



Breaking the Seizure Randomness Myth: Evidence for a Recurring Ebb and Flow of Seizure Risk on the Continuum of Time

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:** Anti-seizure 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.

Commentary

The randomness of seizure occurrence is conventionally a hallmark characteristic and often ranked one of the most debilitating features of epilepsy.¹ This unpredictability necessitates a standing, chronic use of anti-seizure medications (ASM). However, often we come across people with epilepsy (PWE) who claim that they more often have seizures at a specific time of the day, or month and even a particular month of the year. Currently, seizure diaries are the gold standard for monitoring seizure frequency in clinical practice and clinical trials. Seizure diaries maintained meticulously over a long time can

potentially reveal seizure patterns, that is, seizure cycles, which would otherwise go unnoticed. The ease of use and accessibility to smartphones and internet-based diaries recently allowed a big data analysis of more than a million self-reported seizures in over 10,000 individuals. A circadian pattern with higher seizure frequency between 7 AM and 10 AM and an increased reportage during the weekdays compared to the weekend was noted during a median reporting period of approximately 3 months.² However, self-reporting of seizures in PWE is sub-optimal. Less than half of PWE provide a precise seizure burden, and they miss a majority of objectively detected seizures.³





Therefore, accurate analysis of seizure variations over time requires objectively measured data, ideally collected over the years to avoid missing risk cycles that span several days to months. In the absence of seizure forecasting devices, evidence for the existence of seizure cycles would provide PWE a sense of seizure predictability, which significantly reduces the epilepsy burden.⁴

Technological advances in continuous intracranial EEG (ciEEG) acquisition by the NeuroVista and responsive neurostimulation (RNS) System (NeuroPace Inc) have helped overcome the above limitations of seizure diaries.^{5,6} These 2 devices have tremendously advanced our knowledge about the temporal variations in interictal epileptiform activity (IEA), their interplay with seizures, and the potential for seizure forecasting. Now, Leguia et al have retrospectively analyzed ciEEG data from 222 PWE with drug-resistant focal epilepsy, a majority (57.2%) being mesial temporal in origin, who participated in the RNS clinical trial with the explicit goal of mapping out discrete patterns of seizure cycles.⁷ They analyzed seizures at 3 distinct time scales and measured the strength of seizure clustering (effect size) by phase-locking value (PLV; ranging from 0 to 1 with PLV >0.4 suggesting strong phase clustering). The seizure data were accrued over a median of 5.9 years, with some PWE monitored for as long as 9.5 years. Circannual (around 1 year; also known as “seasonal epilepsy”) seizure cycles were infrequent (24/194; 12%) and had weak phase clustering (mean PLV of 0.17). In contrast, the circadian and multidien (ranging from >2 days to several weeks) seizure cycles were highly prevalent and had similar, moderate strength of phase clustering (mean PLV of 0.34). Circadian seizure cycles were noted in 89% (76/85) PWE, similar to the prevalence reported in studies from NeuroVista and Seizure-Tracker, a self-reported seizure diary.⁸ Multidien seizure cycles were noted in 60% (112/186) of PWE. The multidien cycles did not align with fixed period lengths such as the day of the week, month, or lunar phase, highlighting the unlikely influence of external or environmental cues and their likely governance by endogenous factors. It is tempting to consider the role of hormonal cycles in modulating the multidien seizure cycles, like in catamenial epilepsy. However, the prevalence of multidien seizure cycle is equal in men and women in the current and another recent study.⁸ Although hormones such as testosterone, cortisol, and aldosterone have multidien fluctuations, we are far from understanding their interactions with the multidien seizure cycles. In contrast, moving from systemic influences on seizure cycles to inherent brain mechanisms provides tempting and concrete evidence for drivers of the multidien seizure cycles in the form of interaction of IEAs and seizures.

Prior studies that relied on short timescale EEG recordings have found an inconsistent relationship between IEA and seizures. In contrast, a previous analysis of 37 PWE with RNS, a subset of the current study population from the same research group, found that IEA show clear circadian and multidien clustering in an individual PWE.⁹ Extending these results, Leguia et al found that most multidien chronotype PWE had electrographic and self-reported seizures clustered around the peak

periodicities of the IEA. These multidien seizure cycles could be divided into 5 distinct patterns occurring at 7, 15, 20, and 30-day periods with one group exhibiting irregular periodicity. A given PWE could have one or more such multidien periodicity, independent of sex, or seizure focus. In contrast, the circadian cycles of electrographic seizures peaked around 00:00, 03:00, 09:00, 14:00, and 18:00 hours but lacked phase association with IEA because the latter consistently peaked during the night on a circadian timescale. Combined, this suggests that while the sleep–wake cycle is the primary modulator of hourly IEA, an interplay between the sleep–wake cycle and endogenous circadian rhythms modulate the circadian seizure chronotypes. The current study relies on data from PWE undergoing neurostimulation. But similar seizure risk cycles are noted using nonstimulation intracranial devices in PWE and animals, with the latter showing that such seizure cycles are independent of ASM usage.¹⁰

The most significant contribution of the study by Leguia et al is its validation of the decades and centuries of clinical observation of the presence of seizure cycles, which turns out to be much more frequent than previously appreciated, especially at multidien timescale. This information may advance the use of chronotherapy, that is, adjusting ASMs based on temporal changes in seizure risk, currently used in nocturnal and catamenial epilepsies. The results of the current study behoove us to consider chronotherapy for well-recognized, individualized multidien cycles. Additionally, the yield of epilepsy monitoring unit evaluation for diagnostics and presurgical evaluation can be improved by timing admissions based on seizure risk cycles.

As most PWE seem to have a relatively strong phase clustering of seizures at circadian and multidien timescales, it is only logical and expected to question the predictability of an upcoming seizure. The science of accurate seizure prediction has advanced by leaps and bounds in the last decade. Researchers have already achieved above-chance accuracy in warning of an imminent seizure in a majority of PWE analyzed using intracranial devices such as NeuroVista and self-reported seizure diaries.^{5,11} Incorporating information of individualized seizure cycles promises to refine prediction accuracy further. The forecasting of seizures by NeuroVista device improved significantly after accounting for circadian chronotypes in PWE.¹² Now, the new found knowledge of the existence of multidien IEA and seizure cycles has helped the research team led by Vikram Rao and Maxime Baud, the senior authors of the currently discussed paper, to push the envelope in seizure prediction further. They recently reported that predictive models that used multidien IEA information could forecast seizure risk, better than chance, a day in advance in two-thirds of the validation cohort. In a few PWE, the forecasting could be performed 3 days in advance.¹³


Continued advancement in the field of seizure forecasting could herald the era of individualized, dynamic ASM management. Although the current study provides a critical blow to the idea of seizures being a random phenomenon, the ultimate benefit of these findings to the wide epilepsy community



cannot be realized until the discovery of noninvasive biomarkers of the IEA and seizure cycles. Nonetheless, the current study in the era of breakneck technological advances raises the hope of wearable technology in the near future that monitors the dynamic and measurable biomarkers of the seizure cycle to provide actionable seizure forecasting.

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