Cycles in Seizure Duration and Their Underlying Dynamics in the Tetanus Toxin Rat Model

Parvin Zarei Eskikand[1*,2], Sepehr Kazemi[1], Mark J. Cook[1,2,3], Anthony N. Burkitt[1,2], David B. Grayden[1,2,3]

1 Department of Biomedical Engineering, The University of Melbourne, Victoria, Australia
2 Graeme Clark Institute for Biomedical Engineering, The University of Melbourne, Victoria, Australia
3 Department of Medicine, St Vincent's Hospital, Melbourne, Victoria, Australia

* pzarei@unimelb.edu.au

Abstract

Seizure duration, a characteristic of epilepsy that is understudied in relation to its relationship with rhythmic cycles, provides critical insights into the severity and temporal dynamics of seizures. This study investigates the rhythmic patterns of seizure duration in the Tetanus Toxin (TT) rat model of epilepsy. Our analysis shows significant cyclical patterns in seizure durations, with periods ranging from 4 to 8 days across rats. The synchronization index and circular-linear correlations revealed phase-locked relationships between seizure durations and cycles, suggesting non-random, predictable temporal dynamics. Further analyses examined the relationship between seizure durations, inter-seizure intervals, and dominant EEG power. The findings highlight that seizure durations exhibit predictable rhythms, which could transform seizure prediction and enable time-based intervention strategies, ultimately improving epilepsy management and patient outcomes. These insights lay the groundwork for personalized, rhythm-aware therapeutic approaches.

Introduction

Epilepsy, a neurological disorder characterized by recurrent, unprovoked seizures, affects millions worldwide. These seizures vary significantly in frequency, duration, and severity, creating challenges for effective management and treatment. A critical aspect of epilepsy care is the ability to predict seizures accurately, as reliable forecasting could vastly improve patient safety and quality of life. Traditionally, research has focused on identifying patterns in seizure frequency [3, 4, 5, 12, 15, 16, 17, 18, 21]. However, duration patterns, which can reveal more about the intensity and potential impact of seizures, remain underexplored.

While research has considered cyclical or rhythmic patterns in seizure occurrence, the present study is the first to systematically investigate the rhythmic evolution of seizure durations over time. This novel approach is grounded in the understanding that temporal dynamics—such as circadian and multi-days rhythms—affect various biological processes and may influence seizure characteristics, including duration. Detecting cyclical patterns in seizure duration could lead to breakthroughs in seizure prediction and time-based intervention strategies, improving outcomes for individuals with epilepsy. Also, understanding the temporal dynamics of seizures provides valuable insights into the underlying neurophysiological mechanisms associated with

epileptic events. Due to the complexity of seizure dynamics within and across subjects, detailed longitudinal studies are essential to unveil these potential rhythmic influences.

The Tetanus Toxin (TT) rat model, which mimics human focal epilepsy by inducing spontaneous seizures following an intra-hippocampal injection of tetanus toxin, provides an ideal environment for exploring these temporal dynamics [7]. This model enables continuous, long-term monitoring of seizure activity, making it particularly useful for identifying multiday cycles and other extended patterns. In this study, we leveraged the TT rat model to analyze seizure duration data collected over a 40-day period, using sinusoidal curve fitting to reveal any underlying rhythmic fluctuations. By calculating the Synchronization Index (SI) and assessing circular-linear correlations, we examined the phase-locked relationship between seizure durations and identified cycles, hypothesizing that seizure duration might exhibit phase-locked behavior indicative of intrinsic neural rhythms.

Beyond rhythmic evolution, this study explored additional factors that might affect seizure duration, specifically inter-seizure intervals and dominant EEG power. By investigating the relationship between seizure duration and the time intervals preceding or following each seizure, we aimed to determine whether longer or shorter intervals might impact seizure duration, offering insights into the temporal dependencies in seizure dynamics. Additionally, we assessed the correlation between seizure duration and the power of the dominant EEG frequency. The role of EEG power, particularly dominant frequency, in influencing seizure duration has been highlighted in recent studies and may reflect neural excitability or synchronization during seizures. Lastly, we considered the impact of external stimuli, specifically low-intensity electrical stimulation or "probing," on seizure dynamics. Probing is commonly used in neurophysiological studies to assess cortical excitability and network connectivity. While probing is generally considered safe, recent research has shown that repetitive stimulation may lower seizure thresholds or extend seizure duration. We analyzed seizure patterns during both probing-on and probing-off periods to explore how probing might modulate seizure frequency and intensity.

As the first study to investigate rhythmic evolution in seizure duration, our findings could offer new insights into the mechanisms that govern seizure dynamics. By characterizing both natural rhythmic patterns and the effects of experimental probing, we aim to contribute to a more comprehensive understanding of seizure activity and advance time-based approaches for managing epilepsy. This research may have implications for improved seizure forecasting and the development of optimized, individualized treatment strategies in epilepsy care.

Materials and methods

Data

The data for this study was collected from a intra-hippocampal TT rat model study [7]. Briefly, six rats were placed in the TT group after intra-hippocampal injection of TT and four rats were placed in the control group after instead administrating phosphate-buffered saline. Six TT rats were used from the original seven as one of the rats died on day 26; the control rats were not considered in this study. Five stainless steel electrodes were implanted into the skull of each rat for intracranial EEG recording. All other methods related to the collection of the data used in our study are contained in the original paper by Crisp et al. (2020) [7]. After around 1-2 weeks, the TT rats started to have spontaneous seizures. The daily numbers of seizures waxed and waned over a period of approximately 6 weeks, as illustrated in Fig 1. Between 4 to 5 weeks after injection, the seizure rate tended to decrease until there were no seizures detected. EEG data were recorded continuously at 2048 Hz sampling rate for 23 hours every day, with 1 hour for daily maintenance checks and back-up of the data.

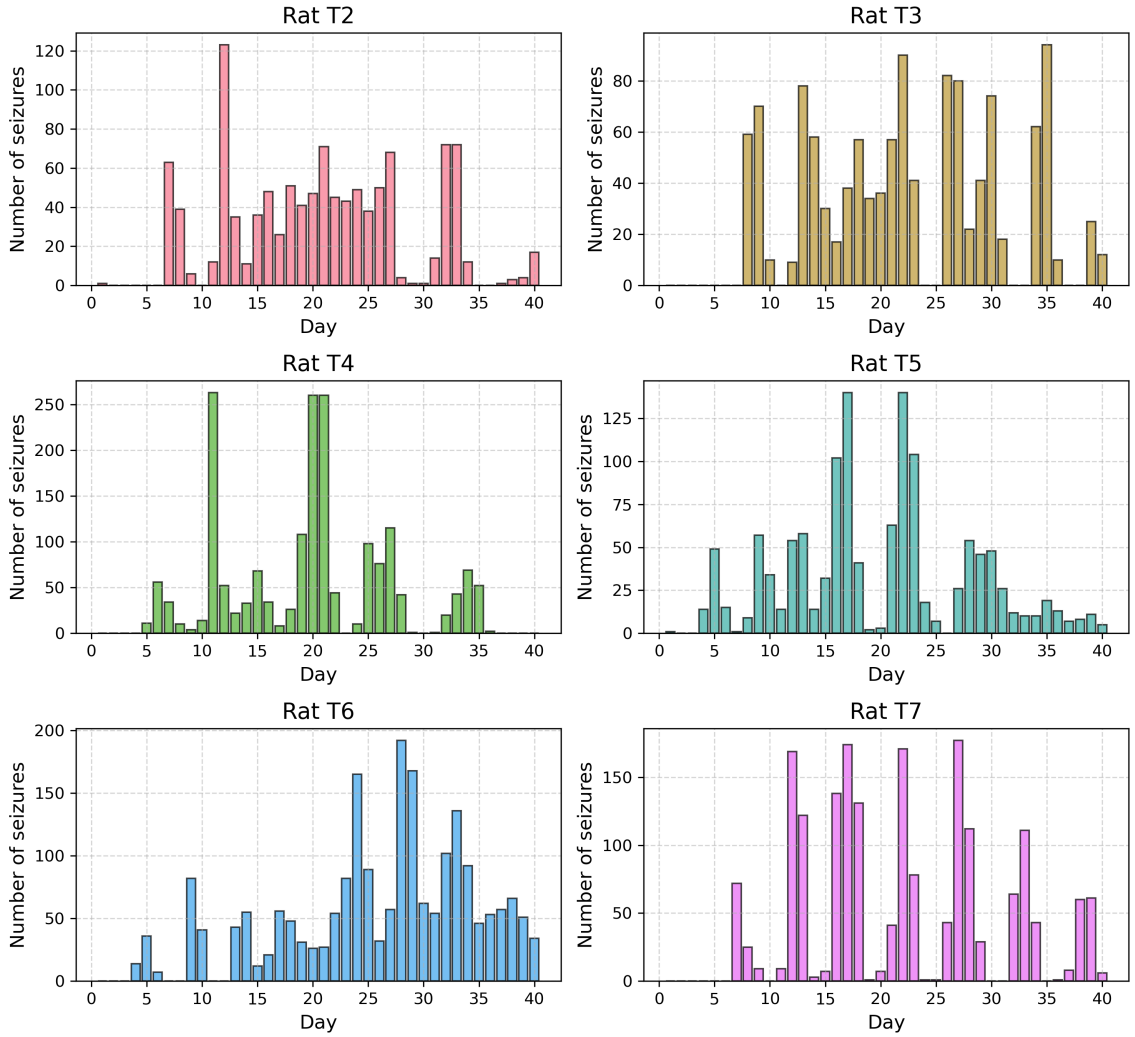


Fig 1. Seizure occurrences over time for TT rats. Each subplot represents data from one rat with the x-axis indicating days since the start of the recording. The y-axis is the total number of seizures that occurred on the specific day.

The experimental protocol included periodic, low-level electrical stimulation or "probing" [7]. The probing-on period consisted of 100 biphasic pulses (pulse-width 0.5 ms and current/phase 1.26 ± 0.024 mA) with inter-stimulus intervals of 3.01 s over a period of about 5 minutes. After each probing-on period, there was a 5 min probing-off period before the start of the next probing-on period.

The research procedures received approval from the St. Vincent's Hospital, Melbourne Animal Ethics Committee and were carried out following the guidelines outlined in the "Australian Code for the Care and Use of Animals for Scientific Purposes, 8th Edition" (2013).

Fig 2A displays a histogram of seizure durations across different rats, highlighting the distribution of seizure durations for each individual rat. Fig 2B displays the ranges number of seizures across different rats over 40 days of recording compared to the average duration of seizures that occurred on each day across all

rats. This figure shows the daily averages across all rats, providing a comparative view of seizure frequency and duration trends over time.

Temporal analysis of the changes in the duration of seizures

We calculated the hourly average of seizure durations over 40 days of recording across multiple rats and analyzed this data to identify the underlying periodic patterns in the changes in seizure duration using sinusoidal curve fitting. The sinusoidal model applied is expressed as

$$f(x) = A \cdot \sin(\omega x + \phi) + c\,, \tag{1}$$

where A represents the amplitude, ω is the angular frequency, ϕ denotes the phase shift, and c is the vertical offset. The optimization process involved minimizing the Sum of Squared Residuals (SSR) between the measured data and the fitted sinusoidal function. The periods corresponding to each rat were determined and documented.

We calculated the Synchronization Index (SI) for the significant periods identified by sinusoidal curve fitting. For each rat, the positional phases of seizures within a cycle were calculated by mapping seizure occurrences to a sinusoidal cycle. To calculate the Synchronization Index (SI), we first converted the seizure phases to their complex exponential representation [18]. The mean resultant vector was computed as

$$R = \frac{1}{N} \sum_{j=1}^{N} e^{i\theta_j}, \tag{2}$$

where θ_j represents the phase of each seizure and N is the total number of seizures. The SI is then defined as the magnitude of the mean resultant vector,

$$SI = |R|. \tag{3}$$

A higher SI value (closer to 1) indicates a stronger synchronization of seizures within the periodic cycle, while a lower value (closer to 0) indicates less synchronization. We reported the SI for each rat, along with the identified periods from the sinusoidal fits as performed by [18].

To assess the relationship between seizure phases within cycles and seizure durations, we calculated the circular-linear correlation. In this analysis, seizure phases represent circular data, while seizure durations are linear data. The circular-linear correlation coefficient is computed as

$$r = \frac{\sum_{j=1}^{N} (D_j - \bar{D}) \sin(\theta_j - \bar{\theta})}{\sqrt{\sum_{j=1}^{N} (D_j - \bar{D})^2} \cdot \sqrt{\sum_{j=1}^{N} \sin^2(\theta_j - \bar{\theta})}}, \tag{4}$$

where D_j is the duration of the j-th seizure, θ_j is its corresponding phase, $\bar{D}$ is the mean seizure duration, and $\bar{\theta}$ is the mean phase. This correlation coefficient quantifies the degree of association between seizure phases within cycle and duration of seizures, ranging from -1 (perfect negative correlation) to 1 (perfect positive correlation), with 0 indicating no correlation.

To evaluate the statistical significance of the circular-linear correlation, we performed a permutation test. This test assesses whether the observed correlation could have arisen by chance. We calculated the observed circular-linear correlation coefficient, r_{obs}, using the actual data. We then randomly shuffled the seizure durations while keeping the phases unchanged. For each permutation, we recalculated the circular-linear correlation coefficient, generating a distribution of correlation coefficients under the null hypothesis (i.e., that there is no relationship between seizure phases and durations. This process was repeated 100,000 times to build a distribution of permuted correlation coefficients. The p-value was determined by comparing r_{obs} to

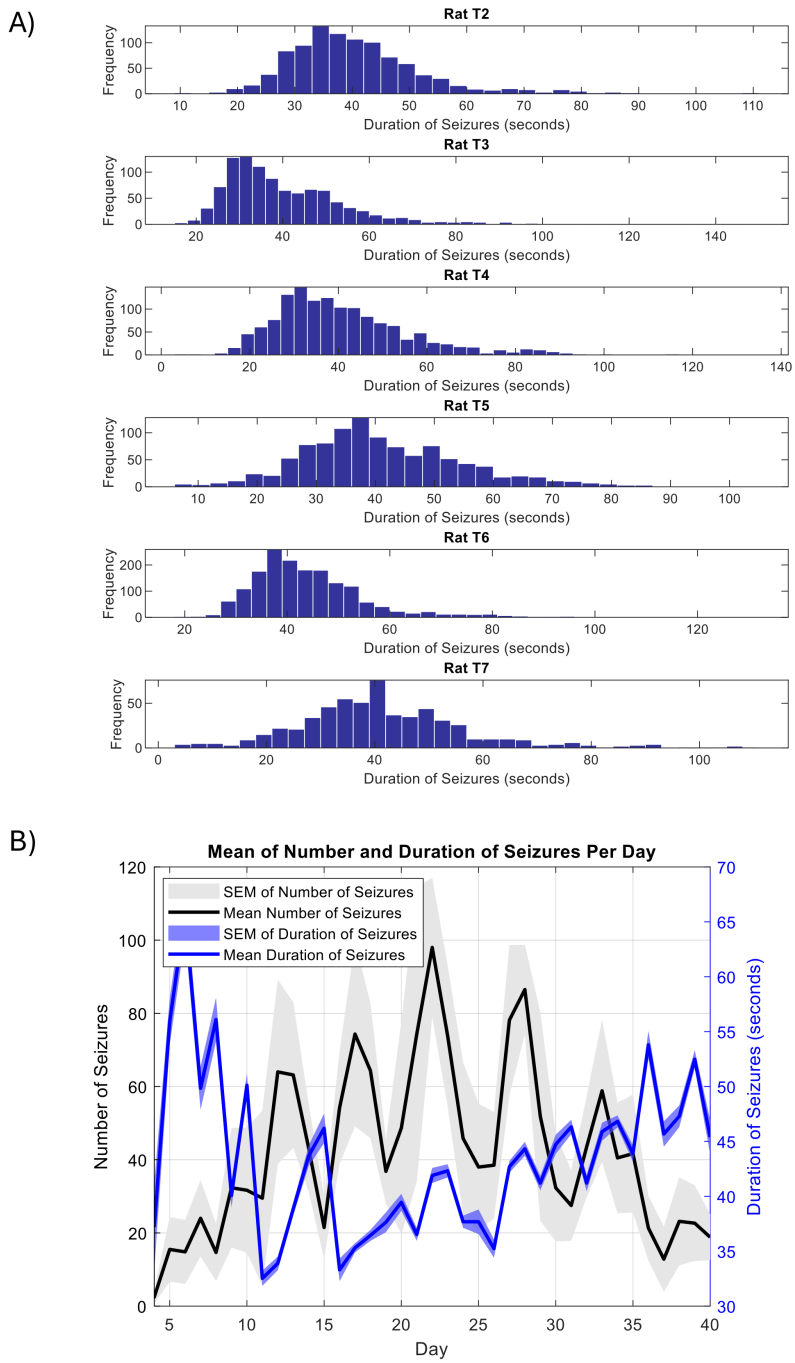


Fig 2. A) Histogram of seizure durations across six rats, showing the frequency of seizure durations regardless of whether they occurred during on or off periods. The x-axis denotes the duration of seizures in seconds, while the y-axis represents the frequency of seizures within each duration bin. **B) The mean number and duration of seizures per day over a 40-day period.** The black line represents the mean number of seizures per day, with the corresponding shaded gray area indicating the standard error of the mean (SEM) for seizure counts. The blue line represents the mean duration of seizures (in seconds), with the shaded blue area representing the SEM of seizure duration. The left y-axis corresponds to the number of seizures, while the right y-axis corresponds to seizure duration in seconds.

the distribution of permuted correlationsr_{per}. Specifically, the p-value was calculated as the proportion of permuted correlations that were as extreme as or more extreme than the observed correlation,

$$p = \frac{\text{number of } |r_{\text{per}}| \geq |r_{\text{obs}}| + 1}{\text{number of permutations} + 1}. \tag{5}$$

To correct for multiple comparisons across rats, the calculated p-value was multiplied by the number of comparisons (i.e., the number of rats), ensuring that the results were adjusted for family-wise error rates. The permutation test ensures a robust assessment of the statistical significance of the circular-linear correlation, with p-values less than 0.05 considered significant. As a final step, the data was divided into 15-day segments (360 hours each) with a 359-hour overlap to better demonstrate changes over time on the cycles as the seizures waxed and waned. Periodic patterns were analyzed over time, and significant cycle within each segment were identified using the method described above.

Is seizure duration determined by the cycle or the time interval between seizures?

We investigated the correlation between the time before a seizure and the duration of the seizure. Additionally, we analyzed whether seizure duration influences the time until the next seizure. Beyond these analyses, we conducted a survival analysis to explore whether the time before a seizure affects the probability of the next seizure occurring (in line with the classical *seizure begets seizure* theory [14]) and whether seizure duration influences the likelihood of a subsequent seizure.

Survival analysis was performed using seizure data from six rats (T2-T7). Two primary variables were used for the analysis: seizure duration and time before seizures (time elapsed since the previous seizure). For each rat, the time to the next seizure was used as the survival time. The survival time was defined as the time between consecutive seizures, while the time before each seizure and duration of seizure were used as two covariates. A Cox proportional hazards model was fitted separately for each rat using the seizure duration and time before seizure as covariates [13]. The `coxphfit` function in MATLAB was used to fit the model, with the formula,

$$\lambda(t) = \lambda_0(t) \exp(\beta_1 \cdot D + \beta_2 \cdot T), \tag{6}$$

where D is the duration of the seizure, T is the time before the seizure, $\lambda(t)$ is the hazard function, $\lambda_0(t)$ is the baseline hazard, β_1 is the coefficient for seizure duration, and β_2 is the coefficient for the time before the seizure.

The values of β_1 and β_2 are estimated from the data using maximum likelihood estimation. The hazard ratios (HR) were calculated by exponentiating the model coefficients, and 95% confidence intervals (CI) were computed for the hazard ratios using the standard errors from the model.

The correlation between dominant frequency power and seizure duration

We also explored whether there is a correlation between the power in the dominant frequency and the duration of seizures. This analysis provides insights into the factors that influence seizure duration and examines the possibility of cycles in EEG power at certain frequencies. To analyze the dominant frequency of the EEG during seizures in probing off periods, logarithmic frequency bands were defined from 1 Hz to 130 Hz. A total of 10 logarithmically spaced frequency bands were created to capture the frequency content of the EEG. For each seizure, the power spectral density (PSD) was computed using the Welch method [20]. The dominant frequency for each seizure was defined as the frequency band with the maximum power.

Results

Periodic patterns and phase-locked rhythms in seizure durations

The analysis of seizure data for six rats over a period of 40 days revealed distinct periodic patterns for seizure duration of each rat. Fig 3A shows the raster plot of the seizure duration and the best fitted sinusoid to the data. We assumed that the cycle frequencies were fixed over the whole recording periods. The results demonstrate clear cyclical patterns in seizure durations across all six rats (T2–T7) over the 40-day recording period. For each rat, the average hourly seizure durations (blue dots) fluctuate over time, and the fitted sinusoidal curves (cyan lines) capture these periodic changes. The periods of the fitted sinusoidal functions vary across the rats, ranging from 4.1 days (Rat T2) to 8.6 days (Rat T5), indicating individual variability in the seizure cycles. The fitted sinusoidal curves highlight the presence of rhythmic fluctuations in seizure durations, suggesting a temporal structure in seizure occurrence that may be tied to underlying physiological or environmental rhythms.

Fig 3B presents the polar histograms of the relationship between seizure durations and the phases of the identified cycles. The results indicate a clear relationship between the phase of the identified cycles and the durations of seizures across all six rats (T2–T7). The clustering of durations of seizures in a specific phase interval implies that seizure durations are not random but follow a predictable pattern. The Synchronization Index (SI) values, which range from 0.14 to 0.51, indicate varying degrees of phase locking, with higher SI values reflecting stronger clustering of seizures at specific phases of the cycle. Rats T4 and T7 exhibit the highest SI values (0.32 and 0.51, respectively), implying a stronger synchronization between seizure durations and the cycle phases. In contrast, Rat T6 shows the weakest phase locking, with an SI value of 0.14. The circular-linear correlations between the phase of the cycles and seizure durations are significant in most rats, as evidenced by the low p-values. These significant correlations suggest that seizure durations are non-randomly distributed across different phases of the cycle, indicating that seizures tend to occur more frequently or with longer durations during certain phases of the cycle. These results highlight a cyclical, rhythmic influence on seizure durations, with substantial individual variability in the strength of phase locking across the rats.

The Tetanus Toxin model of epilepsy is characterized by fluctuating activity over the weeks of recording, with seizure properties evolving over time [7]. To examine these temporal changes, the data was divided into 360-hour (15-day) segments, with each segment advancing by 1 hour. This method enabled the analysis of seizure cycles across various time windows during the 40-day recording period. A sinusoidal curve was fitted to the data for each segment to capture periodic patterns. Fig 4 illustrates the periods of cycles in seizure durations over 40 days of recording. The results reveal dynamic changes in seizure cycles over time for all six rats (T2–T7). In each subplot, significant periods of cyclical seizure durations are identified. These periods are represented by horizontal lines, with their color indicating the significant of correlations between seizure phases and duration of seizures across overlapping 15-day segments. The figure reveals that the periodicity of seizure durations changes over time, with different rats exhibiting varying patterns and strengths of significant cycles across the recording period. Rat T7 shows a relatively stable cyclic pattern throughout the entire recording period, with significant cycles consistently detected, indicating a more consistent rhythm. In contrast, the cycles in other rats fluctuate more frequently, with more variability in the detected periods and strengths of correlations over time. The presence of strong correlations (low p-values) suggests that seizure durations follow rhythmic, cyclical patterns during these periods.

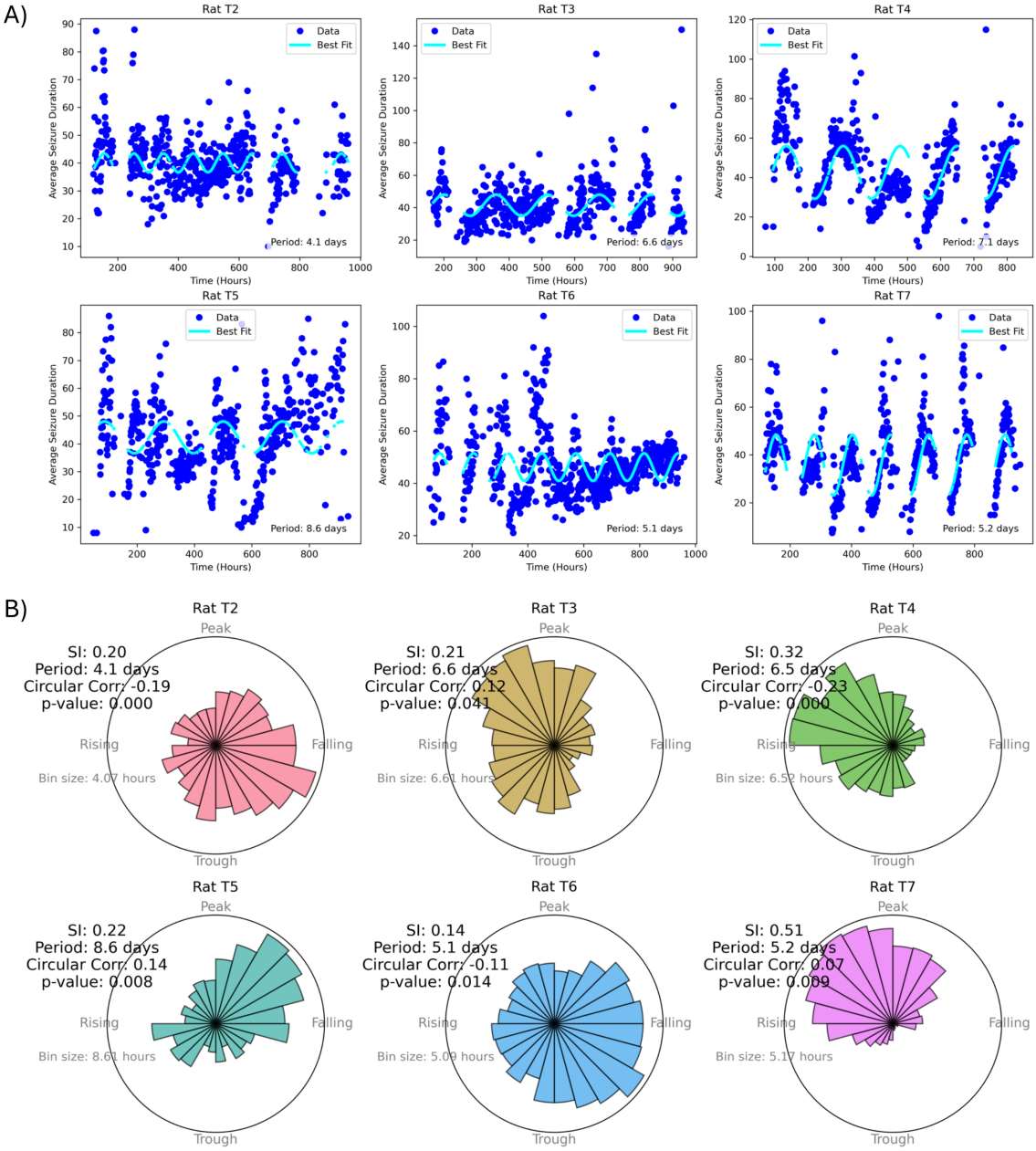


Fig 3. A) Raster plots of seizure durations over 40 days (960 hours) of recording for six rats (T2–T7). Each blue dot represents the average seizure duration recorded over a one-hour interval. The cyan curve represents the best-fit sinusoidal function to the data, capturing periodic patterns in seizure durations. The period of the fitted sinusoidal is indicated for each rat, revealing distinct cyclical patterns in seizure durations. **B) Polar histograms displaying the relationship between seizure durations and the phases of the identified cycles.** Each subplot represents a different rat (T2 through T7). Each radial bar represents the distribution of seizure duration within different phases of the cycle. The predominant period and the Synchronization Index (SI), Eq. (3), are annotated on each plot, with higher SI values indicating stronger phase locking. Circular-linear correlations between the phase of the cycles and seizure durations are provided, with significant p-values indicating that seizure durations are non-randomly distributed across the phases in most rats.

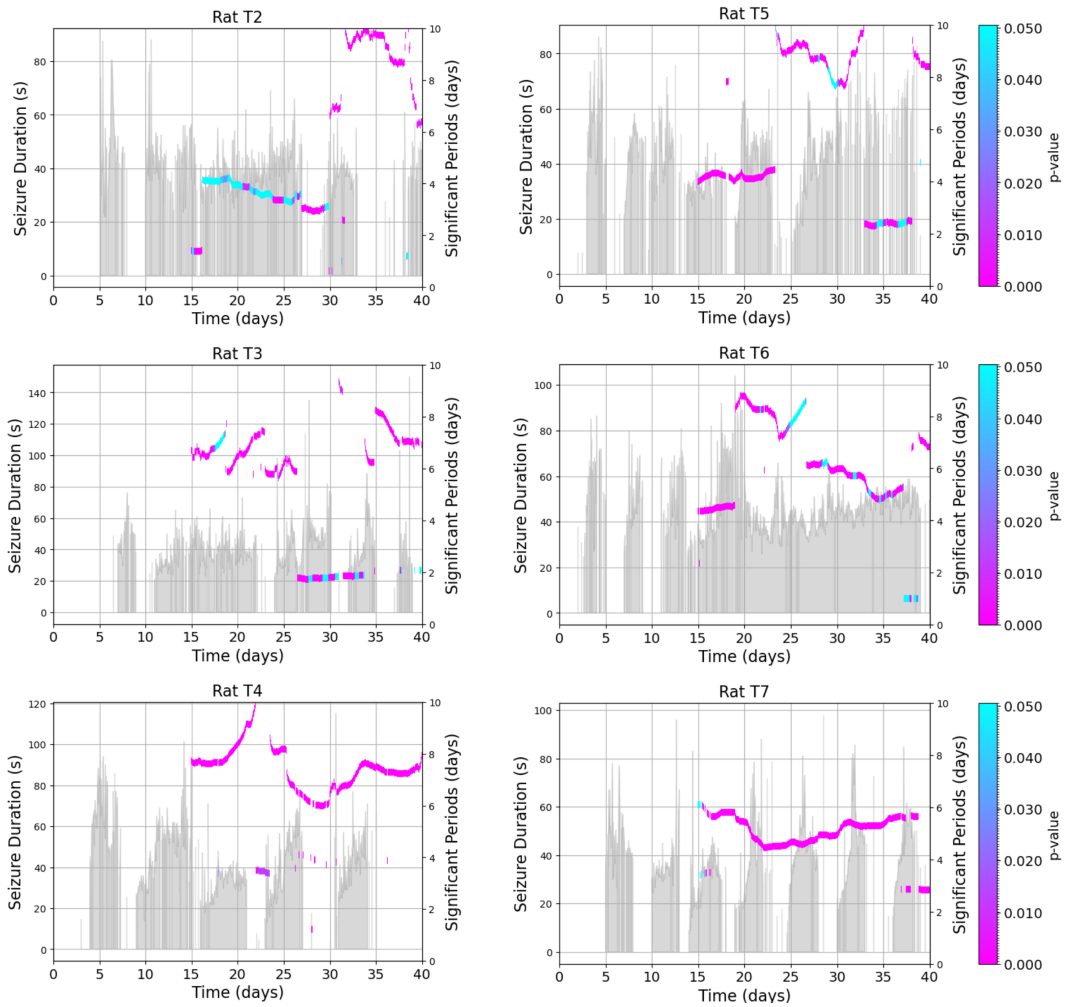


Fig 4. Changes in seizure cycles over time for six rats (T2–T7). Each subplot displays the significant periods (in days) of cyclical changes in seizure durations as horizontal lines, plotted against time (in days) across multiple segments. Each segment lasts 360 hours (15 days) and overlaps with the next segment by 359 hours, providing continuous monitoring of cyclical patterns. The color of each line represents the p-value of the correlation between seizure durations and the phase of the cycle, with the color bar on the right of the figure indicating the p-value scale. High p-values are represented in blue, while low p-values (indicating more significant correlations) are shown in purple. The gray histogram on the left axis of each subplot shows the hourly seizure duration over the 40 days of recording, providing context for the duration of seizures throughout the study period.

Is there a relationship between the time interval between seizures and the duration of seizures?

The results suggest that there is a relationship between the time intervals separating seizures (only in extreme cases where the interval is either very short or very long) and the durations of seizures. Extreme cases were selected for this analysis, comparing very long intervals (greater than or equal to 1 day) and very short intervals (less than 1.5 minutes) between seizures. The threshold of 1.5 minutes was chosen to ensure a relatively equal number of data points in comparison to the longer time intervals (greater than or equal to 1 day).

Seizures that occur after a long interval ($\geq$ 1 day) tend to have shorter durations, with a median seizure duration of approximately 20-25 seconds. When the next seizure occurs after a long interval ($\geq$ 1 day), the seizure duration appear to be longer, with a median duration of around 40-45 seconds. Seizures occurring after a very short interval (less than 1.5 minutes) are relatively shorter, with median durations around 35 seconds. Seizures that are followed by another seizure within a short interval (less than 1.5 minutes) tend to be shorter as well, with median durations of 35 seconds (Fig 5A).

The results of the Cox proportional hazards model analysis for seizure duration and time before seizure across six rats (T2 through T7) are shown in Fig 5B. The left panel presents the hazard ratios for seizure duration, indicating if longer seizure durations are associated with a reduced risk of subsequent seizures. The hazard ratios for seizure duration across all rats are slightly below 1, suggesting that an increase in seizure duration is associated with a modestly reduced risk of a subsequent seizure. In the right panel, the hazard ratios for the time before the previous seizure are depicted. These hazard ratios are close to 1 but exhibit some variability across rats. For most rats, the time before the previous seizure has no effect on the risk of the next seizure. In both analyses, the hazard ratios remain close to 1, indicating that neither seizure duration nor time before seizure has a strong influence on the likelihood of subsequent seizures.

Dominant frequency and the duration of seizures

We investigated whether there is a correlation between seizure duration and the power of the dominant EEG frequency during the probing off period. The results, displayed in Fig 6A, indicate that there is a statistically significant correlation between these two variables across all six rats (T2 to T7). All rats exhibit moderate to strong positive correlations between seizure duration and dominant EEG power. This suggests that, for these rats, longer seizures tend to be associated with higher dominant EEG power.

Looking at the distribution of dominant frequencies for each rat (T2 through T7) at Fig 6B, we can observe the range of frequencies in relation to known EEG frequency bands. The dominant frequencies in rat T2 are mostly distributed in the alpha range, with the majority of the data clustered between 5-15 Hz. This indicates that many seizures in this rat are associated with activity in the alpha band. Similar to T2, Rat T3 exhibits a broad distribution of frequencies, but with a slightly higher range, including both alpha and low beta frequencies (13-20 Hz). There is a greater spread in the data, though the frequencies still tend to be within or just above the alpha range. The dominant frequencies for Rat T4 are mostly concentrated in the delta range (1-4 Hz), with very few instances exceeding the alpha range. This suggests that seizure activity in Rat T4 is more likely associated with lower-frequency EEG activity, potentially indicating different neural dynamics compared to other rats. The distribution of frequencies for Rat T5 is extending well into the alpha range and higher. While some frequencies fall into the theta (4-8 Hz) and delta ranges, there are significant occurrences of dominant frequencies in the alpha range, similar to Rats T2 and T3. The frequencies for Rat T6 are primarily concentrated in the alpha range (8-12 Hz) and theta range (4-8 Hz). The distribution for Rat T7 is focused at the lower end of the spectrum, with many values in the delta range, similar to Rat T4. This suggests seizure activity that is more associated with low-frequency oscillations.

Seizure durations during probing on periods compared to probing off periods

Fig 7 displays a histogram of seizure durations across different rats that are occurred during the probing on periods compared to probing off periods. The results indicate notable differences in the distribution of seizure durations between the probing on and off periods across all six rats (T2–T7). The histograms show a higher frequency of seizures during the on periods compared to the off. The results in Fig 7b show distinct differences in seizure durations between probing on periods and probing off periods for several rats. Rats

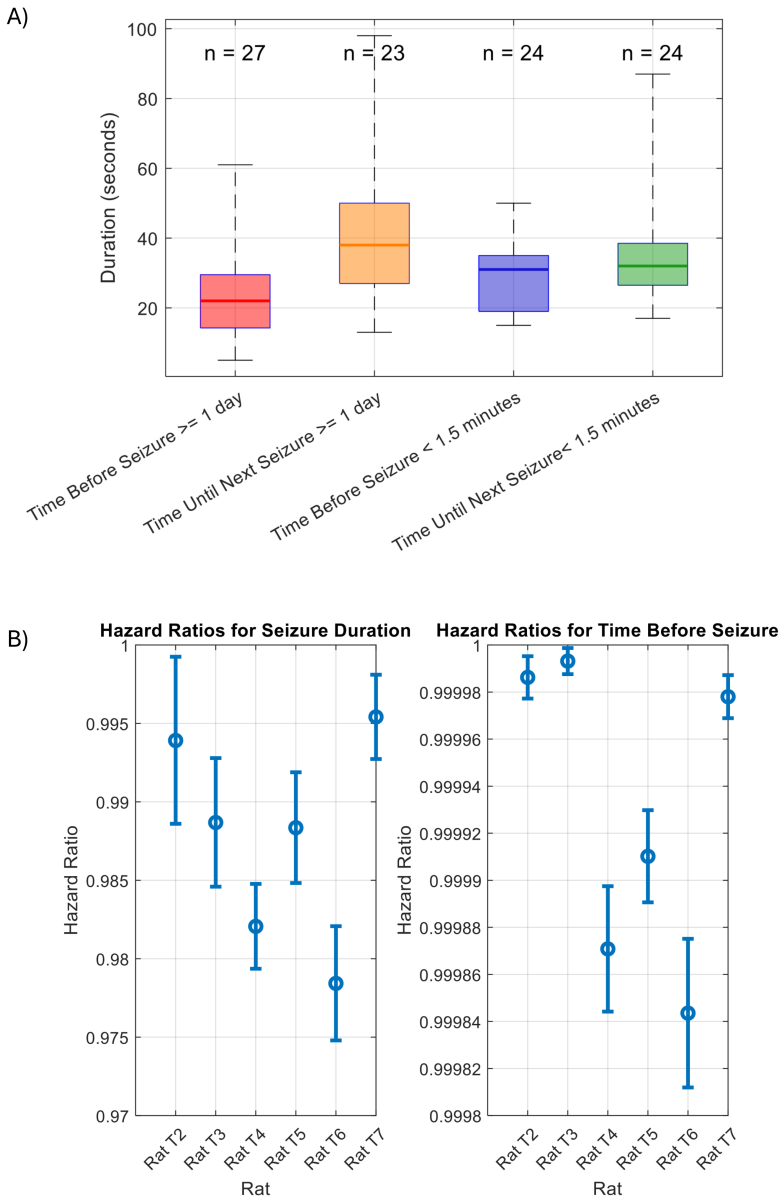
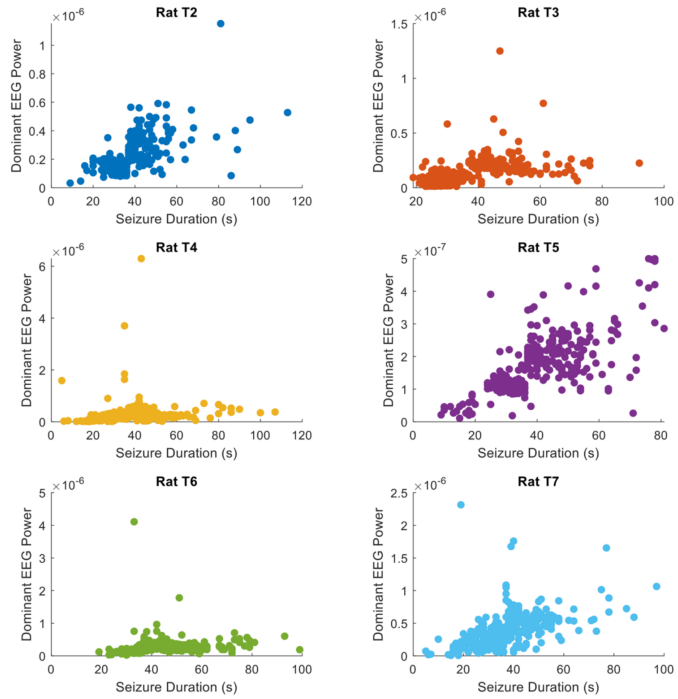


Fig 5. A) Boxplot illustrating the relationship between the time interval separating seizures and the duration of seizures. Four extreme conditions are shown: time before the previous seizure is greater than 1 day, time until the next seizure is greater than 1 day, time before the previous seizure is less than 1.5 minutes, and time until the next seizure is less than 1.5 minutes. Each box represents the distribution of seizure durations (in seconds) for the respective condition, with the horizontal line in the box indicating the median duration. The number of seizures (n) for each condition is displayed above the box. This comparison explores whether the time interval between seizures influences the duration of the subsequent seizure. **B) Hazard ratios for seizure duration and time before seizure across rats.** The plot on the left shows the hazard ratios for the effect of seizure duration on the risk of subsequent seizures in each rat, with confidence intervals. The plot on the right shows the hazard ratios for the effect of time before the previous seizure on the risk of subsequent seizures. Data is presented for rats T2 through T7, with hazard ratios below 1 indicating a reduced risk of seizure occurrence as the covariates increase. Error bars represent 95% confidence intervals.

A)



Rat	Correlation Coeff	p value
T2	0.589	<0.0001
T3	0.445	<0.0001
T4	0.139	<0.0036
T5	0.689	<0.0001
T6	0.189	0.0006
T7	0.547	<0.0001

B)

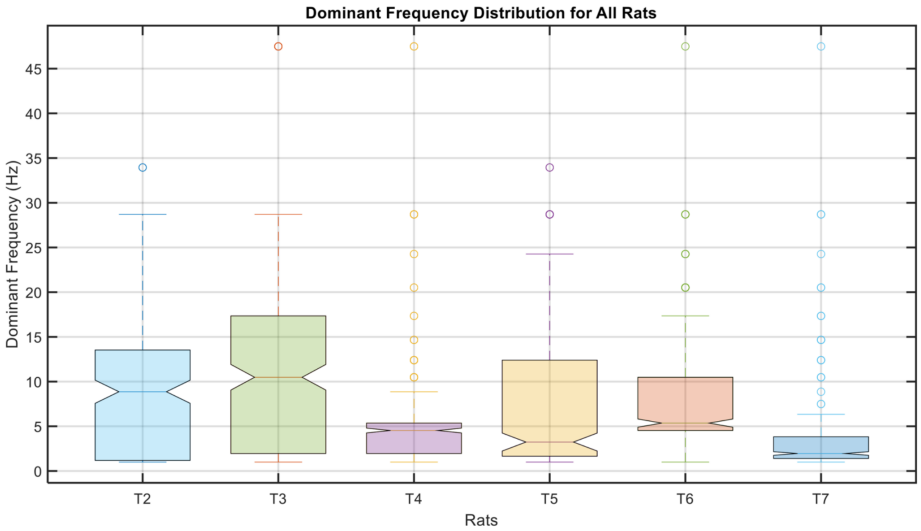


Fig 6. Relationship between seizure duration and power of dominant frequency during the probing off period. A) Scatter plots display the correlation between seizure duration and power of dominant frequency for six rats (T2 to T7). Each plot represents the individual relationship between seizure duration and the dominant EEG power recorded during that seizure. The table on the right summarizes the correlation coefficients and corresponding p-values for each rat. B) Distribution of dominant EEG frequencies for all rats. The notched box plots display the distribution of the dominant EEG frequencies (in Hz) for each rat (T2 through T7) during seizures. The notches indicate the confidence interval around the median, and the whiskers show the range of the data. Outliers are represented by individual points beyond the whiskers. These dominant frequencies were found to have strong correlations with seizure duration, as shown in Fig 6A.

T2, T3, T4, and T7 exhibit significant differences in seizure durations, as indicated by p-values below 0.05. In these cases, seizures during the on periods tend to have longer durations compared to those during off periods.

Data availability statement

Data are available upon reasonable request from the corresponding authors. Code is available on Github (https://github.com/ParvinZE/Cycles-in-Epilepsy).

Discussion

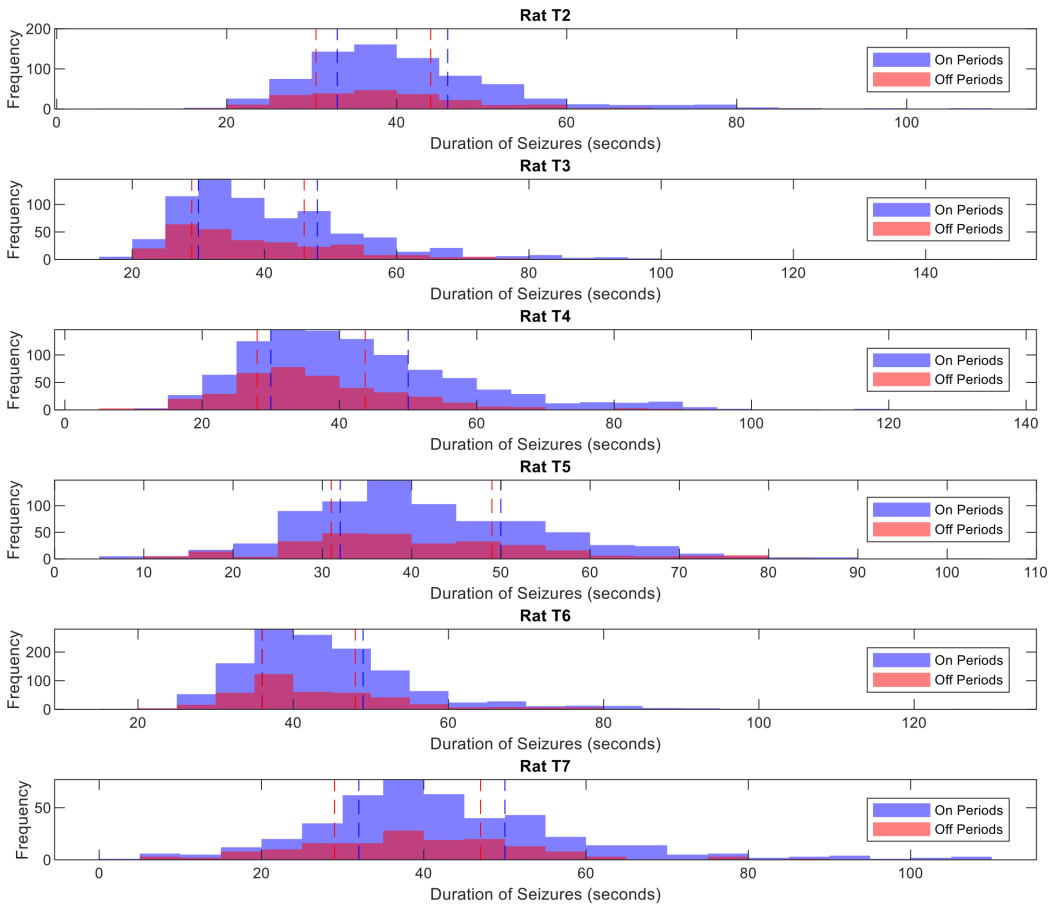
In this study, we explored the factors that could influence the duration of seizures, aiming to better understand what controls the severity of seizures. Specifically, we investigated the presence of rhythmic patterns in seizure duration and examined whether the interval between seizures affects the duration of the next seizure. Through a comprehensive analysis of seizure data from six rats, we identified several key insights into the temporal dynamics of seizure duration and the potential factors contributing to its variability.

Cyclical patterns in seizure duration

The results of this study highlight the presence of significant cyclical patterns in seizure durations across six rats (T2–T7) over the 40-day recording period. The sinusoidal fits to the seizure duration data captured clear rhythmic fluctuations for each rat, suggesting that seizure durations follow predictable temporal structures. These findings support the idea that seizure duration may be influenced by underlying physiological or environmental rhythms that manifest as distinct cycles. While all rats exhibited rhythmic patterns, the strength and regularity of these cycles varied, with periods ranging from 4.1 days in rat T2 to 8.6 days in rat T5, highlighting the individual variability in the temporal dynamics of seizure durations. Despite these differences in periodicity, the presence of clear cyclical patterns in all six rats suggests that seizure durations are not randomly distributed but are instead governed by time-based processes.

The polar histograms and Synchronization Index (SI) analyses further supported these observations, revealing significant relationships between seizure durations and the phases of identified cycles. The clustering of seizure durations at specific phases of the cycle, particularly in rats with higher SI values (T4 and T7), suggests that seizure timing and duration are influenced by underlying cyclic rhythms. This phase locking of seizure durations reflects a non-random distribution of seizures, reinforcing the idea that seizure occurrence and duration are governed by predictable temporal dynamics. The circular-linear correlations between seizure durations and the phases of the identified cycles further reinforce the notion of non-random patterns in seizure activity. These correlations are significant in all rats, indicating that seizure durations are not uniformly distributed across the cycle phases. Instead, certain phases of the cycle correspond to longer or shorter seizure durations, suggesting a predictable relationship between seizure timing and seizure duration.

A)



B)

Rat	p value
T2	0.001
T3	0.004
T4	<0.001
T5	0.696
T6	0.061
T7	0.007

Fig 7. Comparing seizure durations during the on and off periods. a) The histograms of seizure duration during the on and off periods.The blue bars represent the distribution of seizure durations during the probing on periods, while the red bars represent those during the probing off periods. Dashed vertical lines indicate the low (left) and high (right) quantiles for each period. b) The p-values in the table correspond to statistical tests comparing seizure durations between on and off periods for each rat, with significant differences observed in most rats (T2, T3, T4, and T7), as indicated by p-values less than 0.05.

Temporal dynamics of seizure duration

The Tetanus Toxin model of epilepsy is known for its evolving seizure activity over time. The dynamic nature of seizure cycles is further underscored by the analysis of changing seizure patterns over time. The use of overlapping time segments allowed for the detection of evolving cyclical patterns throughout the 40-day recording period. In rats like T7, where significant cycles were consistently detected, there appears to be a more stable rhythmic influence on seizure durations over time. In contrast, the more variable cycles observed in other rats highlight the dynamic nature of seizure patterns. Despite these variations, the results also reveal a general decreasing pattern in the periods of cycles during the mid-recording phase, particularly between day 20 and day 30 for Rats T2, T4, and T6. In these rats, the periods of significant seizure duration cycles become shorter over this time window, indicating a shift in the underlying rhythmic processes.

We compared these results with the dynamics of the cycles in the occurrence of seizures studied by [22]. There are some similarities between the evolving patterns of the periods of cycles in the number of seizures and the duration of seizures across the rats studied. For instance, in rat T2, there is a general reducing pattern in the periods of cycles from day 15 to day 30 in both the number of seizures and seizure durations. This reduction in period length across both metrics suggests the possibility of a shared underlying rhythm that affects both the frequency of seizures and their duration over this specific time window. Similarly, rat T7 shows a stable periodicity in both seizure number and duration throughout the entire 40-day period. The consistent cycles in both figures suggest a strong, predictable rhythm influencing both aspects of seizure activity, indicating that the temporal dynamics of seizure occurrence and duration are tightly linked in this rat. In rat T4, a distinct pattern emerges between day 30 and day 40, where the identified period fluctuates slowly around 7 days in both the seizure number and seizure duration.

These specific examples illustrate that the cycles governing seizure frequency and duration are synchronized. However, the degree of similarity between seizure number and duration cycles varies across the rats, indicating individual variability in the rhythmicity of seizures. This underscores the importance of further investigating these temporal patterns to improve seizure forecasting and develop personalized epilepsy management strategies.

The relationship between seizure duration and inter-seizure intervals

The relationship between the time interval separating seizures and the duration of seizures reveals interesting patterns, particularly in extreme cases where the interval is either very short (less than 1.5 minutes) or very long (greater than or equal to 1 day). The results suggest a potential link between the duration of seizures and both the time before and the time until the next seizure, though this effect is only pronounced in these extreme cases. Seizures that occur after a long interval of greater than or equal to 1 day tend to have shorter durations, with a median duration of 20–25 seconds. This pattern suggests that longer recovery periods between seizures may result in briefer seizure events. Conversely, when seizure durations are relatively long, there is often a longer interval until the next seizure, with the median duration of these longer seizures being around 40–45 seconds. This relationship is particularly evident in extreme cases where the time until the next seizure exceeds 1 day, indicating that longer seizure events may be associated with greater spacing between seizures in these instances. This is in agreement with the study by Ferastraoaru et al. (2016) on humans with focal epilepsy, which showed that the terminal seizure (the last seizure in a cluster) tends to be longer, similar in duration to isolated seizures [10].

In order to further investigate the relationship between the time interval separating seizures and seizure duration, we conducted a survival analysis using the Cox proportional hazards model. This analysis allowed us to assess whether longer seizure durations or the time before the previous seizure influence the risk of a

subsequent seizure. The results of this analysis, presented in Fig 5B, show the hazard ratios for both seizure duration (left panel) and the time before the previous seizure (right panel) across six rats (T2 through T7). The hazard ratios for seizure duration are all slightly below 1, suggesting that longer seizure durations are modestly associated with a reduced risk of a subsequent seizure. This pattern implies that longer seizures may provide some protective effect, potentially increasing the interval until the next seizure. However, this effect is relatively small, as the hazard ratios remain close to 1.

Taken together, these results suggest that neither seizure duration nor the time before the previous seizure has a strong influence on the timing of subsequent seizures. While longer seizure durations may slightly reduce the risk of another seizure, the overall impact is minimal. These findings highlight the complex nature of seizure dynamics and suggest that factors other than seizure duration and interseizure intervals, such as the dynamic cycles, play a more critical role in determining seizure timing. The study by Cook et al. (2016) [6] conducted on human subjects with focal epilepsy also showed that no linear association between seizure intervals and durations, suggesting that a longer buildup (seizure interval) does not necessarily result in a proportionally longer seizure duration (discharge). However, in two subjects, the study was able to investigate a logistic relationship between seizure intervals and durations, which revealed that short-duration seizures were more likely to follow short intervals, and longer intervals were more likely to be followed by longer seizures [6].

Correlation between seizure duration and dominant EEG frequency: insights into neural oscillations and stability of seizure cycles

The relationship between seizure duration and the power of the dominant EEG frequency was explored to determine if longer seizures are associated with higher EEG power during the probing off period. The results, as shown in Fig 6A, reveal a statistically significant positive correlation between seizure duration and dominant EEG power across all six rats (T2 to T7). This consistent pattern of moderate to strong correlations suggests that, in these rats, longer seizures tend to be linked with increased dominant EEG power, indicating a possible interaction between seizure intensity and neural oscillations. For example, rat T5 exhibited the strongest correlation ($r = 0.689$), while Rat T4 showed the weakest ($r = 0.139$), though still statistically significant. These findings imply that seizure dynamics, particularly duration, may be closely tied to the dominant EEG power. In general, this suggests that, as seizures last longer, the power of the dominant EEG frequency during those events increases, possibly reflecting greater neural involvement or heightened brain activity during prolonged seizures.

The distribution of dominant frequencies across the six rats, displayed in Fig 6B, provides additional context to the correlations observed. The dominant frequencies for most rats tend to fall within known EEG frequency bands, though there are individual variations. For example, rats T2, T3, T5, and T6 primarily exhibit dominant frequencies in the alpha range (8-12 Hz), indicating that their seizures are associated with higher-frequency brain activity. This could reflect more synchronous neural firing patterns during these seizures. In contrast, rats T4 and T7 have dominant frequencies that are concentrated in the delta range (1-4 Hz), which is characteristic of slower, large-scale neural oscillations. Interestingly, these two rats also display more stable periods of cycles during the entire recording compared to the other rats and have a stronger Synchronization Index (SI) with the identified periods from sinusoidal fitting. This suggests a potential relationship between the dominance of delta-range frequencies and the stability of the seizure cycles. The lower-frequency oscillations in the delta range may reflect a more regular, rhythmic neural activity, which could result in more stable cyclic patterns observed in rats T4 and T7. The differences in frequency distribution between rats suggest distinct neural dynamics underlying their seizure activity. For instance, the delta-dominated seizures in rats T4 and T7 may involve different neural circuits or states compared to the alpha-dominated seizures in other rats.

Several studies have examined the changes in power of the dominant frequency during ictal periods. For example, Bragin et al. (2005) [2] showed that in chronic seizure models using rats, 70% of seizures began with an increase in the frequency of interictal EEG spikes (hypersynchronous type), which evolved into low-voltage fast patterns [2]. Fisher et al. (1992) [1] demonstrated a significant increase in spectral power above 35 Hz during electrodecremental events at the start of seizures in patients with partial seizures, with power increasing up to fivefold in the 80-120 Hz portion of the spectrum [1]. In the study by Khosravani et al. (2009) [19], low-frequency oscillations (0–100 Hz) were found to increase in absolute magnitude during seizures. Furthermore, while high-frequency oscillations (HFOs) tend to be of low amplitude, they often override the larger, slower frequency waveforms that dominate the early phases of electrographic seizures, indicating a dynamic interplay between these frequency ranges during seizure activity [19]. While these studies provide valuable insight into the changes in dominant frequency power during seizures, they do not directly explore the relationship between seizure duration and dominant EEG power. Our study focuses on this relationship, providing novel insights into how dominant EEG power might influence seizure length.

Probing increases seizure likelihood and prolongs seizure duration in rats

The results presented in Fig 7 highlight the effect of probing on seizure occurrence and duration. Across all six rats (T2–T7), there is a higher frequency of seizures during the probing on periods compared to the off periods, suggesting that the probing stimulus used in the experiments increased the likelihood of seizures. This observation aligns with the notion that external stimulation, even at low levels, can act as a trigger for seizure activity, possibly lowering the threshold for seizure initiation. Frauscher et al. (2023) emphasized that stimulation can significantly impact brain dynamics, triggering seizures in some cases to aid in seizure onset localization and to provide insight into epileptic network connectivity [11].

Additionally, our results indicate significant differences in seizure durations between probing-on and probing-off periods in several rats, particularly in T2, T3, T4, and T7, with longer seizure durations observed during the probing-on periods ($p < 0.05$). This suggests that probing not only increases seizure frequency but may also enhance seizure intensity, potentially through the stimulation's cumulative effect on neural activity.

Clinical implications

Understanding the cyclic patterns in seizure duration offers valuable insights into the underlying neurophysiological sources of epilepsy and provides a basis for designing targeted interventions to control seizure severity. The discovery of rhythmic fluctuations in seizure duration suggests that epileptic activity is not purely random but may be influenced by intrinsic or extrinsic cycles, potentially linked to circadian rhythms, neurochemical fluctuations, or underlying neural network dynamics. By identifying these cycles, we can gain a clearer picture of the factors that drive seizure activity and develop strategies to mitigate its impact.

The presence of rhythmicity in seizure duration could indicate specific oscillatory processes within the brain that contribute to seizure generation and propagation. For instance, if seizure duration follows predictable patterns tied to the brain's natural cycles, such as sleep-wake or hormone cycles, then interventions could be timed to periods of increased vulnerability or reduced threshold for prolonged seizures. This approach could help in developing therapies that are in sync with these cycles, either by introducing medication, neurostimulation, or other therapeutic techniques precisely when they are most needed or when the brain is most responsive to intervention.

Additionally, by understanding seizure duration cycles, clinicians and researchers could explore more

deeply the structural or functional network changes that influence these patterns. For example, prolonged seizures that follow particular cycles might be connected to heightened activity in specific neural circuits or regions. Targeting these circuits with individualized treatments, such as responsive neurostimulation, could help regulate seizure duration more effectively. Further, recognizing cycles in seizure duration allows for a proactive, rather than reactive, approach to epilepsy management, enabling personalized care strategies that reduce the intensity or duration of seizures based on anticipated changes in cycle phases.

Future directions

An exciting direction for future research involves the use of computational models to understand the neural circuitry underlying the observed cycles in both seizure frequency and duration. By simulating neural networks and brain circuits, computational models can help us explore the specific mechanisms that contribute to cyclic patterns in seizure activity. Such models could provide a virtual testing ground for hypotheses about the oscillatory behavior of neural circuits, enabling researchers to investigate how intrinsic rhythms, connectivity patterns, and external influences interact to shape seizure dynamics [8, 9, 23].

Computational models could incorporate external factors, such as circadian or hormonal cycles, to simulate how these systems might interact with brain circuits to influence seizure cycles. This could help us understand why certain times of day or physiological states are associated with increased seizure frequency or duration and guide the timing of interventions to align with the brain's natural rhythms. Moreover, models that simulate the impact of periodic or rhythmic interventions—such as targeted neurostimulation delivered in sync with identified cycles—could reveal optimized stimulation protocols aimed at modulating or disrupting seizure patterns more effectively. By advancing our understanding of these neural mechanisms, computational modeling could accelerate the development of innovative, rhythm-aware treatments aimed at mitigating seizure frequency and duration through targeted modulation of the underlying circuits. As these models become increasingly sophisticated and data-driven, they hold promise for transforming our approach to epilepsy management, paving the way for more effective, personalized care.

Conclusion

This study provides novel insights into the cyclical patterns governing seizure duration, emphasizing the presence of significant rhythmic fluctuations in seizure dynamics. Through detailed analysis of six rats over a 40-day recording period, we identified that seizure duration follows predictable temporal structures, with distinct periodicities varying across individuals. Additionally, this work explored the influence of inter-seizure intervals and dominant EEG power, offering a broader perspective on the factors that may modulate seizure severity. The finding that seizure durations align with specific phases within identified cycles, supported by Synchronization Index (SI) analysis, reinforces the notion that seizure activity is governed by underlying temporal dynamics rather than occurring randomly. These insights hold potential clinical implications, suggesting avenues for time-based therapeutic interventions and personalized epilepsy management.

Our results highlight that understanding rhythmic patterns in seizure duration could aid in identifying neural mechanisms that contribute to epileptic activity and influence seizure characteristics. By establishing links between seizure duration and specific EEG frequencies, as well as exploring the impact of probing, this study contributes to a growing understanding of seizure modulation in epilepsy research. Future work, including computational modeling of seizure cycles, may further clarify the neural circuitry behind these rhythms, leading to targeted approaches that mitigate seizure severity through informed, rhythm-aware interventions.

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