Circadian and circaseptan rhythms in human epilepsy: a retrospective cohort study

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Summary

Background Epilepsy has long been suspected to be governed by cyclic rhythms, with seizure rates rising and falling periodically over weeks, months, or even years. The very long scales of seizure patterns seem to defy natural explanation and have sometimes been attributed to hormonal cycles or environmental factors. This study aimed to quantify the strength and prevalence of seizure cycles at multiple temporal scales across a large cohort of people with epilepsy.

Methods This retrospective cohort study used the two most comprehensive databases of human seizures (SeizureTracker [USA] and NeuroVista [Melbourne, VIC, Australia]) and analytic techniques from circular statistics to analyse patients with epilepsy for the presence and frequency of multitemporal cycles of seizure activity. NeuroVista patients were selected on the basis of having intractable focal epilepsy; data from patients with at least 30 clinical seizures were used. SeizureTracker participants are self selected and data do not adhere to any specific criteria; we used patients with a minimum of 100 seizures. The presence of seizure cycles over multiple time scales was measured using the mean resultant length (R value). The Rayleigh test and Hodges-Ajne test were used to test for circular uniformity. Monte-Carlo simulations were used to confirm the results of the Rayleigh test for seizure phase.

Findings We used data from 12 people from the NeuroVista study (data recorded from June 10, 2010, to Aug 22, 2012) and 1118 patients from the SeizureTracker database (data recorded from Jan 1, 2007, to Oct 19, 2015). At least 891 (80%) of 1118 patients in the SeizureTracker cohort and 11 (92%) of 12 patients in the NeuroVista cohort showed circadian (24 h) modulation of their seizure rates. In the NeuroVista cohort, patient 8 had a significant cycle at precisely 1 week. Two others (patients 1 and 7) also had approximately 1-week cycles. Patients 1 and 4 had 2-week cycles. In the SeizureTracker cohort, between 77 (7%) and 233 (21%) of the 1118 patients showed strong circaseptan (weekly) rhythms, with a clear 7-day period. Between 151 (14%) and 247 (22%) patients had significant seizure cycles that were longer than 3 weeks. Seizure cycles were equally prevalent in men and women, and peak seizure rates were evenly distributed across all days of the week.

Interpretation Our results suggest that seizure cycles are robust, patient specific, and more widespread than previously understood. They align with the accepted consensus that most epilepsies have some diurnal influence. Variations in seizure rate have important clinical implications. Detection and tracking of seizure cycles on a patient-specific basis should be standard in epilepsy management practices.

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Introduction

The human body is a collection of thousands of clocks, each cycling in accordance with their own pacemaker.[1] Cells such as neurons can track time with millisecond accuracy.[2] Hormonal cycles might have longer periods than cells of 24 h (eg, cortisol), 28 days (eg, oestrogen), or more. The presence of many metabolic cycles with their various peaks and troughs has a fundamental effect on human health. For example, sleep cycles are linked to healthy brain function.[3] Understanding the cyclic nature of disease progression is vital for treating diseases that continuously fluctuate through stages of severity, rather than steadily worsening.

Cycles of disease severity have been extensively studied in epilepsy, with data accumulating over hundreds of years. The rate of seizures has long been shown to oscillate regularly over the course of days,[4] months,[5,6] and years.[7,8] Modern research has provided extensive documentation of circadian patterns of seizures.[9–11] Longer cycles of seizure frequency are less easily studied, although they have been recorded.[12,13] Monthly seizure rhythms are often interpreted as catamenial seizures that coordinate with hormonal cycles.[14,15] Notably, multiple studies have identified approximate monthly cycles that did not appear to be more prevalent in women.[5,16,17] Individuals vary in circadian rhythms of epilepsy, with different patients having distinct times of peak seizure onset.[16,17]

Although the existence of seizure cycles is clear, their cause is somewhat controversial. Peak seizure times might arise purely from behavioural changes, such as different stress levels at the weekend, or seasonal variation in sleep quality. Alternatively, innate and persistent biological drivers, such as those that govern sleep, menstruation, hibernation, or breeding cycles (eg,

Research in context

Evidence before this study

We searched for studies on epilepsy and cycles published in MEDLINE from Jan 1, 1946, to Nov 1, 2016, and Embase from Jan 1, 1974, to Nov 1, 2016, using comprehensive electronic search strategies combining terms "epilepsy", "seizures", "convulsions", "cycles", "circadian", "diurnal", "patterns", "circaseptan", and "catamenial" with no language restrictions. Historical publications relating to the same search terms were identified through Google Books. We identified a small number of studies in between 1946 and Aug 23, 2018, and some older historical texts relating to these terms, mostly in relation to cycles of the moon and the postulated connection with seizures. Although many authors have appreciated that cycles in the patterns of epileptic seizures exist, these have been poorly defined, chiefly because no accurate databases of seizure activity over sufficiently long timeframes were available.

Added value of this study

We used two unique databases of seizure activity: the NeuroVista study, which captured continuous EEG recordings from intracranial electrodes for up to 3 years, and the SeizureTracker study, which has data from more than 12 000 patients for periods of up to 8 years. The NeuroVista study captured much higher-resolution data over a shorter period than SeizureTracker, though SeizureTracker contains a much larger sample of seizures from a greater number of patients. This allowed hypotheses regarding the underlying patterns of seizure activity identified in the NeuroVista study to be validated in a much larger population.

Implications of all the available evidence

Marked and highly individual patterns of seizure activity were seen in patients over multiple time scales. Circadian rhythms were most common, but a notable minority of patients had 7-day cycles (circaseptan), as well as much longer cycles (>3 weeks). These cycles were similarly prominent in men and women. The identification of these patterns might allow the development of personalised chronotherapies, more accurate seizure prediction algorithms, and provide an insight into the biological basis of culturally ubiquitous calendar measures such as the week.

in mammals) might affect seizure cycles. Increasing evidence shows that seizures are co-modulated with subclinical epileptic activity that also adheres to patient-specific circadian and multiday cycles. In 2018, Baud and colleagues[16] reported that seizures preferentially occurred within a particular phase of the underlying cycles of epileptic activity (referred to as phase locking). Karoly and colleagues[17] had previously hypothesised that circadian rhythms of seizure and spike-wave discharges occur with aligned phases. Taken together, these results suggest that subclinical epileptic activity and seizures share similar regulatory factors. Underlying oscillation in metabolic or regulatory factors would modulate both seizure susceptibility and the rate of interictal discharges. A better understanding of seizure cycles might provide new targets for treatment.

Even without fully understanding the mechanisms of seizure cycles, temporal patterns can be incorporated into patient management plans. Chronotherapy, or scheduling medication so that drug concentrations coincide with times of peak seizure propensity has been explored in the treatment of epilepsy.[18,19] Daily cycles of seizures might be caused by peaks and troughs in drug effectiveness due to metabolic cycles. Hence, trying to treat these seizure cycles by drug scheduling might simply shift the timing of patient's peak seizure risk, unless long-acting drugs with stable blood concentrations are used. By contrast, longer monthly cycles are less likely to be caused by medication. There is evidence that longer cycles of epileptic activity might be as strong as circadian rhythms;[16] however, the possibility of titrating therapy over weekly or monthly cycles has not yet been explored.

A better understanding of seizure cycles will help advance our understanding and treatment of epilepsy. However, scarcity of reliable, long-term records of patients' seizure times has restricted the ability to investigate temporal rhythms. The study of patterns greater than 24 h is particularly challenging because of the requirement of very long recording periods. Documentation of monthly and annual cycles has generally been limited to small cohorts of tens of patients.[15] Other, larger studies have not taken patient-specific patterns into account. Given the individual nature of epilepsy, where each person's seizures might be uniquely caused by the specific wiring of their brain, population approaches will probably never reveal all facets of epilepsy progression. In this retrospective cohort study, we investigated whether repeating (cyclic) patterns of seizure onset aligned with a particular phase of (ie, are phase locked to) an underlying periodic signal in patients with epilepsy.

Methods

Study design and data sources

We used two unique seizure datasets to investigate cyclic patterns. The first dataset from a study by Cook and colleagues[20] (NeuroVista data; Melbourne, VIC, Australia) is the longest continuously recorded electrocorticography in humans. To confirm findings across a large population, we also used self-reported seizures recorded from a study using SeizureTracker (USA).[21]

In the NeuroVista study,[20] epileptic seizures were recorded from 15 participants with focal epilepsy. Participants were each implanted with a single device, consisting of 16 intracranial electrodes and a subclavicular component, for 6 months to 3 years. Approval

for the NeuroVista study[20] and this study was obtained though the Human Research Ethics Committees of the three participating clinical centres: Austin Health, The Royal Melbourne Hospital, and St Vincent's Hospital of the Melbourne University Epilepsy Group (LRR145/13).

SeizureTracker is a website with connected mobile apps through which patients can self report and track their seizures. The data was managed in a deidentified format, consistent with the recommendations of the US Department of Health and Human Services Office for Human Research Protections, protocol number 12301. Patients consented to sharing their data under the terms of the SeizureTracker privacy policy.

Because data from SeizureTracker is self reported, we used several preprocessing steps to improve the quality of the data. Seizures with no duration were removed, as were seizures with duration longer than 1 h. Because of recording protocol, seizures reported without onset times were saved at 1 am in the SeizureTracker database; therefore, we removed all seizures recorded at 1 am. We analysed people with at least 3 months of data collection and at least 100 recorded seizures.

Procedures

The presence of cyclic patterns over many time scales was measured using the magnitude of the mean resultant vector for different periods. The mean resultant vector can be intuitively understood by realising that circular quantities, such as time, can be expressed as positions on a clock (ie, as unit vectors with a direction corresponding to the elapsed time allotted for each cycle). The vector sum of all the clock hands gives the mean resultant vector.[22,23] Hence, the length of the mean resultant vector, or mean resultant length (R value), measures how well seizures aligned to the same phase of a given underlying period. The R value is the complement of the circular variance—ie, it inversely corresponds to the variance of seizure onset phase. Higher R values reflect stronger alignment to some phase of an underlying cycle (an R value of 0 reflects a random distribution and an R value of 1 suggests all seizures occurred at precisely the same time of every cycle; appendix).

In this study, the actual phase (the angle of the mean resultant vector) was not considered. Instead, the strength and significance of phase alignment (R value) was measured for different time scales. The R value was calculated for periods of 6 h to 3 months to enable many time periods to be viewed simultaneously for each patient (by plotting the cycle period *vs* R value). Peaks in the R value highlight the presence of an underlying cycle regulating seizure onset for that particular time scale. The same R value analysis was done for NeuroVista and SeizureTracker data.

To calculate the mean resultant vector, seizure times were represented as phases, depending on when they occurred in a cycle of a given period (ie, for a 24-h period, seizure times are 0–24 h, for a 1-week period seizure times are 0–168 h). To avoid clustered seizures artificially increasing the estimation of the R value, seizures occurring within the same hour were removed. For time scales longer than 48 h, seizures occurring on the same day were also removed (meeting a commonly used clinical definition for clustered seizures).[24] Seizures occurring on the same day were not removed for cycles with only 1-day or 2-day periods, because this could bias results making seizures appear more common in the early hours of the morning (as any later seizures on the same day would be removed). Clustered seizures were also analysed separately (appendix).

We hypothesised that seizure times were phase locked to an underlying periodic signal. Therefore, instead of looking for a periodic signal in the rate of seizures, this study explicitly measured how well seizure onset aligned to the phase of a given underlying period (ie, a day, week, or month). The data were treated as a one-dimensional signal (seizure times), an approach inspired by techniques for analysis of neural spike trains, which might be phase locked to many different periodic signals. Several key techniques from circular statistics were used in this analysis that are also used in the analysis of spiking neurons.

For the **SeizureTracker privacy policy** see https://seizuretracker.com/MainPrivacy.php

Statistical analysis

Minimum seizure numbers were selected on the basis of simulation results (appendix). For the NeuroVista study,[20] the minimum seizure number was set to 30 seizures, resulting in 12 patients (from the original cohort of 15). For the SeizureTracker data,[21] the minimum threshold was set at 100 seizures, resulting in 1118 patients (from the original cohort of 12 947).

Because of known discrepancies between electrocorticography data (NeuroVista data)[20] and self-reported seizures (SeizureTracker data),[21] a quantitative comparison across these two different datasets was not done. Instead, this study aimed to detect qualitative similarities relating to the existence, prevalence, and distribution of multiday seizure cycles.

The Rayleigh test can be used to measure the non-uniformity of circular data (under the assumption that data are normally distributed),[22] as well as confidence intervals for the mean of circular quantities.[25] In this study, the Rayleigh test was used to reject the null hypothesis that the phase of seizure times was uniformly distributed around a circle. The Rayleigh test assumes data are normally distributed (ie, follow a von-Mises distribution, which is the equivalent of a Gaussian for circular data). The Stephens modified Watson test[26] was used to establish whether data followed a von-Mises distribution or not.

In addition to the Rayleigh test, the Hodges-Ajne test[27] was used to test for circular uniformity. Although the Hodges-Ajne test is less powerful than the Rayleigh test, it works well for unimodal, bimodal, and multimodal distributions and does not make assumptions about the underlying distribution of the data.

See **Online** for appendix

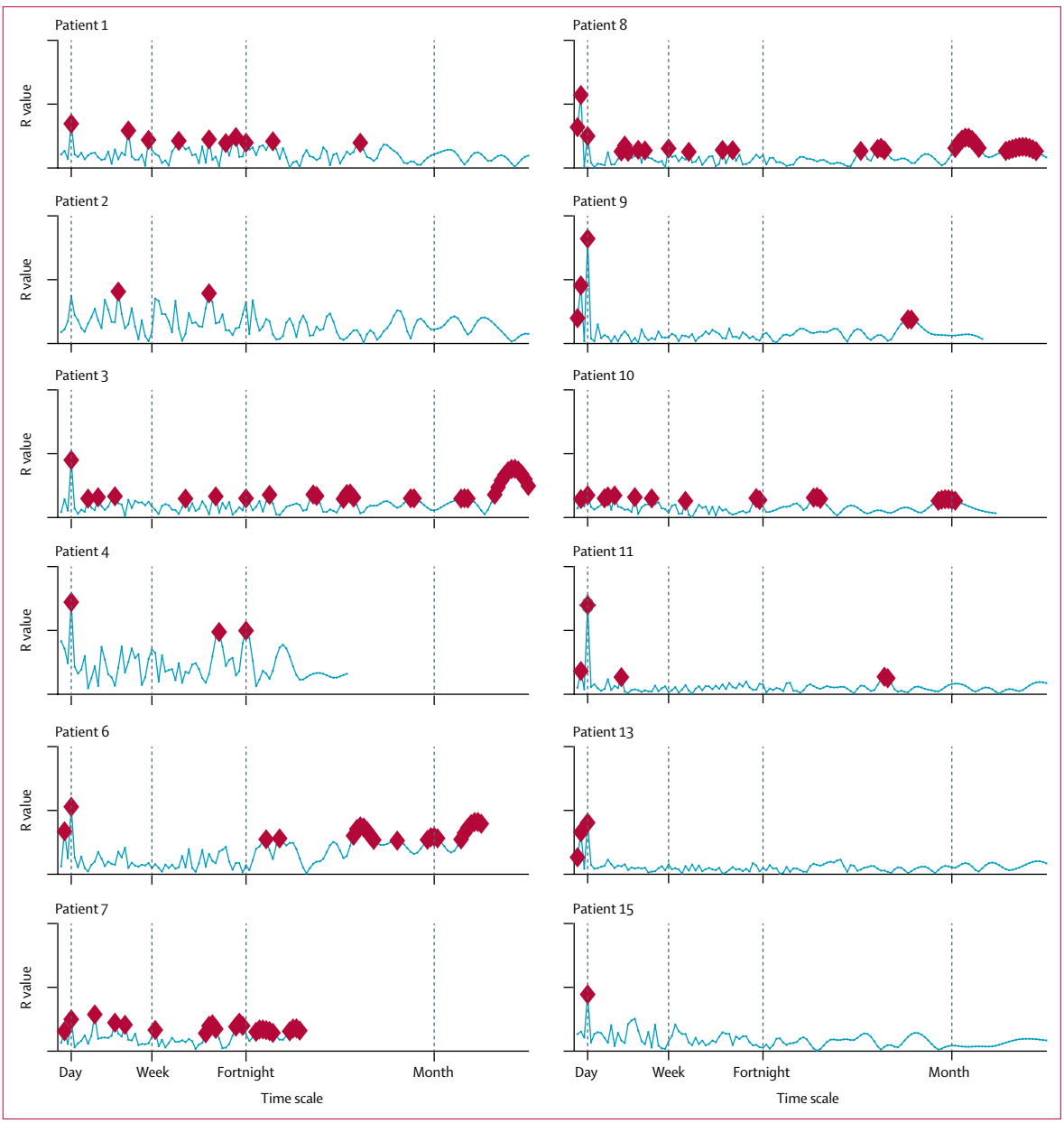

Figure 1: **Seizure cycles in electrocorticography data**
R values were calculated from the 12 patients from the NeuroVista database. Each subpanel shows the R value for a patient's seizure times (y axis) at a given time cycle (x axis). The presence of significant cycles is highlighted as pink diamonds (p<0·05, corrected for comparisons across multiple time cycles). R values were not computed for every time scale shown on the x axis, but the data were linearly interpolated for display.

Because there are no established distribution-free statistics for the R value,[28] Monte-Carlo simulations were also done using a Poisson or negative binomial model for seizure times to confirm the results of the Rayleigh test for seizure phase. From the distribution of R values over multiple simulations, it was possible to calculate the magnitude of the mean resultant vector that was expected to occur by chance for our data (p<0·05; appendix). All significance was assessed after correcting for multiple comparisons (testing was done at multiple time scales for each patient). All analyses were done in MATLAB (version 2017a) using the Circular Statistics Toolbox.

Role of the funding source

The funders of this study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all study data and the corresponding author had final responsibility for the decision to submit for publication.

Results

From the NeuroVista study,[20] we used data from 12 people (eight men and four women) who had at least 30 clinical seizures, recorded between June 10, 2010, and Aug 22, 2012. Mean recording duration was 1·4 years (SD 0·5). All patients showed a significant oscillation for at least one time scale (figure 1). 11 (92%) of 12 patients had strong rhythms at 24 h. One person (patient 8) had a stronger 12-h cycle than 24-h cycle, showing two peaks in seizure probability per day. From the general behaviour of the R value, a 24-h cycle should also show a smaller peak at 12 h (but no peak at 48 h). More generally, when phase alignment for some period occurs, the R value will also increase for half that period but would not increase at double the period (the phases cancel out). In an ideal case, in which seizure times show perfect alignment to a given phase, the R value does not decrease at half periods. For example, someone who always had a seizure at precisely 0800 h would have an R value of 1 at 6 h, 12 h, and 24 h. However, any noise (small deviations from 0800 h) always favours the true cycle—ie, the largest R value appears at 24 h. Other multiples of the period do not show this effect. For example, a patient who always had a seizure sometime on a Monday would show a peak R value at 7 days, a slightly smaller peak at 3·5 days, but no peak at 24 h.

Patient 8 also had a significant cycle at precisely 1 week. Two others (patients 1 and 7) also had approximately 1-week cycles. Patients 1 and 4 had 2-week cycles. Some people (patients 3, 6, 7, and 10) had stronger rhythms at time scales longer than 24 h, which suggests that circadian regulation was not necessarily the strongest modulating factor of epileptic activity.

The SeizureTracker database contained 12 947 patients with diverse types of epilepsy and recording durations of up to 8 years (median 1·8 years [IQR 0·9–3·8], mean 2·5 years [SD 2·7]). All data were obtained from self-reported seizure diaries, extracted from Jan 1, 2007, to Oct 19, 2015. After preprocessing of seizure times in the SeizureTracker data, people with less than 100 seizures were excluded, leaving 1118 patients (500 women, 476 men, and 142 sex not recorded). Notably, despite the initially large cohort, only 3918 people had more than ten reported seizures (1782 had more than 50 seizures). It was necessary to set a cutoff for seizure numbers, because the 95th percentile of the R values begins to rapidly increase at less than about 50–100 seizures (appendix). To ensure a high degree of rigour in all statistical tests, a threshold of 100 seizures was chosen; however, results were qualitatively similar for a cutoff of 50 seizures (appendix). Notably, a mean of 40% (SD 27) of seizures occurred in a cluster (median 37% [IQR 16–61]), and a mean of 19% (20) of lead seizures became clusters (median 13% [2–30]). The effect of clustering on cycles was assessed separately (appendix).

One patient in the SeizureTracker cohort mostly had seizures during the day (between 0800 h and 2000 h; figure 2A). Another patient had most seizures on Sundays and Fridays (figure 2B). Another patient (figure 2C) had no seizures in the final week of each month.

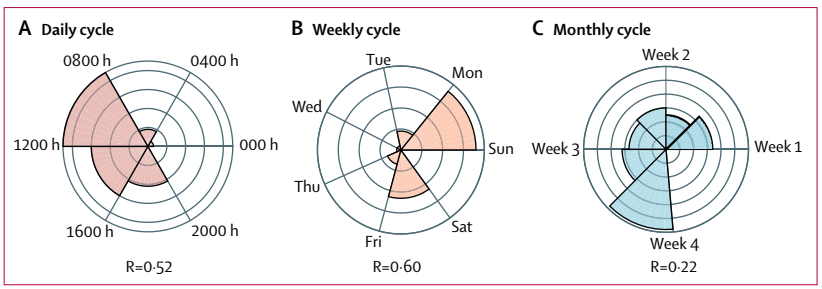

Figure 2: **Example R values and histograms for multiday seizure cycles**
Circular histograms of seizure times of three patients from the SeizureTracker database. For each histogram, the number of seizures is given on the radial axis, with each division representing ten seizures. (A) A patient with a daily cycle, seizures most prevalent in the morning. (B) A patient with a weekly cycle, seizures predominately on Friday and Sunday. (C) A patient with a monthly cycle, no seizures during 1 week of each 4-week period.

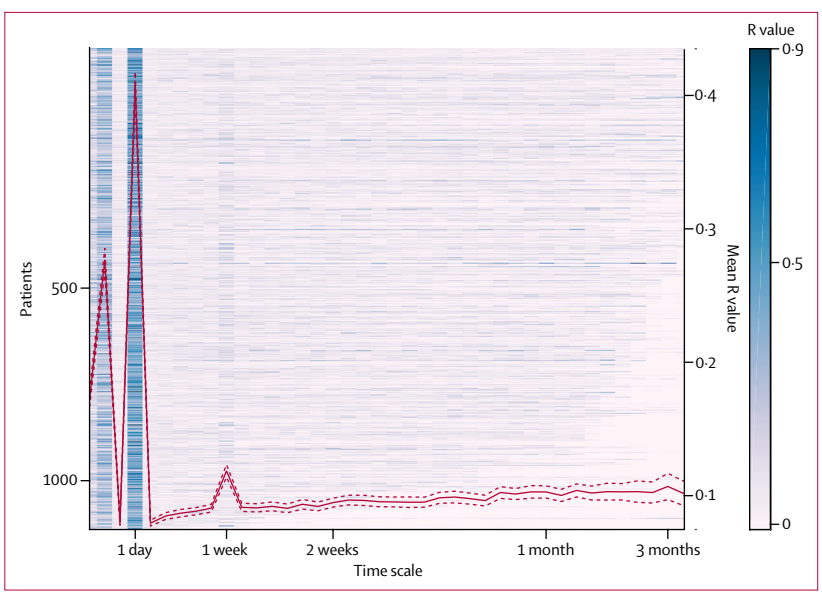

Figure 3: **Raster plot of seizure cycles from SeizureTracker patient diaries**
The colour code shows the mean resultant length (R value) for all 1118 patients (y axis) over different time scales (x axis). The R value was computed for 80 different time scales ranging from 6 h to 3 months. The red line shows the mean R value across all patients (right y axis). Dotted lines are 95% CI for the SEM. Peaks at 12 h and 24 h (circadian rhythms) and a smaller peak at 1 week are visible. The R value was computed for 80 different timescales ranging from 6 h to 3 months. Multiple patients also showed significant alignment for longer periods. A graphical representation of the exact p values is in the appendix.

In the SeizureTracker cycles heatmap, dark vertical bands are visible at 12 h and 24 h, suggesting that most patients show circadian oscillations of their seizure occurrence (figure 3; appendix). Repeating cycles with a period of 1 week was also common, evidenced by the vertical band, and small peak in the average phase locking value at 7 days. Many patients also showed some evidence of cycles lasting up to a month, although no obvious preference for longer periods, such as a 28-day cycle, was seen.

In 45% of the SeizureTracker data, the null hypothesis that the seizure phases belonged to a von-Mises (normal) distribution was rejected. Hence, the results of the Rayleigh test might not be reliable.

	Rayleigh test	Hodges-Ajne test	Monte-Carlo simulation
At least one cycle	990 (89%)	965 (86%)	958 (86%)
More than one cycle	811 (73%)	829 (74%)	720 (64%)
24-h cycle	912 (82%)	914 (82%)	891 (80%)
7-day cycle	107 (10%)	233 (21%)	77 (7%)
>3-week cycle	249 (22%)	247 (22%)	151 (14%)

Significant cycles had p<0·05, with a Bonferroni correction for testing at multiple time scales. The Rayleigh and Hodges-Ajne tests are used to reject the null hypothesis that seizure phases are randomly distributed around a circle. Monte-Carlo simulation was also done to measure the significance of the R value. Further details on simulation and graphs of exact p values are provided in the appendix.

Table: **Prevalence of significant seizure cycles in the SeizureTracker cohort (n=1118)**

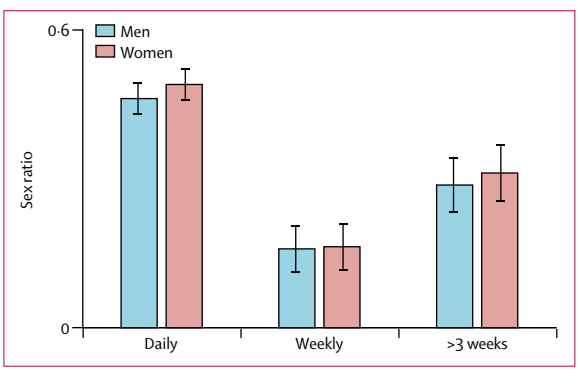

Figure 4: **Distribution of men and women**
Proportion of men and women in the SeizureTracker cohort with significant daily, weekly, and longer (>3 weeks) cycles with 95% CIs. Exact p values for each proportional difference were as follows: p=0·2179 for daily cycles, p=0·5217 for weekly cycles, and p=0·6495 for longer cycles (using a two-sided *z* test).

At least 86% of people showed one significant cycle in their seizure times (965 [86%] of 1118 with the Hodges-Ajne test, 990 [87%] with the Rayleigh test, and 958 [86%] with the Monte-Carlo simulation; at least 64% had more than one cycle; table). Most cycles were circadian, with at least 891 (80%) of 1118 people showing significant 24-h cycles. Some discrepancies were noted between statistical measures for 7-day cycles; 77 (7%) people with the Monte-Carlo simulation and 233 (21%) people with the Hodges-Ajne test had significant 7-day cycles. Between 151 (14%) and 247 (22%) people had significant cycles of longer than 3 weeks.

Some relevant probabilities were computed to gain an intuitive understanding of the significance of the results. 5% of patients are expected to show a significant cycle by chance alone (appendix). In a cohort of 1118 patients, the chance that two or more patients would randomly share a cycle is greater than 60%. However, this chance rapidly decreases for more then two people sharing a cycle, so the probability that six patients will share a cycle is less than 1%. The probability that 77 patients would randomly share a specific cycle (such as a 7-day cycle) is infinitesimal. The chance that 151 patients would share a cycle longer than 3 weeks is greater: about 39 patients would be expected to be in this group by chance (appendix).

No significant pattern difference was seen between men and women for patients with seizure cycles at different key time scales (figure 4). We also investigated whether the epilepsy syndromes were markedly different for people with significant cycles compared with the rest of the cohort (appendix). Overall, the distribution of syndromes for people with daily, weekly, and longer seizure cycles did not greatly differ from the total cohort. Similarly, different seizure types were not strongly associated with the propensity to cycle (appendix). Weekly cycles showed the only notable differences in seizure types. People with weekly seizure cycles showed a higher proportion of focal onset aware seizures and a lower proportion of tonic-clonic events and focal seizures with loss of awareness (appendix).

For the analysis of where peak seizure rates occurred for patients who had significant daily (figure 5A) and weekly (figure 5B) cycles, the correction for multiple comparisons was dropped from the Rayleigh significance test because it is now specifically investigating a daily and weekly cycle. With this less stringent limit, 959 (86%) of the 1118 patients had a 24-h cycle, and 296 (26%) patients had a 7-day cycle. The patients with significant daily cycles tended to have a peak in seizures around breakfast (293 [32%] of 914 had peaks at 0600–0900 h) and dinner time (163 [18%] had peaks at 1800–2100 h), although actual meal times and hours of sleep and wake were unknown in both datasets. No seizures were recorded at 0100 h because of data processing restrictions. Otherwise, patients had peak seizure times at all hours of the day (results were not unduly affected when seizures at 0100 h were included; appendix). Not many patients recorded their highest seizure rate during the night; although 164 001 (45%) of all 365 161 seizures in the SeizureTracker dataset were reported to occur between 2100 h and 0900 h (appendix; 1528 [52%] of 2911 for the NeuroVista seizures). In the subset of people with significant circadian cycles, 411 (45%) of 914 still reported seizures between 2100 h and 0900 h. Weekly cycles were more evenly distributed; however, more patients had their peak seizure day as either a Tuesday or Wednesday compared with other days (figure 5B).

Discussion

Using two independent datasets, we showed that cycles in seizure propensity occur across different time scales in different people. Cycles occurred in more than 80% of all patients. These cycles were most often circadian (24 h), but they also included circaseptan (7 day) and longer periods. The cycles did not appear to be associated with sex. Furthermore, our findings show that it is possible to identify the subset of patients with significant cycles and their specific cycles using self-reported diaries. Cyclic patterns established from seizure diaries can be used as statistical priors to develop patient-specific models of seizure likelihood.[29] These models have applications for seizure forecasting and chronotherapy.

Tools that monitor individuals' seizure cycles can augment epilepsy management. For example, by standardising treatment decisions to avoid inconsistencies (ie, where a new drug appears to be effective simply because the individual is in the decreasing phase of their cycle). Similarly, tracking seizure cycles during clinical trials is important to properly judge the effect of treatment. The therapeutic benefits that might be achieved through a knowledge of seizure cycles are yet to be tested, and several important considerations affect the actual clinical use of tools, such as the R value, to measure patient seizure cycles. For example, the ability to accurately measure the R value is related to the rate of seizure occurrence (appendix).

Times of peak seizure likelihood were patient specific. For people with strong circadian rhythms, the peak time of day for seizures was distributed across all hours of the day, although more seizures occurred in the morning (around 0800 h) and evening (around 2000 h) than at other hours of the day. However, patients with more than 100 seizures reported a similar number of seizures between 0900 h and 2100 h as between 2100 h and 0900 h (with 0100 h events excluded), suggesting that these daytime peaks were not driven by reporting bias (patients more likely to report seizures during the day). The proportion of nocturnal (2100 h to 0900 h) seizures was the same for people with circadian cycles as the overall cohort.

Historical data has shown a bimodal distribution of peak seizure times; for example, Langdon-Down and Brain[4] observed in 1929 that seizure occurrence peaked on awakening and in the late afternoon in a closely monitored cohort. Furthermore, Gowers[30] noted in a study of 840 patients with epilepsy that diurnal peaks were more common (361 patients [43%]) than nocturnal peaks (176 patients [21%]). Previous work has also noted the presence of morning and evening preferred times in cycles of epileptiform activity.[9,16] Associations between seizures and the sleep cycles have been well studied.[31] In 1968, Janz[32] noted that the link between sleep and seizures was particularly strong for tonic-clonic seizures, although our study did not find a strong association between circadian cycles and seizure types (appendix). Observed morning and evening peaks might also have coincided with troughs in drug concentrations. The data in this study did not specify times of sleeping or waking or medication times; the future collection of this information will shed further light on the underlying causes of circadian cycles.

In this study, weekly cycles did not strongly favour any day of the week. Slightly more patients had high seizure rates on Tuesdays and Wednesdays. Other diseases show weekly trends. Cardiovascular diseases and stroke are known to have a Monday peak,[33] and some evidence shows that people are more health aware early in the week.[34] Awareness might be linked to increased recognition and reporting of seizures. The question of whether 7-day weeks are arbitrary, or have some endogenous, biological underpinning has long been debated. By contrast,

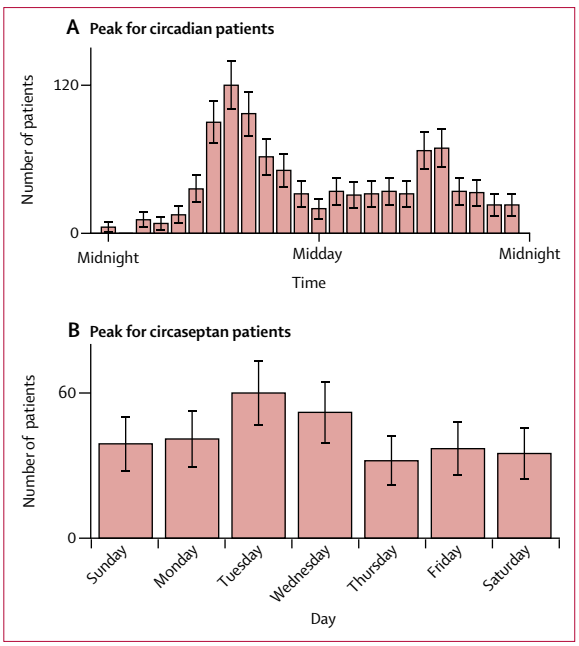

Figure 5: **Distribution of peak seizure rates in the SeizureTracker cohort**
(A) Number of patients with peak seizure rates at each hour of the day with 95% CIs. Only patients with significant 24-h cycles are shown. (B) Number of patients with peak seizure rates at each day of the week with 95% CIs. Only patients with significant 7-day cycles are shown.

circadian and seasonal cycles can plausibly be entrained by the rotation of the earth around its axis and orbit.[35] No clear celestial triggers exist for 7-day cycles; yet evidence of their existence has been shown across a range of diseases,[33,36,37] metabolic function,[38,39] and human behaviours.[34] Some studies have argued that the cause of weekly periodicity is primarily environmental;[40] however, some evidence shows that the 7-day week is endogenous.[41] The fact that seizure occurrence did not favour a particular day of the week provides some support that cycles were not purely due to environmental causes or reporting biases (in the case of SeizureTracker data).

Most metabolic, behavioural, and neurological functions show some circadian component.[42] The presence of longer periodic rhythms is more intriguing, because the underlying physiological mechanisms have not been as well studied as circadian patterns. Monthly cycles of seizure frequency have previously been linked to menstruation.[15] However, our results and those from previous studies[16,17] have shown that cycles are equally common in men and women. Historically, there has been great interest in longer cycles of seizure activity: Langdon-Down and Brain (1929),[4] Griffiths and Fox (1938),[5] and Bercel (1964)[6] provided documentation of monthly seizure rhythms in residents of an epilepsy colony, which were equally prevalent in men. Mead (1748)[7] and Andree (1753)[43] postulated that monthly seizures cycles were in some way linked to the phases of the moon. The hypothetical link between lunar cycles and seizures has been debated over millennia and is testament to the

longstanding association between the moon and mental health.[44] However, even hundreds of years ago, remarkably precise records of seizure times in large patient cohorts were able to debunk the presence of a lunar influence.[45,46] Studies from the 21st century have renewed the possibility of increased seizures during the full moon;[47] but, for the most part, results have been discredited or attributed to more mundane explanations such as sleep deprivation.[48–50] A study published in 2013 showed that the phase of the moon had a detectable effect on sleep quality,[51] providing a candidate explanation for why the moon cycle influences seizure occurrence. The results of our study showed that long cycles of 3 weeks or more occurred in about 20% of people. At least some of these people's cycles will probably align with the lunar phase or menses simply by chance, without signifying any deeper causal link.

Our study showed that seizure onset is more likely at certain phases of underlying multiday cycles. It seems likely that seizures at least partly track the underlying cycle of subclinical epileptic activity,[16] and we have previously shown alignment between the likelihood of seizures and spike-wave discharges.[17] Given the ubiquity of seizure cycles, which occur in most people with epilepsy despite the diversity of their syndromes, we speculate that underlying physiological changes (possibly environmental and endogenous) might bring the brain closer to some threshold for seizure occurrence. That is to say, epilepsy is not driving the presence of cycles, but cycles are driving the propensity for seizures. Regardless of whether this hypothesis is correct, linking cycles to seizure likelihood might be valuable to patients. For example, Baud and colleagues[16] explored the possibility of using tailored risk profiles for people's seizures. We have also previously shown how a probabilistic model of seizure susceptibility can be constructed from multiple underlying rhythms.[29] These models for seizure susceptibility could guide drug doses, aiming for a higher concentration at the time of day when patients are shown to have a higher chance of seizures. We hope that future human studies and clinical trials will investigate the usefulness of seizure risk profiles for improving quality of life, and the potential therapeutic effect of titrating drug concentrations on the basis of multiday cycles.

Limitations of self-reported seizure diaries are well documented.[52–54] Patients might under-report or over-report events or have other reporting biases. Although the limitations of seizure diaries do impose restrictions on the type of analysis that can be done, data derived from diaries still provides important scientific insight. In our study, patient inaccuracy does not invalidate cycle detection provided that most reported seizures were real and that erroneous seizures were evenly distributed in time. Missing seizures (ie, diary fatigue) would not obscure cyclic patterns. Incorrect seizures would act as an overlaid noise on a true cyclic trend. Provided enough true seizures are recorded, the signal can be distinguished from the noise. The assumption of evenly distributed noise sources is common for statistical analyses, and often difficult to prove. In our analysis, we could not distinguish which seizures were erroneous. Therefore, cyclic patterns might arise purely from patterns of human bias. However, if human biases are assumed to be socially driven, then population-level trends (eg, more reports on weekends or no reports during the night) should be recorded. The results showed that seizure times were evenly distributed over times of day, days of the week, and months of the year, which provides some support that the results were not entirely driven by reporting bias.

Our study was limited to investigating cyclic trends of up to 3 months. Despite the length of recordings, more cycles would be required to measure the statistical significance of annual trends (eg, seasonal variation, holiday periods, or daylight saving time). The median recording duration of the SeizureTracker database was 1·8 years (IQR 0·9–3·8) and mean NeuroVista recording duration was 1·4 years (SD 0·5). Therefore, most patients have only a couple of samples (cycles) from which to measure annual cycles. On a population level, seizures did not clearly favour a particular month (appendix). However, given the patient specificity of other seizure cycles, combining patients' seizures in this way would probably dilute any potential annual trends.

To the best of our knowledge, this study is the largest investigation of patient-specific seizure rhythms. The results show that multiday cycles modulate seizure activity in humans. In addition to strong circadian modulation of seizures, clear weekly rhythms and longer periodic cycles were recorded. Notably, findings from long-term electrocorticography recordings were backed up by seizure times obtained from self-reported seizure diaries. This suggests that diaries can provide a valuable clinical tool to detect and monitor repeating patterns of seizures. The ubiquity of seizure cycles indicates that this is an important clinical phenomenon that affects most patients. The ability to identify unique cyclic patterns in individuals could lead to new opportunities in seizure forecasting tools, as well as improved treatment.

For the **Seizure cycles analysis code** see https://github.com/pkaroly/seizure-cycles

For more on **SeizureTracker data access restrictions** see http://www.seizuretracker.com/SeizureSuccess/Seizure_Tracker_Research/index.php

Contributors

PJK, DMG, DRF, and MJC conceived the study and had roles in study design and data analysis. WHT, DBG, and REM contributed to writing and data analysis. PJK, DMG, and MJC wrote the article.

Declaration of interests

PJK is supported by an Australian Government Research Training Program Scholarship, outside of this study. DMG receives funding from National Institutes of Health grant T32NS048005, outside of this study. REM is a co-founder of SeizureTracker.com and receives funding from the Tuberous Sclerosis Alliance, outside of this study. All other authors declare no competing interests.

Data sharing

Data sharing of the SeizureTracker.com participants will be facilitated by the International Seizure Diary Consortium. Population exports are done through an online request process. The available data include deidentified participant data that underscore the results reported in this article (text, tables, figures, and appendix). Analysis code is available online. Data access is restricted to researchers who have submitted study aims for review by an independent panel established for this purpose. Submitted aims are reviewed for user interest and patient impact.

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References

1 Nagoshi E, Saini C, Bauer C, Laroche T, Naef F, Schibler U. Circadian gene expression in individual fibroblasts: cell-autonomous and self-sustained oscillators pass time to daughter cells. *Cell* 2004; **119:** 693–705.

2 Panzeri S, Ince RA, Diamond ME, Kayser C. Reading spike timing without a clock: intrinsic decoding of spike trains. *Phil Trans R Soc Lond B Biol Sci* 2014; **369:** 20120467.

3 Alvarez GG, Ayas NT. The impact of daily sleep duration on health: a review of the literature. *Prog Cardiovasc Nurs* 2004; **19:** 56–59.

4 Langdon-Down M, Brain WR. Time of day in relation to convulsions in epilepsy. *Lancet* 1929; **213:** 1029–32.

5 Griffiths G, Fox JT. Rhythm in epilepsy. *Lancet* 1938; **232:** 409–16.

6 Bercel NA. The periodic features of some seizure states. *Ann N Y Acad Sci* 1964; **117:** 555–63.

7 Mead R, Stuck T. A treatise concerning the influence of the sun and moon upon human bodies, and the diseases thereby produced. London: J Brindley, 1748: 36–47.

8 Reynolds JR. Epilepsy: its symptoms, treatment, and relation to other chronic, convulsive diseases. *Am J Psychiatry* 1862; **19:** 198–209.

9 Anderson CT, Tcheng TK, Sun FT, Morrell MJ. Day–night patterns of epileptiform activity in 65 patients with long-term ambulatory electrocorticography. *J Clin Neurophysiol* 2015; **32:** 406–12.

10 Loddenkemper T, Vendrame M, Zarowski M, et al. Circadian patterns of pediatric seizures. *Neurology* 2011; **76:** 145–53.

11 Quigg M. Circadian rhythms: interactions with seizures and epilepsy. *Epilepsy Res* 2000; **42:** 43–55.

12 Laidlaw J. Catamenial epilepsy. *Lancet* 1956; **271:** 1235–37.

13 Newmark ME, Penry JK. Catamenial epilepsy: a review. *Epilepsia* 1980; **21:** 281–300.

14 Herzog AG, Klein P, Ransil BJ. Three patterns of catamenial epilepsy. *Epilepsia* 1997; **38:** 1082–88.

15 Herzog AG, Fowler KM, Sperling MR, Massaro JM. Distribution of seizures across the menstrual cycle in women with epilepsy. *Epilepsia* 2015; **56:** e58-62.

16 Baud MO, Kleen JK, Mirro EA, et al. Multi-day rhythms modulate seizure risk in epilepsy. *Nat Commun* 2018; **9:** 88.

17 Karoly PJ, Freestone DR, Boston R, et al. Interictal spikes and epileptic seizures: their relationship and underlying rhythmicity. *Brain* 2016; **139:** 1066–78.

18 Ramgopal S, Thome-Souza S, Loddenkemper T. Chronopharmacology of anti-convulsive therapy. *Curr Neurol Neurosci Rep* 2013; **13:** 339.

19 Stanley DA, Talathi SS, Carney PR. Chronotherapy in the treatment of epilepsy. *ChronoPhysiol Ther* 2014; **4:** 109–23.

20 Cook MJ, O'Brien TJ, Berkovic SF, et al. Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. *Lancet Neurol* 2013; **12:** 563–71.

21 Goldenholz DM, Moss R, Scott J, Auh S, Theodore WH. Confusing placebo effect with natural history in epilepsy: a big data approach. *Ann Neurol* 2015; **78:** 329–36.

22 Fisher NI. Statistical analysis of circular data. Cambridge University Press; 1995.

23 Jammalamadaka SR, Sengupta A. Topics in circular statistics. Multivariate analysis vol. 5. Singapore: World Scientific, 2001: 107–30.

24 Haut SR. Seizure clusters: characteristics and treatment. *Curr Opin Neurol* 2015; **28:** 143–50.

25 Brazier KTS. Confidence intervals from the Rayleigh test. *Mon Not R Astron Soc* 1994; **268:** 709–12.

26 Stephens MA. Use of the Kolmogorov-Smirnov, Cramér-Von Mises and related statistics without extensive tables. *J R Stat Soc Ser B Methodol* 1970; 115–22.

27 Zar JH. Biostatistical analysis. Chennai: Pearson Education India, 1999: 616–58.

28 Kutil R. Biased and unbiased estimation of the circular mean resultant length and its variance. *Statistics* 2012; **46:** 549–61.

29 Karoly PJ, Ung H, Grayden DB, et al. The circadian profile of epilepsy improves seizure forecasting. *Brain* 2017; **140:** 2169–82.

30 Gowers WR. Epilepsy and other chronic convulsive diseases: their causes, symptoms, and treatment. London: Churchill, 1881: 196–99.

31 Hofstra WA, de Weerd AW. The circadian rhythm and its interaction with human epilepsy: a review of literature. *Sleep Med Rev* 2009; **13:** 413–20.

32 Janz D. The grand mal epilepsies and the sleeping-waking cycle. *Epilepsia* 1962; **3:** 69–109.

33 Gallerani M, Pala M, Fedeli U. Circaseptan periodicity of cardiovascular diseases. *Heart Fail Clin* 2017; **13:** 703–17.

34 Ayers JW, Althouse BM, Johnson M, Dredze M, Cohen JE. What's the healthiest day?: circaseptan (weekly) rhythms in healthy considerations. *Am J Prev Med* 2014; **47:** 73–76.

35 Duffy JF, Wright KP. Entrainment of the human circadian system by light. *J Biol Rhythms* 2005; **20:** 326–38.

36 Cantwell K, Morgans A, Smith K, Livingston M, Dietze P. Temporal trends in cardiovascular demand in EMS: weekday versus weekend differences. *Chronobiol Int* 2015; **32:** 731–38.

37 Cugini P, Romit A, Di Palma L, Giacovazzo M. Common migraine as a weekly and seasonal headache. *Chronobiol Int* 1990; **7:** 467–69.

38 Blank M, Cornélissen G, Halberg F. Circasemiseptan (about-half-weekly) and/or circaseptan (about-weekly) pattern in human mitotic activity? *In Vivo* 1995; **9:** 391–94.

39 Haus E. Chronobiology of hemostasis and inferences for the chronotherapy of coagulation disorders and thrombosis prevention. *Adv Drug Deliv Rev* 2007; **59:** 966–84.

40 Hildebrandt G. The time structure of adaptation. In: Haus E, Kabat HF, eds. Chronobiology 1982–1983. Basel: Karger Publishers, 1984: 263–67.

41 Reinberg AE, Dejardin L, Smolensky MH, Touitou Y. Seven-day human biological rhythms: an expedition in search of their origin, synchronization, functional advantage, adaptive value and clinical relevance. *Chronobiol Int* 2017; **34:** 162–91.

42 Bass J. Circadian topology of metabolism. *Nature* 2012; **491:** 348–56.

43 Andree J. Cases of the epilepsy, hysteric fits, and St. Vitus dance, with the process of cure: interspersed with practical observations. To which are added cases of the bite of mad creatures, treated after the method of Dr. Desault, with some additional means of my own; observations upon the same, and remedies proposed for the cure of the hydrophobia. London: W Meadows and J Clarke in Cornhill, 1753: 110–26.

44 Temkin O. The falling sickness. A history of epilepsy from the Greeks to the beginning of modern neurology. Baltimore: Johns Hopkins Press, 1971: 90–98, 264.

45 Moreau JJ. De l'étiologie de l'épilepsie: et des indications que l'étude des causes peut fournir pour le traitement de cette maladie. Paris: J-B Bailliere, 1854: 94.

46 Leuret M. Recherches sur l'epilepsie. *Arch Gen Med* 1843; **2:** 32–50.

47 Polychronopoulos P, Argyriou AA, Sirrou V, et al. Lunar phases and seizure occurrence: just an ancient legend? *Neurology* 2006; **66:** 1442–43.

48 Raison CL, Klein HM, Steckler M. The moon and madness reconsidered. *J Affect Disord* 1999; **53:** 99–106.

49 Benbadis SR, Chang S, Hunter J, Wang W. The influence of the full moon on seizure frequency: myth or reality? *Epilepsy Behav* 2004; **5:** 596–97.

50 Otte WM, van Diessen E, Bell GS, Sander JW. Web-search trends shed light on the nature of lunacy: relationship between moon phases and epilepsy information-seeking behavior. *Epilepsy Behav* 2013; **29:** 571–73.

51 Cajochen C, Altanay-Ekici S, Münch M, Frey S, Knoblauch V, Wirz-Justice A. Evidence that the lunar cycle influences human sleep. *Curr Biol* 2013; **23:** 1485–88.

52 Blum DE, Eskola J, Bortz JJ, Fisher RS. Patient awareness of seizures. *Neurology* 1996; **47:** 260–64.

53 Hoppe C, Poepel A, Elger CE. Epilepsy: accuracy of patient seizure counts. *Arch Neurol* 2007; **64:** 1595–99.

54 Kerling F, Mueller S, Pauli E, Stefan H. When do patients forget their seizures? An electroclinical study. *Epilepsy Behav* 2006; **9:** 281–85.