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Short Communication

Endogenous multidien rhythm of epilepsy in rats

Maxime O. Baud[a,b,*,1], Antoine Ghestem[c], Jean-Jacques Benoliel[d,e], Christel Becker[d], Christophe Bernard[c]

[a] Sleep-Wake-Epilepsy Center and Center for Experimental Neurology, Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Switzerland
[b] Wyss Center for Bio and Neuro-engineering, Geneva, Switzerland
[c] Aix Marseille Univ, INSERM, INS, Inst Neurosci Syst, Marseille, France
[d] INSERM UMR-S 1124, Paris Descartes University, Sorbonne Paris Cité, 45, rue des Saints-Pères, Paris 75006, France
[e] Service de Biochimie Endocrinienne et Oncologique, Hôpital de la Pitié-Salpêtrière, Paris, France

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ABSTRACT

Recent trials of chronic EEG in humans showed that epilepsy is a cyclical disorder of the brain with rhythms at multiple time-scales: circadian, multi-day (multidien) or even seasonal. Here, we analyzed chronic EEG data (> 30 days) in male epileptic rats and unraveled not only circadian but also, slower, multidien rhythms of interictal epileptiform activity with periodicity of about 2–3 and 5–7 days. Importantly, seizures were not uniformly distributed over time, but rather clustered at preferential phases of these underlying rhythms, delineating critical circadian times and multidien phase of heightened seizure risk. Multidien rhythms were not synchronous across animals or with human intervention suggesting an endogenous generator. In epilepsy, across species, unknown factors modulate seizure timing in cyclical patterns over multiple days.

1. Introduction

Epilepsy is overtly manifested by seizures that recur spontaneously at non-random periodic intervals (Griffiths and Fox, 1938). The recent use of chronic implanted EEG in humans (Baud et al., 2018; Karoly et al., 2016) further unraveled the existence of covert rhythms of Interictal Epileptic Activity (IEA, e.g. spike rate). Both IEA and seizure probability peak at preferential phases of circadian (Karoly et al., 2016; Spencer et al., 2016) or multidien (Baud et al., 2018) cycles. Emerging evidence shows that the relationship between IEA and seizures is fixed for any given subject and that circadian and multidien fluctuations in IEA help evaluate the likelihood of seizure occurrence (Baud et al., 2018).

In animal models of epilepsy, just like in humans, seizures tend to occur in clusters (Williams et al., 2009). Circadian rhythmicity in IEA has also been described (Pitsch et al., 2017; Quigg et al., 1998) and multidien rhythms have been studied in relationship to the menstrual cycle in females (D'Amour et al., 2015; Maguire et al., 2005), but not in males, to our knowledge. The aim of the current paper is to determine whether multidien cycles exist in two rat models of Temporal Lobe Epilepsy (TLE, Pilocarpine and Kainate i.p.). Long-term (> 30 days) continuous EEG data during latent and chronic periods of TLE were included for retrospective analysis.

2. Methods

2.1. Animals and surgery

The protocol was approved by the French Ministry of National Education, Superior Teaching, and Research (approval 01451-02). We used three cohorts of animals. In the first cohort, 5 male Sprague Dawley rats were injected with kainic acid i.p. to trigger Status Epilepticus (SE) and EEG was recorded between post-SE day 3 and 45–50 to assess epileptogenesis (group Kainate i.p. latent period). In the second cohort, we used the same protocol to trigger SE in 5 male Sprague Dawley rats, but recordings started 45 days later for a duration of 57–70 days (group Kainate i.p. chronic period). In the third cohort, we injected pilocarpine i.p. to trigger SE in five male Wistar rats and recordings started 45 days later for a duration of 57–70 days (group Pilocarpine i.p. chronic period). For EEG, recording and reference skull screws were secured above hippocampal CA1 (−4.0 mm posterior, −2.0 mm lateral) and cerebellum, respectively, and connected to the wireless telemetry probe implanted under the skin (Data Science International [DSI], St Paul, MN). After surgery, the animals were

Abbreviations: IEA, interictal epileptiform activity; PLV, phase-locking value; TLE, temporal lobe epilepsy

* Corresponding author at: Sleep-Wake-Epilepsy Center and Center for Experimental Neurology, Department of Neurology, Inselspital, Bern, Switzerland.
E-mail address: maxime.baud.neuro@gmail.com (M.O. Baud).

[1] http://www.neuro-elab.com

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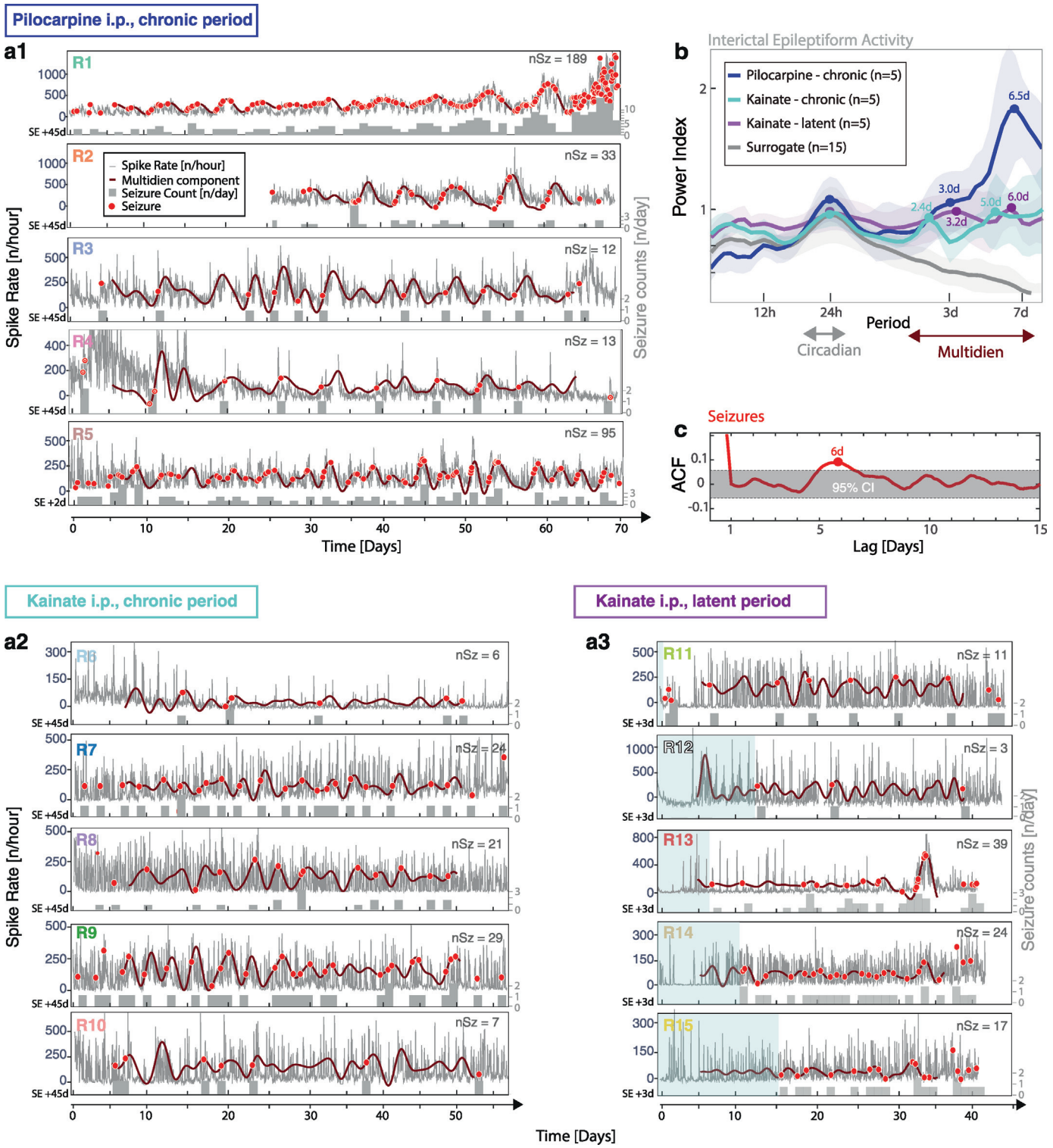

Fig. 1. Circadian and multidien rhythms of epileptic activity in 15 male rats. **(a1-3)** Raw epileptiform activity counts (interictal and ictal) for the Pilocarpine (R1–5) and kainate (R6–15) i.p. models of epilepsy recorded at variable distance from induction of Status Epilepticus (SE, delay in black on the left of x-axis). Grey vertical bars represent daily count of spontaneous seizures (total indicated as nSz). Multidien rhythms with an about-six-day periodicity (range 5 to 7 days) are readily visible from the raw epileptic spike rates (grey time-series) in the first five rats and are detected by a wavelet analysis in all (dark-red curves). Visual inspection of seizure timing (red dots) and daily seizure counts further reveals clustering effects during the rising phase of the spike rate over days. **(b)** Average wavelet periodograms (± SD) per group revealed greater rhythmicity in the pilocarpine than in the kainate model, although IEA periodicity was similar across animals peaking at 24 h, 2–3 d and 5–7 d. Use of surrogate data show that these peak periodicities are specific to fluctuations over several days. **(c)** Average autocorrelation function of the seizure time-series (red dots) reveals periodicity at about 6 days (grey box is 95% confidence interval).

housed in individual cages with access to food and water ad libitum and a light schedule from 7:30 AM to 7:30 PM. During the chronic period (pilocarpine and kainate groups, $n = 10$), sawdust change and weighting of animals occurred every Monday, but otherwise the animals had no interactions with human beings. In the kainate latent period group, animals interacted with human beings during one hour everyday (7/7) of the week.

2.2. EEG data

The EEG was acquired at 500 Hz sampling rate. Interictal spike and seizure counts were formatted as hourly rates and represent the raw data in this study. For seizure detection, we used an algorithm (Neuroscore, DSI) based on a spike detector and a spike train detector. The minimum spike interval was set to 1 ms, the maximum to 1 s, the minimum spike train duration to 2 s, and the minimum number of spikes to 10. After visual verification on synchronous video recordings, the duration of seizures was adjusted, and all false positives were removed. Only seizures with tonic and/or tonico-clonic phase were considered for later analysis. For automated spike detection, false positives were minimized by adjusting parameters for each rat with an amplitude threshold (minimum value between 250 μv and 400 μv) a rejection value (between 2 mV and 4 mV) a minimum duration of 1 ms and a maximum duration of 300 ms. Movement artifacts were visually rejected. All spikes detected during a seizure were discarded from interictal spike counts (Chauvière et al., 2012).

2.3. Signal analysis

We applied the same analytical methodology as in a recent human study (Baud et al., 2018). Power and phase of the hourly IEA time-series were obtained using a Morlet wavelet transform for 89 period bins (scales) with increasing spacing: 1.2 h between 2.4 and 31.2 h, 2.4 h between 33.6 and 48 h, 4.8 h between 2.2 and 4 d, and 12 h between 4.5 and 10 d. Temporary EEG disconnection for animal care resulted in occasional short gaps in data acquisition, which were interpolated using a linear trend with variance matching the two peri-gap windows, only for scales with periodicity five-times greater than gap duration as previously detailed (Baud et al., 2018). A cone of influence considering a full period for each wavelet was discarded at the extremities of recordings. Power index in periodograms was estimated as the absolute value (square-rooted) of wavelet coefficients. To show the specificity of this analysis, surrogate data was created for each of the 15 rats by normalizing (Z-score) spiking rate for each calendar day. The circadian rhythm was divided in 24 (15°) bins for instantaneous phase calculation. The multidien rhythm encompassed a band of wavelet coefficients between 2.0 and 8.0 d as to accommodate variation in exact periodicity and component rhythms. Its phase was calculated as the angle of wavelet coefficients divided into 18 (20°) bins. The orientation of resultant vectors in polar plots represent the average phase and their length correspond to the Phase Locking Value (PLV), an index of phase clustering varying between 0 and 1.

2.4. Statistics

Within-subject Circular Statistics were done on 14/15 rats with > 5 total number of seizures using the 2012 CircStat Matlab toolbox (http://www.eye-tuebingen.de/berenslab/) including functions for circular mean and Rayleigh test. Phase lag between two peaks was tested using a one-sample t-test. Correlation between variables was evaluated using a simple linear fit. The autocorrelation function was calculated on the seizure time-series after smoothing data over 24 h. Autocorrelation in spike rate was calculated as rho Pearson coefficient in the spectral domain and averaged for the entire time-series. Distribution of seizures over days of the week was evaluated with a Kruskal-wallis test. A sign-test on the median was used to evaluate if IEA changed before and after seizures. Relative Risk (RR) was calculated for a given phase as (TP/(TP + FP)) / (FN/(TN + FN)). Values were expressed as mean ± standard deviation (SD) and plotted as dots and error-bars.

3. Results

3.1. Chemically-induced epilepsy

After status epilepticus, all animals developed spontaneous seizures per inclusion criteria. In the chronic phase (≥ 45 days after status epilepticus, R1-R10, Fig. 1a1-2), animals had varying seizure frequencies (median 2.8 per week, range 0.8–18.9). The median latency to first spontaneous seizure observed in 5 animals recorded during the latent period (R11–15) was 14 days (range 3–18, blue shading in Fig. 1a3). Importantly, it should be noted that the time-scale of Fig. 1a is very different than previous studies looking at increases in IEA hours after seizures. Here, trends are shown at the level of multiple days.

3.2. Circadian rhythms of IEA

All animals showed a circadian peak (24 h exactly) in IEA with higher activity during the sleep period (daytime) and lowest in the middle of the active period in most animals. Four animals also showed a low-magnitude ultradian component at 6 or 12 h.

3.3. Multidien rhythms of IEA

During the chronic phase, multidien rhythms of IEA were visible in all 10 animals (solid dark-red line) in the raw spike-rate or seizure time-series, albeit subtly so in R6 (Fig. 1a2). Although pilocarpine and kainate groups had similar periodicity, the magnitude of multidien rhythms was stronger in the pilocarpine group. Some animal displayed a multidien rhythm that was stronger than the circadian rhythm and readily visible by eye (best examples R2 and R3). Other animals had weak circadian and multidien rhythms, that could only be detected in the spectral domain (weaker rhythms in R6 and R13). Although limited to qualitative assessment by the low number of animals, multidien rhythms of IEA seemed absent during the first few days of the latent phase (R11–15, Fig. 1a3), but appeared after one week in some animals (R12 and R14), and were present in all after day 30. Interestingly, in R12 and R14 they appear before the first seizure suggesting that seizures are not the driver of these rhythms.

In the spectral domain (Fig. 1b), all animals showed one to two multidien (here: 2 to 8 days) peaks in IEA rhythmicity with the most common robust periodicities found in all animals between 5 and 7 days (mean 6.5 d). All animals also had a shorter and subtler periodicity between 2.4 and 3.8 days (mean 2.6 d). The comparison between original data and surrogate data where spiking rate was normalized on 24-hour windows, shows that the multidien peaks were specific to long-term fluctuations in IEA (Fig. 1b). The average IEA autocorrelation over time in the spectral domain was rho = 0.19 ± 0.14 for periodicities below 1.9 day (i.e. circadian), and rho = 0.62 ± 0.22 for periodicities of 2.0 days and above, indicating robust multidien rhythms with relatively stable periodicity in this dataset.

3.4. Multidien rhythms of seizures

The average autocorrelation function (ACF) on seizure hourly counts showed a significant peak at about 6 days across animals (Fig. 1c), confirming multidien periodicity from clinical data that is independent from EEG.

3.5. Asynchrony with environment

Many studies report a circadian regulation of seizures and IEA in

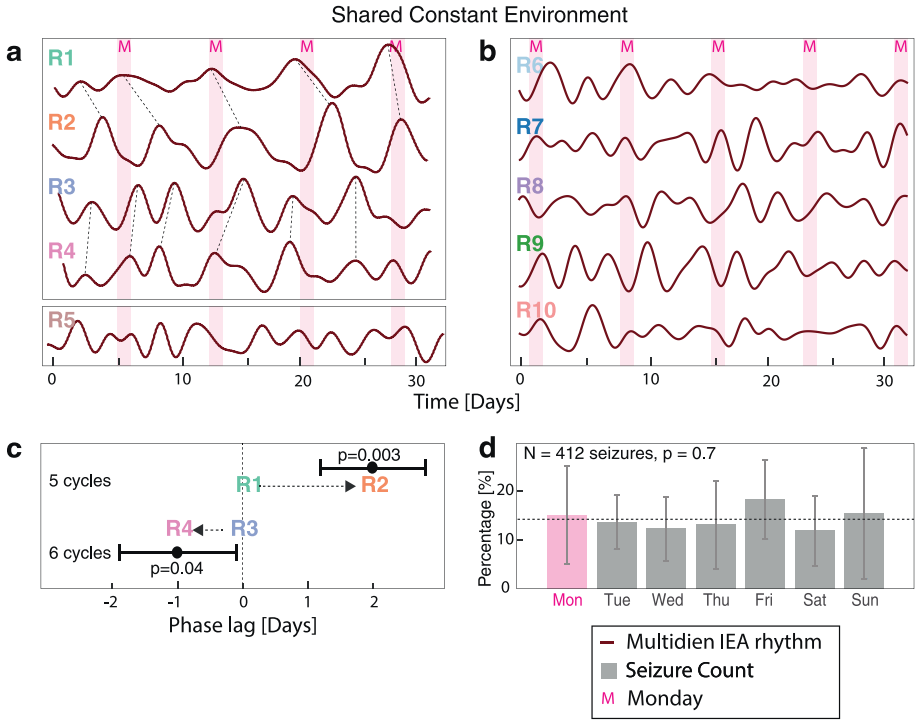

Fig. 2. Asynchrony with the environment and across animals. **a)** Four pilocarpine rats recorded simultaneously did not show synchrony with environmental factors (human intervention on Mondays, M). Examination of the wavelet-derived IEA fluctuations (dark-red curves, same as in Fig. 1) reveals a lag of one to two days for peak IEA between animals (c). This lack of synchrony in multidien rhythms, suggests independent endogenous modulation. R5 in lower box recorded separately did not show phase synchrony with environment. **(b)** Five kainate rats were also recorded simultaneously and did not show synchrony across animals or with the environment. **(d)** Seizure likelihood was not statistically different on different days of the week.

patients and experimental models imposed by the light and day cycle (in particular in a controlled environment like an animal facility). We thus tested whether the multidien cycles were imposed by external factors. In the chronic period groups, the weekly human intervention on Mondays could have acted as a Zeitgeber. However, there was no phase preference of multidien IEA rhythms for Mondays across 10 animals (Fig. 2a-b, PLV = 0.18, p = .16, Rayleigh test n = 77 observations on Mondays). Furthermore, the distribution of seizures was not significantly different over the different days of the week (p = .7, Kruskal-Wallis test, Fig. 2d). Finally, we did not find any synchrony in multidien rhythms across 4 pilocarpine (R1–4) and 5 kainate animals (R6–10) recorded simultaneously (Fig. 2a-b). Rather, there were an unequal number of cycles over a given period of time, and a significant phase shift across animals with the same number of cycles ($p < .05$, one-sample t-test, Fig. 2c). Together these data suggest that relatively stable multidien rhythms are specific to each individual animal and that they are not entrained by the environment in conditions that were nearly constant over multiple days.

3.6. Relationship between IEA and seizures

A phase analysis on 14 animals with > 5 seizures confirmed significant seizure clustering at preferential time of the day in 11 rats, between 9 AM and 5 PM with PLV ranging from 0.31 to 0.79 ($p < .02$, Rayleigh test, Fig. 3a). At the multidien level, seizure significantly clustered in the rising phase or close to the peak of IEA in 12 animals with PLV ranging from 0.32 to 0.87 ($p < .03$ for all except R14–15, Rayleigh test, Fig. 3d). The magnitude of the effect varied from animal to animal, but across animals the absolute phase of seizure clustering remained the same. For example, R4 had a PLV of 0.84 (high consistency), because a few seizures occurred almost exactly at the same rising phase of the multidien rhythm, as can be seen in the raw data (figure 1a1). In contrast, R1 had a PLV of 0.31 (moderate consistency) because many seizures occurred outside the preferential rising phase, but a modulatory effect of the multidien rhythm remained (more seizures before peak IEA). A negative linear correlation was found between seizure frequency and multidien PLV among the 12 animals ($R2 = 0.63$, $b = -0.20 \pm 0.05$, p = .002). A linear relationship between PLV and seizure frequency was absent at the circadian level (p = .49). We assessed the effect size of using phases of underlying cycles as predictors of the relative seizure risk. At the circadian and multidien level, the risk of seizure was three times greater during the daytime or the rising phase of IEA as compared to the nighttime and downslope of IEA, respectively (Fig. 3f). This shows that circadian and multidien rhythms are equally important modulators of seizure timing. Finally, we evaluated whether in addition to these long time-scales rhythms of IEA, seizures themselves could have an impact on IEA. We did not find such a relation in our dataset when comparing pre- and post-seizure IEA (sign test on the median, p = .95, Fig. 3c).

4. Discussion

Our results show that circadian and multidien modulation of epileptic brain activity exist in rat models of temporal lobe epilepsy, with striking resemblance to human data (Baud et al., 2018). In particular, over many cycles, seizures recur at the same phases of the underlying circadian and multidien rhythms. This may account for the clustering of seizures observed in rodent studies (Williams et al., 2009). Multidien rhythms were relatively robust over time but varied in magnitude from one animal to the other, with a tendency to be more marked in the first group, that was injected with pilocarpine. As compared to humans, multidien rhythms were shorter in periodicity and more consistent across subjects, although not synchronous. The main periodicity seems to be set around six days in male rats and was not related to external factors. Circadian rhythms were not as strong as those found in humans, possibly related to polyphasic sleep in rodents.

A recent study in mice showed that circadian rhythmicity in seizures appeared as soon as four days after status epilepticus (Pitsch et al., 2017). We recorded animals during different periods (chronic vs. latent) post status epilepticus, with different stages of brain injury, and we also found that cycles of epileptic activity were present early after status epilepticus. Whether multidien rhythms of brain activity are present before the induction of status epilepticus was not assessed in this study.

While external circadian cues were present during these recordings (light-dark cycle), the multidien rhythms more likely reflect

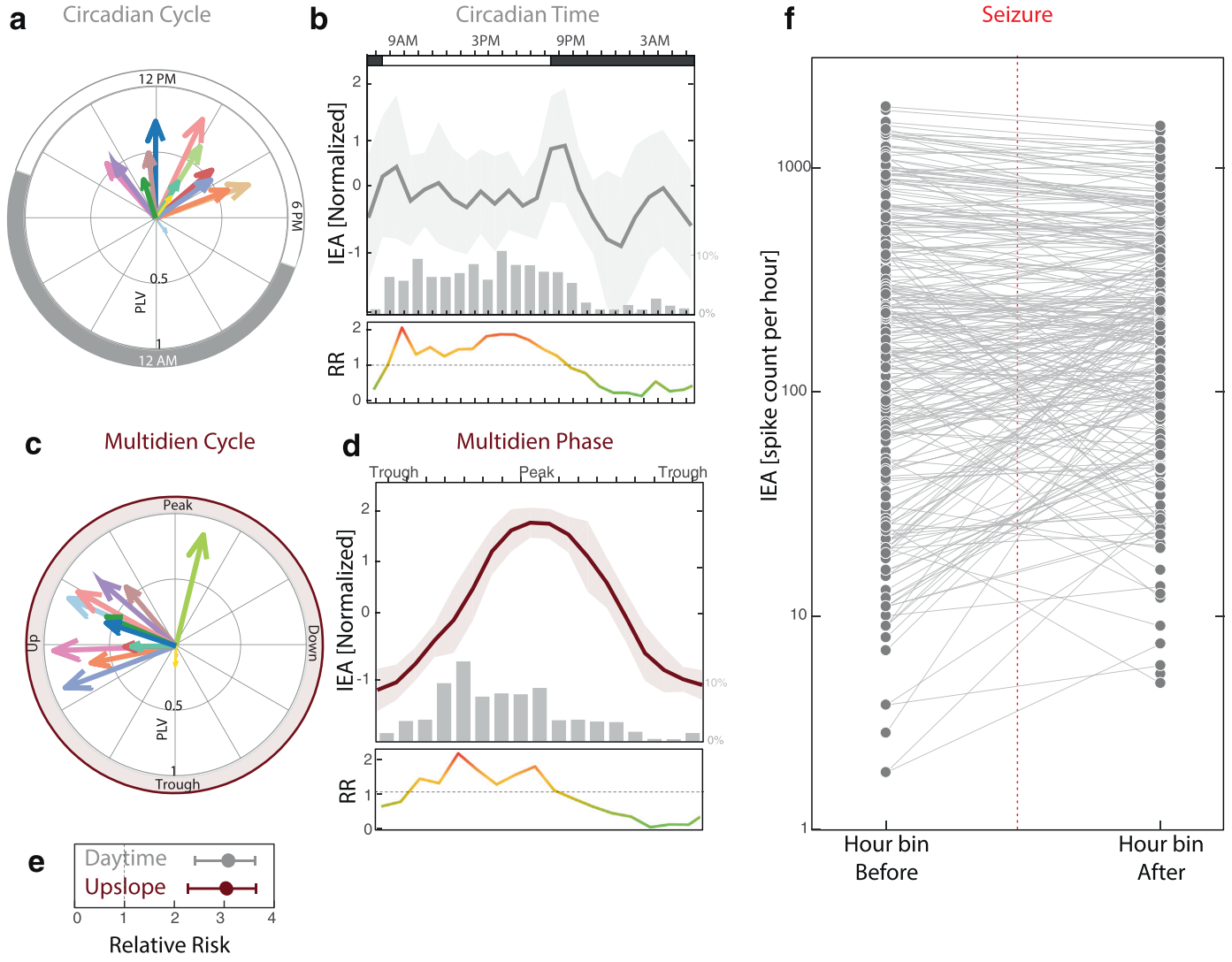

Fig. 3. Relationship between IEA and seizures. **(a, c)** Seizure clustering shown in polar plots for circadian time and multidien phase, respectively) representing each rat (colours match those of Fig. 1) as a vector pointing to the peak seizure time and with length representing the phase-locking value (PLV), an index of phase clustering. **(b)** Average normalized hourly spike rate (mean ± SD) and seizure probability density (grey bars) over the circadian cycle. White and grey rectangles represent daytime and nighttime, respectively. Note the overall clustering effect during daytime. Relative risk (RR) associated with each circadian time is plotted below as a colour gradient with green and red showing relatively low and high risk, respectively. **(d)** Average normalized daily spike rate (mean ± SD) and seizure probability density as a function of multidien phase. Note the overall clustering effect during the rising phase or close to the peak of the multidien cycle. High risk is present during the rising phase and near the peak. **(e)** Similar effect sizes shown as relative seizure risk (RR, 95% confidence interval) for daytime versus nighttime and upgoing (trough to peak) versus down going slope (peak to trough) for circadian and multidien cycles, respectively. **(f)** Effect of seizures on IEA, measuring IEA in hour bins before and after the occurence of a seizure. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

endogenous, rather than environmental mechanisms because different animals housed together did not show synchrony in nearly constant environment. This raises the question of the origin of multidien rhythms in epilepsy. Four-day multidien rhythm of IEA (D'Amour et al., 2015) and seizure likelihood (Maguire et al., 2005) synchronous to the ovarian cycle were shown in female rats and mice, respectively. It is tempting to speculate that, in addition to their circadian secretory profile, steroid hormones may also have a longer cycle in male rats (Jozsa et al., 2005). The existence of biological mechanisms regulating IEA in epilepsy on a slow time scale raises the possibility that such mechanisms may also regulate physiological activity in control individuals, a key issue that now needs to be addressed. Rodent models are well suited for the study of such slow rhythms in epilepsy and controls, as the periodicity (less than one week) is manageable experimentally. It is important to stress that, as for humans, each animal must be studied as an individual, as multidien rhythms are subject-specific.

It has been proposed that seizures can influence subsequent IEA (Gotman and Marciani, 1985). Under this hypothesis, multidien cycles of IEA observed here could be the result of occurrence of seizures at regular intervals (here with an about-six-day periodicity). However, IEA continued to cycle even in the absence of seizure. Moreover, seizures did not have an impact on IEA in the next hour in our dataset. Rather than looking for causal relationship, we propose that IEA and seizures are two facets of epileptic activity that are co-regulated by underlying biological rhythms. Their relationship is complex and can vary from one rat to the other, just like in humans (Baud et al., 2018). When focusing on the hours after seizures, IEA could be decreasing at the circadian level but increasing at the multidien level.

Limitations to this study include the fact that even during the chronic period of these models, epileptic brain activity may be non-stationary and still evolving in severity. To mitigate this limitation, we

opted to decompose the IEA signal using a wavelet methodology as it evaluates rhythms locally. Considering constant environmental conditions and measuring other brain variables that may fluctuate as well (e.g. sleep-wake cycle) will be important in future work. Here, the endogenous nature of multidien rhythms of epilepsy in rats is an inference rather than a conclusion resulting from a specifically designed chronobiological study with constant conditions. Such measures as varying or randomizing vivarium cleaning times, evaluating amounts of exposure to potential entraining influences such as light, noise, investigator contact, and others is necessary to demonstrate the exogenous vs. endogenous origin of such biological rhythms. A reasonable alternative conclusion regarding the idiosynchrasy of each animal's multidien rhythm is that they may arise from external rhythmic controllers that interact in unforseen ways to create rhythms that may not have physiologic importance. This preliminary work suggests that rigorous chronobiological experiments would be worthwile to undertake.

After decades of controversy on the immediate (within hours) relationship between spiking-rate and seizures, a general principle is emerging across species at larger time-scales that can only be comprehended with the use of long-duration chronic EEG. These cycles need to be taken into account to study the mechanisms of the chronobiology of epilepsy and improve seizure forecasting.

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Author contribution

MOB and CBer designed the study. AG, JB, and CBec collected the data. MOB and AG analyzed the data. MOB and CBer wrote the manuscript.

Potential conflicts of interest

None of the author has any conflict of interest to declare.

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