Control of absence seizures induced by the pathways connected to SRN in corticothalamic system

Bing Hu · Daqing Guo · Qingyun Wang

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Abstract The cerebral cortex, thalamus and basal ganglia together form an important network in the brain, which is closely related to several nerve diseases, such as parkinson disease, epilepsy seizure and so on. Absence seizure can be characterized by 2–4 Hz oscillatory activity, and it can be induced by abnormal interactions between the cerebral cortex and thalamus. Many experimental results have also shown that basal ganglia are a key neural structure, which closely links the corticothalamic system in the brain. Presently, we use a corticothalamic-basal ganglia model to study which pathways in corticothalamic system can induce absence seizures and how these oscillatory activities can be controlled by projections from the substantia nigra pars reticulata (SNr) to the thalamic reticular nucleus (TRN) or the specific relay nuclei (SRN) of the thalamus. By tuning the projection strength of the pathway “Excitatory pyramidal cortex–SRN”, “SRN–Excitatory pyramidal cortex” and “SRN–TRN” respectively, different firing states including absence seizures can appear. This indicates that absence seizures can be induced by tuning the connection strength of the considered pathway. In addition, typical absence epilepsy seizure state “spike-and-slow wave discharges” can be controlled by adjusting the activation level of the SNr as the pathways SNr–SRN and SNr–TRN open independently or together. Our results emphasize the importance of basal ganglia in controlling

absence seizures in the corticothalamic system, and can provide a potential idea for the clinical treatment.

Keywords Basal ganglia · Absence seizures · Control

Introduction

Absence seizure or “petit mal” seizure is one of the main characteristic form of generalized epilepsy. In 1941, Jasper and Kershman firstly analyzed the electroencephalograms (EEGs) of patients with petit mal absence seizures. They found that absence seizures were characterized by an abrupt onset and termination of the SWDs in two brain hemispheres and by a high interhemispheric synchronization of spike-wave activity (Jasper and Kershman 1941). And, it has been shown that the spike-wave activity is mainly with the frequency of 2–4 Hz (Crunelli and Leresche 2002). In addition, the absence seizures can originate from the mutual roles between the cerebral cortex and the thalamus, which form the corticothalamic circuits. This can be witnessed by a number of clinical researches and computational modeling studies (Breakspear et al. 2006; Coenen and van Luijckelaar 2003; Marten et al. 2009; Robinson et al. 2002; Timofeev and Steriade 2004). For example, Roberts and Robinson (2008) used a physiologically based continuum model (i.e., the mean-field model) of the corticothalamic system to explain the basic mechanisms of the seizure activity. In particular, they emphasized the effect of delays of the thalamocortical and corticothalamic projections on the onset and termination of seizures. Rodrigues et al. (2009) explored the dynamic transition behavior between spike-wave oscillations and epileptic seizures. Marten et al. (2009) studied the onset of polyspike complexes in a mean-field of human and its application to

B. Hu · Q. Wang (✉)
Department of Dynamics and Control, Beihang University,
Beijing 100191, China
e-mail: nmqingyun@163.com

D. Guo
Key Laboratory for Neuro Information of Ministry of Education,
School of Life Science and Technology, University of Electronic
Science and Technology of China, Chengdu 610054, China

absence epilepsy. Interestingly, by a computational modeling, Volman et al. (2011) have shown that under some circumstances, gap junctions among neurons can control the collective activity with the seizures. Recently, a brief history on the oscillating roles of thalamus and cortex in absence seizures was elaborated in Ref. (Massimo 2012).

The basal ganglia are mainly composed of the striatum, subthalamic nucleus (STN), globus pallidus external segment (GPe), globus pallidus internal segment (GPi), substantia nigra pars reticulata (SNr), substantia nigra pars compacta (SNc) (Humphries and Gurney 2012), which are the important structure in the brain and closely related to Parkinson's disease, motor control, epilepsy and so on (Gatev and Wichmann 2008; Groenewegen 2003; Park and Rubchinsky 2012; Paz et al. 2005). Based on the viewpoint of anatomy, it is well known that the basal ganglia and the corticothalamic circuit closely contact with each other. The corticothalamic circuit sends many projections to the basal ganglia, and in turn the basal ganglia sends direct and indirect outputs to the corticothalamic circuit (van Luijtelaaar and Sitnikova 2006). Resultantly, the basal ganglia can have a great impact on the activity of the corticothalamic circuit. Hence, it is expected that the basal ganglia can play an important role in the control of absence seizures in the corticothalamic circuit. Some existing experimental results can support this viewpoint (Biraben et al. 2004; Deransart and Depaulis 2002). However, due to the complicated interactions between the basal ganglia and corticothalamic, the mechanism on how the activities of the basal ganglia influence absence seizures in corticothalamic circuit is still unclear (Chen et al. 2014).

We have known that the basal ganglia mainly send inhibitory projections to thalamic reticular nucleus (TRN) and specific relay nuclei (SRN) of thalamus by substantia nigra pars reticulata (SNr). And, many experimental data show that variation of the firing rates in SNr can greatly affect seizure activity in corticothalamic circuit (Deransart et al. 1998; Kase et al. 2012). The effect of outputs in SNr on the firing activity of corticothalamic circuit can directly project to TRN or SRN (Gulcebi et al. 2012), or from the SNr to thalamic reticular nucleus relaying at SRN by the indirect pathway (Deransart et al. 1998). In particular, main question involved in the present study is how to control SWDs in the corticothalamic system with changing projection strength of different pathways. Recently, Chen et al. (2014) used a mean-field model to study the precise roles of some direct basal ganglia-thalamic pathways in controlling absence seizures, where SWDs were induced by the inhibitory projection from TRN to SRN and the delay, which is related to the slow kinetics induced by $GABA_B$ receptors in the SRN. However, the factors of the absence seizure activity in the

corticothalamic circuit are not only limited to the inhibitory pathway (Crunelli and Leresche 2002; Marten et al. 2009; Paz et al. 2011). Hence, theoretical explorations should be still further made to well understand the generation and control mechanism of the absence seizures.

To further understand the seizure and mediating mechanisms of absence epilepsy in the brain, we will use the mean-field model containing the corticothalamic circuit and basal ganglia as developed in Chen et al. (2014) to study control of absence seizures. We find that absence seizures can also be induced by excitatory projections from excitatory pyramidal neurons to SRN or conversely, or through the excitatory pathway from SRN to TRN. And then, absence seizures can be controlled by the direct pathway of SNr to TRN and SNr to SRN, which can be independent or together in certain conditions. Our results complement the recent findings on controlling the absence seizures as obtained in Ref. (Chen et al. 2014).

Model description

Based on the previous works (van Albada et al. 2009; van Albada and Robinson 2009), Chen et al. (2014) extended a mean-field model to explore seizure and control mechanism of absence seizures. Here, we still use the mean-field model developed in Ref. (Chen et al. 2014). The studied network model contains nine neural populations as shown in Fig. 1. They are denoted as follows, e = excitatory pyramidal neurons; i = inhibitory interneurons; r = TRN; s = SRN; d_1 = striatal D1 neurons; d_2 = striatal D2 neurons; p_1 = SNr; p_2 = globus pallidus external (GPe) segment; ζ = subthalamic nucleus (STN). Because SNr and GPi have similar cytology and function, as well as inputs and outputs of them are close. Similar to previous studies (Chen et al. 2014; van Albada et al. 2009; van Albada and Robinson 2009), we consider GPi and SNr as a single population in our model. Three types of neural projections are contained in the basal ganglia corticothalamic (BGCT) network. We employ different line types and heads to distinguish them (see Fig. 1). The lines with arrow heads denote the excitatory projections mediated by glutamate, whereas round heads represent the inhibitory projections mediated by $GABA_A$ and $GABA_B$, respectively.

In what follows, by means of the simple mean-field model, we can effectively study the macroscopic dynamics of neural populations. The detailed mathematical equations describing the mean-field model can be found in some existing literatures (Chen et al. 2014; van Albada and Robinson 2009; van Albada et al. 2009). Some descriptions and explanations of the model can be described as follows.

Fig. 1 Framework of the basal ganglia-corticothalamic network. Neural populations include e = excitatory pyramidal neurons; i = inhibitory interneurons; r = thalamic reticular nucleus (TRN); s = specific relay nuclei (SRN); d_1 = striatal D1 neurons; d_2 = striatal D2 neurons; p_1 = substantia nigra pars reticulata (SNr); p_2 = globus pallidus external (GPe) segment; ζ = subthalamic nucleus (STN). Lines with arrow heads denote the excitatory projections mediated by glutamate receptors. Solid lines with dot heads represent the inhibitory projections mediated by $GABA_A$ receptors. Dashed line means the inhibitory projection from TRN–SRN mediated by $GABA_B$ receptors, where three pathways denoted with “*” are main factors considered in this paper to induce the Absence seizure activity

For each neural population, the dependence of the mean firing rate Q_a on the cell-body potential V_a is modeled by a sigmoid function (van Albada and Robinson 2009), given by

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

where $a = e, i, r, s, d_1, d_2, p_1, p_2, \zeta$ represent different neural populations, the quantity $Q_a^{\max}$ is the maximum firing rate, θ_a is the mean threshold potential, and σ is the standard deviation of firing thresholds. The neural population can attain an average firing rate Q_a with membrane potential V_a above the threshold potential θ_a .

The change in the mean cell-body potential of type a population is modeled as (van Albada et al. 2009),

$$D_{\alpha\beta} V_a(t) = \sum_{b \in A} S(v_{ab}) \cdot v_{ab} \cdot \phi_b(t) \quad (2)$$

$$D_{\alpha\beta} = \frac{1}{\alpha\beta} \left[\frac{\partial^2}{\partial t^2} + (\alpha + \beta) \frac{\partial}{\partial t} + \alpha\beta \right] \quad (3)$$

where the differential operator $D_{\alpha\beta}$ is a physiologically realistic representation of dendritic and synaptic integration of incoming signals. α and β are the decay and rise rates of the cell-body potential. v_{ab} is the coupling strength from the neural population of type b to type a. A is a set of populations projecting to population a. $S(v_{ab})$ is

a positive or negative signal; if the input from b to a is excitatory, then $S(v_{ab}) = 1$; otherwise, $S(v_{ab}) = -1$. $\phi_b(t)$ is the incoming pulse rate from the neural population of type b. For simplicity, we do not consider the axonal time delay for signals traveling among neural populations in the present work. However, because the $GABA_B$ functions via second messenger processes, a delay parameter τ should be introduced to the pathway from TRN to SRN to show its slow synaptic kinetics. Hence, this results in a delay differential equation to describe the pulse transmission from TRN to SRN receptor by $GABA_B$. It is noted that the delay is not a main factor considered in this paper. Hence, we all set $\tau = 0.05$ s throughout the whole paper.

Finally, a damped wave equation is taken to describe the propagation effect of field ϕ_a generated from neural population a to other populations, which is connected by the velocity v_a (Chen et al. 2014):

$$\frac{1}{\gamma_a^2} \left[\frac{\partial^2}{\partial t^2} + 2\gamma_a \frac{\partial}{\partial t} + \gamma_a^2 \right] \phi_a(t) = Q_a(t) \quad (4)$$

where $\gamma_a = v_a/r_a$ is the damping rate, r_a is the characteristic axonal range. In fact, the axons of all neural populations except cortical excitatory pyramidal neurons are too short to support the wave propagation on the relevant scales, which imply that $\phi_c = F(V_c)(c = i, r, s, d_1, d_2, p_1, p_2, \zeta)$ (van Albada et al. 2009; van Albada and Robinson 2009). Accordingly, we only model propagation effects along the cortical surface due to long-range excitatory connections via a damped-wave equation with source term $Q_e(t)$:

$$\frac{1}{\gamma_e^2} \left[\frac{\partial^2}{\partial t^2} + 2\gamma_e \frac{\partial}{\partial t} + \gamma_e^2 \right] \phi_e(t) = Q_e(t) \quad (5)$$

Because the intracortical connectivity are proportional to the numbers of the involved synapses, we can further simplify our model by setting $V_i = V_e$ and $Q_i = Q_e$, as appeared in some previous studies (Chen et al. 2014; Marten et al. 2009; Massimo 2012; Roberts and Robinson 2008; Rodrigues et al. 2009).

Nextly, we rewrite the above Eqs. (1)–(5) in the first-order form for all neural populations as follows,

$$\begin{aligned} \frac{d\phi_e(t)}{dt} &= \dot{\phi}_e(t) \\ \frac{d\dot{\phi}_e(t)}{dt} &= \gamma_e^2 [-\phi_e(t) + F(V_e(t))] - 2\gamma_e \dot{\phi}_e(t) \\ \frac{dX(t)}{dt} &= \dot{X}(t) \\ X(t) &= [V_e(t), V_{d_1}(t), V_{d_2}(t), V_{p_1}(t), V_{p_2}(t), V_{\zeta}(t), \\ &\quad V_r(t), V_s(t)]^T \end{aligned}$$

$$\begin{aligned}
\frac{d\dot{V}_e(t)}{dt} &= \alpha\beta(v_{ee}\phi_e + v_{ei}F(V_e) + v_{es}F(V_s) - V_e(t)) \\
&\quad - (\alpha + \beta)\dot{V}_e(t) \\
\frac{d\dot{V}_{d_1}(t)}{dt} &= \alpha\beta(v_{d_1e}\phi_e + v_{d_1d_1}F(V_{d_1}) + v_{d_1s}F(V_s) - V_{d_1}(t)) \\
&\quad - (\alpha + \beta)\dot{V}_{d_1}(t) \\
\frac{d\dot{V}_{d_2}(t)}{dt} &= \alpha\beta(v_{d_2e}\phi_e + v_{d_2d_2}F(V_{d_2}) + v_{d_2s}F(V_s) - V_{d_2}(t)) \\
&\quad - (\alpha + \beta)\dot{V}_{d_2}(t) \\
\frac{d\dot{V}_{p_1}(t)}{dt} &= \alpha\beta(v_{p_1d_1}F(V_{d_1}) + v_{p_1p_2}F(V_{p_2}) + v_{p_1\zeta}F(V_\zeta) \\
&\quad - V_{p_1}(t)) - (\alpha + \beta)\dot{V}_{p_1}(t) \\
\frac{d\dot{V}_{p_2}(t)}{dt} &= \alpha\beta(v_{p_2d_2}F(V_{d_2}) + v_{p_2p_2}F(V_{p_2}) + v_{p_2\zeta}F(V_\zeta) \\
&\quad - V_{p_2}(t)) - (\alpha + \beta)\dot{V}_{p_2}(t) \\
\frac{d\dot{V}_\zeta(t)}{dt} &= \alpha\beta(v_{\zeta e}\phi_e + v_{\zeta p_2}F(V_{p_2}) - V_\zeta(t)) - (\alpha + \beta)\dot{V}_\zeta(t) \\
\frac{d\dot{V}_r(t)}{dt} &= \alpha\beta(v_{re}\phi_e + v_{rp_1}F(V_{p_1}) + v_{rs}F(V_s) - V_r(t)) \\
&\quad - (\alpha + \beta)\dot{V}_r(t) \\
\frac{d\dot{V}_s(t)}{dt} &= \alpha\beta(v_{se}\phi_e + v_{sp_1}F(V_{p_1}) + v_{sr}^A F(V_r) \\
&\quad + v_{sr}^B F(V_r(T - \tau)) - V_s(t) + \phi_n) - (\alpha + \beta)\dot{V}_s(t)
\end{aligned}$$

where the parameter ϕ_n denotes the constant nonspecific subthalamic input onto SRN. Unless otherwise noted, we use the parameter values as listed in Appendix for numerical simulations. These values result from physiological experiments, and can be found in previous studies (Breakspear et al. 2006; Chen et al. 2014; Robinson et al. 1998, 2001, 2003). At the same time, some parameter values are slightly adjusted to generate stable SWDs oscillation in corticothalamic circuit. Thus, they are also in the range of the physiological significance.

Numerical simulation method

All simulations are performed under the MATLAB environment, with dynamical equations being integrated by the standard fourth-order Runge-Kutta method. Firstly, we perform the bifurcation analysis for several pathway parameters (i.e., v_{se} , v_{rs}) of the model to investigate transitions between different dynamical states. The bifurcation diagram is obtained by plotting the local minimum and maximum values of cortical excitatory axonal fields (i.e., ϕ_e) as we change the corresponding parameter with the temporal state of the system being discarded. Then, regions of different firing states in the two-parameter space are derived. In addition, the power spectral analysis from the

time series ϕ_e is used to estimate the dominant frequency of neural oscillations.

Main results

Seizure activities induced by the pathway from excitatory pyramidal neurons to SRN

Absence seizures are generated in the corticothalamic circuit. Projection between the cortex and thalamus neurons has been shown as an important factor for inducing seizures (Breakspear et al. 2006; Marten et al. 2009; Paz et al. 2011). For example, Breakspear et al. studied general seizure phenomena induced by v_{se} in a corticothalamic network (Breakspear et al. 2006). Extending existing results, we will investigate the absence seizure activities induced by the projection from excitatory pyramidal population to SRN (i.e., v_{se}), and how the pathways in the basal ganglia (i.e., SNr–SRN and SNr–TRN) to control these seizure activities. First, we explore the transition of state behaviors of the neural populations as the excitatory coupling strength v_{se} varies. Figure 2 depict the corresponding bifurcation diagram and some typical time series of ϕ_e , which reveal that different dynamical states can emerge in the studied model for different values of v_{se} . In particular, it is shown in Fig. 2a that as v_{se} is relative small, low firing of the cortex neurons can be observed and no oscillation behavior occurs (corresponding to region (1) of Fig. 2a). A typical state can be clearly seen in Fig. 2b. As v_{se} is increased to about 0.9 mV s, it can be seen from Fig. 2a that the system behaves as a simple oscillation state with a maximum value and a minimum value of ϕ_e in every period (corresponding to region (2) of Fig. 2a, c). This phenomenon can be characterized by the Hopf bifurcation (Marten et al. 2009; Rodrigues et al. 2009). With further increasing v_{se} , excitatory pyramidal neurons can exhibit typical SWDs with two pairs of maximum and minimum peaks in one period (region (3) of Fig. 2a), which implies the occurrence of epilepsy seizures with relatively large v_{se} (Crunelli and Leresche 2002; Marten et al. 2009; Paz et al. 2011). Figure 2d is a typical time series of ϕ_e , as the value of v_{se} is taken in the region (3) of Fig. 2a. Finally, when v_{se} is increased to about 2 mV s, the firing activity of the model comes into saturation state (4) (high firing state), where the firing of cortical neurons is very high as shown in Fig. 2e.

Next, we explore the effects of the pathway SNr–SRN and SNr–TRN in the basal ganglia on controlling the seizure activities. Because the SNr is the main output population from the basal ganglia to thalamus, we mainly investigate how the activation level of SNr influences the dynamics generated in corticothalamic circuit as reported

Fig. 2 **a** Bifurcation diagram of ϕ_e as a function of the excitatory coupling strength v_{se} from the excitatory pyramidal neurons to SRN. Four typical dynamical states can be observed: (1) low firing; (2) simple oscillations; (3) SWDs; (4) saturation. **b–d** The typical time series of ϕ_e corresponding to the above four regions. We choose $v_{se} = 0.6$ mV s, $v_{se} = 1.1$ mV s, $v_{se} = 1.6$ mV s, $v_{se} = 2.1$ mV s in (b)–(e), respectively

in some experiments (Kase et al. 2012; Paz et al. 2007). Firstly, we discuss the roles of the isolated pathway SNr–TRN on controlling seizures (i.e., cut off the pathway SNr–SRN). In particular, we obtain both the state regions and frequency characteristics in the two-dimensional parameter space ($v_{se}, v_{p1\zeta}$) with $v_{sp1} = 0$. From Fig. 3a, we see that state regions of the studied system are divided into four parts (1)–(4) as defined in Fig. 2. It is obvious that when v_{se} is relatively small, the system stays at low firing state irrespectively of $v_{p1\zeta}$ in the considered region of the parameters. We also can observe that for the moderate v_{se} , decreasing $v_{p1\zeta}$ can push the model from the seizure state

Fig. 3 **a, b** The state and frequency analysis in parameter space ($v_{se}, v_{p1\zeta}$). v_{se} is the projection strength from excitatory pyramidal neurons to SRN, $v_{p1\zeta}$ is the excitatory coupling strength of the STN–SNr pathway. Four different states are represented by different colors: (1) low firing; (2) simple oscillations; (3) SWDs; (4) high firing. Seizures can be controlled by decreasing $v_{p1\zeta}$ (indicated by the *down* arrow) or increasing $v_{p1\zeta}$ (indicated by the *upward* arrow). The typical 2–4 Hz SWD region is remarked by “SWD” in (b) corresponding to the parameter ranges in (a). **c, d** Two bifurcation diagrams of ϕ_e as a function of $v_{p1\zeta}$, set $v_{se} = 1.2$ mV s and $v_{se} = 1.8$ mV s, respectively

(3) to simple oscillations (2), then to the low firing state (1). As v_{se} is within the interval (1, 1.4), the state of the system can be translated from seizure state (3) to simple oscillations (2) as directed by the downward arrow in Fig. 3a by decreasing $v_{p1\zeta}$. With v_{se} further increasing to enough large, it is seen that increasing $v_{p1\zeta}$ can drive the model from the seizure state (3) to the high firing state (4). For more clearer vision, Fig. 3c, d show two specific bifurcation diagrams with $v_{se} = 1.2$ mV s and $v_{se} = 1.8$ mV s, respectively as $v_{p1\zeta}$ varies, where we can clearly observe transition of different firing states of the systems. Furthermore, we calculate the frequency of oscillations of the system, which corresponds to Fig. 3a. The obtained results are shown in Fig. 3b, where we can find a typical 2–4 Hz SWDs region denoted as “SWD” in Fig. 3b. In addition, it can be seen that the SWDs frequency can enhance with increasing of $v_{p1\zeta}$.

However, the inner biophysical mechanism on how the pathway SNr–TRN suppresses SWDs in the corticothalamic circuit is complicated, and still unclear. We try to explain it from the studied model as illustrated in Fig. 1. When v_{se} is relative small, decreasing the activation level of SNr can enhance the active level of TRN, which in turn leads

inactivate effects in SRN, and finally reduce the excitatory projection from SRN to the cortex. Resultantly, the seizure activities of the cortex are controlled. When the value v_{se} is large enough, the excitatory input from cortex to SRN is so large that it can induce the high activation level of TRN, which in turn inhibits the activation level of SRN. Therefore, it can be inferred that the activation level of TRN must be inhibited to control the SWDs, which can be achieved by increasing the inhibitory input with the pathway SNr–TRN.

Then, for more physiological significance, we would like to consider the combination effects of the pathway SNr–TRN and SNr–SRN on controlling seizures. Here, we introduce a scale coefficient K (Chen et al. 2014) to show the ratio between strength of v_{sp1} and v_{rp1} , i.e., $v_{rp1} = Kv_{sp1}$. Numerical results of the state and frequency analysis are exhibited in Fig. 4a, b, respectively. We can observe that as K is relatively small, the model stays either at the simple oscillation state or at the low firing state. With increasing the value of K and moderate value of $v_{p1\zeta}$, a region of the state 3 can appear as shown in Fig. 4a, b, where the seizures activity of the model occur. In addition, it can be found that as $K > 0.6$, there is a region, where both activation and inactivate level of the SNr (i.e., increasing or decreasing $v_{p1\zeta}$) can inhibit the seizure activity as illustrated by the *double arrow* in the *right side* of Fig. 4a. This can be caused by the complicated competition mechanism between the pathway SNr–TRN and SNr–SRN. Further investigation shows that there exists a typical 2–4 Hz SWDs region denoted as “SWD” in Fig. 4b, which is almost consistent with the parameter range in Fig. 4a. For clearer vision, a typical bifurcation plot at $K = 0.8$ is shown in Fig. 4c as $v_{p1\zeta}$ changes, where clear transition from the state 2 to 3 and finally to 1 can be observed.

Seizure activities induced by the pathway from SRN to excitatory pyramidal neurons

In this section, we study seizure activities induced by the projection from SRN to excitatory pyramidal neurons (i.e., v_{es}), and how the pathways in the basal ganglia (i.e., SNr–SRN and SNr–TRN) to control these seizure activities. Similar to the above investigation, the corresponding bifurcation diagram and four typical time series of ϕ_e are shown in Fig. 5a–e, respectively. They reveal different dynamical states in the studied system for different values of v_{es} . Clearly, as the projection strength from SRN to excitatory pyramidal neurons (i.e., v_{es}) is changed, the excitatory input can affect the cortex directly. Resultantly, the four states can emerge as shown in Fig. 5a with increasing v_{es} . And, some typical representations are illustrated in Fig. 5b–e, respectively, where we can clearly see different firing states of the model.

Fig. 4 a, b The state and frequency analysis in the plane $(K, v_{p1\zeta})$. K represents the ratio between strength of v_{sp1} and v_{rp1} , i.e., $v_{rp1} = Kv_{sp1}$, $v_{p1\zeta}$ is the excitatory coupling strength of the STN–SNr pathway. Three different states are represented by different colors: (1) low firing; (2) simple oscillations; (3) SWDs. Inhibition can occur when K is relatively large, and it is shown by the *double arrow* (a). The typical 2–4 Hz SWD region is remarked by “SWD” in (b), which corresponds to the parameter ranges in (a). c Bifurcation diagram of ϕ_e as a function of $v_{p1\zeta}$, set $K = 0.8$. For all simulations, we set $v_{se} = 1$ mV s

By careful investigation, it is found that the isolated control effect of the pathway SNr–TRN or SNr–SRN is not obvious. So, we only consider the combination effects of SNr–TRN and SNr–SRN on controlling seizures. As the parameters vary, Fig. 6a, b exhibit the variations of the state and frequency of the system, respectively. We can find that the system mainly locates at the state 1 and 3 in the considered range of parameters, and the range of parameters is very small for the state 2 and 4. Hence, the seizures can be eliminated in all range of K by enhancing the activation level of the SNr as shown by the upward arrow in Fig. 6a. It can also be concluded that the control effect is relatively good in this case, because the model can directly be pushed from the SWDs states to the low firing state. Besides, a clear transition of the system can be observed from a typical bifurcation diagram as shown in Fig. 6c. In addition, based on frequency analysis, a typical 2–4 Hz SWDs region denoted as “SWD” can be found in Fig. 6b, which is almost consistent with the parameter range of the states in Fig. 6a. Following above results, we can infer that we can reduce the activation level of the SRN to control the seizure activity. And when the activation level of the SNr increases, the inhibitory effect on SRN by the direct pathway SNr–SRN also increases, but the inhibitory effect on SRN by the indirect pathway SNr–TRN–SRN decreases. Finally, the inhibitory effect by the

Fig. 5 **a** Bifurcation diagrams of ϕ_e as a function of the excitatory coupling strength v_{es} from the SRN to excitatory pyramidal neurons. Four different dynamical states can be observed: (1) low firing; (2) simple oscillations; (3) SWDs; (4) high firing. **b–e** The typical time series of ϕ_e corresponding to the above four regions are shown as $v_{es} = 0.4$ mV s, $v_{es} = 1$ mV s, $v_{es} = 1.5$ mV s, $v_{es} = 1.8$ mV s, respectively

direct pathway SNr–SRN is in the dominative position due to their competition. Hence, the seizure activity can be controlled.

Seizure activities induced by the excitatory input from SRN to TRN

Until now, it is shown that there are three main arguments about origin of the epileptic seizures: (1) SWDs generated in cortex neurons; (2) SWDs generated in thalamus neurons; (3) SWDs appeared in cortex neurons, and it transforms from a “spindles” wave generated in thalamus neurons (Breakspear et al. 2006). Hence, the thalamus neurons can play a vital role in the generation of epileptic seizures (Breakspear et al. 2006; Deransart et al. 1998; Paz

Fig. 6 **a, b** The state and frequency analysis in the plane $(K, v_{p1\zeta})$. K represents the ratio between strength of v_{sp1} and v_{rp1} , i.e., $v_{rp1} = Kv_{sp1}$, $v_{p1\zeta}$ is the excitatory coupling strength of the STN–SNr pathway. Four different states are represented by different colors shown in (a). Inhibition occurs in all the range of K in (a), shown by the up arrow. The typical 2–4 Hz SWD region is remarked by “SWD” in (b) corresponding to the parameter ranges in (a). **c** Bifurcation diagram of ϕ_e as a function of $v_{p1\zeta}$, set $K = 0.5$. For all simulations, we set $v_{es} = 1.208$ mV s

et al. 2007). Thus, theoretical exploration about this from the modeling should be conducted to well understand the generation of epileptic seizures. Recently, Chen et al. proposed a corticothalamic-basal ganglia model based on the previous modeling (van Albada et al. 2009; van Albada and Robinson 2009) to study control of the epileptic seizures (Chen et al. 2014). They mainly investigate the effects of the inhibitory projection strength of the pathway TRN to SRN and delays of the pathway on the epileptic seizures, and found that the seizures can be controlled by pathways in the basal ganglia. Inspired by this work, we will consider how seizure activity can be induced by excitatory projection from SNr to TRN, and how it can be controlled by the basal ganglia.

Firstly, by changing v_{rs} , the bifurcation diagram is shown in Fig. 7a. It is shown that there exist four firing states. They are denoted as state (1)–(4), respectively. From Fig. 7a, we can observe that the seizure activity can abruptly appear from high firing to SWDs as v_{rs} increases. And it ends with a simple oscillation by further increasing v_{rs} . Finally, when v_{rs} is large enough, the system enters into a low firing. For different states, four typical time series that correspond to (1)–(4) are presented in Figs. 7b–e, respectively, which can give a good vision on the firing transition.

Next, we study the control role of the pathway SNr–TRN when we cut off the pathway SNr–SRN. Figure 8a

Fig. 7 **a** Bifurcation diagrams of ϕ_e as a function of the excitatory coupling strength v_{rs} from the SRN to TRN. Four different dynamical states can be observed: (1) low firing; (2) simple oscillations; (3) SWDs; (4) high firing. **b–e** The typical time series of ϕ_e corresponding to the above four regions. We choose $v_{rs} = 0.4$ mV s, $v_{rs} = 0.6$ mV s, $v_{rs} = 1.4$ mV s, $v_{rs} = 2.2$ mV s, respectively

presents the state transition in the two-dimensional parameter space $(v_{rs}, v_{p1\zeta})$, where four types of states that are denoted by different colors appear. In particular, as v_{rs} increases to the vertical dotted line, decreasing $v_{p1\zeta}$ (i.e., reducing the activation level of SNr) can push the system from SWDs state to a simple oscillation state, i.e., the seizure activity can be controlled. By further increasing v_{rs} to large enough, the model can also run into the low firing state (1). A typical bifurcation diagram at $v_{rs} = 1.4$ mV s is shown in Fig. 8c, where we can see state transition from state 2 to 3 as $v_{p1\zeta}$ varies. Additionally, a typical 2–4 Hz region denoted as “SWD” can be found in Fig. 8b. From Fig. 8b, we see that $v_{p1\zeta}$ has a little effect on the frequency. But, the frequency enhances with increasing v_{rs} . Based on above analysis, we can conclude that when v_{rs} is small, the activation level of TRN is low, so the inhibitory effect on

Fig. 8 The control role of the isolated pathway SNr–TRN. **a, b** The state and frequency analysis in the parameter plane $(v_{rs}, v_{p1\zeta})$. v_{rs} is the projection strength from SRN to TRN, $v_{p1\zeta}$ is the excitatory coupling strength of the STN–SNr pathway. Four different states are represented by different colors: (1) low firing; (2) simple oscillations; (3) SWDs; (4) high firing. The control effect occurs in the right side of the vertical dotted line, shown by the down arrow. The typical 2–4 Hz SWDs region is remarked by “SWD”. **c** A bifurcation diagram of ϕ_e as a function of $v_{p1\zeta}$, set $v_{rs} = 1.25$ mV s in (a)

SRN by v_{sr} is small, which finally leads to the large excitatory projection strength from SRN to the cortex. Hence, the model exhibits high frequency firing. As v_{rs} becomes large, the inhibitory role by the pathway TRN–SRN will increase, which results in decreasing the excitatory input from SRN to the cortex. Consequently, the SWDs, simple oscillations and low firing state can appear as v_{rs} increases. In sum, the seizure activity in the cortex can be controlled by reducing the activation level of SNr.

Thirdly, we study the control effect of the pathway SNr–SRN when the pathway SNr–TRN is cut off. Similarly, Fig. 9a, b show the variations of the state and frequency of the system in two dimensional parameter plane, respectively. It is shown that as v_{rs} changes for fixed value of small or moderate value of $v_{p1\zeta}$, different states can appear. And we can find that increasing $v_{p1\zeta}$ can push the system from state 3 to 1 or 2, which implies that the seizures can be controlled by large value of $v_{p1\zeta}$. Especially, when v_{rs} is relative small (in the left side of the dotted line), the state can directly transfer from SWDs oscillations to the low firing state with increasing of $v_{p1\zeta}$. As v_{rs} arrives at the right side of the vertical dotted line with an upward arrow as shown in Fig. 9a, Enhancing the activation level of SNr (i.e., increasing $v_{p1\zeta}$) can firstly push the system from the SWDs state to the simple

Fig. 9 The control role of the isolated pathway SNr–SRN. **a, b** The variation of state and frequency in the plane $(v_{rs}, v_{p1\zeta})$. v_{rs} is the projection strength from SRN to TRN, $v_{p1\zeta}$ is the excitatory coupling strength of the STN–SNr pathway. Four different states (1)–(4) can appear as parameters change. The seizure activity can be controlled by increasing $v_{p1\zeta}$, shown by the upward arrow in the region (3). The typical 2–4 Hz SWD region is remarked by “SWD” in (b) corresponding to the parameter ranges in (a). **c** A typical bifurcation diagram of ϕ_e as a function of $v_{p1\zeta}$, and $v_{rs} = 0.7$ mV s in (a)

oscillations state, then to the low firing state. Finally, the seizure activity can be controlled with the activation level of SNr being increased. However, for the large value of $v_{p1\zeta}$, the system always stays at low firing state irrespectively of the value of $v_{p1\zeta}$. The variation of the corresponding frequency is also shown in Fig. 9b, in which a typical 2–4 Hz SWDs region appears as denoted “SWD”. In the “SWD” region, when $v_{p1\zeta}$ is increasing, the oscillation frequency is decreasing. Based on our model as shown in Fig. 1, for the moderate $v_{p1\zeta}$, we can infer that when v_{rs} is relative small, the activation level of TRN is low, then in turn the inhibitory effect on SRN by v_{sr} is small. This results in the large excitatory projection strength from SRN to cortex. Hence, high firing can appear in the model for this case. As v_{rs} becomes large, the inhibitory role by the pathway TRN–SRN is strong, and then the excitatory input from SRN to cortex gradually decreases. So the model can exhibit SWDs, simple oscillations and low firing state with suitable parameters. It is also concluded that when the v_{rs} located in the region SWDs, the direct inhibitory role on SRN by pathway SNr–SRN can be improved by enhancing the activation level of SNr. And then, the excitatory input from SRN to cortex reduces gradually, so the seizure activity in the cortex is controlled. For the fixed value $v_{rs} = 0.75$ mV s,

Fig. 10 **a, b** The state and frequency analysis in the parameter plane $(K, v_{p1\zeta})$. K represents the ratio between strength of v_{sp1} and v_{rp1} , i.e., $v_{rp1} = K v_{sp1}$, $v_{p1\zeta}$ is the excitatory coupling strength of the STN–SNr pathway. Three different states are represented by different colors: (1) low firing; (2) simple oscillations; (3) SWDs. Inhibition occurs in the right side of (a) when K is relative large, shown by the down arrow. The typical 2–4 Hz SWD region is remarked by “SWD” in (b). **c** Bifurcation diagram of ϕ_e as a function of $v_{p1\zeta}$, where we set $K = 0.75$. For all simulations, we set $v_{rs} = 1.08$ mV s

we plot a typical bifurcation diagram as shown in Fig. 9c to have a good vision on the present results as $v_{p1\zeta}$ changes.

Finally, we simultaneously open the pathway SNr–TRN and SNr–SRN, and study their effects on controlling epileptic seizure. Similar to the previous analysis, Fig. 10a, b show the corresponding state and frequency analysis, respectively, which can help us to explore the competition mechanism between the two pathways. We can find that when K is small, the model stays either at the simple oscillations state or the low firing state, which depends on the value of $v_{p1\zeta}$. As K becomes large, the seizures activity can appear with the large value of $v_{p1\zeta}$. And then, it is shown that reducing the activation level of the SNr (i.e., decreasing $v_{p1\zeta}$) can push the activity of model from state 3 to 2 as shown by the arrow in the right side of Fig. 10a. This can inhibit the seizure activity, which is similar to the isolated control role of pathway SNr–TRN shown in Fig. 8a. In Fig. 10b, the typical 2–4 Hz SWDs region can also be found, and the frequency in this region decreases with increasing of $v_{p1\zeta}$. Furthermore, as indicated in Fig. 10c with a typical bifurcation plot, transition from state 3 to 2 is clear. The mechanism of this case is excepted to be similar to that of the control effect of the isolated pathway SNr–TRN.

Conclusion

To summarize, based on the corticothalamic-basal ganglia model, we have considered the origin and control of the epileptic seizures as the two main excitatory pathways e–s and s–r are introduced to generate the seizures, respectively. By regulating the strength in two pathways (i.e., v_{se} , v_{es} and v_{rs}), four types of the firing states can appear such as (1) low firing; (2) simple oscillations; (3) SWDs; (4) high firing. We have found that the transitions of four types of firing states are different as the parameters change. Furthermore, it is found that the epileptic seizures can be controlled by pathway SNr–TRN and SNr–SRN in the basal ganglia. In particular, we have investigated the effects of strength of the related pathways SRN on controlling the epileptic seizures. And, we have also tried to explain the mechanism of the control by the model. The results obtained in this paper extended the bidirectional control theory developed in Chen et al. (2014), which shows that SWDs induced by many pathological factors in corticothalamic can be controlled by the basal ganglia. However, there also exists some pathways which are not considered due to the lack of clinical data. Perhaps, SNr can become an important stimulating target for future clinical research. In addition, because the mean-field model is simplified for tractability. Hence, it is hoped that our results can have an important guidance to understand the origin and therapy of the epileptic seizures.

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Appendix

Unless otherwise noted, we use these parameter values for simulations as follows (Chen et al. 2014; Marten et al. 2009; Massimo 2012; Paz et al. 2007; Roberts and Robinson 2008; Rodrigues et al. 2009; van Albada et al. 2009; van Albada and Robinson 2009).

Parameter	Mean	Value
Q_e^{max}, Q_i^{max}	Cortical maximum firing rate	250 Hz
$Q_{d_1}^{max}, Q_{d_2}^{max}$	Striatum maximum firing rate	65 Hz
$Q_{p_1}^{max}$	SNr maximum firing rate	250 Hz
$Q_{p_2}^{max}$	GPe maximum firing rate	300 Hz
Q_{ζ}^{max}	STN maximum firing rate	500 Hz
Q_s^{max}	SRN maximum firing rate	250 Hz
Q_r^{max}	TRN maximum firing rate	250 Hz

Parameter	Mean	Value
θ_e, θ_i	Mean firing threshold of cortical populations	15 mV
$\theta_{d_1}, \theta_{d_2}$	Mean firing threshold of striatum	19 mV
θ_{p_1}	Mean firing threshold of SNr	10 mV
θ_{p_2}	Mean firing threshold of GPe	9 mV
θ_{ζ}	Mean firing threshold of STN	10 mV
θ_s	Mean firing threshold of SRN	15 mV
θ_r	Mean firing threshold of TRN	15 mV
γ_e	Cortical damping rate	100 Hz
τ	Time delay due to slow synaptic kinetics of $GABA_B$	50 ms
α	Synaptodendritic decay time constant	50 s ⁻¹
β	Synaptodendritic rise time constant	200 s ⁻¹
σ	Threshold variability of firing rate	6 mV
ϕ_n	Nonspecific subthalamic input onto SRN	2 mV s

Coupling strength	Source	Target	Value (mV s)
v_{ee}	Excitatory pyramidal neurons	Excitatory pyramidal neurons	1
v_{ei}	Inhibitory interneurons	Excitatory pyramidal neurons	-1.8
v_{re}	Excitatory pyramidal neurons	TRN	0.05
v_{rs}	SRN	TRN	0.5
$v_{sr}^{A,B}$	TRN	SRN	-0.48
v_{d_1e}	Excitatory pyramidal neurons	Striatal D1 neurons	1
$v_{d_1d_1}$	Striatal D1 neurons	Striatal D1 neurons	-0.2
v_{d_1s}	SRN	Striatal D1 neurons	0.1
v_{d_2e}	Excitatory pyramidal neurons	Striatal D2 neurons	0.7
$v_{d_2d_2}$	Striatal D2 neurons	Striatal D2 neurons	-0.3
v_{d_2s}	SRN	Striatal D2 neurons	0.05
$v_{p_1d_1}$	Striatal D1 neurons	SNr	-0.1
$v_{p_1p_2}$	GPe	SNr	-0.03
$v_{p_1\zeta}$	STN	SNr	0–0.6
$v_{p_2d_2}$	Striatal D2 neurons	GPe	-0.3
$v_{p_2p_2}$	GPe	GPe	-0.075
$v_{p_2\zeta}$	STN	GPe	0.45
$v_{\zeta p_2}$	GPe	STN	-0.04
v_{es}	STN	Excitatory pyramidal neurons	1.8
v_{se}	Excitatory pyramidal neurons	SRN	2.2
$v_{\zeta e}$	Excitatory pyramidal neurons	STN	0.1
v_{sp_1}	SNr	SRN	-0.035
v_{rp_1}	SNr	TRN	-0.035

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