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Seizure Cycles in Focal Epilepsy

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IMPORTANCE Focal epilepsy is characterized by the cyclical recurrence of seizures, but, to our knowledge, the prevalence and patterns of seizure cycles are unknown.

OBJECTIVE To establish the prevalence, strength, and temporal patterns of seizure cycles over timescales of hours to years.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study analyzed data from continuous intracranial electroencephalography (cEEG) and seizure diaries collected between January 19, 2004, and May 18, 2018, with durations up to 10 years. A total of 222 adults with medically refractory focal epilepsy were selected from 256 total participants in a clinical trial of an implanted responsive neurostimulation device. Selection was based on availability of cEEG and/or self-reports of disabling seizures.

EXPOSURES Antiseizure medications and responsive neurostimulation, based on clinical indications.

MAIN OUTCOMES AND MEASURES Measures involved (1) self-reported daily seizure counts, (2) cEEG-based hourly counts of electrographic seizures, and (3) detections of interictal epileptiform activity (IEA), which fluctuates in daily (circadian) and multiday (multidien) cycles. Outcomes involved descriptive characteristics of cycles of IEA and seizures: (1) prevalence, defined as the percentage of patients with a given type of seizure cycle; (2) strength, defined as the degree of consistency with which seizures occur at certain phases of an underlying cycle, measured as the phase-locking value (PLV); and (3) seizure chronotypes, defined as patterns in seizure timing evident at the group level.

RESULTS Of the 222 participants, 112 (50%) were male, and the median age was 35 years (range, 18-66 years). The prevalence of circannual (approximately 1 year) seizure cycles was 12% (24 of 194), the prevalence of multidien (approximately weekly to approximately monthly) seizure cycles was 60% (112 of 186), and the prevalence of circadian (approximately 24 hours) seizure cycles was 89% (76 of 85). Strengths of circadian (mean [SD] PLV, 0.34 [0.18]) and multidien (mean [SD] PLV, 0.34 [0.17]) seizure cycles were comparable, whereas circannual seizure cycles were weaker (mean [SD] PLV, 0.17 [0.10]). Across individuals, circadian seizure cycles showed 5 peaks: morning, mid-afternoon, evening, early night, and late night. Multidien cycles of IEA showed peak periodicities centered around 7, 15, 20, and 30 days. Independent of multidien period length, self-reported and electrographic seizures consistently occurred during the days-long rising phase of multidien cycles of IEA.

CONCLUSIONS AND RELEVANCE Findings in this large cohort establish the high prevalence of plural seizure cycles and help explain the natural variability in seizure timing. The results have the potential to inform the scheduling of diagnostic studies, the delivery of time-varying therapies, and the design of clinical trials in epilepsy.

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Supplemental content

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Over the centuries, scholars and laymen have sought to explain the periodicity of epileptic seizures by invoking divine[1] or demonic[2] interventions, celestial motions,[3] and hormonal cycles.[4] In 1881, Gowers[5] described daily seizure patterns, which he termed *nocturnal*, *diurnal*, and *diffused*. In 1938, Griffiths and Fox[6] described longer rhythms, ranging from weeks to months, in institutionalized children, men, and women with epilepsy. Today, biological rhythms are known to be ubiquitous,[7] with myriad manifestations in medicine. Practicing neurologists commonly encounter patients reporting seizures occurring at the same time of the day[6,8,9] or month,[6,10] or even during a particular season,[6] although such anecdotal clinical observations are seldom quantified.

In the century since initial phenomenological descriptions of seizure cycles, few studies[10-12] have applied rigorous statistics to analyze the cyclical organization of seizure timing, to our knowledge. The advent of inpatient seizure monitoring enabled studies of seizure cycles over several days, necessarily with cross-sectional designs,[13-15] but short recording durations precluded identification of longer cycles. Recent studies avoided this limitation by using online diaries of self-reported seizures collected longitudinally outside the hospital.[16,17] Despite the limited accuracy of such diaries,[18,19] these studies confirmed circadian seizure cycling in many individuals and suggested the existence of longer periodicities,[16,17] albeit with weaker effects.[17] However, critical questions about the prevalence, strength, and patterns of seizure cycles remain unanswered, in part because diary studies could not correlate self-reported seizures with concurrent recordings of brain activity.

In the last decade, the availability of continuous electroencephalography (cEEG) provided a unique opportunity to study seizure cycles at long timescales with objective data and suitable statistics.[20,21] Using the 2 existing cEEG data sets, NeuroVista[22] and NeuroPace,[23] studies[20,24,25] uncovered the striking cyclical organization of interictal epileptiform activity (IEA) and electrographic seizures (ie, those apparent on electroencephalograms) in a limited number of patients. However, without larger, longer studies incorporating patient-reported seizures, the generalizability and clinical relevance of these findings remain unclear. Here, we uncover seizure chronotypes—discrete, robust, and prevalent patterns of seizure timing—in a retrospective data set including up to 10 years of seizure diary data and concurrent cEEG data from individuals participating in a clinical trial of an implanted neurostimulation device for epilepsy.[23]

Key Points

Question What are the prevalence, strength, and patterns of seizure cycles in focal epilepsy?

Findings In this cohort study of 222 patients who received an implantable continuous electroencephalographic recording device, the prevalence was 12% of weak circannual seizure cycles, 60% of moderate multidien seizure cycles, and 89% of moderate circadian seizure cycles. Prevalent cycles were further classified into 5 multidien (7, 15, 20, and 30 days and irregular) and 5 circadian (morning, mid-afternoon, evening, early night, and late night) seizure chronotypes.

Meaning The findings establish the high prevalence of circadian and multidien seizure cycles and reveal the existence of distinct seizure chronotypes in focal epilepsy.

Methods

Patients

We analyzed retrospective data from a total of 222 out of 256 adults with medically refractory focal epilepsy who participated in clinical trials of the RNS System (NeuroPace Inc), an implanted device that treats seizures with responsive neurostimulation.[23,26] The RNS System provides a limited form of cEEG by continuously monitoring intracranial EEG from the seizure focus or foci and quantifying detections of epileptiform activity (eFigures 1 and 2 in the Supplement). In addition, participants in the clinical trials kept diaries of seizures classified as simple motor, simple other, complex partial, and generalized tonic-clonic, without knowledge of the recorded epileptiform activity. According to the 2017 International League Against Epilepsy classification,[27] we considered complex partial and generalized tonic-clonic seizures as the disabling seizures with impaired awareness studied here and excluded patients without disabling seizures. For analyses of seizure cycles at 3 timescales, we used the following selection criteria (eFigure 3 in the Supplement): (1) For circannual seizure cycles, we included 194 patients who kept continuous diaries for 2 years or more showing 24 days or more with disabling seizures, based on the rationale that a uniform distribution over the months of the year would result in 2 seizures per month. (2) For multidien seizure cycles, we included 186 patients with 24 or more self-reported days with disabling seizures over a period with 6 months or more of continuous cEEG count data after discarding the initial segment (median, 131 days) to avoid the "implant effect" (the changes in EEG signal and reduction in seizure frequency that can occur after placement of intracranial electrodes).[22,28,29] (3) For circadian seizure cycles, we included 85 patients with 48 hours or more with nonzero counts of electrographic seizures in 6 months or more of continuous cEEG, based on the rationale that a uniform distribution over the 24-hour clock would result in 2 seizures per hour. Retrospective data analysis was approved by the institutional review boards of participating centers,[23,30,31] and written informed consent was obtained from the participants.

Data Acquisition and Selection

We analyzed the following 3 distinct types of data (eFigure 1 in the Supplement): (1) Self-reported disabling seizures were recorded in participants' diaries as counts per calendar day; timestamps were not recorded, so self-reported seizures were analyzed only at multidien and circannual timescales. (2) Electrographic seizures were recorded by the RNS System with timestamps; owing to the limited storage of electrocorticograms by the device, electrographic seizures were identified

through sustained detections of epileptiform activity (termed *long episodes*) exceeding a clinically prespecified duration, typically 15 to 40 seconds (eFigure 2 in the Supplement). The reliability of long episodes as a proxy for electrographic seizures depends on device detection settings, which are periodically adjusted for clinical purposes. For each patient and each epoch of stable detection settings, a board-certified epileptologist (V.R.R.) evaluated by visual inspection whether 90% or more of long episodes corresponded to electrographic seizures (ie, clear organization and spatiotemporal evolution of epileptiform activity) in the subset of long episodes that had stored electrocorticograms (median, 274 reviewed per patient), as described in detail previously.[20,32] A software tool that uses deep learning to group electrocorticograms based on electrographic feature similarity facilitated this visual analysis.[33] For patients with at least 1 epoch meeting this criterion (162 patients had none), electrographic seizures from a varying number of epochs were aggregated for analysis at circadian and multidien timescales. The frequency of changes in detection settings precluded analysis of electrographic seizures at the circannual timescale. (3) Interictal epileptiform activity was available for all patients and defined as hourly counts of detections of short-lived epileptiform discharges (eFigure 2 in the Supplement).[20,32]

Data Processing

Data were preprocessed as described previously,[20] with minor adjustments (eMethods in the Supplement). To resolve periodicity in epileptic activity at 3 timescales, a Morlet wavelet transform[20,21] was applied to (1) hourly counts of IEA (circadian: 0.8-1.2 days), (2) daily counts of IEA calculated by summing the hourly counts over a calendar day (multidien: broadband 4-45 days), and (3) detrended timeseries of self-reported seizures (circannual: broadband 90-450 days; eMethods in the Supplement).

Statistical Analysis

Sample size was evaluated by the availability of data for each timescale. Individuals in the cohort can be viewed as independent replications of the statistical tests described here. Circular statistics (CircStat toolbox, Matlab; MathWorks) allow equivalence of 0° and 360° and can elucidate phase associations between a recurrent event and an underlying cycle. "Phase clustering" reflects skewness of a circular distribution and is quantified by the phase-locking value[34] (PLV), where PLV tends to 0 for a uniform distribution of events over phases of a cycle, and the PLV is 1 when all events occur exactly at the same phase (eMethods in the Supplement). This quantification of effect sizes in circular data revealed the strength of diverse seizure cycles; that is, the tendency for seizures to cluster into phases of cycles of hourly or daily IEA, lunar phases, calendar months, weekdays, and clock times. At the individual level, the statistical significance of PLVs was tested against 1000 surrogate time series,[35] built by repeated random shuffling of seizure counts and intervals between seizure days.[36,37] This procedure serves as a control, testing the null hypothesis that a single seizure or a group of seizures occurs without association with underlying cycles as it destroys the original sequence of seizure counts while conserving its main internal statistics, such as mean, variance, and tendency for temporal clustering (eMethods in the Supplement).[21,36] To estimate prevalence, we adjusted the *P* value of significance such that the false discovery rate was 0.1 or less for each tested cycle. *P* values were from 1-sided tests and results were deemed statistically significant at $P < .05$, adjusted for the false discovery rate.

For individual analyses at the circannual timescale, self-reported seizure time series were cropped to encompass a multiple of 12 months of data, to avoid overrepresentation of certain months when calculating the distribution of seizures in monthly bins (eMethods in the Supplement).

To find recurring cyclical patterns across individuals at the multidien timescale, we used nonnegative matrix factorization,[38] an unsupervised soft clustering algorithm (eMethods in the Supplement). We grouped patients into 5 clusters based on individual characteristic periodograms derived from fluctuations in IEA.

For individual analyses at the circadian level, we clustered individual circadian peak times for electrographic seizures using a K-means algorithm and a rank of 5 (eMethods in the Supplement).[8]

At the population level, we estimated 99% CIs around population mean PLVs using bootstrapping.[39] The "peakedness" of the circular distribution of angles of individual mean resultant vectors was measured using a calculation of circular kurtosis,[34] which has a value of 1 if all the individual angles coincide with the mean angle and decreases as individual angles diverge (eMethods in the Supplement).

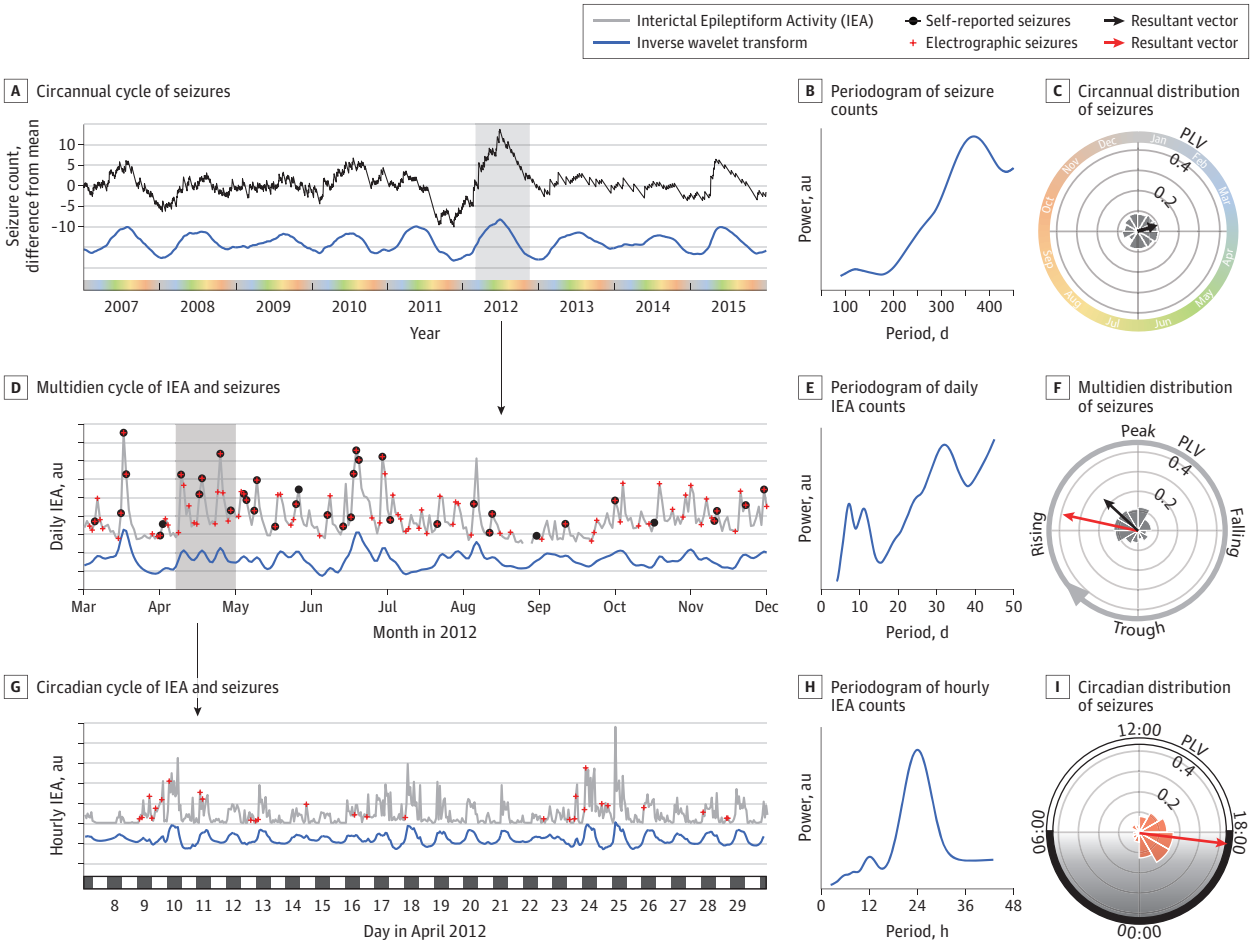
Results

We analyzed cEEG and seizure diary data from a total of 222 participants in the RNS System clinical trials (median age, 35 years [range, 18-66 years]; 112 men [50%] and 110 women [50%]) who had diverse focal epilepsies: 127 mesio-temporal (57.2%), 31 frontal (14.0%), 22 neocortical-temporal (9.9%), 9 parietal (4.1%), 3 occipital (1.4%), and 30 multifocal (13.5%) (eResults and eFigure 3 in the Supplement). The total data amounted to 1118 patient-years of cEEG (median, 5.9 years [range, 6 months to 9.5 years]), 754 108 electrographic seizures (median, 1436 [range, 67-148 073]), and 313 995 self-reported seizures (median, 422 [range, 26-64 882]).

Coexisting Seizure Cycles at Different Timescales

In **Figure 1**, we show data from an exemplar patient who had cycles in electrographic and self-reported seizures at timescales ranging from hours to years. During 9 years of recording, this patient had a weak circannual cycle, with a peak around 365 days in the corresponding periodogram and a slight increase in seizure rate in the spring (PLV, 0.1; $P = .002$; Figure 1A-C). This patient also had coexisting approximately 7-day multidien cycles and approximately 30-day multidien cycles of IEA that did not consistently align with particular days of the week or month.[40] Electrographic and self-reported seizures showed preference for the rising phases of IEA cycles

Figure 1. Illustrative Patient With Seizure Cycles at 3 Timescales: Circannual, Multidien, and Circadian



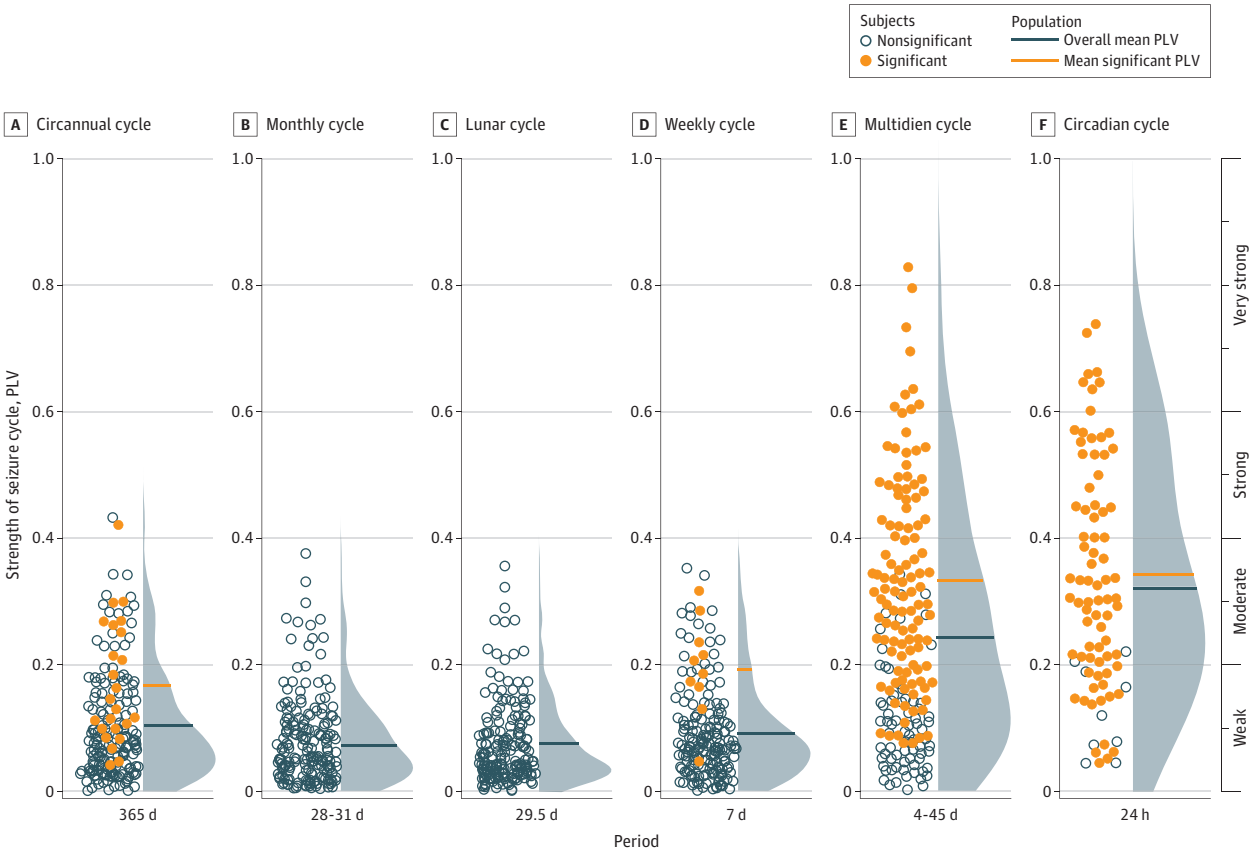
A, Circannual cycle of seizures over 9 years, apparent in detrended seizure rate fluctuations around the running mean. Positive values indicate increased seizure counts over running mean and negative values indicate decreased seizure counts over the running mean. Gradient shows phases as months of the year. Blue curve is the corresponding inverse wavelet transform between 90 and 450 days. B, Corresponding wavelet-periodogram with peak near 365 days underscoring the presence of a circannual cycle. C, Corresponding resultant vector and circannual distribution showing that seizures occur year-round but have slight seasonal preference for spring. D, Multidien cycle over 9 months (shaded area in panel A) apparent in daily interictal epileptiform activity (IEA; averaged over calendar days) along with wavelet-derived cycles from 4 to 45 days (blue trace), self-reported seizures (black dots), and electrographic seizures (red crosses). Higher linear density of black dots and crosses in the left half of the timeseries corresponds to increase in the seizure rate in panel A. E, Corresponding periodogram of daily IEA counts in panel D, showing peaks at 7, 12, and 32 days. F, Corresponding circular distribution and resultant vectors showing preferential multidien phase of occurrence for electrographic (black) and self-reported (red) seizures. G, Circadian cycle apparent in hourly IEA over 20 days (shaded area in panel D) along with wavelet-derived circadian periodicity (blue curve) and electrographic seizures. Black boxes represent nights and white boxes represent days. H, Corresponding periodogram of hourly IEA counts in panel G, showing peak at 24 hours. I, Corresponding circadian distribution and resultant vector showing a preferred time for seizure occurrence around 18:00. The expected value of histogram bins for a uniform distribution depends on total number of bins: 12 monthly bins in panel C, 18 20° bins in panel F, and 24 hourly bins in panel I. au indicates arbitrary units; and PLV, phase-locking value.

over days, with a PLV of 0.40 for electrographic seizures (P = .02) and 0.25 for self-reported seizures (P = .001; Figure 1D-F). At the circadian timescale, electrographic seizures showed preferential timing around 18:00 (PLV, 0.45; P = .001; Figure 1G-I), corresponding in this case to the rising phase of the circadian IEA cycle.

Prevalence and Strength of Seizure Cycles

Among included patients, the prevalence of statistically significant seizure cycles was 12% (24 of 194) at the circannual timescale, 60% (112 of 186) at the multidien timescale, and 89% (76 of 85) at the circadian timescale (**Figure 2**). In addition to their individual statistical significance, we quantified the strength of seizure cycles (ie, circular effect size measured as the PLV; see Methods). At the population level, circannual seizure cycles were weaker (mean [SD] PLV, 0.17 [0.10]) than multidien seizure cycles (mean [SD] PLV, 0.34 [0.17]) and circadian seizure cycles (mean [SD] PLV, 0.34 [0.18]) (Figure 1), which did not differ significantly in strength (eFigure 4 in the Supplement). External cycles of fixed period length, such as calendar days[17] and lunar phases,[41] have been proposed to explain seizure periodicity. However, across patients, only 5% (10 of 186) had weak fluctuations of seizure rates according to days of the week (mean

Figure 2. Prevalence and Strength of Seizure Cycles at Multiple Timescales



Distribution of phase-locking values (PLVs; y-axis) for seizures in association with 6 underlying cycles (x-axis). Dots are individual patients and violin contours are based on kernel density estimates to highlight the shape of the distribution. A, Circannual cycle: phases are 12 months of year. B, Monthly cycle: phases are 28 to 31 days of the month. C, Lunar cycle: 20 phases of the moon. D, Weekly cycle: phases are 7 days of the week. E, Multidien cycle: 20 phases of the fluctuations in interictal epileptiform activity (averaged over calendar days) are obtained by wavelet transform. F, Circadian cycle: phases are 24 hourly bins. Significance was tested individually against surrogate time series with *P* values adjusted for multiple comparisons within each of the 6 categories (orange dots). Empty dots indicate nonsignificant PLVs. Seizure cycle strength (effect sizes) can be interpreted as weak (PLV ≤0.2), moderate (PLVs >0.2 to ≤0.4), strong (PLVs >0.4 to ≤0.6), and very strong (PLV >0.6). Statistics for comparison of population means are in eFigure 4 in the Supplement. In all calculations periods are fixed, except for multidien cycles where period length can be variable within individuals.

[SD] PLV, 0.19 [0.08]), and none had seizures modulated by days of the month or phases of the moon (Figure 2B-D). We next examined patterns of seizure timing at each timescale.

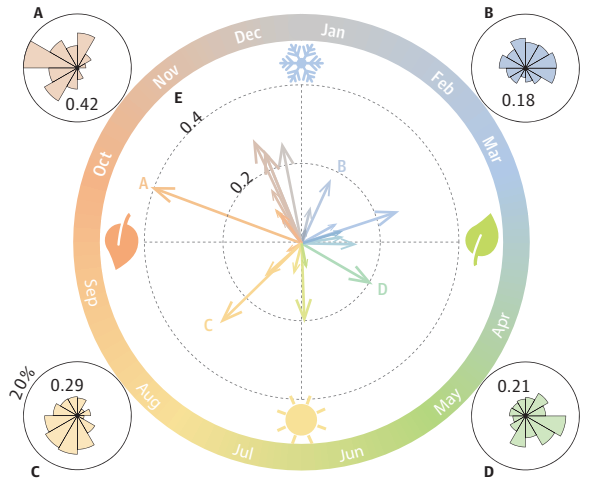
Circannual Seizure Chronotype

Among the 24 patients with a significant circannual cycle of self-reported seizures, individuals demonstrated weak to moderate seasonal seizure preference for the fall (**Figure 3**A), winter (Figure 3B), spring (Figure 3C), or summer (Figure 3D), without a group trend for seasonality (ie, circannual phase). In addition to this supervised approach, we found an approximately 365-day periodic fluctuation in seizure rate, using a wavelet transform on detrended seizure time series (eFigure 5 in the Supplement).

Multidien Seizure Chronotypes

Across the 112 patients with significant multidien cycles of self-reported seizures, an unsupervised pattern recognition method extracted 5 distinct, recurrent features of IEA fluctuations, corresponding to peak periodicity at 7, 15, 20, and 30 days, as well as 1 feature accounting for more irregular periodicity (**Figure 4**A and B; eFigure 6 in the Supplement). These features represent shared periodicities in multidien cycles of IEA within the whole cohort, but a given patient could have 1 or more periodicities (Figure 4A), independent of sex (eFigure 7 in the Supplement) or seizure focus (eTable in the Supplement). For visualization, we show mean periodograms for patients clustered by dominant periodicity in Figure 4B. To characterize the association between IEA and seizures, we evaluated the tendency of seizures to recur at particular phases of multidien cycles of IEA (ie, phase clustering; see Methods). For most patients, electrographic (Figure 4C) or self-reported (Figure 4D) seizures occurred preferentially on the rising phase, close to the peak, highlighting that IEA increases during days around seizures, independent of a specific multidien period length. This consistent phase association between multidien IEA phases and both electrographic and self-reported seizures was apparent at the individual level (84 of 112 [75.0%] with PLV

Figure 3. Circannual Cycles of Seizures



A-D, Circannual distribution of self-reported seizures over 9 years in 4 representative patients, each with a preferential phase at a distinct season of the year: autumn, winter, spring, and summer. The outer circle corresponds to 20% probability. E, Self-reported seizures with significant circannual cycles in 24 of 194 patients. Each resultant vector represents 1 individual, its angle is the mean preferential phase for seizure occurrence, and its length is the phase-locking value. Note the absence of a group trend and overall weak to moderate seizure cycle strength. See also eFigure 5 in the Supplement for corresponding periodogram.

>0.2; Figure 4D) and across patients, with a high circular kurtosis of 0.58 (Figure 4D) indicating excellent correspondence between fluctuations in electrographic and clinical seizures over days (Figure 4C and D).

Circadian Seizure Chronotypes

Across the 76 patients with significant circadian cycles of electrographic seizures at any localization, we observed 5 main seizure peak times, centered around 00:00 (N1), 03:00 (N2), 09:00 (D1), 14:00 (D2), and 18:00 (D3) (**Figure 5**A), corroborating historical observations.[6,8,9] Individuals with frontal lobe epilepsy tended to have nocturnal seizures (eTable in the Supplement).[32] Regardless of peak seizure time, hourly IEA consistently peaked during the night (Figure 5B; eFigure 8 in the Supplement); thus, for a given patient, seizures could be in phase or out of phase with peak circadian IEA (eFigure 9 in the Supplement). Across patients, we found a slight preference of seizures for the rising phase of circadian cycles of IEA (eFigure 9 in the Supplement), although this phase association was less consistent (circular kurtosis = 0.13) than for multidien cycles of IEA and seizures.

Discussion

Using the largest existing cEEG data set, collected over years from ambulatory patients with epilepsy living in natural conditions,[23] we identified seizure chronotypes at multiple timescales. Circadian and multidien seizure cycles were equally strong and highly prevalent, whereas circannual seizure cycles were weaker and observed in a minority of patients. Thus, seizure cycles underlie the natural variability of seizure rates observed in clinical practice, and the proposed typology may help personalize care for individuals with focal epilepsy.

Seizure Chronotypes

Circannual cycles of seizures were found in only 12% of patients, but, to our knowledge, this represents the first quantitative investigation of "seasonal epilepsy," a rare seizure chronotype. Circannual modulation of seizure timing might be superimposed on circadian effects and be associated with changes in photoperiod,[40,42] as observed in cluster headache.[43]

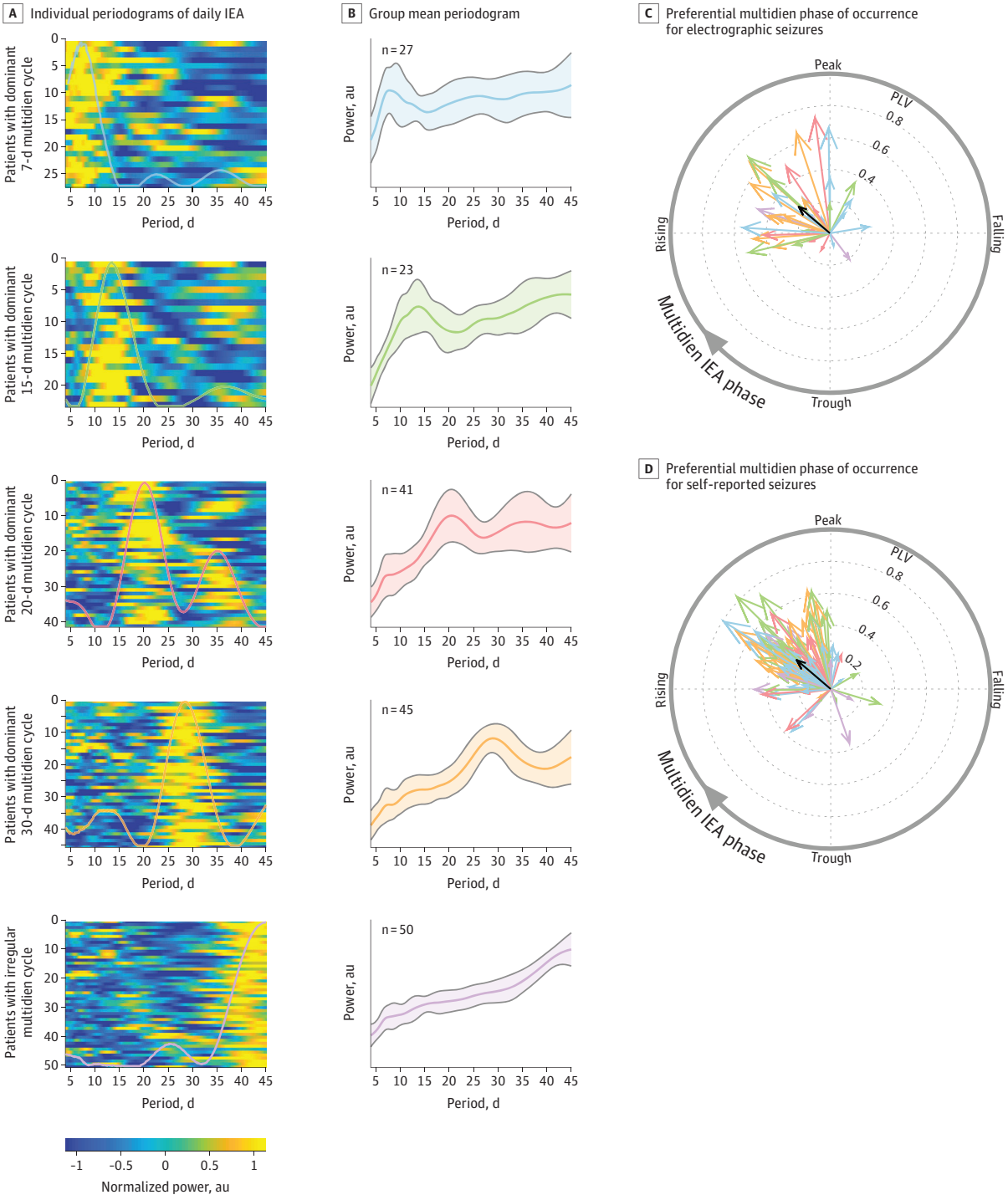
Multidien cycles of seizures were found in 60% of patients, with periods centered at 7, 15, 20, and 30 days, corroborating the historical description of "rhythm in epilepsy" and representing prevalent multidien seizure chronotypes.[6] Despite greater awareness of catamenial and circadian influences on seizures in current practice,[44] we found that multidien cycles were as strong modulators of seizure timing and equally prevalent in men and women. Unlike the circadian period, multidien period length characteristically varies from cycle to cycle within individuals, and underlying periodicity was often apparent only in the alignment between seizures and IEA.[20] To account for this, we used spectral-domain methods that are more flexible than time-domain methods for elucidating cycles in epilepsy.[20,21] Here, seeking seizure cycles with fixed periodicity (days of the week,[17] days of the month,[17] and lunar phases[41]) failed to reveal the full extent of multidien cycles. As a result, and despite stringent statistical criteria, the prevalence of multidien cycles was here 2 to 4 times higher than reported (15%-30%) in calendar-based studies,[16,17] underscoring the advantage of tracking phases of multidien cycles of epileptic brain activity that are frequently nonstationary.[21] This suggests that multidien cycles in epilepsy are free running; that is, they have an endogenous generator and are not paced by the environment.[40]

Circadian cycles of seizures were as prevalent in our study (89%) as previously reported.[16,17,32] Our description of circadian patterns provides contemporary analogs to Gowers'[5] seizure chronotypes and corroborates historical descriptions of 5 peak seizure times as follows[8,9]: early and late peaks for nocturnal seizures and early morning, midafternoon, and evening peaks for diurnal seizures. In our cohort, an early morning peak occurred in only a few patients, possibly owing to the lack of included patients with generalized epilepsy.

Association Between IEA and Seizures

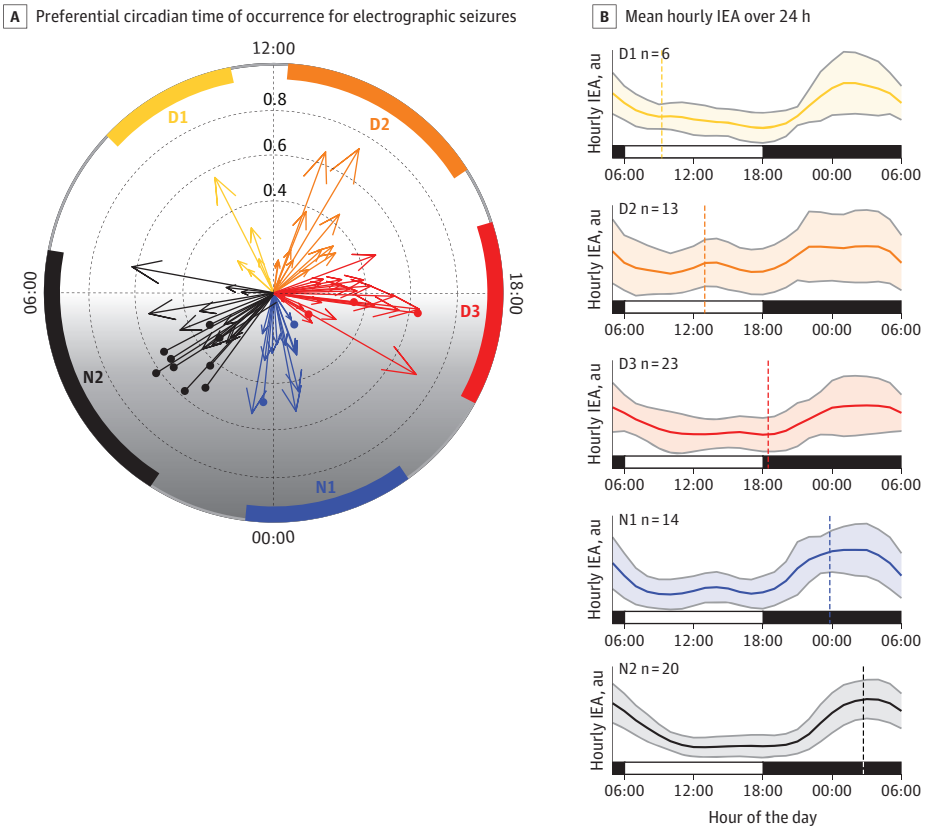
Finally, our findings shed light on the association between IEA and seizures. At the timescale of hours, IEA consistently peaked during the night, but peak seizure times were dispersed around the clock, resulting in a loose circadian phase association between IEA and seizures.[20,24] In contrast, at the timescale of days, self-reported and electrographic seizures consistently occurred on the rising phase of multidien cycles of IEA, corroborating results from other human[20,25] and animal[45] studies. Thus, unique mechanisms may underlie multidien cycles in epilepsy. Sex hormones fluctuate with

Figure 4. Multidien Cycles of Seizures and Interictal Epileptiform Activity (IEA)



Significant multidien cycles of IEA and seizures in 112 of 186 patients. A, Patterns of cyclical IEA fluctuations across patients. Each row represents 1 individual mean periodogram derived from fluctuations in mean daily IEA over days. Grouping of patients into 5 clusters is based on weights associated with 5 features derived by nonnegative matrix factorization (overlaid color trace; see Methods and eFigure 6 in the Supplement). B, Group mean periodogram for individuals belonging to the same cluster. Shaded area is ±1 SD. These clusters were labeled based on the mean periodogram. Some clusters contain more than 1 period (eg, middle panel with 20-day and 35-day peaks, which tend to occur together in individuals). C, Circular distribution of electrographic seizures in association with multidien IEA phases in a subset of patients with adequate data. Each resultant vector represents 1 individual, its angle is the mean preferential phase for seizure occurrence, and its length is the phase-locking value (PLV). The grand mean across all patients (black vector) points to the rising phase of IEA cycles before the peak, regardless of individual periodicities (color-coded to match panel B). D, Same as in panel C, but for self-reported seizures. High phase-consistency between panel C and panel D indicates that electrographic and self-reported seizures tend to cluster on the same days. au indicates arbitrary units.

Figure 5. Circadian Cycles of Seizures and Interictal Epileptiform Activity (IEA)



A, Significant circadian cycles of electrographic seizures in 76 of 85 patients. Each resultant vector represents 1 individual, its angle is the mean phase (preferential time on the 24-hour clock) for seizure occurrence, and its length is the phase-locking value. Five color-coded clusters were obtained by K-means. Dot and arrowheads represent frontal and extrafrontal localizations, respectively. For the influence of seizure localization on timing, see the eTable in the Supplement. B, Corresponding mean (±1 SD) hourly IEA over 24 hours (06:00 AM duplicated) for the 5 clusters. Mean IEA tends to peak at night, regardless of preferential seizure timing (cluster mean shown as dotted vertical line). Individual seizure and IEA phase associations are shown in eFigures 8 and 9 in the Supplement. au indicates arbitrary units; D1, early morning peak for diurnal seizures; D2, midafternoon peak for diurnal seizures; D3, evening peak for diurnal seizures; N1, early peak for nocturnal seizures; and N2, late peak for nocturnal seizures. Clustering consistent with historical description of 5 seizure circadian peaks.[8]

the menstrual cycle in women and possibly with a 20-day and 30-day periodicity in men,[46] and cortisol may have a 7-day cycle,[47] suggesting a possible hormonal basis for multidien cycles of seizures and IEA.[13]

Strengths and Limitations

This work has some strengths, complementing and extending previous studies[16,17,20,24,25] in several ways. First, we analyzed separate data sets of electrographic and self-reported seizures, and the inclusion of the latter increases clinical relevance. Second, these well-curated data sets spanned an unprecedented number of individual cycles across many participants, enabling estimation of the prevalence of distinct seizure chronotypes. Third, we adopted a conservative statistical approach, based on surrogate time series testing,[35] that can elucidate cycles beyond the well-known clinical phenomena of within-day or within-hour temporal clustering,[48] as demonstrated by our recent computational study.[21] Fourth, in addition to their statistical significance, we estimated the strength of individual seizure cycles, from weak modulation (slightly skewed circular distributions) to strong effects (seizures occurring over a narrow range of phases) that are likely to be clinically relevant.

This study also has some limitations. First, although our cohort included diverse focal epilepsies, all participants were treated with an implanted neurostimulation device, which limits its generalizability of the results. However, although precise timestamps of delivered stimulations were not available for analysis in our data set, neurostimulation does not appear to cause the observed cycles, which persist when the stimulator is turned off[20]; in addition, similar phenomena are found in rats[45] and dogs with epilepsy,[49] as well as in humans who did not receive neurostimulation.[6,8,9,24,25] Second, we included long-term self-reports of seizures, which remain the standard criterion in epilepsy trials but may be inaccurate.[18,19] This potential inaccuracy and the fact that our methods may not fully resolve some bimodal circular distributions or times when multidien IEA cycles vanish could have been associated with the underestimation of the prevalence and strength of seizure cycles. However, we found excellent correlation between IEA, electrographic seizures, and self-reported seizures over long timescales. Additional factors, such as sleep-wake cycles and sleep homeostasis, may play a role in seizure timing but were not examined here.

Clinical Implications

Our findings have several clinical implications. First, in a given patient, apparent patterns of seizure timing often defy explanation, leading to spurious correlations with behavioral or environmental factors.[40] Our results help demystify fluctuations in seizure rates and refocus the dialogue between clinicians and patients on objective metrics associated with long-term disease course. Second, diagnostic studies intended to capture seizures, such as inpatient

video EEG, might have a higher yield if they are scheduled based on times of highest seizure likelihood.[50] Similarly, knowledge of seizure cycles could directly inform chronotherapy, the time-varying adjustment of medications, and other interventions to reduce seizures.[51] Third, given the variability of seizure rates across and within patients, short-term clinical trials in epilepsy encounter sampling issues that limit interpretation of the results.[52,53] The design of future clinical trials in epilepsy and efforts toward seizure forecasting[54] will benefit from accounting for seizure cycles.

Conclusions

The chronobiology of epilepsy is undergoing a renaissance fueled by recent technological developments. Broader use of minimally invasive devices[55] capable of monitoring cycles in epileptic brain activity could help personalize diagnosis and treatment in epilepsy, and long-term recordings from such devices may help elucidate the mechanistic basis of seizure chronotypes.

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