determined by the knee-point (MATLAB function knee_pt.m[39]) in the sorted variance values (threshold = ¼ knee-point value). The ACC signal equaled the root-mean-squared three-axis ACC recording. ACC and TEMP data were removed when the device was off the body (TEMP outside of 29–40°C). The EDA signal can be prone to movement artifacts, and the signal quality index was defined as the rate of raw EDA amplitude change over 1-s epochs[38] with the 10th percentile of extreme values removed, coupled with the BVP-based signal quality assessment using ½ knee-point value threshold.

HR was calculated from the raw BVP signal: $HR = 1/IBI$, where IBI = interbeat interval. Beat-to-beat HRV was defined as: $HRV = \left(IBI_{i+1} - IBI_i\right)^2$. As previously described,[36,37] the raw preprocessed EDA data were low pass filtered using a zero-phase shift 4th order Butterworth filter with .045-Hz cutoff frequency to generate EDAt, whereas EDAp was equal to the amplitude of the .05–.25-Hz band of the continuous Morlet wavelet transform.

Denoised data were used to generate hourly average values for all wearable signals: ACC, HR, HRV, EDAt, EDAp, and TEMP. If fewer than 30 epochs (5 s per epoch) were retained after denoising in an hour, the hour was discarded from analysis. Example tracings are shown in Figure 1D, with 10-point smoothing.

2.3 | Interictal epileptiform activity and electrographic seizure detection

The RNS device provides limited intracranial EEG (iEEG) recordings, and uses clinician-defined detectors to quantify IEA and electrographic seizures (Figure 1), as previously described.[4,40] The device records hourly rates of IEA, which were used to assess cycles in IEA activity. The device also stores between 60 and 180 s of time series data (a "long episode") when the seizure detector is triggered, with capacity for approximately 10 min of time series data on the device. "Long episode" recordings are overwritten in chronological order when memory is full. Data are transferred approximately daily using an at-home telemetry device to a cloud-based system for clinician review. As previously described,[40] EEG seizures were verified by a board-certified epileptologist (N.M.G.) and experienced reader (B.J.). Seizure analyses were limited to subjects for whom "long episodes" available for visual confirmation did not exceed the device's storage capacity except rarely. Only visually reviewed "long episode" recordings were considered for seizure classification. At least 20 seizures were required for analysis.

2.4 | Data discontinuities

Missing data were interpolated using a 49-h moving median (accounting for slow fluctuations in physiology), with circadian cycle correction using Pearson system random numbers drawn from the distribution of data corresponding to the same hour of the day (Pearson system random numbers accommodate for nonnormal skew and kurtosis; Figure S2). Subjects had excellent device adherence (Table S1). The entire recording duration was included for analyses to maintain consistency in record durations and seizure counts for each channel.

2.5 | Circadian and multiday cycles in epilepsy

2.5.1 | Time–frequency analyses of wearable recordings

Circadian and multiday cycles in chronic wearable and brain recordings were analyzed using previously described methods.[6] Here, circadian refers to cycles of approximately 24 h and does not distinguish sleep–wake state changes and endogenous circadian rhythms. Amplitude spectral density (ASD) plots were generated from the time-averaged continuous Morlet wavelet transform of hourly averaged brain and wearable data (similar to prior work,[29] but using wavelet amplitude as opposed to power [proportional to amplitude squared]; Figure S3). A 1000-trial simulation using normally distributed noise defined the 5th percentile significance threshold. Cycles were defined as relative maxima in the ASD plots for circa 12-h, 1-day, weekly (5–9 days), bi-/triweekly (10–24 days), and monthly (25–35 days) cycles. Multiday groupings are consistent with

multiday chronotypes.[12] At most one period was included per multiday category to assess seizure phase locking; the cycle of shortest period length per category was used. We additionally assessed cycles by subject-specific significance threshold defined by resampled surrogate data, which provided comparable results (Figures S4 and S5).

With cycles of interest identified for each brain and wearable channel, the filter–Hilbert analytic signal determined instantaneous phase, frequency, and amplitude, as described previously.[6] Filtering was performed with third-order zero-phase shift (noncausal) finite impulse response filters, with center periods in units of days of .3 to 2.0 incremented by .1, 2.5 to 10 incremented by .5, and 11 to the maximum period length incremented by 1.0. Maximum period length was determined by the record duration and filter spread. Data within the influence of boundary effects were excluded.[6]

2.5.2 | Regression of behavioral covariates (ACC)

Physical activity can influence physiology measured by wearables, unrelated to brain excitability or seizure propensity (e.g., HR change with exercise). We evaluated covariation between ACC (proxy for behavioral physical activity) and all wearable signals to characterize the impact of physical activity. The MATLAB Curve Fitting Tool was used to fit and regress the ACC signal from each wearable channel (see Supplemental Information for regression model). Goodness of fit was assessed by the coefficient of determination (R^2). These analyses were performed on the 2-day moving average of signals to prevent the circadian cycle from dominating the correlation. The residual signals after regression of ACC were evaluated for multiday cycles. Multiday cycle periods in residual signals were defined as relative maxima in the ASD plot, similar to prior work.[6]

2.6 | Seizure phase locking to cycles in epilepsy

Seizure timing was assessed relative to the instantaneous phase of circadian and multiday cycles. Endogenous cycles in physiology may vary around a central period tendency and shift relative to clock time.[25,41,42] To accommodate for this, the Hilbert-transform analytic signal was calculated from the average bandpass composite centered at the period duration of interest (within ±25% of central period), as described.[6] Circular statistics characterized seizure phase locking to physiological cycles.

Coherence provides a frequency band-specific measure of the correlation between signals. The magnitude squared coherence of brain and wearable recordings was evaluated at circadian and multiday cycle durations of interest. The association between brain–wearable coherence and seizure phase locking (R-value amplitude) was evaluated for multiday cycles using a linear regression model.

2.7 | Phase–phase plots

Phase–phase plots characterize the association of seizure timing with circadian and multiday cycles, that is, the idealized seizure risk (noncausal analyses). Phase–phase plots can represent multiscale seizure risk, depicting phase data from different cycles for each seizure. Phase–phase plots were generated with surface fitting (surface linear interpolation) of three-dimensional histograms of seizure timing in phase–phase space. Seizure risk states (high, medium, low) were categorized using thresholds such that approximately 5%–10% of phase–phase space time was spent in the high-risk state, 10%–20% in medium risk, and 70%–80% in low risk.

2.8 | Statistics

Circular statistics provide a framework for analyzing directional data, recently reviewed for epilepsy applications,[3] and our approach has been described previously.[6] The MATLAB CircStat Toolbox[43] was used for analyses including generation of circular histograms, and resultant vector determination (amplitude and phase angle of the resultant vector, or R-value, of seizure timing relative to the phase of physiological cycles). An R-value = 0 indicates events have no phase preference for a given cycle; an R-value = 1 indicates that events always recur at the same phase of a cycle. The Rayleigh and Hodges–Ajne Omnibus tests were used to characterize statistical significance of seizure phase locking; statistical significance reflects the Rayleigh test unless otherwise indicated. Statistics were evaluated at the .05 significance level. Statistical tests were two-sided. Benjamini–Hochberg false discovery rate correction was applied to circular statistics using $n = 7$ recording channels. The association between brain–wearable coherence and seizure phase locking (R-value) was evaluated using a linear regression model with p-value determination.

3 | RESULTS

3.1 | Subjects

Fourteen subjects were enrolled in the study; 10 subjects met inclusion criteria, seven of whom had reliable RNS

seizure detections (Table S1). Four subjects had insufficient device adherence to meet inclusion criteria.

3.2 | Chronic wearable sensor and brain recordings

For the 10 subjects analyzed, there was excellent implanted and wearable device adherence (Table S1). Remote monitoring of participant data uploads identified rare wearable device malfunction, and the device was replaced.

3.3 | Multiscale cycles in physiological signals

There was a high prevalence of ultradian (cycle frequency faster than daily), circadian, and multiday cycles across subjects and signals (Figure 2). Prominent circadian cycles were seen in ACC, HR, HRV, EDAt, TEMP, and IEA more so than EDAp. Significant multiday cycles were seen in all subjects for all channels; however, there was relatively greater amplitude of cycles in IEA compared to wearable signals. Circa weekly and biweekly cycles were prominent in wearable recordings for some subjects.

3.4 | Circadian cycles and seizure risk in epilepsy

Circadian cycles were common across all recording channels and seen with ACC, HR, HRV, and TEMP ($n = 10$ subjects), EDAt and IEA ($n = 9$), and EDAp ($n = 6$). Daily cycles were evaluated relative to fixed clock time (Figure 3A), and to circadian fluctuations in physiology (Figure 3B).

Three of seven subjects had seizure phase locking to circadian EDAp cycles; six of seven subjects had seizure phase locking to circadian cycles for all other signals (Figures 3B and 4C). There was no clear group-level circadian phase preference for seizure timing.

3.5 | Behavioral activity and wearable recordings

HR had the strongest correlation with ACC (Figure S7), with median $R^2 = .32$, whereas median R^2 was <.10 for each remaining wearable channel, ($p = .0025$, two-sample t-test; Figure S7B). Seizure cycles were assessed using the residual HR signal following regression with ACC (Figure S8).

3.6 | Multiday cycles and seizure risk

Multiday cycles were evaluated for all signals and subjects (Figure 2). Seizure phase locking to multiday cycles were common: TEMP ($n = 5/7$ subjects), HR and EDAp (four subjects), ACC, HRV, and EDAt (three subjects), IEA (six subjects). Figure 4C shows the total number of multiday cycles with significant seizure phase locking across all subjects (evaluated for circa weekly, bi-/triweekly, and monthly cycles). The residual HR signal (after ACC regression), compared to the original HR, had an increase from four to six subjects with seizure phase locking to multiday cycles, with an increase from five to eight total multiday cycles. Table S2 provides data on subject clinical characteristics and seizure cycles.

At the group level, there was a preference for seizure phase locking to the peak (late rising/peak/early falling) phase of the residual HR signal (Figure 4B), and group level

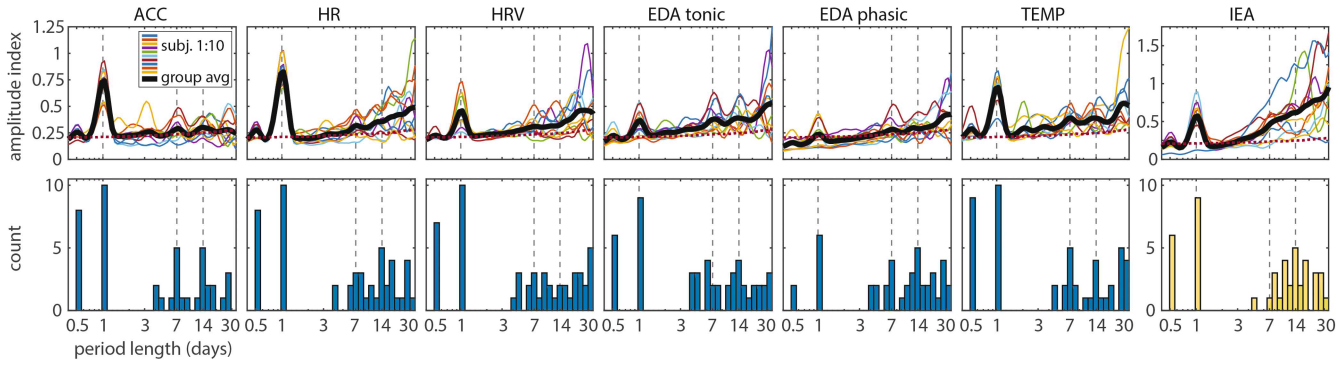

FIGURE 2 Amplitude spectral density (ASD) of chronic brain and wearable device recordings. The top row presents the time-averaged ASD for each channel across all subjects. The bottom panel shows the count of relative maxima for multiday cycles in the ASD above the 95th percentile of normally distributed white noise (red dotted line). Vertical gray dashed lines mark daily, 7-day, and 14-day cycle periods. ACC, accelerometry; EDA, electrodermal activity; HR, heart rate; HRV, HR variability; IEA, interictal epileptiform activity; TEMP, temperature.

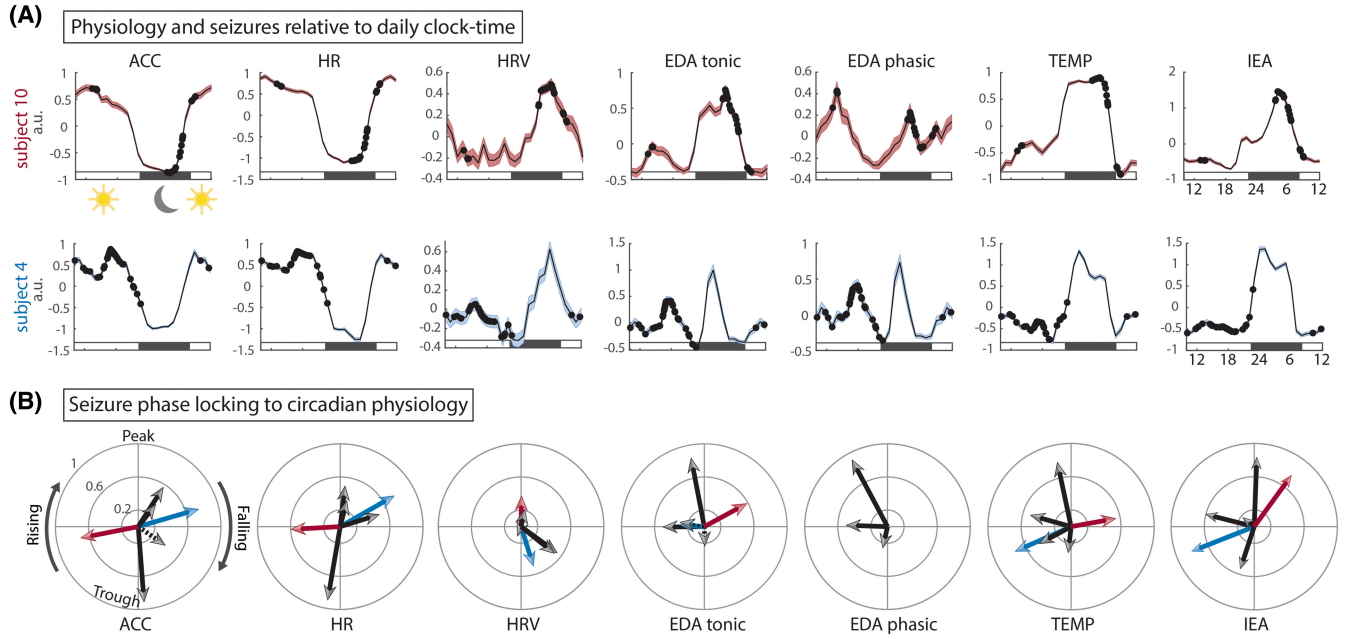

FIGURE 3 Circadian cycles of seizure risk. (A) Daily average wearable sensor and brain recordings over the duration of monitoring, relative to clock time. Error bars reflect SEM. Seizures relative to daily clock time are marked by black circles. (B) Resultant vector of seizure phase locking to circadian physiology. Only statistically significant resultant vectors are shown (dashed vectors indicate statistical significance by Rayleigh but not Omnibus test). Red and blue arrows correspond to the subjects in A and black arrows correspond to the remaining subjects. ACC, accelerometry; EDA, electrodermal activity; HR, heart rate; HRV, HR variability; IEA, interictal epileptiform activity; TEMP, temperature.

phase preference was less prominent in other wearable signals. There was a group preference for seizure phase locking to the rising phase of multiday IEA cycles (one outlier; Figure 4A), consistent with previous reports.[3,4] Table S3 compares results using the Rayleigh versus Omnibus tests.

Figure 4D shows the *R*-value amplitude of seizure phase locking to all multiday cycles across recording channels (limited to one cycle per multiday category). *R*-value amplitudes were generally larger for IEA than wearable signals. Seizure phase locking to the residual HR signal was increased compared to raw HR data.

3.7 | Coherence between wearable sensor and brain recordings

There were high levels of coherence between wearable and brain recordings for circadian cycles (median coherence of IEA to: ACC = .89, HR = .89, HRV = .81, EDAt = .75, EDAp = .60, TEMP = .83). For multiday cycles, a regression model of wearable signals to IEA coherence and seizure phase locking *R*-values did not demonstrate a consistent association (Figure S9). The linear fit model evaluating coherence and seizure phase locking to multiday cycles had a slope of .24, $R^2 = .10$, $p = .21$ for residual HR, compared to slope of .075, $R^2 = .0085$, $p = .73$ for the original HR signal. A direct comparison of IEA and each wearable signal did not demonstrate any strong associations (Table S4; median $R^2 < .04$ for each wearable signal).

3.8 | Multiscale cycles and seizure risk

The association between multiscale (circadian and multiday) cycles and seizure risk is shown in Figure 5. Figure 5A shows individual examples of circadian and multiday cycles in wearable brain recordings; circadian cycles are evident in the high-frequency component of the tracing, whereas multiday fluctuations in physiology are apparent in the 2-day moving average, reflected in circadian and multiday filtered tracings. Seizure timing was greatest during periods of co-occurrence of the high-risk phases of circadian and multiday cycles. Figure 5D shows the group averaged phase–phase plots for all significant circadian and multiday cycles.

Figure 5D shows a continuum of seizure risk levels indicated by the seizure burden color scale. Alternatively, data can be categorized into discrete seizure risk states. To illustrate this, high risk (>.4), medium risk (≥.15 and ≤.4), and a low risk (<.15) thresholds were assigned, and relative seizure burden and time in a risk state were calculated (Table 1). Risk thresholds were constant across signals. For true seizure forecasting applications, risk category thresholds could be individualized. The residual HR signal provided the best

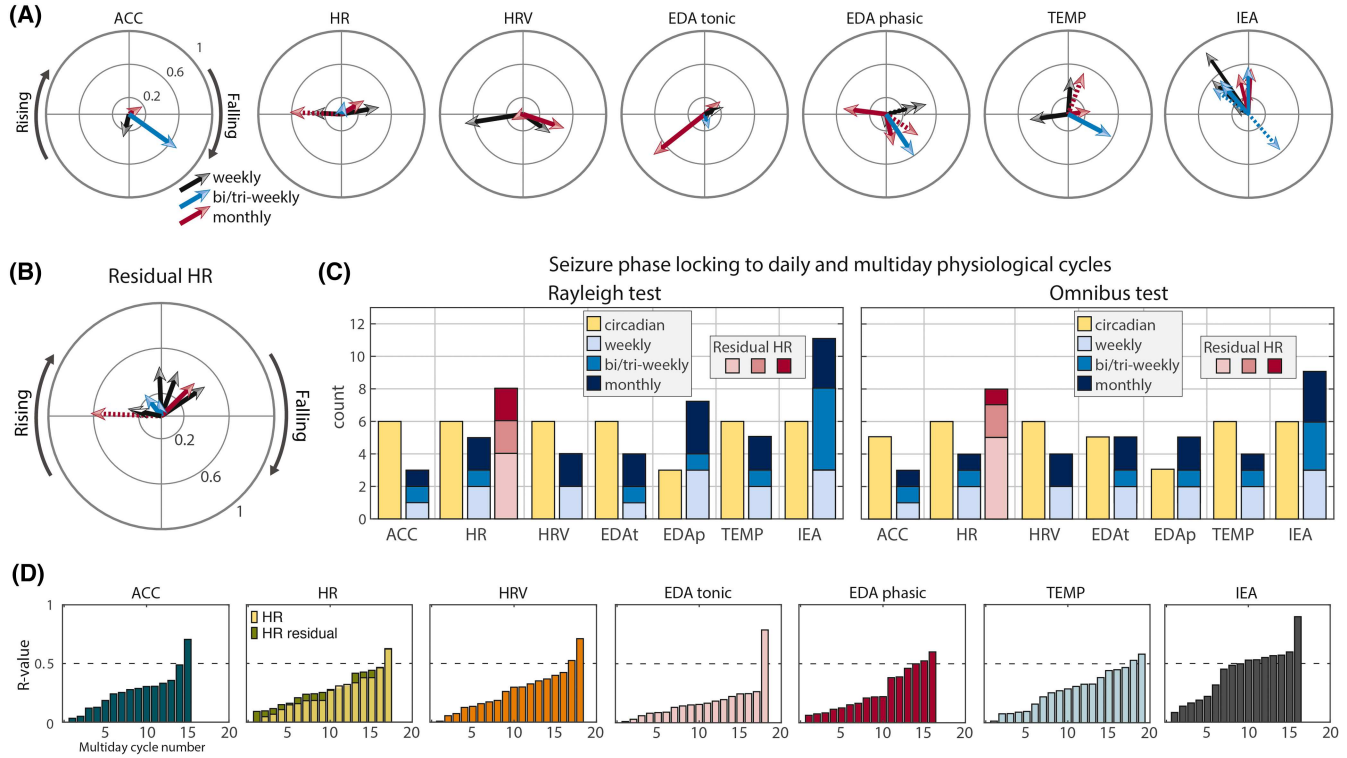

FIGURE 4 Multiday cycles of seizure risk. (A) Polar plots of the resultant vector of seizure phase locking to multiday cycles of chronic brain and wearable recordings (dashed vectors indicate statistical significance by Rayleigh but not Omnibus test; a single white/black arrowhead in [A] EDA tonic and one in [B] HR residual indicate statistical significance on Omnibus but not Rayleigh test). (B) Polar plot of the resultant vector of seizure phase locking to multiday cycles of residual HR. (C) Histogram showing the prevalence of significant seizure phase locking to circadian and multiday cycles. Seizure phase locking to residual HR after regression of behavioral activity (ACC) is marked in shades of red. (D) Sorted resultant vector amplitude (*R*-value) for seizure phase locking to multiday cycles. The HR plot shows seizure phase locking *R*-values for HR cycles and residual HR cycles. Plots show *R*-value for all significant peaks in amplitude spectral density plots (not limited to cycles with significant seizure phase locking as in A–C). ACC, accelerometry; EDA, electrodermal activity; EDAp, phasic EDA; EDAt, tonic EDA; HR, heart rate; HRV, HR variability; IEA, interictal epileptiform activity; TEMP, temperature.

combination of risk discrimination and subject inclusion, followed by TEMP, HR, and EDAp, followed by ACC with good seizure phase locking but few subjects, and finally EDAt and HRV with poor seizure phase locking and few subjects (Table 1). IEA had the best overall combination of risk discrimination and subject inclusion.

4 | DISCUSSION

This work demonstrates that circadian and multiday cyclical changes in a diverse set of noninvasive measures of physiology are common in people with drug-resistant focal epilepsy, and that seizure timing is linked to preferred phases of these cycles for most people. Circadian and multiday cycles of seizure risk were seen across chronic wearable recording channels, which included ACC, HR, HRV, EDAt, EDAp, and TEMP; multiscale cycles were present in concurrent brain recordings of IEA, consistent with prior reports.[3,4] This work used a unique dataset of ultra-long-term ambulatory recordings from a wrist-worn device and a clinical RNS brain implant, containing >2300 days of recordings from 10 participants, and 535 electrographic seizures from the seven participants with reliable electrographic seizure detections.

Seizure phase locking to multiday cycles was most common for the HR and EDAp ($n = 4/7$ subjects) and TEMP ($n = 5$). There was increased seizure phase locking to residual HR (HR after regression of physical activity) multiday cycles, with phase locking seen in six subjects. In comparison, six subjects had seizure phase locking to multiday IEA cycles. To our knowledge, this is the first study to assess the chronobiology of people with epilepsy with chronic multimodal physiological recordings and iEEG confirmation of seizures. These findings suggest that seizure timing is linked to cycles in human physiology for some individuals with focal epilepsy, and highlights the importance of chronobiology in epilepsy.

Seizure phase locking to circadian cycles was observed across wearable device and brain recording channels (less so for EDAp). Circadian changes in epilepsy are well known,[23] and circadian chronotypes are evident in

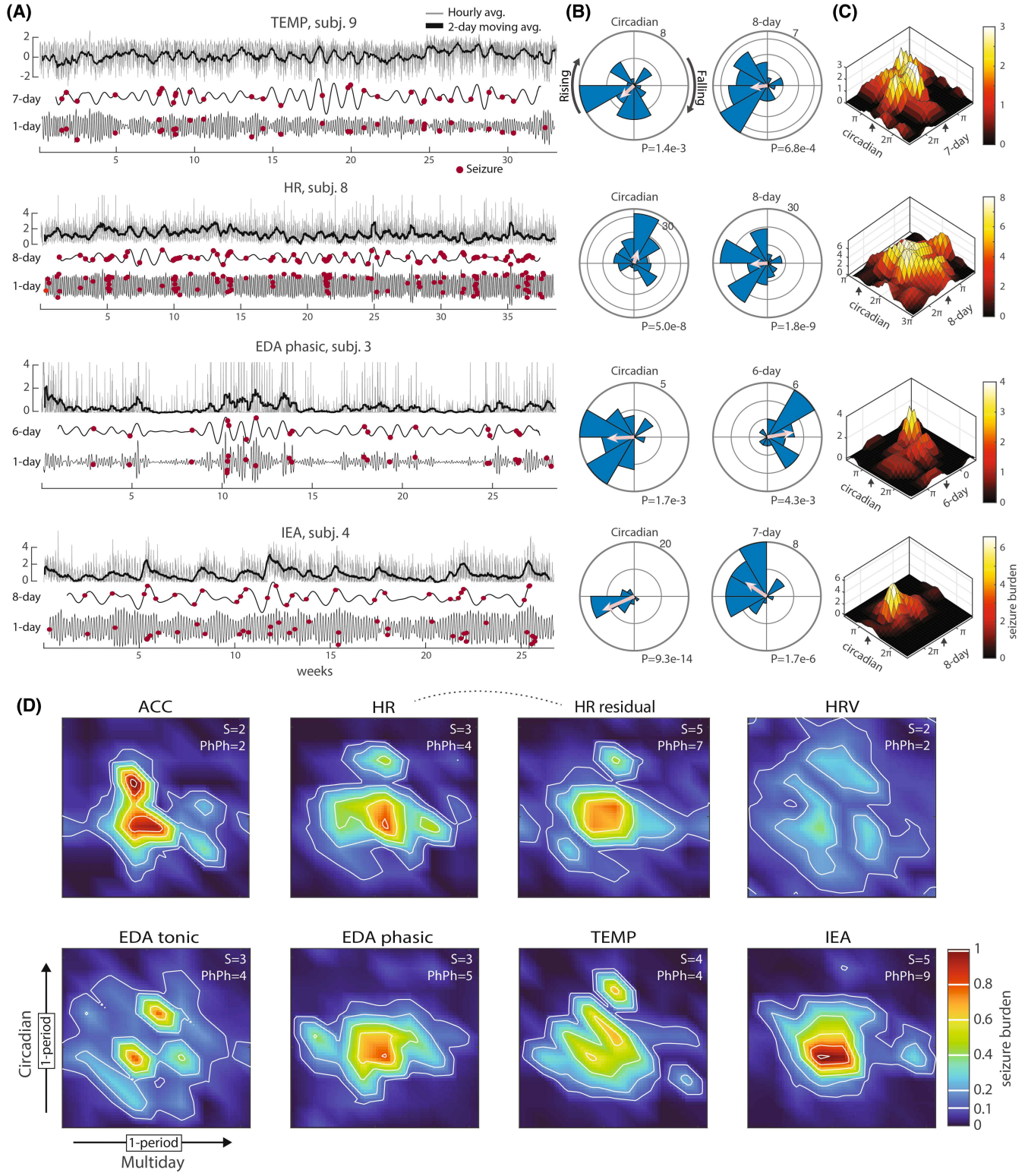

FIGURE 5 Multiscale cycles of seizure risk. (A) Examples of chronic wearable sensor and brain and recordings, and below, circadian and multiday bandpass filtered tracings and seizure onset times. (B) Corresponding polar histogram plots, with pink arrows indicating *R*-value. The outer ring number is seizure count; for *R*-value amplitude, the outer ring = 1. (C) Corresponding phase–phase plots show seizure counts with respect to circadian and multiday cycles. Π = cycle trough, 0 and 2Π = peak, and ↑/↓ = rising or falling phase. (D) Group averaged phase–phase plots for all significant (Rayleigh test) circadian and multiday cycles. Phase–phase plots were normalized to the total number of seizures per subject, and the median circadian and multiday phases were centered prior to averaging. The color map scale has a fixed proportional scale relative to the total seizure count for each channel, for direct comparisons between channels. The top right inset script is the number of subjects (S) and phase-phase analyses (PhPh) included in the group plot. ACC, accelerometry; e = power of 10 (1e2 = 1 × 102); EDA, electrodermal activity; HR, heart rate; HRV, HR variability; IEA, interictal epileptiform activity; TEMP, temperature.

TABLE 1 Multiscale idealized seizure risk categorization.

	ACC	HR	HRV	EDAt	EDAp	TEMP	HR residual	IEA
High risk: time in	.08	.08		.04	.07	.09	.07	.08
Seizure burden	.44	.33		.17	.35	.37	.34	.44
Medium risk: time in	.13	.18	.31	.23	.17	.18	.16	.15
Seizure burden	.26	.38	.54	.42	.35	.39	.31	.29
Low risk: time in	.79	.75	.69	.73	.76	.72	.77	.77
Seizure burden	.30	.29	.46	.42	.30	.24	.35	.27
Subjects, *n*	2[a]	3[b]	2[a]	3[b]	3[b]	4[b]	5[c]	5[c]
Phase–phase analyses, *n*	2[a]	4[b]	2[a]	4[b]	5[b]	4[b]	7[c]	9[c]

Note: "Time in" is the proportion of phase–phase space in that state. The "time in" high risk + medium + low = 1. "Seizure burden" is the proportion of seizures that occur in that risk category. "Seizure burden" high risk + medium + low = 1. The last two rows list the total number of subjects included per signal, and the total number of phase–phase analyses per signal.

Abbreviations: ACC, accelerometry; EDA, electrodermal activity; EDAp, phasic EDA; EDAt, tonic EDA; HR, heart rate; HRV, HR variability; IEA, interictal epileptiform activity; TEMP, temperature.

[a]Low subject and phase–phase analyses counts.

[b]Moderate subject and phase–phase analyses counts.

[c]High subject and phase–phase analyses counts.

chronic brain recordings.[12] The strong circadian coherence between wearable (particularly ACC and HR) and brain recordings suggests wearables can track circadian cycles of seizure risk, and accommodate changing behavioral and sleep/wake patterns.

This work is particularly notable for the presence of seizure phase locking to multiday cycles in wearable recordings. This finding is similar to seizure phase locking to multiday cycles in brain recordings, seen here and in prior work.[3,4,6,7,13] Of the wearable signals, seizure phase locking to multiday cycles was most common for the residual HR signal, and additionally TEMP, EDAp, and original HR.

The physiological signals measured by the wearable device in this study can be impacted by behavioral activities (reflected in ACC), which may be uncorrelated with endogenous physiological cycles. HR was found to have significantly greater correlation with ACC than the remaining wearable channels, and a residual HR channel (HR after regression of the ACC signal) had greater phase locking to multiday cycles ($n = 6/7$ subjects) compared to the original HR signal ($n = 4$). Additionally, there was a group-level preference for seizure phase locking to the peak (late rising/peak/early falling) phase of residual HR cycles. This suggests that models controlling for behavioral covariates in wearable recordings may better reflect the endogenous regulation of physiology, with a greater association with seizure risk.

Each seizure occurrence can be described relative to the instantaneous phase of both circadian and multiday cycles to characterize multiscale cycles and seizure burden. When evaluating multiscale cycles, relevant variables include (1) the proportion of seizures that occur in each risk state, (2) the proportion of time in each risk state, and (3) the number of subjects for whom cycle-based analyses were applicable. Seizure timing relative to wearable recordings was most strongly linked to the residual HR signal, followed by TEMP, EDAp, and HR, followed by ACC with poor subject counts but reasonable risk state classification, and finally EDAt and HRV with poor subject counts and poor risk state classification. Perhaps unsurprisingly, across all signals, seizures were most strongly linked to IEA.

Exactly how physiologically diverse human chronobiology and epilepsy interact requires further study. Interactions between brain excitability and autonomic arousal is one possible mechanism, although in this study an assessment of IEA and wearable coherence, and seizure phase locking to multiday cycles was not significant, suggesting wearables may provide information relevant to seizure risk that is independent from IEA. Activation of several brain regions has been implicated in the regulation of autonomic arousal, including the amygdala,[31] anterior cingulate, insula, thalamus, and prefrontal cortex,[44] suggesting that brain activity changes may be associated with autonomic arousal. Cardiac function and EDA are under direct autonomic regulation. EDA is a measure of sympathetic arousal,[36,37] and changes in sympathetic arousal, reflecting cognitive and physical stress, may affect seizure risk. Some work suggests divergent mechanisms for the regulation of EDAp versus EDAt,[44] and drift in the EDAt signal is a concern for long recording periods.[36] Here, EDAp was more strongly associated with multiday seizure risk. Evidence of seizure phase locking to surface temperature is intriguing, and surface temperature tracks the phase of sex hormone-related physiological changes over the menstrual cycle.[45]

Seizure phase locking to multiscale cycles in HR corroborates recent findings from a long-term study of seizure risk and HR cycles using patient-reported seizure diaries and a fitness watch.[29] Our work supports these findings with electrographic confirmation of seizures and multimodal wearable recordings. Prior work has shown ictal and interictal HR changes in epilepsy[30]; concurrent ultra-long-term wearable and EEG recordings are needed to explore these relationships.

Chronic ambulatory monitoring poses particular challenges. Wearable recordings are prone to artifacts, and EDA is particularly susceptible to movement artifacts and signal drift.[36] This work relied on previously validated[38] signal quality indices to remove noisy epochs. The long timescales of interest here allowed for stringent signal quality controls, and hourly averaged signals further limit the impact of artifacts. The use of objective EEG seizure detection[35] avoided the unreliability of patient-reported diaries, but could not distinguish electrographic from electroclinical seizures. The impact of RNS stimulation on multiday cycles is not known; however, the lack of correlation between IEA (and associated RNS stimulation) and wearable signals should limit this concern.

Ultra-long recordings are challenging to acquire, but bolster the reliability of results despite the small cohort, in which seven subjects had reliable EEG seizure detections. Larger diverse cohorts are needed to evaluate the generalizability of these findings across different epilepsy types and seizure networks. This retrospective analysis of long timescale seizure dynamics, consistent with prior efforts,[3,4,6,12–14,29] used zero-phase shift noncausal analyses, and efforts are underway to apply cycle-based seizure forecasting to prospective trials. Seizure risk forecasting may be improved by combining long timescale seizure risk cycles with an acute forecast algorithm, which has shown early promise with multimodal wearables.[40] The relative ease of implementation of wrist-worn sensor recordings, low cost, and patient preference for a wrist-worn form factor[38] make this an important area of study.

This work provides evidence that long timescale cycles in noninvasive measures of human physiology are common in focal epilepsy, and that for many individuals, seizures occur at preferred phases of these cycles. Improvements in medical and consumer wearable devices will likely lead to wider adoption over time and advance the study of the chronobiology of epilepsy.

AUTHOR CONTRIBUTIONS

Conceived and designed the work: Nicholas M. Gregg, Benjamin H. Brinkmann, Dean R. Freestone, Mark P. Richardson, Gregory A. Worrell. Acquired, analyzed, or interpreted data: Nicholas M. Gregg, Tal Pal Attia, Mona Nasseri, Boney Joseph, Gregory A. Worrell, Benjamin H. Brinkmann. All authors substantively drafted and revised the manuscript.

ACKNOWLEDGMENTS

This research was supported by the Epilepsy Foundation Epilepsy Innovation Institute My Seizure Gauge, NIH grants UH3-NS95495 and R01-NS09288203, American Epilepsy Society Research and Training Fellowship for Clinicians (N.M.G.), and National Science Foundation grant CBET-2138378 (M.N.). The authors acknowledge technical and administrative support from Sherry Klingerman CCRP.

CONFLICT OF INTEREST STATEMENT

G.A.W. and B.H.B. declare intellectual property licensed to Cadence Neuroscience. N.M.G. and G.A.W. are investigators for the Medtronic Deep Brain Stimulation Therapy for Epilepsy Post-Approval Study. E.S.N., P.K., M.J.C., B.H.B., and D.R.F. declare a financial interest in Seer Medical. The other authors have nothing to report.

ORCID

Nicholas M. Gregg https://orcid.org/0000-0002-6151-043X
Tal Pal Attia https://orcid.org/0000-0003-3456-9628
Boney Joseph https://orcid.org/0000-0002-1576-9344
Philippa Karoly https://orcid.org/0000-0002-9879-5854
Jie Cui https://orcid.org/0000-0003-1000-8869
Rachel E. Stirling https://orcid.org/0000-0002-4698-3773
Pedro F. Viana https://orcid.org/0000-0003-0861-8705
Ewan S. Nurse https://orcid.org/0000-0001-8981-0074
Andreas Schulze-Bonhage https://orcid.org/0000-0003-2382-0506
Mark J. Cook https://orcid.org/0000-0002-8875-4135
Gregory A. Worrell https://orcid.org/0000-0003-2916-0553
Mark P. Richardson https://orcid.org/0000-0001-8925-3140
Dean R. Freestone https://orcid.org/0000-0003-2411-5358
Benjamin H. Brinkmann https://orcid.org/0000-0002-2392-8608

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SUPPORTING INFORMATION

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How to cite this article: Gregg NM, Pal Attia T, Nasseri M, Joseph B, Karoly P, Cui J, et al. Seizure occurrence is linked to multiday cycles in diverse physiological signals. Epilepsia. 2023;00:1–13. https://doi.org/10.1111/epi.17607