Controlling absence seizures by tuning activation level of the thalamus and striatum

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Abstract

¹ In this paper, we use a basal ganglia-corticothalamic model(BGCT) to study control effect of the absence epilepsy seizure. It is shown that the seizure state can be well controlled by tuning activation level of the thalamic reticular nucleus (TRN), specific relay nuclei (SRN), striatal D1 neurons and striatal D2 neurons. And then, one type of deep brain stimulation voltage employed on SRN, we find that seizure activities can also be controlled by tuning the period (P) and the duration of effective current (D) in a period into some appropriate ranges. So, we infer that the thalamic and striatal tissue may become effective target regions in clinical treatment of epilepsy in the future.

Keywords: Spike-and-slow wave discharges, Basal ganglia-thalamocortical network, Activation level, Deep brain stimulation

1. Introduction

Epilepsy is a neurological disease characterized by spontaneously occurring seizures which have great negative impact on all people of the whole society. These seizures not only interfere with normal life of people but can also cause great harm to spirit and body, and in some extreme situations, even endanger life [1]. Absence epilepsy (AE) which occurs mainly in childhood (three to nine years old) can cause devastating effects on learning, memory, movements and other normal physiological functions[2]. AE is characterized by frequent absences with short time for each attack, but the degree of loss of consciousness is heavy. During the onset of the patients, the **electroencephalogram (EEG)** displays the bilateral symmetric **spike-and-slow wave discharge (SWD)** in the background of normal activities, which are thought to be generated due to abnormal interactions between cor-

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tical and thalamic neurons, although the pathophysiology mechanism of it remains to be uncertain now[3].

Recently, more and more computational models are used to study the pathogenesis and control mechanism of epileptic disease from the viewpoint of individual neurons or neural networks and have put forward many new hypotheses[4], especially the mean field models [5-8]. Where, Rodrigues et al. used a mean field model of human thalamic and corticothalamic neurons to study the genesis of spike-wave oscillations, they found that the abnormal interaction between thalamus and cortex plays an important role in generating epileptic seizures[6]. And then, in 2009, Rodrigues et al. completely explained seizure mechanisms of the absence epilepsy in a human cortico-thalamic mean-field model [7]. Marten et al. employed a mean-field model to study the onset and transition mechanisms of different types of absence epilepsy [8]. Recently, Chen et al. study shown that absence epilepsy seizures can be well controlled by tuning the activation level of **the substantia nigra pars reticulata (SNr)**, and the SNr may be a potential target for clinical practice, where the model used is a basal ganglia-corticothalamic model(BGCT) [9]. Hu et al. have studied the onset of absence seizures induced by the excitatory pathways related to thalamic relay nuclei(SRN)in corticothalamic system and its controlling effect in BGCT [10]. And then, in 2015, Hu and Wang applied one type of deep brain stimulation(DBS) voltage on the SNr and **the excitatory pyramidal neurons of cortex** in BGCT, and they found that seizures can be well controlled by tuning some parameters of the stimulation current into appropriate ranges [11]. Recently, Chen et al. found that the direct **γ -aminobutyric acid (GABAergic)** pallido-cortical pathway also plays a key role in controlling absence epilepsy [12]. They are good tools for predicting seizures in theory [3,7,10,12] and some even may guide strategies for therapy epilepsy by pharmacological, surgical and electrical stimulation techniques[5, 9, 11].

Deep brain stimulation technology is currently acknowledged as an effective method to treat the intractable epilepsy [13,14]. How to select suitable target areas and optimal protocols for different patients is still a difficult medical problem. Recently, there are a large number of clinical and experimental results shown that the anterior nucleus of the thalamus might be the most well-established target for DBS in the treatment of intractable epilepsy[13,15,16]. **Therefore, the thalamus region is more and more attended by researchers.** The thalamus is a structure remote from, but closely related to the cortex, which is necessary to maintain seizure activity, and closed-loop optogenetic control of thalamus can be

used as a tool to interrupt seizures[17]. Li et al. found that seizures can be suppressed by inactivation of thalamus by tetrodotoxin[18]. Some clinical trial results have shown that deep brain stimulation acted on anterior thalamic nucleus can effectively reduce seizures in patients [19]. Vallone’s computational simulations shown that the generation and termination of seizure-like behaviour can be controlled by adjusting outputs from thalamic neurons to cortical neurons[20]. Wu et al. proposed that the thalamic outputs obviously affected the cortical excitability and can desynchronize cingulate seizures[21]. For drug-resistant partial epilepsy, the thalamic stimulation is also a long-term efficacy and safety treatment prescription[22]. Recently, research results shown in [23] that appropriate stimulus intensities and frequencies can consistently suppress seizure duration by stimulating medial dorsal thalamic nucleus for limbic seizures. However, the evidence to support these points from the view of mathematic model is very few and the theoretical mechanism of thalamic neuronal activity is how to regulate seizures is still unknown. Striatum is the main target area of cortex output and is also the main input organization to the basal ganglia structure of the brain [24,25], which is a telencephalic structure closely related to the execution of movement functions[26,27]. Recently, there are some research results indicated that electrophysiological activity of neurons in the striatum was closely related to epilepsy seizures [28-30]. Kahane and Depaulis commented that striatal low-frequency stimulation (LFS) was effective in a considerable part of epileptic patients, although lacking of control protocols [28]. Nagel and Najm in their review article also pointed that interictal epileptic activity and seizure propagation was reduced by low-frequency stimulation on the caudate nucleus (a part of the striatum) of the brain [29]. However, the striatum nucleus is not becoming common target area of epilepsy treatment in clinical practice by now, and its physiological activity is how to influence seizures is unknown and is our interesting. In this paper, we first use a basal ganglia-corticothalamic model [9-11] to study whether the absence epilepsy seizure can be controlled by tuning the activation level of thalamus and striatum. Then, we employ one type of deep brain stimulation voltage on SRN to verify the obtained results.

We introduce the model and method in section 2; The controlling effects of absence seizures by tuning the activation level of thalamus and striatum are given in section 3 and section 4, respectively. And then, in section 5, one type of deep brain stimulation voltage is applied on SRN to verify the obtained results.

2. Model description

In this section, we first give the framework of the model in Fig.1, which contains nine neural populations (Also see Ref. [9-11]). Anatomically, the basal ganglia enable to influence the dynamics of the corticothalamic system by sending direct and indirect projections to the thalamus and in turn receives multiple projections from both the cortex and thalamus. Therefore, the cortex, thalamus and basal ganglia form an interaction loop system as depicted in Fig.1. For a convenience, they are abbreviated as follows, e=excitatory pyramidal neurons (EPN); i=inhibitory interneurons; r=thalamic reticular nucleus (TRN); s=specific relay nuclei (SRN); d_1 =striatal D1 neurons; d_2 =striatal D2 neurons(Here, the striatal neurons are classified based on their main type of dopamine receptor D1 or D2); p_1 =substantia nigra pars reticulata(SNr); p_2 =globus pallidus external (GPe) segment; ζ =subthalamic nucleus (STN). In Fig.1, we use different line types and heads to denote different types of connections between nerve nuclei. The excitatory projections mediated by glutamic acid are indicated by lines with arrows, and round heads denote inhibitory projections regulated by the γ -aminobutyric acid A ($GABA_A$) receptor (solid line) and the γ -aminobutyric acid B ($GABA_B$) receptor (dotted line), respectively. Where, the lines with blue color are the routes which may induce the changing of activation level of thalamus and striatum as considered in this paper.

Here we will employ the mean field theory to describe the network in Fig.1. Firstly, we give equations to describe the physiological activity of single neural population as follows,

The first part, the mean firing rate of the population a ($a = e, i, r, s, d_1, d_2, p_1, p_2, \zeta$) Q_a is expressed as a function of the cell-body potential V_a of itself [11,12,13,42,43],

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

where, the maximum firing rate is denoted as Q_a^{max} , the mean threshold potential of the population here is represented as θ_a , and σ is the standard deviation of firing thresholds. In this model, we suppose that the neural population firing with rate Q_a if and only if when the membrane potential V_a is more than the mean threshold potential θ_a .

The change of the cell-body potential V_a is given by the following differential equations [9,10,11,31,32],

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

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

Figure 1: Schematic diagram of the studied basal ganglia-corticothalamic model(Also can refer to Ref. [9-11]). Nerve nuclei are expressed as follows, e = excitatory pyramidal neurons (EPN); 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 mean excitatory projections. Solid lines with round heads represent inhibitory projections mediated by $GABA_A$ receptor and the dashed line denotes the inhibitory output from TRN to SRN mediated by $GABA_B$ receptor. Routes that may induce the changing of activation level of thalamus and striatum are denoted by blue lines.

where, the axon and dendritic integrals of input pulse signals are described by the differential operator $D_{\alpha\beta}$. α and β taken as two constants to represent the attenuation and rising rate of the cell-body potential V_a , respectively. v_{ab} is the projection intensity from the neural population b to a. A is a set of all populations projecting to the population a. And, $S(\nu_{ab})=1$ means projections from b to a are excitatory; otherwise, $S(\nu_{ab})=-1$. The input pulse rate from the population b to a is expressed as $\phi_b(t)$ in the equation. τ is a delay parameter introduced to describe the slow synaptic kinetics of the pathway “ $TRN \rightarrow SRN$ ”, which caused by the second messenger process [9,10,11,31,32].

The second part, the propagation effect of pulsed field ϕ_a of the population a is described as the following damped wave equation [9,10,11,31,32],

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

where $\gamma_a = v_a/r_a$ is the damping rate, v_a is the speed of pulse propagation, and the characteristic axonal range is denoted as r_a .

In this model, we suppose that the axon of all populations except EPN are all too short to support pulse propagations, so it is clear that $\phi_c = F(V_c)(c = i, r, s, d_1, d_2, p_1, p_2, \zeta)$ [9-11]. Specifically, the pulse spreading effect of EPN can be described individually as follows,

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

As considered in many studies that intracortical connectivities are proportional to the numbers of synapses involved, so we can continue to simplify our model by setting $Q_i = Q_e$ and $V_i = V_e$ [8,9,10,11,33]. One can also read related important literatures [8,9,10,11,31,32,33] for more detailed instructions of this field model.

Now, for the convenience of numerical calculation, we rearrange equations (1)-(5) in the first-order form as describing the network model in Fig.1 [9-11],

$$\begin{aligned}
\frac{d\phi_e(t)}{dt} &= \dot{\phi}_e(t) \\
\frac{d\dot{\phi}_e(t)}{dt} &= \gamma_e^2[-\phi_e(t) + F(V_e(t))] - 2\gamma_e\dot{\phi}_e(t) \\
\frac{dX(t)}{dt} &= \dot{X}(t) \\
X(t) &= [V_e(t), V_{d_1}(t), V_{d_2}(t), V_{p_1}(t), V_{p_2}(t), V_\zeta(t), \\
&\quad V_r(t), V_s(t)]^T \\
\frac{d\dot{V}_e(t)}{dt} &= \alpha\beta(v_{ee}\phi_e + v_{ei}F(V_e) + v_{es}F(V_s) - V_e(t)) \\
&\quad -(\alpha + \beta)\dot{V}_e(t) \\
\frac{d\dot{V}_{d_1}(t)}{dt} &= \alpha\beta(v_{d_1e}\phi_e + v_{d_1d_1}F(V_{d_1}) + v_{d_1s}F(V_s) - V_{d_1}(t)) \\
&\quad -(\alpha + \beta)\dot{V}_{d_1}(t) \\
\frac{d\dot{V}_{d_2}(t)}{dt} &= \alpha\beta(v_{d_2e}\phi_e + v_{d_2d_2}F(V_{d_2}) + v_{d_2s}F(V_s) - V_{d_2}(t)) \\
&\quad -(\alpha + \beta)\dot{V}_{d_2}(t) \\
\frac{d\dot{V}_{p_1}(t)}{dt} &= \alpha\beta(v_{p_1d_1}F(V_{d_1}) + v_{p_1p_2}F(V_{p_2}) + v_{p_1\zeta}F(V_\zeta) \\
&\quad - V_{p_1}(t)) - (\alpha + \beta)\dot{V}_{p_1}(t) \\
\frac{d\dot{V}_{p_2}(t)}{dt} &= \alpha\beta(v_{p_2d_2}F(V_{d_2}) + v_{p_2p_2}F(V_{p_2}) + v_{p_2\zeta}F(V_\zeta) \\
&\quad - V_{p_2}(t)) - (\alpha + \beta)\dot{V}_{p_2}(t) \\
\frac{d\dot{V}_\zeta(t)}{dt} &= \alpha\beta(v_{\zeta e}\phi_e + v_{\zeta p_2}F(V_{p_2}) - V_\zeta(t)) - (\alpha + \beta)\dot{V}_\zeta(t) \\
\frac{d\dot{V}_r(t)}{dt} &= \alpha\beta(v_{re}\phi_e + v_{rp_1}F(V_{p_1}) + v_{rs}F(V_s) - V_r(t)) \\
&\quad -(\alpha + \beta)\dot{V}_r(t) \\
\frac{d\dot{V}_s(t)}{dt} &= \alpha\beta(v_{se}\phi_e + v_{sp_1}F(V_{p_1}) + v_{sr}^A F(V_r) \\
&\quad + v_{sr}^B F(V_r(T - \tau)) - V_s(t) + \phi_n) - (\alpha + \beta)\dot{V}_s(t)
\end{aligned}$$

where ϕ_n means the constant nonspecific subthalamic input into SRN, and we suppose that $v_{sr}^A \equiv v_{sr}^B$ throughout the paper.

Almost all the parameter values used in numerical calculation are derived from real experimental data. Although some of them made appropriate changes, they are still in the range of physiological significance, the specific interpretation referred to [8,9,10,11,31,32,33,34]. Unless otherwise noted, all the parameter values used are listed in appendix. **The equations are solved by the standard fourth-order RungeCKutta method and the delay is handled in**

the 4th-order RungeCKutta routine by the iterative technology, and the detailed numerical calculation method referred to [9-11]. In this paper, seizure activities induced by changing the coupling strength $-v_{sr}$ on route “ TRN $\rightarrow$ SRN ” [9].

3. Controlling absence seizures by tuning the activation level of thalamus

Fig. 2(a) and Fig. 2(b) are the bifurcation diagrams of ϕ_e with varying of $-v_{sr}$ and v_{rs} , respectively. The position and number of points for each $-v_{sr}$ or v_{rs} are different, which mean four different states (1)-(4). Fig. 2(c) is the state bifurcation diagram in the plane $(-v_{sr}, v_{rs})$ derived from Fig. 2(a) and Fig. 2(b). With changing of $-v_{sr}$ and v_{rs} , the low firing state(1), the simple oscillation state (2), the SWD oscillation state (3) and the saturation state (4) can appear, we distinguish them by different colors. From Fig. 1, we can infer that when the EPN stays in the seizure state (3), we may control seizures by enhancing (which may push EPN into the state (4)) or reducing (which may push EPN into the state (1) or (2)) the activation level of EPN. In turn, it is can be realized by decreasing or increasing the inhibitory output of the route “ TRN $\rightarrow$ SRN ”. Finally, the seizure state (3) may be controlled by increasing or decreasing activation level of TRN, shown by double arrow in Fig. 2(c). Fig. 2(d) is the dominate frequency analysis result corresponding to Fig. 2(c), it is shown that the dominate frequency of the state (3) mainly falls in the range of 2-4 Hz (which is the typical oscillation frequency interval for absence epilepsy) surrounded by white dotted line, denoted by “SWD”. Figs. 2(e)-2(h) are four specific time series of states (1)-(4), we set $-v_{sr}=0.4$ mV s, $v_{rs}=0.4$ mV s in Fig. 2(e); $-v_{sr}=0.8$ mV s, $v_{rs}=0.4$ mV s in Fig. 2(f); $-v_{sr}=0.26$ mV s, $v_{rs}=1.9$ mV s in Fig. 2(g) and $-v_{sr}=3$ mV s, $v_{rs}=1.8$ mV s in Fig. 2(h), respectively. Here, we can clear see that oscillating frequency and the number of extreme points in one period(corresponding to number of points in Fig. 2(a) and Fig. 2(b) for each fixed coupling strength) are different for each state. Especially, the state (3) has four extreme points in a shock period, which is the typical EEG feature of absence epilepsy patients[35-38].

By changing the output from STN to SRN (i.e., ϕ_n), we obtained a state bifurcation analysis diagram in Fig. 3(a). We see that the seizure state (3) can be controlled by decreasing ϕ_n , shown by the downward arrow. Its mechanism can be easily explained in Fig. 1. The coupling strength of “ SRN $\rightarrow$ EPN ” reduced with decreasing of ϕ_n . In turn, activation level of EPN reduced. Finally, the state (3) is transited to the low frequency oscillation state (1) or the simple oscillation state (2), i.e., seizures controlled. Fig. 3(c)

Figure 2: (a),(b): The bifurcation diagram of ϕ_e with varying of $-v_{sr}$ and v_{rs} , respectively. Where, $-v_{sr}$ is the inhibitory projection strength of the route “TRN $\rightarrow$ SRN”, v_{rs} is the excitatory projection strength of the route “SRN $\rightarrow$ TRN”. The number of points and oscillating frequencies on the bifurcation diagram are different for each fixed $-v_{sr}$ or v_{rs} , which means four different states (1)-(4). (c),(d): The state and dominate frequency analysis results in the plane $(-v_{sr}, v_{rs})$ derived from (a) and (b). From (c), we see that four different states (1)-(4) appeared with changing of parameters, distinguished by four colors. The state (3) may disappear by increasing or decreasing the activation level of TRN, shown by the double arrow. The region denoted as “SWD” in (d) is the typical 2-4 Hz absence seizure region corresponding to the state (3) in (c). (e)-(h): Four specific time series of states (1)-(4) obtained by setting $-v_{sr}=0.4$ mV s, $v_{rs}=0.4$ mV s (e); $-v_{sr}=0.8$ mV s, $v_{rs}=0.4$ mV s (f); $-v_{sr}=0.26$ mV s, $v_{rs}=1.9$ mV s (g) and $-v_{sr}=3$ mV s, $v_{rs}=1.8$ mV s (h), respectively.

Figure 3: (a): The state bifurcation analysis in the parameter plane $(-v_{sr}, \phi_n)$. $-v_{sr}$ is the inhibitory coupling strength of the route “TRN $\rightarrow$ SRN”, ϕ_n represents the output from STN to SRN. Clearly, the seizure state (3) can be controlled by decreasing ϕ_n , this trend denoted by the downward arrow. (b): The corresponding dominated frequency analysis result. We mark the absence seizure region by “SWD”. (c): A bifurcation diagram obtained by fixing $-v_{sr}=1.2$ mV s in (a).

is a specific bifurcation diagram obtained by fixing $-v_{sr}=1.2$ mV s in Fig. 3(a), here we can clear see the transition process between the state (1), (2) and (3). Fig. 3(b) is the corresponding frequency analysis result, we also denote the 2-4 Hz region by “SWD”. Clearly, the seizure frequency increased with increasing of the strength of ϕ_n .

4. Controlling absence seizures by tuning the activation level of striatum

In this section, we try to control absence seizures by tuning activation level of striatum neurons. Fig. 4(a)-(b) and Fig. 4(c)-(d) are state and dominate frequency analysis results in the plane $(-v_{sr}, v_{d1e})$ and $(-v_{sr}, v_{d2e})$, respectively. v_{d1e} is the excitatory coupling strength from EPN to d_1 and v_{d2e} is the excitatory coupling strength from EPN to d_2 , which can adjust activation level of striatum D1 neurons and striatum D2 neurons, respectively. Clearly, we can see that the state (3) can be controlled by decreasing the corresponding activation level of striatum, shown by downward arrows. Fig. 4(e) describes linear increase of v_{d2e} with

time. Fig. 4(f) is a time series bifurcation diagram of ϕ_e when $-v_{sr}$ fixed at 1.15 mV s in (c), which clearly shows the state transition process between the simple oscillation state (2) and the seizure state (3) with changing of v_{d_2e} . The mechanisms of them are complicated, hardly explained directly from Fig. 1. However, we may infer from the above result that striatum might be a potential target for controlling the epilepsy seizure.

4.1. Controlling absence seizures by adding the deep brain stimulation voltage on SRN

In this section, we apply one type of deep brain stimulation voltage ($V = I_{DBS} * R$) on SRN to study controlling effect of seizures. In general, we set the resistance $R=1$, and the deep brain stimulation current I_{DBS} is a common square wave stimulation current as follows,

$$I_{DBS} = A \times H(\sin(\frac{2\pi t}{P})) (1 - H(\frac{\sin(2\pi(t+D))}{P})) \quad (6)$$

where, H is the Heaviside step function. A is the amplitude of DBS current, P is the period of DBS current, D is the duration of effective output in one period. In particular, a specific square stimulation current is shown in Fig. 5.

When DBS is applied, we can rewrite equations (1)-(5) as follows, which called a modified

Figure 4: (a),(b): The state and dominate frequency analysis in the plane $(-v_{sr}, v_{d1e})$. Where, $-v_{sr}$ is the inhibitory coupling strength of the route “TRN $\rightarrow$ SRN”, v_{d1e} is the excitatory coupling strength from EPN to d_1 . (c),(d): The state and dominate frequency analysis in the plane $(-v_{sr}, v_{d2e})$, v_{d2e} is the excitatory coupling strength from EPN to d_2 . From (a) and (c), we see that the seizure state (3) may be controlled by decreasing the activation level of d_1 or d_2 , shown by downward arrows. (e): The increasing of v_{d2e} with time. (f): The time series bifurcation diagram of ϕ_e as $-v_{sr}$ fixed at 1.15 mV s in (c).

Figure 5: The common square wave stimulation current employed in model. Here, we set the period $P = 2$ ms, the amplitude of current $A = 10$ pA, the duration of effective output in one period $D = 1$ ms.

model:

$$\begin{aligned}
\frac{d\phi_e(t)}{dt} &= \dot{\phi}_e(t) \\
\frac{d\dot{\phi}_e(t)}{dt} &= \gamma_e^2[-\phi_e(t) + F(V_e(t))] - 2\gamma_e\dot{\phi}_e(t) \\
\frac{dX(t)}{dt} &= \dot{X}(t) \\
X(t) &= [V_e(t), V_{d_1}(t), V_{d_2}(t), V_{p_1}(t), V_{p_2}(t), V_\zeta(t), \\
&\quad V_r(t), V_s(t)]^T \\
\frac{d\dot{V}_e(t)}{dt} &= \alpha\beta(v_{ee}\phi_e + v_{ei}F(V_e) + v_{es}F(V_s) - V_e(t)) \\
&\quad -(\alpha + \beta)\dot{V}_e(t) \\
\frac{d\dot{V}_{d_1}(t)}{dt} &= \alpha\beta(v_{d_1e}\phi_e + v_{d_1d_1}F(V_{d_1}) + v_{d_1s}F(V_s) - V_{d_1}(t)) \\
&\quad -(\alpha + \beta)\dot{V}_{d_1}(t) \\
\frac{d\dot{V}_{d_2}(t)}{dt} &= \alpha\beta(v_{d_2e}\phi_e + v_{d_2d_2}F(V_{d_2}) + v_{d_2s}F(V_s) - V_{d_2}(t)) \\
&\quad -(\alpha + \beta)\dot{V}_{d_2}(t) \\
\frac{d\dot{V}_{p_1}(t)}{dt} &= \alpha\beta(v_{p_1d_1}F(V_{d_1}) + v_{p_1p_2}F(V_{p_2}) + v_{p_1\zeta}F(V_\zeta) \\
&\quad - V_{p_1}(t)) - (\alpha + \beta)\dot{V}_{p_1}(t) \\
\frac{d\dot{V}_{p_2}(t)}{dt} &= \alpha\beta(v_{p_2d_2}F(V_{d_2}) + v_{p_2p_2}F(V_{p_2}) + v_{p_2\zeta}F(V_\zeta) \\
&\quad - V_{p_2}(t)) - (\alpha + \beta)\dot{V}_{p_2}(t) \\
\frac{d\dot{V}_\zeta(t)}{dt} &= \alpha\beta(v_{\zeta e}\phi_e + v_{\zeta p_2}F(V_{p_2}) - V_\zeta(t)) - (\alpha + \beta)\dot{V}_\zeta(t) \\
\frac{d\dot{V}_r(t)}{dt} &= \alpha\beta(v_{re}\phi_e + v_{rp_1}F(V_{p_1}) + v_{rs}F(V_s) - V_r(t)) \\
&\quad -(\alpha + \beta)\dot{V}_r(t) \\
\frac{d\dot{V}_s(t)}{dt} &= \alpha\beta(v_{se}\phi_e + v_{sp_1}F(V_{p_1}) + v_{sr}^A F(V_r) \\
&\quad + v_{sr}^B F(V_r(T - \tau)) - V_s(t) + \phi_n + I_{DBS}R) \\
&\quad -(\alpha + \beta)\dot{V}_s(t)
\end{aligned}$$

Initially, we study control effect of DBS by varying the period P of DBS current. Fig. 6(a) shows the bifurcation diagram of state transitions in the two-dimensional parameter plane $(-v_{sr}, P)$. It can be observed that by tuning the period P , seizure activities can be controlled as indicated by double arrows in Fig.6(a). The corresponding dominant frequency analysis is shown in Fig.6(b). Through careful observation we can see that frequencies of the state (3) are almost 2-4 Hz. For a clearer vision, one specific bifurcation process of ϕ_e is shown in Fig.6(c)(setting $-v_{sr} = 0.6$ mV s in Fig.6(a)) with P changing. It is shown that the SWD may be controlled within suitable values of P by transferring into the state (4).

Next, we wonder if seizure activities can be controlled by varying the parameter D in current. Similarly, we calculate the bifurcation diagram of state transitions in the parameter plane $(-v_{sr}, D)$. It is shown in Fig. 7(a)($A=4$ pA) and Fig. 7(c)($A=-4$ pA) that SWD can be controlled into either the state (4) or the state (1) as the D is turned into some suitable ranges. Additionally, the corresponding frequency analysis are shown in Fig. 7(b) and Fig. 7(d).

5. The polyspikes of absence epilepsy

The polyspikes-slow wave discharges (PSWD) is also a common clinical EEG feature of absence epilepsy[37,38]. In this paper, we find that the PSWD appeared by turning the delay on the route “ $TRN \rightarrow SRN$ ”. Fig. 8(a) shows a four-polyspikes wave, Fig. 8(b) shows a three-polyspikes wave and Fig. 8(c) is a five-polyspikes wave, the delay set as 0.11 s, 0.15 s and 0.2 s, respectively. We may infer from Fig. 8 that delay is a key parameter to induce the polyspikes phenomenon. Fig. 9 is a state bifurcation diagram of ϕ_e as varying of v_{rs} . In Fig. 9(b), we can see that the polyspikes state can be well controlled by transferring to the low firing state or the saturated state with varying of v_{rs} . Fig. 10 is the state bifurcation diagram of ϕ_e as varying of v_{d_1} . In Fig. 10(b), we can also see that the seizure state disappeared with increasing of v_{d_1} . So, we may infer that the polyspikes-slow wave discharges and other epilepsy diseases can also be controlled by the way presented in this paper.

6. Conclusion

In this paper, based on a basal ganglia-corticothalamic model, we study the controlling problem of the absence epilepsy seizure. We find that seizures can be well controlled by

Figure 6: (a),(b): The transition of different states and dominative frequency analysis result in the parameter plane $(-v_{sr}, P)$. $-v_{sr}$ is the inhibitory coupling strength of the route “TRN $\rightarrow$ SRN”, P is the period of the stimulation current. Here, we set $A = 10$ pA, $D = 0.0006$ ms, $v_{p1\zeta} = 0.1$ mV s. Seizure states can be controlled by tuning the period P into some appropriate intervals shown by double arrows. Combining with (a), the typical 2-4 Hz region can be observed in (b). (c): A bifurcation diagram of ϕ_e as a function of P obtained by setting $-v_{sr} = 0.6$ mV s in (a).

Figure 7: The state transitions and dominative frequency analysis in the parameter plane $(-v_{sr}, D)$. $-v_{sr}$ is the inhibitory coupling strength of the pathway “ $TRN \rightarrow SRN$ ”, D is the duration of effective input in one period of the DBS current. Here, $P = 1$ ms, $v_{p1}\zeta = 0.1$ mV s. (a),(b): $A = 4$ pA; (c),(d): $A = -4$ pA. Clearly, we can see that the seizure state (3) controlled by tuning D into some appropriate values.

Figure 8: The polyspikes phenomenon of absence epilepsy. We set $\tau = 0.11s$, $\tau = 0.15s$ and $\tau = 0.2s$ in (a), (b) and (c), respectively. In this simulation, we set $-v_{sr} = 1.6mVs$ and $v_{rs} = 0.2mVs$.

Figure 9: The state bifurcation diagram of ϕ_e as varying of v_{rs} . v_{rs} is the excitatory coupling strength in the pathway “ $SRN \rightarrow TRN$ ” and (a) is the time series of v_{rs} . In (b), we can clear see the transition dynamics behavior between the seizure state, the low firing state and the saturated state. In this simulation, we set $\tau = 0.3$ s, $-v_{sr} = 1.15$ mV s, $v_{d_2}e = 0.9$ mV s .

Figure 10: The state bifurcation diagram of ϕ_e as varying of $v_{d1}e$. $v_{d1}e$ is the connection strength from excitatory pyramidal neurons to striatum D1 neurons and (a) is the time series of $v_{d1}e$. With increasing of $v_{d1}e$, the seizure state transferred to the simple oscillating state shown in (b). In this simulation, we set $\tau = 0.3$ s, $-v_{sr} = 1.15$ mV s and $v_{d2}e = 0.9$ mV s.

tuning the activation level of SRN, TRN, striatum D1 neurons and striatum D2 neurons, which imply that these populations may be potential candidate targets for the deep brain stimulation treatment in the future. Then, one type of square wave stimulation current employed on SRN, and we find that the seizure activity can also be controlled by tuning the period and the duration of effective current in one period into some appropriate ranges. The method presented here can also be extended to the control of the polyspikes-slow wave discharges and other epilepsy diseases. Therefore, the results obtained may provide a good theoretical basis for selecting thalamus and striatum as the deep brain stimulation region in the future clinical treatment.

7. Appendix

Unless otherwise noted, we use the follow parameter values for simulations [8,9,10,11,12,31,32,33,34],

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
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
v_{ee}	Excitatory pyramidal neurons	Excitatory pyramidal neurons	1 mV s
v_{ei}	Inhibitory interneurons	Excitatory pyramidal neurons	-1.8 mV s
v_{re}	Excitatory pyramidal neurons	TRN	0.05 mV s
v_{rs}	SRN	TRN	0.5 mV s
$v_{sr}^{A,B}$	TRN	SRN	(-3.8)-(-0.1)mV s
v_{d_1e}	Excitatory pyramidal neurons	Striatal D1 neurons	1 mV s
$v_{d_1d_1}$	Striatal D1 neurons	Striatal D1 neurons	-0.25 mV s
v_{d_1s}	SRN	Striatal D1 neurons	0.1 mV s
v_{d_2e}	Excitatory pyramidal neurons	Striatal D2 neurons	0.7 mV s
$v_{d_2d_2}$	Striatal D2 neurons	Striatal D2 neurons	-0.3 mV s
v_{d_2s}	SRN	Striatal D2 neurons	0.05 mV s
$v_{p_1d_1}$	Striatal D1 neurons	SNr	-0.1 mV s
$v_{p_1p_2}$	GPe	SNr	-0.03 mV s
$v_{p_1\zeta}$	STN	SNr	0.1 mV s
$v_{p_2d_2}$	Striatal D2 neurons	GPe	-0.3 mV s
$v_{p_2p_2}$	GPe	GPe	-0.09 mV s
$v_{p_2\zeta}$	STN	GPe	0.4 mV s
$v_{\zeta p_2}$	GPe	STN	-0.04 mV s
v_{es}	STN	Excitatory pyramidal neurons	1.6 mV s
v_{se}	Excitatory pyramidal neurons	SRN	1.8 mV s
$v_{\zeta e}$	Excitatory pyramidal neurons	STN	0.1 mV s
v_{sp_1}	SNr	SRN	-0.04 mV s
v_{rp_1}	SNr	TRN	-0.04 mV s

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