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

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ABSTRACT

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.

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 cortical 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

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[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 4.1, 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 [11–13,31,32],

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

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 [9–11,31,32],

$$D_{\alpha\beta}V_a(t) = \Sigma_{b\in A}S(v_{ab}).v_{ab}.\phi_b(t) \tag{2}$$

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

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(v_{ab})=1 means projections from b to a are excitatory; otherwise, S(v_{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 [9–11,31,32].

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

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

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,

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

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 $V_i = V_e$ [8–11,33]. One can also read related important literatures [8–11, 31–33] 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],

$$\frac{d\phi_e(t)}{dt} = \dot{\phi}_e(t)$$