Dynamic Multiday Seizure Cycles in a Tetanus Toxin Rat Model of Epilepsy: Evolving Rhythms and Implications for Prediction

Parvin Zarei Eskikand[1*,2], 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

Epilepsy is characterized by recurrent, unpredictable seizures that impose significant challenges in daily management and treatment. One emerging area of interest is the identification of seizure cycles, including multiday patterns, which may offer insights into seizure prediction and treatment optimization. This study investigated multiday seizure cycles in a Tetanus Toxin (TT) rat model of epilepsy. Six TT-injected rats were observed over a 40-day period, with continuous EEG monitoring to record seizure events. Wavelet transform analysis revealed significant multiday cycles in seizure occurrences, with periods ranging from 4 to 7 days across different rats. Synchronization Index (SI) analysis demonstrated variable phase locking, with some rats showing strong synchronization of seizures with specific phases of the cycle. Importantly, the study revealed that these seizure cycles are dynamic and evolve over time, with some rats exhibiting shifts in cycle periods during the recording period. This suggests that the underlying neural mechanisms driving these cycles may change as the epileptic state progresses. The identification of stable and evolving multiday rhythms in seizure activity, independent of external factors, highlights a potential intrinsic biological basis for seizure timing. These findings offer promising avenues for improving seizure forecasting and designing personalized, timing-based therapeutic interventions in epilepsy. Future research should explore the underlying neural mechanisms and clinical applications of multiday seizure cycles.

Introduction

Epilepsy, a chronic neurological disorder characterized by recurrent seizures, affects millions worldwide, presenting a significant burden on individuals and healthcare systems. Despite advancements in treatment, many patients continue to experience unpredictable seizure occurrences, highlighting the complex and heterogeneous nature of the disease. One of the most challenging aspects of epilepsy is the apparent randomness of seizure occurrences, which significantly complicates the lives of patients. Understanding and studying the temporal patterns and cycles in epilepsy can provide valuable insights into seizure forecasting and also the underlying mechanisms of seizure generation and progression.

Multi-day cycles in epilepsy refer to recurrent patterns in seizure occurrence over extended periods, often displaying rhythmic variations in frequency and intensity. Understanding these patterns is crucial as they

hold potential implications for seizure prediction, treatment optimization, and ultimately, improving patient outcomes. By deciphering the temporal dynamics of epilepsy through multi-cycle analysis, researchers aim to uncover predictive biomarkers, refine therapeutic strategies tailored to individualized seizure patterns, and advance our understanding of the disease's pathophysiology. Recent research has increasingly recognized the importance of temporal patterns and cycles in epilepsy, beyond mere sporadic events [14, 15]. Over the past decade, the analysis of extensive EEG datasets has advanced significantly, revealing substantial evidence that epilepsy cycles occur at various timescales—such as circadian, multidien, and circannual. These cyclical patterns are widely observed in both human and animal studies of epilepsy, with evidence from sources like implantable devices, electronic seizure diaries, and wearable monitoring systems [1, 2, 4, 9, 12, 13, 18].

In this study, we focus on the Tetanus Toxin (TT) rat model of epilepsy to investigate the presence and characteristics of multiday cycles in seizure occurrences. The TT model, known for its robust and reproducible induction of chronic epilepsy, provides an excellent platform for studying the temporal dynamics of seizures. By analyzing long-term EEG recordings from this model, we aim to identify and characterize multiday cycles, providing insights into their potential mechanisms and implications for therapeutic interventions.

Materials and methods

Data

The data used in this study was obtained from a intra-hippocampal Tetanus Toxin (TT) rat model of epilepsy [5]. In brief, six rats received intra-hippocampal injections of TT, forming the TT group, while four control rats were injected with phosphate-buffered saline. Each rat had five stainless steel electrodes implanted into their skulls to allow for intracranial EEG recording. Approximately 1-2 weeks after the TT injection, the TT rats began experiencing spontaneous seizures. The number of daily seizures fluctuated over a span of about six weeks, as shown in Fig. 1. Around weeks 4 to 5 post-injection, the seizure frequency started to decline, eventually resulting in no detectable seizures. EEG data was continuously recorded at a sampling rate of 2048 Hz for 23 hours each day, with 1 hour allocated for daily maintenance and data backup. Of the original seven TT rats, six completed the study, as one died on Day 26.

Fig. S1 shows the distribution of seizure frequencies per hour over a period of 40 days for six rats. Some hours of the day show a drop in the number of seizures, and this pattern varies between different rats. Fig. 2 shows the number of seizures recorded on specific days from day 1 to day 40, as well as at particular hours of the day.

The experimental design involved periodic low-level electrical stimulation, referred to as "probing" [5]. Each probing-on phase consisted of delivering 100 biphasic pulses, with a pulse width of 0.5 ms and a current of 1.26 ± 0.024 mA per phase, spaced by inter-stimulus intervals of 3.01 s, lasting for approximately 5 minutes. This was followed by a 5 minute probing-off phase before the next probing-on session began. The study was conducted in compliance with ethical standards, receiving approval from the St. Vincent's Hospital Melbourne Animal Ethics Committee, in accordance with the "Australian Code for the Care and Use of Animals for Scientific Purposes, 8th Edition" (2013).

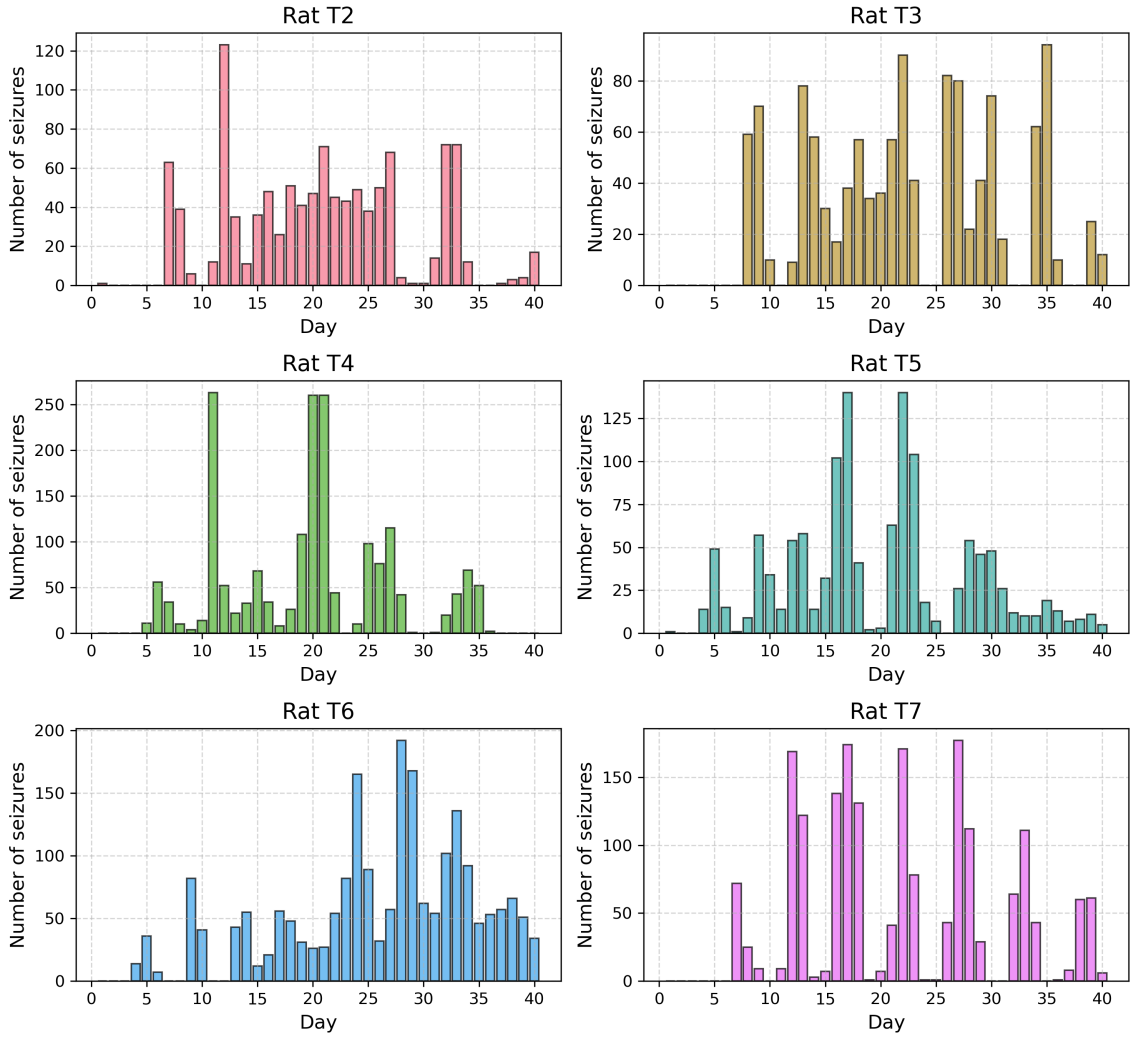

Fig 1. Seizure occurrences over time for TT rats. Each subplot represents data from one rat with the x-axis indicating days since the start of the recording. The y-axis is the total number of seizures that occurred on the specific day.

Temporal analysis of seizure occurrences

The number of daily seizures occurring per hour over a 40-day recording period for six rats was collected. This data was analyzed to identify underlying periodic patterns using Wavelet transforms and sinusoidal curve fitting [15]. We utilized the Continuous Wavelet Transform (CWT) to analyze the temporal patterns and multi-day cycles in seizure occurrences recorded over a span of 40 days. The dataset comprised hourly seizure counts across multiple rats, each represented as a time series. The CWT was applied using a Morlet wavelet, a well-suited wavelet for analyzing time series with transient signals [15]. This wavelet transformation facilitated the decomposition of the seizure count time series into its frequency components, revealing both localized and global power spectra. To identify significant frequency components corresponding to multi-day cycles, a range of frequencies spanning from 4 hours cycles per day up to 240 hours (10 days) cycles was

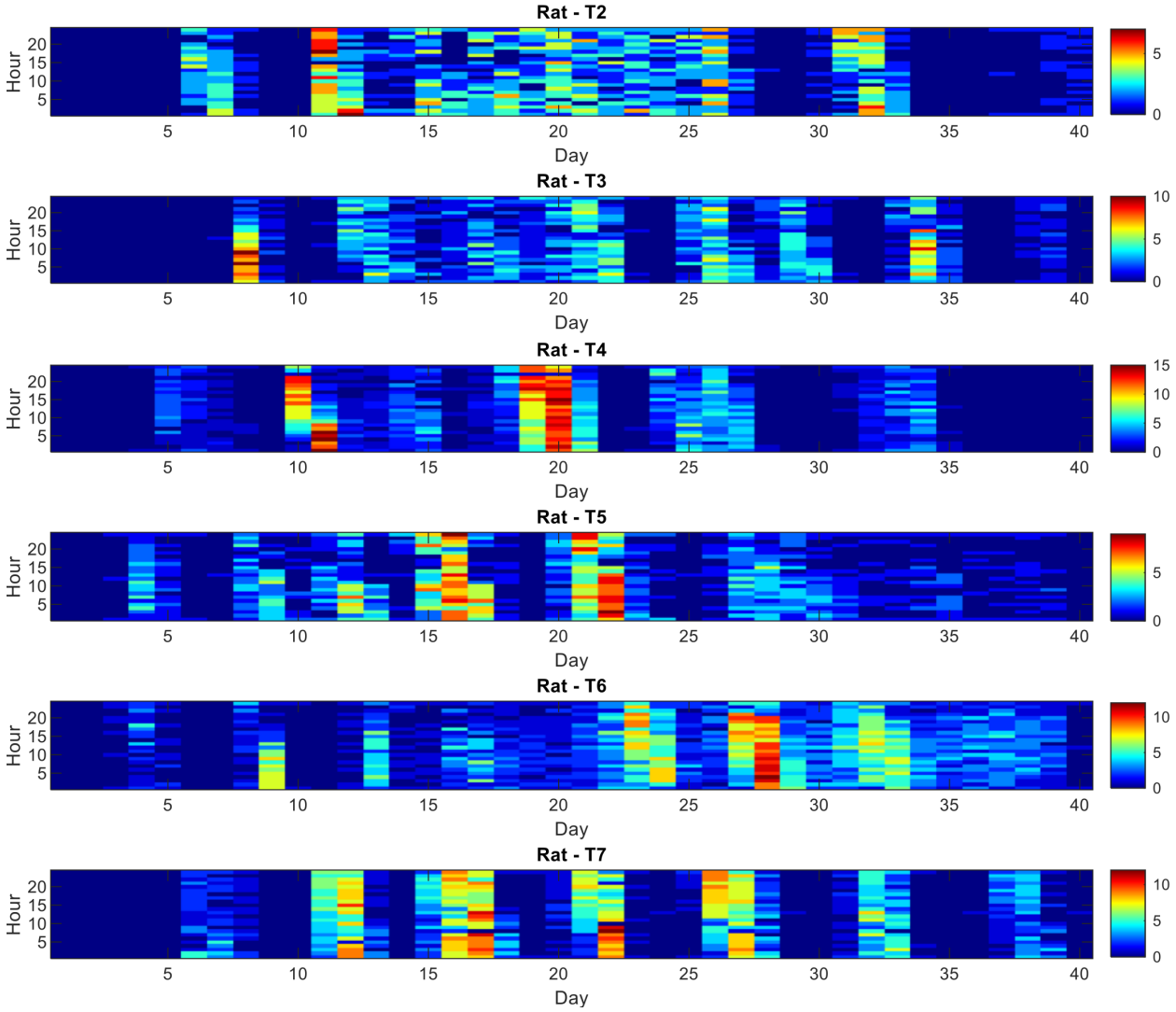

Fig 2. Seizure distribution across days and hours for six TT rats. The distribution of seizures recorded over a period of 40 days, plotted against hours of the day. The x-axis represents the day of recording, while the y-axis denotes the hour of the recording session. Colors ranging from red to blue indicate varying frequencies of seizures, with red indicating higher frequencies and blue indicating lower frequencies.

explored. We set the maximum to 10 days to be able to observe at least four cycles of the data over 40 days.

Significance testing was performed to distinguish meaningful frequency components from noise. Significant peaks in the global wavelet power were determined using a time-averaged significance test as described in [20]. This is done by comparing the observed wavelet power against the distribution of power expected under the null hypothesis that the data is generated by the chosen background noise model (in this case, a red-noise process), with the significance level at 95% to account for autocorrelation properties and multiple comparisons [15]. Peaks exceeding the 95% significance level in the wavelet power spectrum were identified as significant cycles. These peaks corresponded to periods where seizure occurrences exhibited pronounced cyclical behavior across the 40-day observation period. The Synchronization Index (SI) was calculated for the significant peaks with the highest power. The SI index measures the phase consistency of seizures within the data. This was done by converting the timestamps of seizures into phase values and computing the mean resultant vector [15]. The SI index, I_S, is a measure of the phase locking of seizure occurrences, with values

ranging from 0 to 1. Higher SI values indicate stronger synchronization in seizure timings. This calculated using the following equation:

$$I_S = \left| \frac{1}{N} \sum_{k=1}^{N} e^{i\theta_k} \right| , \tag{1}$$

where N is the number of events, θ_k is the phase of the k-th seizure, and $e^{i\theta_k}$ represents the complex exponential of the phase. The SI is the magnitude of the mean resultant vector, calculated by taking the absolute value of the average of these complex exponentials. The SI value ranges from 0 to 1, where 0 indicates no synchronization and 1 indicates perfect synchronization [15].

For better visualization of the cycles, we also fitted a sinusoid to the hourly number of seizures for each rat. The sinusoidal function used is defined as:

$$f(x) = A \cdot \sin(\omega x + \phi) + c \,, \tag{2}$$

where A is the amplitude, ω is the angular frequency, ϕ is the phase shift, and c is the offset. The optimization was performed by minimizing the Sum of Squared Residuals (SSR) between the observed data and the sinusoidal model. The periods identified for each rat were recorded and reported.

As the final step, to better illustrate the effect of Tetanus Toxin on the cycles, the data was segmented into 15-day intervals (360 hours each) with 359 hours overlap to analyze periodic patterns over time. For each segment, the significant peaks in the cycles were calculated using the method described above.

We also calculated the significance of the peak by comparing the observed power at that frequency to the global significance threshold obtained from the wavelet power spectrum.

$$S = \frac{\text{Power} - \text{Significance Level}}{\text{Significance Level}} \,, \tag{3}$$

where Power is the observed power at the specific frequency and Significance Level is the threshold power level determined by the global significance test. Higher S values indicate greater significance, with the color transitioning from cooler tones (e.g., blue) for lower S values to warmer tones (e.g., purple) for higher S values. This allows for a visual representation of the relative strength of each significant peak in the frequency domain.

Results

The analysis of seizure data for six rats over a period of 40 days revealed distinct periodic patterns for each rat. Fig. 3 illustrates the wavelet power spectrum analysis results for each rat. The power spectrum depicts the distribution of power across different periods (in hours), highlighting significant peaks where seizure occurrences exhibited pronounced cyclical behavior over the 40-day observation period. Significant peaks were determined using a time-averaged significance test ($\alpha = 0.05$), accounting for autocorrelation properties and multiple comparisons. Significant peaks in the global wavelet power spectrum were identified as periods where the period of seizure occurrences were statistically higher than expected by chance. These peaks, marked in the figure as 'Significant Peaks', indicate intervals of heightened seizure activity that recur periodically within each rat's data. Peaks exceeding the 95% significance level (black dashed line) were considered robust indicators of cyclic behavior in seizure occurrence. Fig. 3 shows the presence of dominant multiple cycles in the seizure occurrence in the Tetanus Toxin (TT) rat model of epilepsy. The cycles found for different rats are listed as follows: Rat T2: 157 hours (6.5 days), 121 hours (5 days), 73 hours (3 days); Rat T3: 159 hours (6.6 days), 104 hours (4.3 days); Rat T4: 174 hours (7.2 days); Rat T5: 145 hours (6 days); Rat T6: 114 hours (4.7 days); Rat T7: 126 hours (5.2 days).

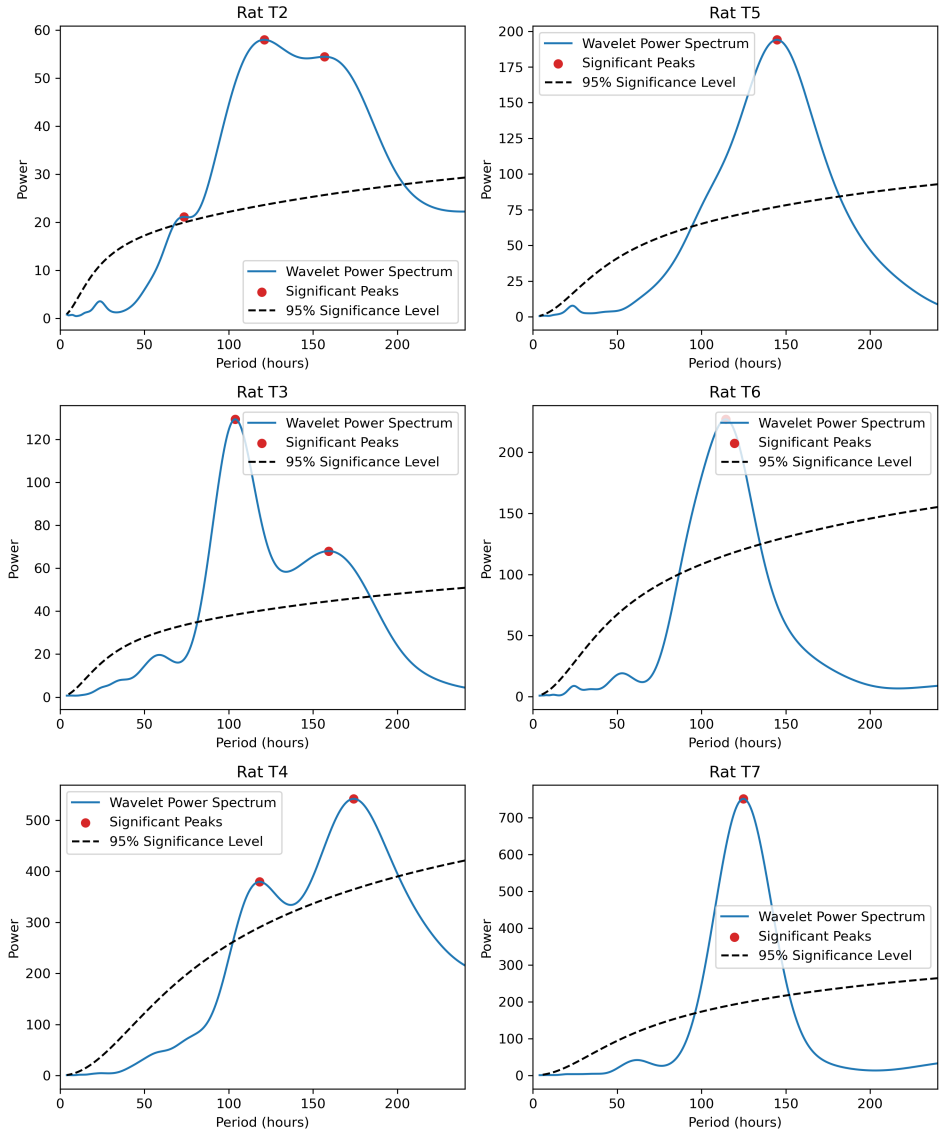

Fig 3. Wavelet power spectrum analysis of hourly seizure occurrences for seizure data recorded over 40 days. Red dots indicate significant peaks in the wavelet power spectra of numbers of seizures occurring per hour, which are indicated by the blue lines showing power at different periods (hours). Each subplot corresponds to a different rat (T2 to T7). The dashed black line represents the 95% significance threshold.

Using sinusoidal curve fitting, we identified the optimal parameters that best describe the cyclic nature of the seizure occurrences, assuming that cycle frequencies were fixed over the whole recording periods. Fig. 4 illustrates the fitted sinusoidal models and the corresponding numbers of seizures per hour for each rat. The observed data points are marked with blue stars, while the fitted curves are depicted in orange. The period of the sinusoidal function is annotated in each subplot, indicating the duration of the cycles in hours (days). The periods identified for each rat are consistent with the results obtained from the wavelet transform analysis that showed the strongest power. This figure better visualizes one of the rhythmic cycles identified in the data. In the following section, the temporal changes in these significant cycles over 40 days of recording are investigated.

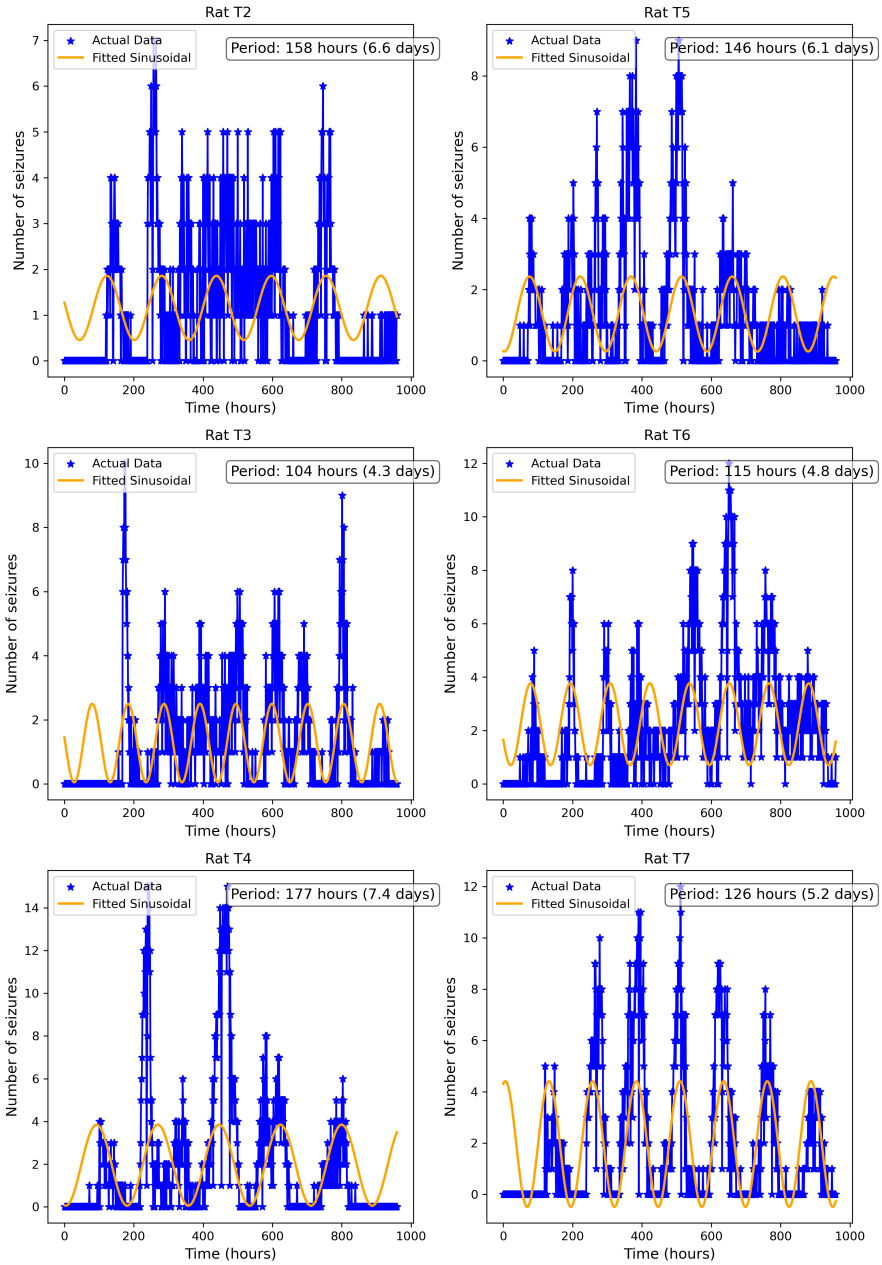

Fig 4. Sinusoidal curve fitting of seizure data. Each subplot displays the actual seizure counts (blue stars) and the fitted sinusoidal model (orange line). The period of the sinusoidal fit is annotated for each subplot, demonstrating the periodic patterns observed in seizure occurrences over time.

To further understand the cyclic nature of seizures in the rats, polar plots were generated to illustrate the distribution of seizure phases within one cycle of the most significant rhythmic period as determined by the wavelet transform analysis. Fig. 5 presents the polar histograms of seizure timings for each rat, based on the periods identified from the wavelet power spectra. These polar plots help illustrate the phase locking of seizures and provide insights into the synchronization index (SI) of seizure occurrences. The histograms are displayed in polar coordinates, where angles represent the phases of the cycle (processing clockwise) and the radial axis indicates the relative number of of seizure occurrences within each phase interval. For example, the polar histogram for Rat T7 demonstrates a strong clustering of seizures around the "Rising" phase, with

very few events occurring during the “Falling” and “Trough” phases. The clustering of seizures in a specific phase interval implies that seizure occurrences are not random but follow a predictable pattern. For example, rat T7 has the highest SI of 0.64, indicating the strongest phase locking of all the rats to their dominant frequencies. This strong synchronization suggests that seizures in Rat T7 are highly predictable throughout the recording and occur predominantly during the “Rising” phase. This predictability could be useful for anticipating seizure events and implementing preventative measures.

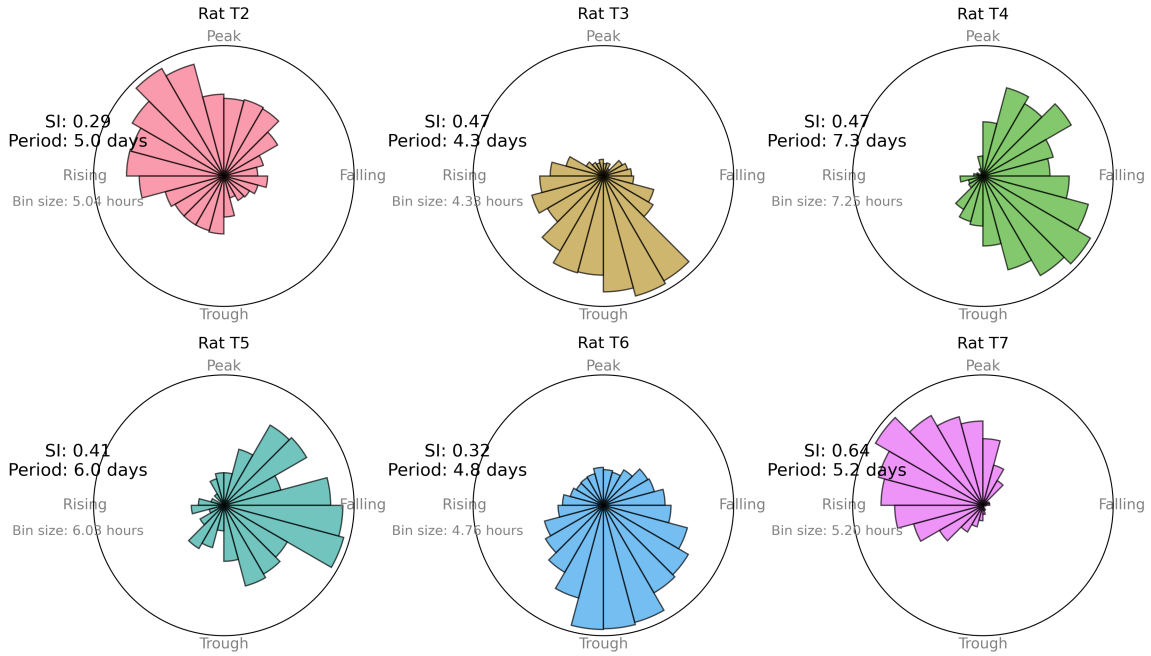

Fig 5. Polar histograms of seizure timings for each rat based on the identified rhythmic periods. Each subplot represents a different rat (T2 through T7). The radial axes indicate the frequency of seizure occurrences within each phase interval, and the angular axes represent the phases of the identified rhythmic cycle. The predominant period and the Synchronization Index (SI), Eq.(1), are annotated on each plot. Higher SI values indicate stronger phase locking and synchronization of seizure occurrences.

The Tetanus Toxin model of epilepsy is known to wax and wane over the weeks of recording, and for the properties of the seizures to change over time [5]. To investigate these effects over time, the data was divided into segments, each 360 hours (15 days) long and advancing 1 hour between consecutive segments. This segmentation approach allowed for the analysis of seizure periods across different time windows along the 40 days of recording. For each segment, the wavelet power spectrum was computed. Peaks were considered significant if their power exceeded the threshold set by the significance level (0.95).

Fig 6 illustrates the significant periods of seizures over the duration of recording. Each subplot represents one rat and displays colored dots corresponding to significant seizure periods over time (days) for multiple segments. The color of each line represents the Peak Significance$S$ value, Eq. (3), shown on a log scale. Higher S values indicate greater significance, with the color transitioning from cooler tones (i.e., blue) for lower S values to warmer tones (i.e., purple) for higher S values. This allows for a visual representation of the relative strength of each significant peak in the frequency domain. Each data point shows the significant cycle(s) determined from the preceeding 360 hours (15 days), as indicated by the dashed lines on the zero y-axes for the first data point.

This analysis presents the evolution of significant cycles in seizure activity over 40 days. The results indicate that the significant cycles are not static but change over time, reflecting dynamic rhythmic patterns in seizure occurrences. Some cycles persist across multiple segments, while others appear or disappear as the

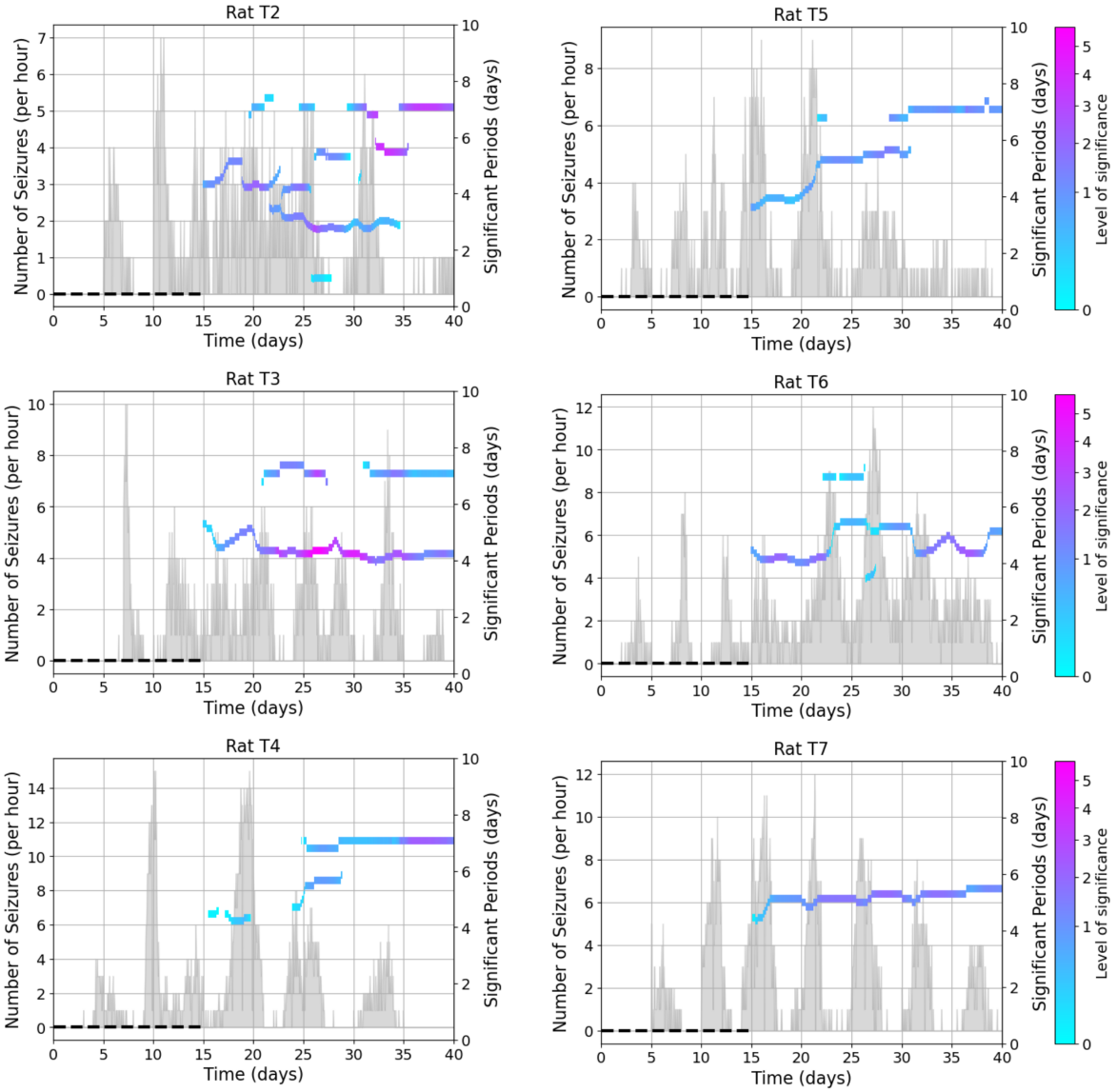

Fig 6. Significant cycles over time for different rats. Each subplot displays the significant periods (days) of seizures as horizontal lines, plotted against time (days) across multiple segments. Each segment lasts 360 hours (15 days) and overlaps with the next segment by 359 hours. The color of each line represents the significance of the peak, with the color bar on the right of each subplot indicating the scale, where lower significance values are shown in blue and higher significance values in purple. The gray histogram on the left axis shows the number of seizures per hour over the 40 days of recording. The dashed line indicated that the power of the wavelet calculated over a 15-day period.

recording progresses. This variation suggests that the underlying neural mechanisms generating these cycles may shift over time.

For Rat T2, the significant cycles show considerable variation throughout the 40-day period. Early in the recording, cycles of around 4-5 days are consistently present, but later segments reveal the emergence of longer cycles (up to 7 days). There is notable variation in the significant periods over time, with some periods disappearing and reappearing. The significance of the power of some periods increases towards the end of the recording, with some high-power cycles (depicted in purple) emerging after 32 and 36 days. The

results suggest that the rhythmic periods of seizures in Rat T2 evolve over time, with certain cycles becoming more pronounced (higher power) later in the recording. This indicates possible changes in the underlying mechanisms driving seizures as the experiment progresses.

Initially, Rat T3 shows significant cycles with periods around 4-5 days (approximately 100-120 hours) during the first 20 days of the recording. However, after day 20, a new dominant cycle with a period of around 7 days (approximately 170 hours) emerged. This 7-day cycle did not remain stable — it disappeared and reappeared intermittently until the end of the recording. This suggests that, while the 4-5-day cycles are consistently present throughout, the 7-day cycle was more transient, appearing sporadically. This variability could reflect changes in the underlying neural activity influenced by the progression of the Tetanus Toxin effect or other factors.

Rat T4 shows more variability in the significant cycles. Early in the recording, cycles were around 4 days, but mid-recording, there was more variation, with cycles ranging from 4-5 days. Towards the end of the recording period, the cycles tended to stabilize around 7 days. This variability indicates a more complex seizure pattern with an increase over time.

In Rat T5, the significant cycles started with a period of around 4 days and gradually increased to around 7 days by the end of the recording. Around day 30, there was a period where two dominant cycles coexisted—one around 5.5 days and the other around 7 days. This indicates a shift in the rhythmic patterns of seizure occurrences.

Rat T6 showed a gradual change in the significant periods over the 40 days of recording. The significant cycles began with a period of around 4 days and then fluctuated, gradually increasing and decreasing over time. Between days 23-27, there were two dominant cycles present simultaneously, one shorter and one longer, indicating a temporary coexistence of different rhythmic patterns.

Rat T7 showed very stable significant cycles, maintaining a cycle length of around 5 days (120-130 hours) throughout the entire 40-day period. The cycles remained stable, indicating a strong rhythmic pattern in seizure occurrence The cycles in Rat T7 were characterized by relatively high significance, reflecting strong synchronization of seizure activity.

Discussion

In this study, we examined the rhythmic patterns of seizure occurrences in a Tetanus Toxin rat model of epilepsy using wavelet transform analysis to identify significant cycles in seizure timing. By analyzing the seizure data recorded over 40 days across six different rats (Rats T2-T7), we uncovered distinct rhythmic patterns that varied in both period and power across individual rats. These findings provide new insights into the complex dynamics of seizure occurrence and the impact of cyclic rhythms in epilepsy.

Wavelet power spectrum analysis

The wavelet power spectrum analysis, shown in Fig. 3, provides a detailed view of the power and significance of different rhythmic periods in the seizure data. Across the six rats, we observed significant peaks corresponding to multi-day cycles, with periods typically ranging from 73-174 hours. For example, the presence of a single dominant peak at 120 hours suggests that Rat T7's seizures were strongly synchronized with a 5-day cycle. The lack of additional significant peaks indicates that this period was the primary driver of rhythmic activity

in Rat T7's seizures, making it a highly consistent and predictable pattern. Some rats, like T5, T6 and T7, displayed one very strong and dominant cycle, while others, like T4, T2 and T3, showed multiple significant periods, indicating more complex seizure patterns. These multiple periods may correspond to different underlying processes that contribute to seizure generation, potentially offering multiple targets for therapeutic intervention. These findings suggest that the seizures in each rat are influenced by specific, recurring rhythms, which vary in strength and periodicity across different individuals.

Temporal dynamics of significant rhythms

The analysis of significant periods over time, as depicted in Fig. 6, showed that the seizure rhythms were not static but evolved during the recording period. Some rats, like T3 and T7, showed stable rhythmic periods, while others, such as T2, exhibited more fluctuation and variability. Some rats, such as T2, T4 and T5, showed an increase in the period of significant cycles toward the end of the 40-days of recording. These findings suggest that the effects of Tetanus Toxin on seizure dynamics may not be uniform across different rats. The observed shifts in rhythmic periods could reflect adaptive or pathological changes in the brain's oscillatory networks, possibly related to the progression of the epileptic state or the brain's response to either sustained seizure activity or the Tetanus Toxin. Understanding the evolution of these significant seizure periods and their power can provide valuable insights into the effects of Tetanus Toxin on neural rhythms and may inform the development of targeted interventions based on the specific rhythmic characteristics of each rat.

Crisp et al. (2020) also observed temporal changes in seizure dynamics in their study, showing that the type of seizure onset evolved over the recording period for these same rats. Initially, seizures were characterized by fast, low-amplitude spiking with a DC shift at the beginning. However, as epileptogenesis progressed, seizures began to exhibit no DC shift, with repetitive bursts and increasing frequency toward the end. Additionally, changes in evoked potentials were noted, reflecting the brain's increasing excitability in response to stimulation as the number of seizures increased [5]. It would be interesting to explore the relationship between the evolving seizure cycles in our study and the changes in seizure types and neural excitability observed by [5]. Specifically, investigating how the rhythmic periods of seizures may influence or be influenced by the underlying neural mechanisms driving these seizure onset dynamics could provide deeper insights into the effects of Tetanus Toxin. This connection between the temporal evolution of seizure rhythms and seizure dynamics will be a focus of future studies.

Importance of studying seizure cycles in animal models compared to humans

In humans, seizure cycles are often influenced by a multitude of external factors, which can complicate the analysis of their underlying physiological causes. For instance, differences in daily activities, such as altered routines during weekends, irregular sleep patterns [19], and increased stress or social interactions, can affect seizure timing [10, 11]. Environmental influences like air pollution [3] and diet [10] also play significant roles in seizure triggers and modulate the rhythms of seizure occurrences. These factors, while highly relevant to real-world human conditions, introduce considerable variability, making it difficult to isolate the core physiological mechanisms that generate seizure rhythms. By maintaining consistent lighting conditions, controlled feeding schedules, and a stable environment for the rats, we can effectively eliminate many of the external factors that complicate human studies.

Our study demonstrated that multi-day cycles in seizure occurrences persist even in the absence of the external factors typically observed in human studies, such as weekly changes in life routines, environmental pollution, and dietary variations. The presence of these multi-day rhythmic patterns in rats, despite the

removal of such external factors, strongly suggests that these cycles have a physiological basis independent of environmental and lifestyle variables. This finding is particularly significant as it underscores the inherent nature of these seizure rhythms, pointing to underlying biological mechanisms—possibly related to circadian rhythms [15], endocrine systems [17], or other neurophysiological processes—that are responsible for generating these cycles. It highlights the importance of considering these intrinsic factors when studying epilepsy and designing interventions, as it indicates that the seizure cycles observed in humans are not solely the result of external influences, but are likely driven by deeper, endogenous processes. This insight provides a more solid foundation for understanding seizure dynamics and developing targeted therapeutic strategies that address the root causes of rhythmic seizure activity for each individual patient.

Multi-days cycles in other rat models of epilepsy

There are other rat models of epilepsy that have been employed to investigate the cyclic nature of seizure occurrences and their underlying mechanisms. Notably, the kainic acid and pilocarpine models of temporal lobe epilepsy have provided valuable insights into the existence of circadian and multidien rhythms in epilepsy. Both of these models show multidien rhythms ranging from 2-7 days. However, these cycles were not as strong as the ones we observed in the Tetanus Toxin (TT) model of epilepsy, particularly in the kainic acid model [2]. There are also other studies that have examined multi-day cycles in female rats in relation to their menstrual cycle, but not in male rats [6, 16].

Clinical implications and future directions

The findings of this study underscore the importance of understanding the temporal dynamics and rhythmic patterns of seizures in epilepsy. The identification of significant rhythmic periods and phase locking in seizure occurrences suggests that these cycles could be exploited for therapeutic purposes, such as timing interventions to coincide with periods of high seizure risk. Additionally, the variability in rhythmic patterns across different rats highlights the need for personalized approaches to epilepsy treatment, taking into account the specific rhythmic dynamics of each patient.

Future studies should aim to further elucidate the mechanisms underlying these rhythmic patterns and their role in seizure generation. Investigating how these rhythms interact with other factors, such as seizure duration and inter-seizure intervals, could provide a more comprehensive understanding of seizure dynamics. Additionally, we plan to explore the neural mechanisms behind these cycles using computational models [7, 8, 21]. Computational modeling offers a powerful approach to simulate and analyze the complex interactions within neural networks that may drive these rhythmic patterns. By incorporating key physiological variables, such as neuronal excitability, synaptic connectivity, and network dynamics, these models will allow us to test various hypotheses about the emergence and stability of seizure cycles, potentially revealing new therapeutic targets[8]. Moreover, exploring the potential for modulating these rhythms through pharmacological or non-invasive interventions could open new avenues for epilepsy treatment.

Conclusion

In conclusion, the analysis of seizure rhythms in this study using a Tetanus Toxin rat model of epilepsy has revealed distinct and dynamic rhythmic patterns that vary in both period and power across individual rats. These findings contribute to our understanding of the temporal organization of seizures and suggest that

rhythmic cycles play a significant role in the timing and predictability of seizure events. This knowledge could inform the development of targeted, timing-based interventions to improve epilepsy management.

Acknowledgments

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Supporting information

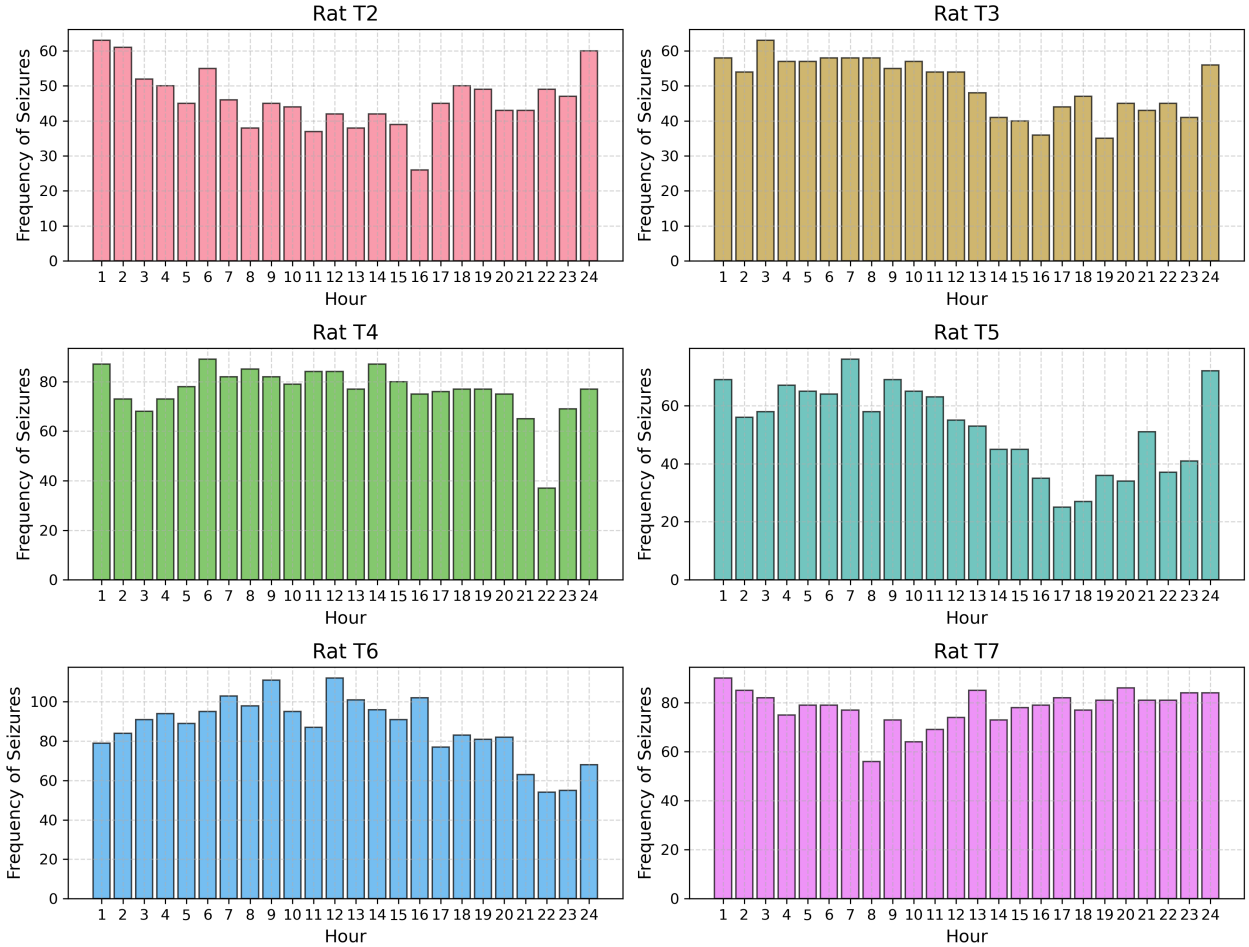

Fig S1. Distribution of seizure frequencies per hour over a period of 40 days for six TT rats. Each subplot represents data from one rat, with the x-axis indicating the hours of the day (from 1 to 24) and the y-axis showing the frequency of seizures occurring during each hour starting from midnight.

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