Self-connection of Thalamic Reticular Nucleus Modulating Absence Seizures

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Abstract. Accumulating evidence has suggested that the corticothalamic system not only underlies the onset of absence seizures, but also provides functional roles in controlling absence seizures. However, few studies are involved in the roles of self-connection of thalamic reticular nucleus (TRN) in modulating absence seizures. To this end, we employ a biophysically based corticothalamic network mean-field model to explore these potential control mechanisms. We find that the inhibitory projection from the TRN to specific relay nuclei of thalamus (SRN) can shape the self-connection of TRN controlling absence seizures. Under certain condition, the self-connection of TRN can bidirectionally control absence seizures, which increasing or decreasing the coupling strength of the self-connection of TRN could successfully suppress absence seizures. These findings might provide a new perspective to understand the treatment of absence epilepsy.

Keywords: Absence seizures · Spike and wave discharges · Thalamic reticular nucleus · Self-connection · Mean-field model

1 Introduction

Absence seizures, recognized as the classical characteristics of absence epilepsy, abruptly start and terminate, during which bilaterally synchronous 2–4 Hz spike and wave discharges (SWDs) can be easily observed on the electroencephalogram (EEG), especially in childhood absence epilepsy patients [1,2]. In the past two decades, a growing body of evidence has suggested that the genesis of absence seizures is closely associated with abnormal excessive neural oscillations within corticothalamic network [3–5]. Based on these findings, it is reasonable to speculate that appropriately tuning interactions between cerebral cortex and thalamus to abate these abnormal neural oscillations might provide a manner to suppress absence seizures.

Both the inside and outside regulations of corticothalamic network have been suggested to successfully terminate absence seizures [6–13]. For example, in terms of the inside modulation, previous animal experimental findings suggested that both thalamic stimulation and closed-loop optogenetic control of thalamus could interrupt epileptic seizures [9,10]. Recently, a computational model study also demonstrated that the thalamic feed-forward inhibition contributes to suppressing absence seizures [13]. Unlike these inside modulations, several external nuclei of corticothalamic network, such as basal ganglia and cerebellar nuclei, also have been suggested to play crucial roles in controlling absence seizures [6–8,11,12,14]. Particularly, computational simulations suggested that the basal ganglia not only could bidirectionally control absence seizures through the direct nigro-thalamic pathway, but also could suppress absence seizures via the pallido-cortical pathway [11,12]. Taken together, both animal experiments and computational simulations suggest that appropriately tuning abnormal interactions within the corticothalamic network could effectively prevent absence seizures.

Anatomically, the thalamic reticular nucleus (TRN) lies like a shell between cerebral cortex and specific relay nuclei of thalamus (SRN), and entirely composes GABAergic neurons. Note that the TRN-SRN pathway has been demonstrated to contribute to modulating absence seizures by the feed-forward or feedback inhibition for SRN neurons [13,15]. Actually, besides the two types of inhibition, the self-inhibition of TRN neurons might also participate in suppressing absence seizures. However, few studies are involved in the potential functional roles of self-connection of TRN in controlling absence seizures [15–18]. Although past animal experimental studies have suggested that loss of recurrent inhibition in TRN in β_3 knockout mice might evoke absence epilepsy [18], how this recurrent inhibition participates in suppressing absence seizures is still poorly understood. Therefore, in this study, we employ a biophysically based corticothalamic network mean-field model to investigate the potential control roles played by the self-connection of TRN. We find that the self-connection of TRN could bidirectionally control absence seizures under certain condition, which might provide some new insights into the treatment of absence epilepsy.

2   Methods and Analysis

2.1   Computational Model

Similar to previous studies [11–13], we use the main epileptogenic factor that the slow kinetics of GABA$_B$ receptors in SRN to induce absence seizures. Here, we modify the corticothalamic network by inducing the self-connection of TRN, as shown in Fig. 1. Notably, four neural populations contained in the corticothalamic network are excitatory pyramidal neurons (E, e), inhibitory interneurons (I, i), TRN (r) and SRN (s). The connections between neural populations are primarily mediated by glutamate (red arrow lines) and GABA (blue lines with round dots), which the solid and dashed blue lines represent the GABA$_A$ and GABA$_B$ mediated inhibitory connections, respectively. The external inputs to the SRN (ϕ_n) show the non-specific thalamic inputs.
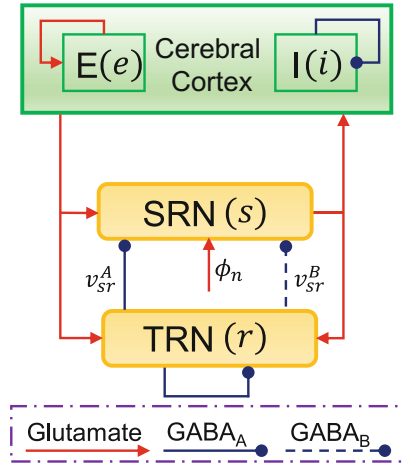
Fig. 1. The framework of the corticothalamic network. In the cerebral cortex, we mainly focus on excitatory pyramidal neurons (E, e) and inhibitory interneurons (I, i). The thalamus consists of thalamic reticular nucleus (TRN, r) and specific relay nuclei (SRN, s). Notably, the red arrow lines show the excitatory connections mediated by glutamate, and the blue lines with round dots depict the inhibitory connections mediated by GABA, including GABA$_A$ (solid blue lines) and GABA$_B$ (the dashed blue line). External inputs to the SRN (ϕ_n) represent the non-specific thalamic inputs (Color figure online)

To describe the neural dynamics of corticothalamic network, we employ the mean-field model proposed by Robinson and his colleagues [19–21], in which for a given neural population a, three main state variables that the mean membrane potential V_a, mean firing rate Q_a and presynaptic activity ϕ_a are considered. Accordingly, we build the corticothalamic network mean-field model, as shown in the Appendix.

It is worth noting that we set $v_{se} = 2.4$ mV s and $\tau = 50$ ms to evoke absence seizures in this model, which is consistent with previous studies [13]. But for more details about the model parameter values and the related physiological significances, we refer the reader to previous literature [11–13, 19–22].

2.2   Data Analysis

In the current study, we use the standard fourth-order Runge-Kutta method with fixed step length of 0.05 ms to solve the corticothalamic network mean-field model, and all model simulations are performed on the MATLAB software (Mathworks, Natick, MA). Here, two primary data analysis techniques adapted from previous studies have been applied to analyze cortical neural oscillations [11–13]. One is the bifurcation analysis that based on the stable local minimum and maximum values of cortical neural oscillations ϕ_e in a single oscillatory period. According to the number of extreme values and amplitude of ϕ_e, we can easily determine the dynamical states of cortical oscillations. The other one is the frequency analysis. We use the Fast Fourier transform to calculate the power

spectral density of ϕ_e, based on which we can identify the dominant frequency that corresponding to the maximum of power spectral density. Combining the dynamical states and dominant frequency of cortical neural oscillations ϕ_e, we can outline the boundary of SWDs in the typical range 2–4 Hz.

3   Results

3.1   Dynamical States of Cortical Oscillations

In the modified corticothalamic network mean-field model, we first examine whether the model could reproduce typical absence seizures. To this end, we calculate the dynamical states and dominant frequency of cortical oscillations ϕ_e in the two-dimensional parameter space $(-v_{sr}^{A,B}, -v_{rr})$ (Fig. 2). We find that
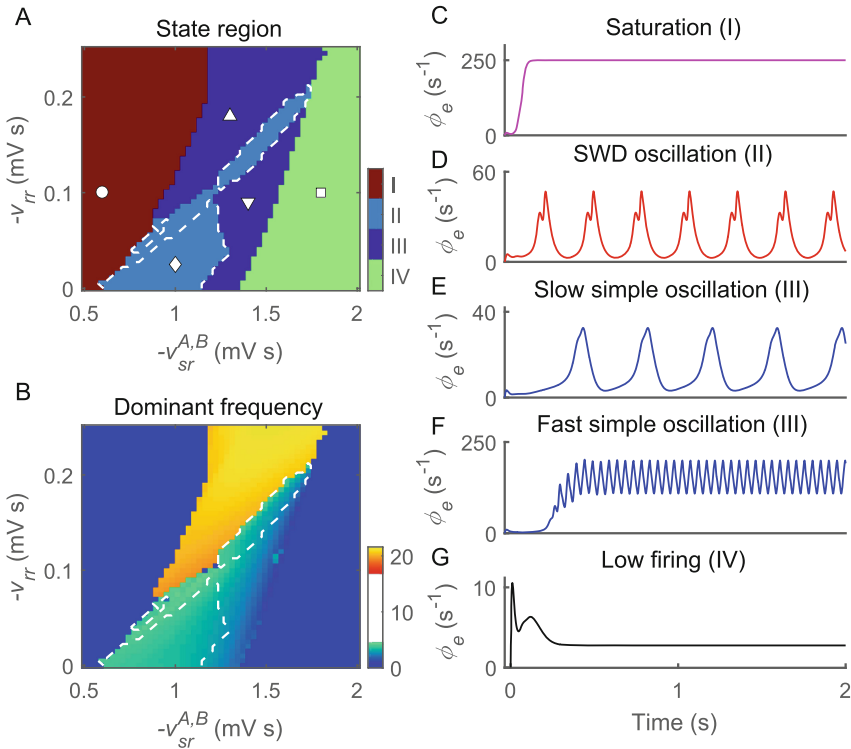

Fig. 2. Dynamical states of cortical oscillations. (A) Four different dynamical states of cortical oscillations distributed in the two-dimensional parameter space $(-v_{sr}^{A,B}, -v_{rr})$ are saturation state (I), SWD oscillation state (II), simple oscillation state (III) including slow and fast simple oscillations, and low firing state (IV). (B) The distribution of dominant frequency of cortical oscillations in the parameter space $(-v_{sr}^{A,B}, -v_{rr})$. Note that the regions of the typical 2–4 Hz SWDs are surrounded by white dashed lines in (A) and (B). (C-G) The time series of cortical oscillations (ϕ_e) and the corresponding parameter values are shown in (A) with different white symbols that "○" (I), "◇" (II), "△" and "▽" (III), and "□" (IV).
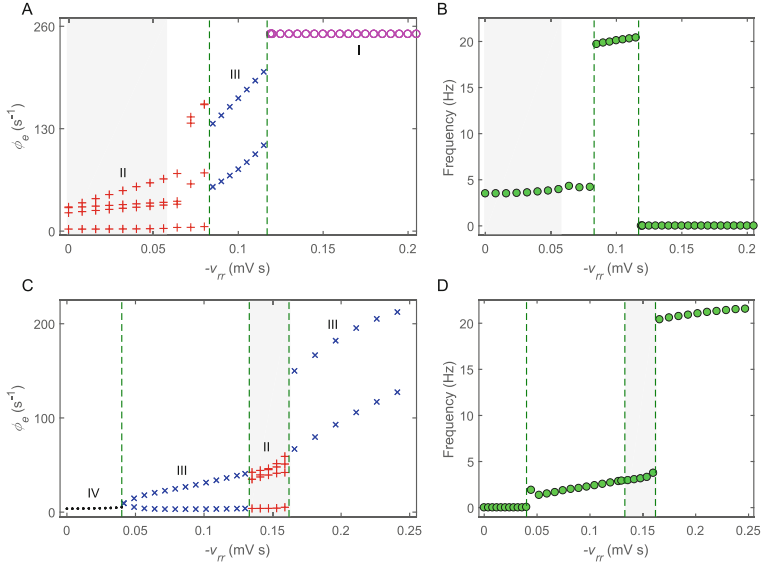
Fig. 3. Roles of self-connection of TRN in modulating absence seizures. (A) The dynamical state analysis of cortical oscillations ϕ_e with $-v_{sr}^{A,B} = 1.0$ mV s. Gradually increasing the coupling strength of self-connection of TRN $(-v_{rr})$ could push cortical oscillations ϕ_e from the SWD oscillation state (II) to simple oscillation state (III) and to saturation state (I). (B) The dominant frequency of cortical oscillations ϕ_e that corresponding to those in (A) changes with the increase of $-v_{rr}$. (C, D) Same as in (A) and (B), but with $-v_{sr}^{A,B} = 1.46$ mV s. The dynamical state analysis (C) and dominant frequency (D) of cortical oscillations ϕ_e changes with the enhancement of $-v_{rr}$. Notably, all gray shaded regions show the range of typical 2–4 Hz SWDs

four dynamical states that the saturation state (I), SWD oscillation state (II), simple oscillation state (III) and low firing state (IV) are distributed in this parameter space (Fig. 2A). Correspondingly, the distribution of the dominant frequency of ϕ_e for each dynamical state can be clearly observed (Fig. 2B). Furthermore, we outline the boundary of regions of the typical 2–4 Hz SWDs (as shown in Fig. 2A and B, the areas surrounded by white dashed lines), for which are often observed in real patients. These findings suggest that the model can replicate absence seizures, as well as other brain dynamical states. Moreover, the coupling strength of self-connection of TRN $(-v_{rr})$ can affect the transition between different dynamical states. Additionally, to show the firing mode of each dynamical state, we select five groups of parameters and calculate the corresponding cortical oscillations ϕ_e (Fig. 2C–G). Interestingly, we find that the strength of $-v_{rr}$ has a significant influence on the dominant frequency of cortical simple oscillation state (III), which relatively strong and weak $-v_{rr}$ are corresponding to fast and slow simple oscillations, respectively (Fig. 2E and F). For this case, we speculate that strong $-v_{rr}$ might weaken the effect of GABA$_B$ in the TRN-SRN pathway.

3.2   The Self-connection of TRN Modulating Absence Seizures

To further uncover the roles of self-connection of TRN in controlling absence seizures, and according to the results obtained in Fig. 2A and B, we select two different values of $-v_{sr}^{A,B}$ to observe the transition of cortical dynamical states. First, we set $-v_{sr}^{A,B}$=1.0 mV s. Gradually enhancing the coupling strength $-v_{rr}$, we find that the cortical dynamical state switches from the SWD oscillation state (II) to the simple oscillation state (III), and to the saturation state (I) (Fig. 3A). Correspondingly, the dominant frequency of ϕ_e smoothly change with the increase of $-v_{rr}$, but significantly increase in the simple oscillation state (III) (Fig. 3B). These findings suggest that appropriately increase the coupling strength $-v_{rr}$ can effectively interrupt absence seizures. Then, we change the value of $-v_{sr}^{A,B}$ to 1.46 mV s. Similarly, we calculate the transition of cortical dynamical states and corresponding dominant frequency. In this case, we find that the cortical dynamical state switches from the low firing state (IV) to the slow simple oscillation state (III) at first, and then to the SWD oscillation state (II), and next to the fast simple oscillation state (III) (Fig. 3C). A sudden jump of the dominant frequency can be observed when the cortical dynamical state is in the fast simple oscillation state (III) (Fig. 3D). Obviously, these findings suggest that there exists a bidirectional control region for the coupling strength $-v_{rr}$, in which appropriately enhancing or decreasing the coupling strength $-v_{rr}$ can achieve the control of absence seizures, implying that $-v_{rr}$ can bidirectionally modulate absence seizures under this condition.

4   Conclusions

In the present study, we found that the self-connection of TRN plays crucial roles in modulating absence seizures. Particularly, the coupling strength of TRN-SRN pathway that mediated by GABA$_\mathsf{A}$ and GABA$_\mathsf{B}$ can shape the self-connection of TRN suppressing absence seizures. Moreover, the coupling strength $-v_{rr}$ has a significant effect on the dominant frequency of cortical oscillations in the simple oscillation state. Importantly, under certain condition, enhancing or decreasing the coupling strength $-v_{rr}$ can terminate absence seizures, implying that the self-connection of TRN could bidirectionally control absence seizures. It should be noted that the corticothalamic network mean-field model makes specific predictions for the functional roles of recurrent inhibition of TRN in suppressing absence seizures that are testable in animal models of absence epilepsy. Therefore, these findings provide a new perspective to design animal experiments, as well as some novel insights into the treatment of absence epilepsy.

Appendix: The Corticothalamic Network Mean-Field Model

To obtain the corticothalamic network mean-field model, we assume that absence seizures are involved in the whole brain, so that the spatial effect is ignored in this model. Also, based on the assumption that intracortical connections are proportional to the synapses involved, we have $V_i = V_e$ and $Q_i = Q_e$. Note that both of these assumptions are in line with previous studies [11–13, 20, 21]. Accordingly, the corticothalamic network mean-field equations are given in the following:

$$\frac{\mathrm{d}\phi_e(t)}{\mathrm{d}t} = \dot{\phi}_e(t) \tag{1}$$

$$\frac{\mathrm{d}\dot{\phi}_e(t)}{\mathrm{d}t} = \gamma_e^2 \left\{ -\phi_e(t) + F[V_e(t)] \right\} - 2\gamma_e \dot{\phi}_e(t) \tag{2}$$

$$\frac{\mathrm{d}V_e(t)}{\mathrm{d}t} = \dot{V}_e(t) \tag{3}$$

$$\frac{\mathrm{d}\dot{V}_e(t)}{\mathrm{d}t} = \alpha\beta \left\{ -V_e(t) + v_{ee}\phi_e(t) + v_{ei}F[V_e(t)] + v_{es}F[V_s(t)] \right\} - (\alpha+\beta)\dot{V}_e(t) \tag{4}$$

$$\frac{\mathrm{d}V_r(t)}{\mathrm{d}t} = \dot{V}_r(t) \tag{5}$$

$$\frac{\mathrm{d}\dot{V}_r(t)}{\mathrm{d}t} = \alpha\beta \left\{ -V_r(t) + v_{re}\phi_e(t) + v_{rs}F[V_s(t)] + v_{rr}F[V_r(t)] \right\} - (\alpha+\beta)\dot{V}_r(t) \tag{6}$$

$$\frac{\mathrm{d}V_s(t)}{\mathrm{d}t} = \dot{V}_s(t) \tag{7}$$

$$D_s = \alpha\beta \left\{ -V_s(t) + v_{se}\phi_e(t) + v_{sr}^A F[V_r(t)] + v_{sr}^B F[V_r(t-\tau)] + \phi_n \right\} \tag{8}$$

$$\frac{\mathrm{d}\dot{V}_s(t)}{\mathrm{d}t} = D_s - (\alpha+\beta)\dot{V}_s(t) \tag{9}$$

Here, ϕ_a ($a = e, i, r, s$) shows the propagating axonal fields of the neural population a, v_{ab} describes the coupling strength from the neural population b to the neural population a. The inverses of α and β represent the decay and rise time constants, respectively. γ_e governs the temporal damping rate of cortical excitatory pulses. V_a denotes the mean membrane potential, through which the mean firing rate Q_a can be obtained with the sigmoid function $F[V_a(t)]$ [11, 12, 20] given by

$$Q_a(t) \equiv F[V_a(t)] = \frac{Q_a^{max}}{1 + \exp[-\frac{\pi}{\sqrt{3}}\frac{(V_a(t)-\theta_a)}{\sigma}]} \tag{10}$$

where Q_a^{max} denotes the maximum firing rate, θ_a shows the mean firing threshold, and σ is the standard deviation of the mean firing threshold.

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