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Circadian control of neural excitability in an animal model of temporal lobe epilepsy

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ABSTRACT

We provide experimental evidence for the emerging imbalance in the firing activity of two distinct classes (type 1 and type 2) of population spikes recorded from the hippocampal area CA1 in an animal model of temporal lobe epilepsy. We show that during the latent period of epileptogenesis following status epilepticus inducing brain injury, there is a sustained increase in the firing rate of type 1 population spikes (PS1) with a concurrent decrease in the firing rate of type 2 population spikes (PS2). Both PS1 and PS2 firing rates are observed to follow a circadian rhythm and are in-phase in control rats. Following brain injury there is an abrupt phase shift in the circadian activity of the PS firing rates. We hypothesize that this abrupt phase shift is the underlying cause for the emergence of imbalance in the firing activity of the two PS. We test our hypothesis in the framework of a simple two-dimensional Wilson–Cowan model that describes the interaction between firing activities of populations of excitatory and inhibitory neurons.
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"Balanced" networks in the brain have been proposed to account for a large variety of observations of cortical activity, including the representation of sensory information, decision-making and sleep and motor control [7]. A loss of balance in the neuronal network activity has been associated with the emergence of a number of neurological diseases including Parkinson's [15], Autism [18], Schizophrenia [22], and Tourette's syndrome [20]. Epilepsy, a neurological disorder of the brain in which patients suffer from recurrent seizures, is associated with an imbalance in the activity of excitatory and inhibitory populations of neurons in the brain, in favor of the former, leading to an abnormal hyper-synchronous state of the brain [4]. A number of *in vitro* studies have demonstrated the mechanism of this hyperexcitability at the synaptic level [8,11]. However, the functional implication of these synaptic changes leading to the progression of the brain to an epileptic state following brain injury in an *in vivo* system is still unknown.

Here we investigate the temporal dynamics of firing rates of high amplitude short time duration (100–200 ms) spatially localized patterns of spontaneous electrical activity referred to as *population spikes* (PS), recorded from the hippocampal CA1 area in an animal model of temporal lobe epilepsy. The PS are the macroscopic physiological features representing the integrated synaptic activity in the extracellular space generated by synchronous firing of populations of neurons in the brain [3,5]. Depending on the shape profile two distinct classes of PS were identified in neural recordings from the hippocampal CA1 area, labeled as type 1 PS (PS1) with a large negative excursion in the measured electrical activity and type 2 PS (PS2) with a large positive excursion in the measure electrical activity.

We observe that the firing rates of the two PS (defined as the number of spontaneous PS events observed per unit of time) exhibit circadian-like 24 h periodicity and are locked in-phase in control rats. However, during the latent period, defined as the time period following brain injury until the time of generation of first spontaneous epileptic seizures, while the firing rates of these PS are circadian, they are now locked in anti-phase. This phase shift is abrupt occurring within a few days post-brain injury and persists throughout the latent period. During the latent period we also observe an evolving imbalance in the firing rate of the two PS (quan-

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tified through an estimate of the drift in the baseline firing rate), such that there is a sustained increase in the firing rate of PS1 with a concurrent sustained decrease in the firing rate of PS2. We theorize that *this evolving imbalance may be implicated in the generation of the first spontaneous epileptic seizure following electrically induced status epilepticus*.

Based on these experimental findings, we hypothesize that the strength of the interactions between the populations of neurons in the hippocampus is dependent on their phase relative to the daily circadian cycle. Brain injury abruptly disturbs the circadian phase, which in turn triggers homeostatic mechanisms [9] producing changes in the interaction strength between the populations of hippocampal neurons which in turn modulates their firing activity. We refer to this as the "circadian-control" (CC) hypothesis. We suggest that this may underlie the cause for the emerging imbalance in the firing activity of the PS in the hippocampal CA1 area.

Our experiment used adult male Sprague Dawley rats ($n = 9$) of age 63 days and weighing between 200 and 265 g, which were implanted with 16 microwire recording electrodes (microelectrodes) bilaterally into the CA1 and the dentate gyrus regions of the hippocampus. In addition, a bipolar, twisted Teflon-coated stainless steel electrode was implanted into the right ventral hippocampus for the induction of brain injury [16]. The experimental details are given in the methods section of the supplementary material accompanying this manuscript. After 1 week of baseline recordings at a sampling rate of 12 kHz, rats ($n = 7$) were electrically stimulated for 30 min until sustained behavioral and electrographic seizures were observed. After the rats stopped seizing they entered a seizure-free latent period. Subsequently, rats were housed in a controlled environment with 24 h symmetric day–night cycle and monitored with continuous video and extracellular brain electrical activity recordings. Videos were screened daily for spontaneous seizures. At the end of the recording session, the rats were sacrificed and the intact brains were excised. The isolated intact brains were imaged with high-field magnetic resonance microscopy to confirm the location of the electrode placement within the CA1 region of the hippocampus [19,21]. In total 7 (E1–E7) rats were electrically stimulated into status epilepticus. A total of 3 rats (E1–E3) entered the chronic phase of epileptic seizures, following an epileptogenic phase with a minimum of a Racine grade 3 first spontaneous seizure. Data presented in this work is primarily derived from these 3 epileptogenic rats. Table 1 in the supplementary methods section summarizes the mean duration of epileptogenic phase and the Racine seizure grade for all the electrically stimulated rats. The rats (E4–E7) provided us with additional data-points to validate epileptogenic circadian modulation in firing activity of PS events following status epilepticus.

In Fig. 1A, we show a representative example of the extracellular activity recorded from the hippocampal CA1 area of an epileptogenic rat during the latent period. Overlaid on the trace, in squares and circles, we show the PS1 and PS2 events, respectively. In Fig. 1B and C, we show the mean shape profile of the PS1 activity and the mean shape profile of the PS2 activity detected from the same rat over a latent time period of 12 days of recordings using a modification of a well-known spike clustering algorithm [12].

The time evolution of the normalized firing rates of PS1 and PS2 from an age-matched control rat (C1) and during the latent period in an epileptogenic rat (E2) is shown in Fig. 2A–D. Key points worth mentioning from Fig. 2 are: (1) there exists a circadian-like modulation in the firing rate of the PS1 and PS2 activity both during the control and the latent time periods; (2) there is no observed drift in the firing rate of the PS1 and PS2 activity in the data obtained from control rats (Fig. 2A and C); (3) during the latent period there is a marked upward drift in the firing rate of PS1 and a corresponding marked downward drift in the firing rate of the PS2 (Fig. 2B and D); (4) the circadian-like modulation of firing rates of PS1 and PS2

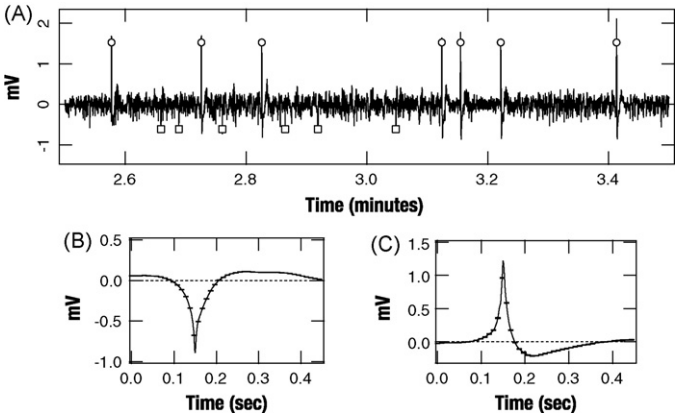

Fig. 1. (A) Sample 1 min trace of extracellularly recorded brain electrical activity from the hippocampal CA1 area. Overlayed on the trace are the times of occurrences of spontaneous population spikes, squares representing the type 1 population spikes (PS1) and circles representing the type 2 population spikes (PS2), (B) mean shape profile of PS1 and (C) mean shape profile of PS2.

are locked in-phase during the control period (Fig. 2E), while during the latent period the two PS oscillate anti-phase with respect to each other (Fig. 2F), with a marked shift in the rhythmic activity of PS1; (5) the average number of PS1 events per hour recorded during the latent period in the three epileptogenic rats are significantly greater ($p \approx 0.0026$; two-sample t-test) than that recorded during the control period, while the average number of PS2 events per hour are less ($p \approx 0.058$; two-sample t-test) during the latent period as compared to the pre-status epilepticus control period in these rat (Fig. 2G and H).

In Fig. 3, we summarize the results on the phase shift in the circadian-like firing activity of the two PS and the imbalance in their firing rates during the latent period from the PS data obtained from 3 epileptogenic (E1, E2, E3) and 2 controls (C1, C2). The imbalance in the firing rates is quantified by estimating the drift $D = \langle df/dt \rangle$ (f: firing rate) in the firing activity of both PS1 and PS2 through a least-squares fit of the drift in the baseline-firing rate to a straight line, $\Delta f = D\,\Delta t + c$. In Fig. 3A, we plot the mean value of D (with error bars representing the standard error corresponding to 95% confidence interval). From Fig. 3A, we see that, while the firing rates are in balance ($D \approx 0$) in controls, $D > 0$ during the latent period in epileptogenic rats ($p \approx 0.0044$, two-sample t-test). This implies an evolving imbalance in the firing activity of the two PS. The phase relationship between the circadian like firing activity of the PS1 and PS2 is quantified through a least squares-fit of the detrended-modulo 24 firing rate data (detrending implies the removal of the drift in the baseline of the circadian-like rhythm of firing rate) with a sinusoidal function $f(t) = a\sin(\omega t + b)$, with $\omega = 7.2722 \times 10^{-5}$ Hz. The phase is associated with the time T_X (X = PS1, PS2) of maximum value obtained by $f(t)$ and is given as: $\Phi_X = 2\pi T_X/24$. The mean value of phase for the two PS (with standard error corresponding to 95% confidence interval) is shown in Fig. 3B. The relative phase difference is quantified as $\Delta\Phi = |\Phi_{PS1} - \Phi_{PS2}|$. In-phase firing activity of the two PS is considered to occur when $\Delta\Phi \leq \pi/2$. We see that during the control period, the two PS events are phase-locked with a lag of around $\pi/4$ radians, however during the latent period, the phase lag increases to approximately $3\pi/4$ radians. The phase shift $\Delta\Phi$ in the relative phase for the epileptogenic rat is significantly greater than that for the control rat ($p \approx 7.3775 \times 10^{-5}$, two-sample t-test).

We have proposed a CC hypothesis, which suggests that the evolving imbalance in the PS1 and PS2 firing rates is the result of an abrupt phase-shift in their circadian activity. In order to study the implications of this hypothesis in the context of our experimental results as presented above, we consider a simple two-dimensional

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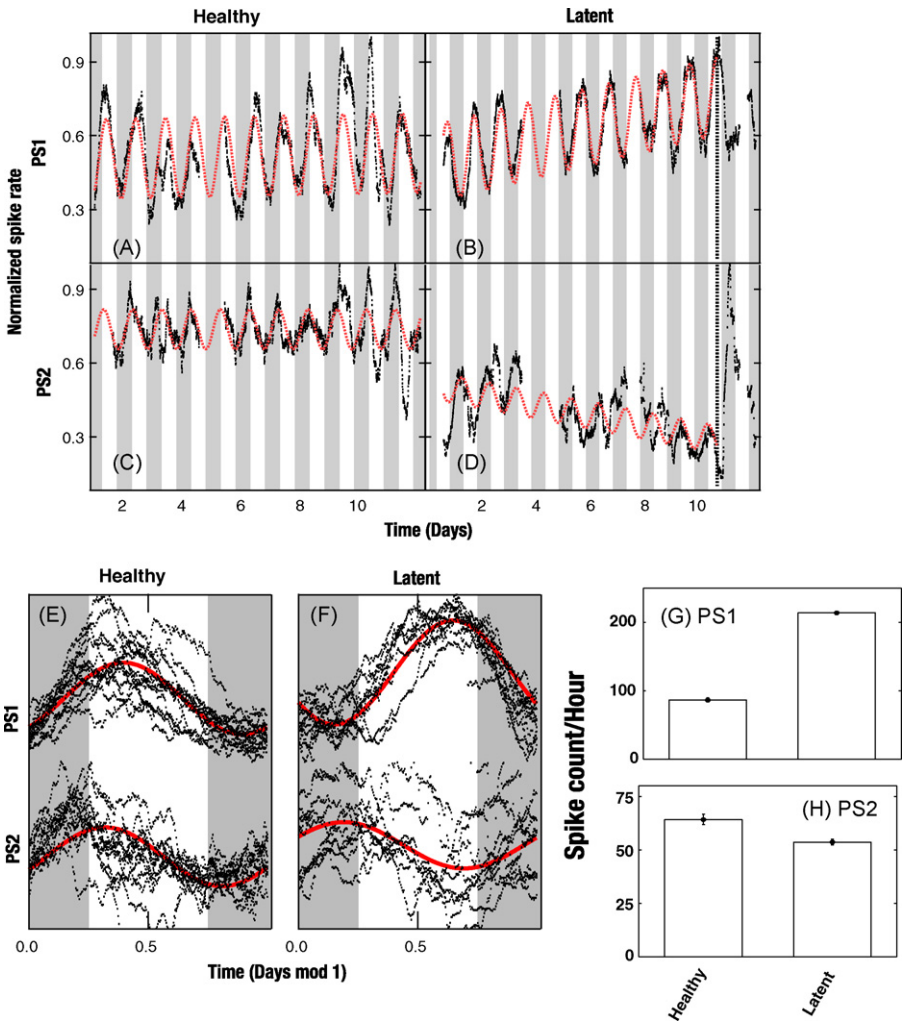

Fig. 2. In A–D we shown the firing rates of type 1 (PS1) and type 2 (PS2) population spikes recorded from a control rat (C1) and an epileptogenic rat (E2) during the latent period. Red dotted lines represent the least-squares fit of the firing rate data to a function $f(t) = at + b\sin((t + c)$ where $\omega = 7.2722 \times 10^{-5}$ Hz. The fitted line is shown as a guide for the eye to follow the circadian pattern in the firing activity of PS. The gaps in the firing rate data (around day 5 in both control and latent period) reflect the absence of recordings on those days due to technical problems. The phase of circadian oscillations of PS1 and PS2 from the control rat and the epileptogenic rat are shown in (E) and (F), respectively. The red line is a least squares fit to the phase data with a function $f(t) = \alpha\sin(\omega t + \beta)$, where $\omega = 2\pi$. The diurnal day–night cycle is shown in the background. The dotted line in (B) and (D) shows the time of occurrence of the first spontaneous epileptic seizure. The average number of PS1 and PS2 events observed per hour during the pre-status epilepticus control time period and the epileptogenic latent period in rat E2 are shown in (G) and (F), respectively.

Wilson–Cowan model for the interaction between the PS1 and PS2 activity. The Wilson–Cowan model describes the dynamics of interaction firing activities of populations of excitatory and inhibitory neurons [23]. In the Fig. 4A and B, we show the schematic diagram of the interactions between the PS in controls and the epileptogenic rats under the assumption that PS1 and PS2 represent the synchronous firing of populations of excitatory and inhibitory neurons, respectively. We have made two specific assumptions in the development of our modified version of the Wilson–Cowan model for PS1 and PS2 interactions. (1) PS1 represents the synchronous firing of populations of excitatory neurons. This assumption is based on the observation that the firing rate of PS1 during the latent period of epileptogenesis increases as one gets nearer in time to the first spontaneous seizure. (2) PS2 events represent the synchronous firing of population of inhibitory neurons. This assumption is based on the observation that the firing rate of PS2 decreases during the latent period of epileptogenesis. These assumptions allow us to incorporate anatomical connectivity patterns within the CA1 region [10,13,14] into the model to test our hypothesis that the relative shift in the circadian phase results in a sustained increase in the firing rate of PS1, and a concurrent decrease in the firing rate of PS2. However, we note that our experimental approach of continuous long-term *in vivo* recording using a chronically implanted microwire electrode array precludes us from conclusively demonstrating the synaptic origin of the population spikes reported here. In summary, epileptic seizures are known to be associated with increased excitability within the CA1 pyramidal cells. Thus, the association of PS1 patterns with excitation and the PS2 pattern with inhibition conforms to the notion of increased excitation within the hippocampus resulting in the development of spontaneous epileptic seizures. If, then, within the framework of our modified Wilson–Cowan model, we take a coupled pair of ordinary differential equations (ODEs) governing the evolution of $X(t)$ and $Y(t)$ representing the firing rates of PS1 and PS2, respectively, we have:

$$\begin{aligned} \tau_x \frac{dX}{dt} &= -X + S(A\ \sin(\omega t + \Delta\Phi) + c_1 X - c_2 Y + P) \\ \tau_y \frac{dY}{dt} &= -Y + S(B\ \sin(\omega t) + c_3 X - c_4 Y + Q) \end{aligned} \tag{1}$$

where $\tau_x \ll \omega^{-1}$ and $\tau_y \ll \omega^{-1}$. $S(x) = [1 + \exp(-\alpha x)]^{-1}$ is the response function [23]. c_j ($j = 1 \ldots 4$) represents the strength of local interactions between the population of excitatory and inhibitory

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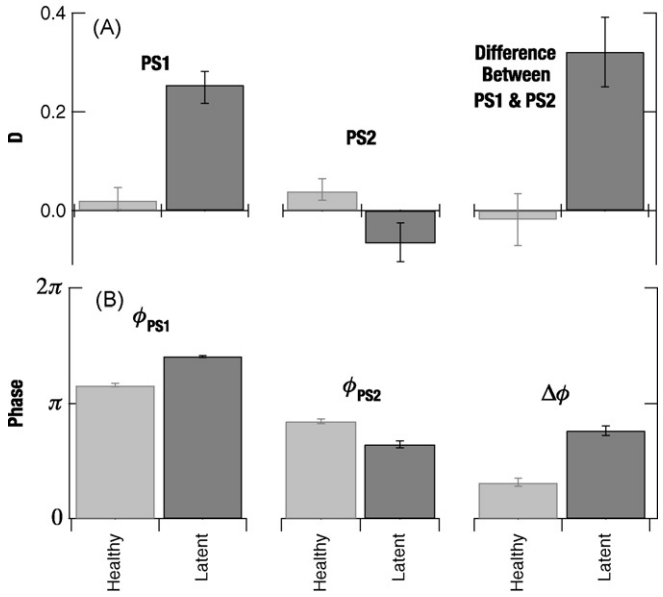

Fig. 3. The mean amplitude of the drift in the firing rate, D and the circadian phase shift in the relative firing activity of the type 1 (PS1) and type 2 (PS2) population spikes during the control and the latent periods are shown in (A) and (B), respectively.

neurons in the CA1 area. The necessary condition for the coupled pair of ODEs in Eq. (1), to exhibit intrinsic stable limit cycle in absence of external sinusoidal driving ($A = B = 0$) is, $c_1 \neq 0$ [17]. However, based on our assumptions (See Fig. 4A and B), c_1 represents the recurrent interaction between populations of excitatory

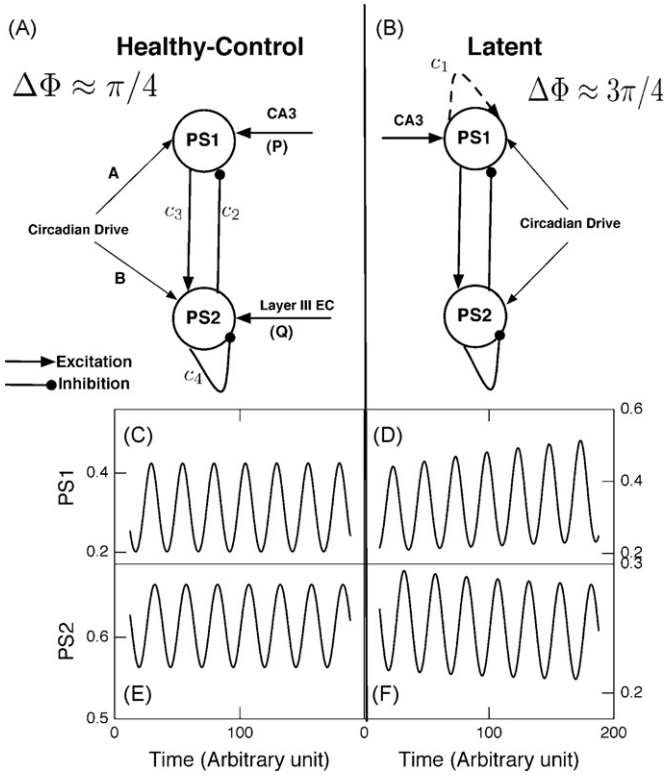

Fig. 4. In A and B we present the schematic diagram of the interaction between the type 1 (PS1) and the type 2 (PS2) population spikes in control and the latent period. The PS1 and PS2 firing activity generated by the model (Eq. (1)) for the control and the latent period are shown in (C) and (D). The model parameters are, $A = 0.5$, $B = 0.25$, $\omega = 2\pi/25$, $\tau_x = \tau_y = 1$, $\tau_L = 200$, and $p = 0.025$ for both the control and the latent time periods. $Q = 1.9$ for control period and $Q = 0$ for the latent time period.

neurons in the CA1 area that give rise to the PS1 activity. Moreover, it is known from the anatomy of network connectivity within the CA1 network, there are sparse recurrent connections between the CA1 excitatory neurons [13]. Additionally, the synaptic time scale of interaction between the populations of neurons in the CA1 is much faster than the circadian-like activity of PS (Fig. 2). Therefore, in our modeling of the firing activity of the two PS through Eq. (1) above, we assume that the origin of circadian-like oscillations in the hippocampal CA1 is from an external source. Although we are not aware of any direct anatomical pathway into the CA1 through which the circadian drive can influence the CA1 activity, there is evidence for the influence of a circadian cycle or drive on synaptic activity within the CA1 [2,6].

Accordingly, the circadian influence in Eq. (1) is modeled through an external sinusoidal input to X and Y. A and B represent the strength of external circadian drive onto both PS1 and PS2 activity, respectively, and $\Delta\Phi$ represents the phase difference in the time of circadian drive to the two classes of population spikes that are modulated following brain injury. P represents the excitatory input from the hippocampal CA3 Shaffer collateral–commissural projections onto the CA1 excitatory neurons [1]. Q represents the excitatory input onto the CA1 interneurons via the temporoammonic pathway from the layer III of the entorhinal cortex [14]. Finally, according to the CC hypothesis, the asymptotic strength of interaction between the PS1 and PS2 activity, c_j^∞ is considered to be dependent on the phase-lag $\Delta\Phi$ of the circadian input that drives the PS1 and PS2 firing activity. The asymptotic strength of the interaction terms is modeled through a linear dependence on $\Delta\Phi$, $c_j^\infty = \alpha_j + \beta_j \Delta\Phi$ and the differential equation governing the evolution of c_j is given by $dc_j/dt = (c_j^\infty - c_j)/\tau_L$, where $\tau_L \ll \omega^{-1}$. The parameters used in our simulation example are $(\alpha_1, \alpha_2, \alpha_3, \alpha_4) = (0.65, -0.015, 0, 0.32)$ and $(\beta_1, \beta_2, \beta_3, \beta_4) = (0, 0.05, 0.1, 0.5)$. In Fig. 4C–F we show the output from our model, simulating the conditions from our experimental findings (Figs. 2 and 3). For $\Delta\Phi = 3\pi/4$, representing the condition observed in controls (Fig. 2A and C), we see from Fig. 4C and E that the firing rates of both PS1 and PS2 exhibit circadian rhythmicity with the maintenance of balance in the relative firing rate of two patterns. During the latency period, there is a sudden shift in the phase of circadian drive onto two populations of interacting neurons resulting in $\Delta\Phi = 3\pi/4$. This, in turn, results in modulation in the interaction terms c_j through the homeostatic learning rule. Additionally, due to the selective loss of neurons in layer III of the entorhinal cortex in the animal model of limbic epilepsy [10], parameter $Q = 0$. As a result, there is a sudden decrease in the firing rate of PS2 activity. The non-linear interaction between the firing rates of PS through Eq. (1), then results in further decrease in firing activity of PS2 and a corresponding increase in the firing rate of PS1 activity (Fig. 4D and F). Thus, using the constraints imposed through the CC hypothesis and the anatomy of network connectivity within the CA1, this simple model (Eq. (1)) is able to replicate our experimental finding of evolving imbalance in firing activity of the two PS following brain injury.

All the simulation results presented above were performed using a 4th order Runge–Kutta method for differential equations. The source code will be made available from SST upon request.

In conclusion, we present experimental evidence for an evolving imbalance in brain excitability following injury, as characterized by the firing activity of the two distinct classes of PS. We note that the synaptic origin of these PS events cannot be discerned in the context of the experimental paradigm of continuous long-term *in vivo* recordings of extracellular activity within the hippocampus. We have shown that the imbalance in the PS firing rates is accompanied with a phase shift in the circadian rhythm of their relative firing activity. Based on this experimental observation we have proposed a circadian control mechanism for the phase-induced

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imbalance in the observed firing activity of the two PS. We test the implications of the circadian control of PS activity using a modified two-dimensional Wilson–Cowan model. Two key assumptions: the recorded PS events in the hippocampal CA1 area represent interaction between excitatory and inhibitory population of neurons, and the firing rate of these PS is under circadian control, allowed us to model the observed temporal dynamics of PS within the framework of the Wilson–Cowan model, under the two conditions of control and epileptogenic state of the brain, in order to elucidate the circadian influence on the pathophysiology of an evolving brain disease.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neulet.2009.03.057.

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