Regulation and control roles of the basal ganglia in the development of absence epileptiform activities

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Abstract

Absence epileptiform activities are traditionally considered to be primarily induced by abnormal interactions between the cortical and thalamic neurons, which form the thalamocortical circuit in the brain. The basal ganglia, as an organizational unit in the brain, has close input and output relationships with the thalamocortical circuit. Although several studies report that the basal ganglia may participate in controlling and regulating absence epileptiform activities, to date, there have been no studies regarding whether the basal ganglia directly cause absence epileptiform activities. In this paper, we built a basal ganglia-corticothalamic network model to determine the role of basal ganglia in this disease. We determined that absence epileptiform activities might be directly induced by abnormal coupling strengths on certain pivotal pathways in the basal ganglia. These epileptiform activities can be well controlled by the coupling strengths of three major pathways that project from the thalamocortical network to the basal ganglia. The results implied that the substantia nigra pars compacta (SNc) can be considered to be the effective treatment target area for inhibiting epileptiform activities, which supports the observations of previous studies. Particularly, as a major contribution of this paper, we determined that the final presentation position of the epileptic slow spike waves is not limited to the cerebral cortex; these waves may additionally appear in the thalamus, striatal medium spiny neurons, striatal fast spiking interneuron, the SNc, subthalamic nucleus, substantia nigra pars reticulata and globus pallidus pars externa. In addition, consistent with several previous studies, the delay in the network was observed to be a critical factor for inducing transitions between different types of absence epileptiform activities. Our new model not only explains the onset and control mechanism but also provides a unified framework to study similar problems in neuron systems.

Keywords Absence epileptiform activities · Basal ganglia · Thalamocortical circuit · Onset and control · State transition

Introduction

Approximately one percent to two percent of people suffer from various types of epilepsy. Excessive synchronous discharge activities in neuronal circuits are common physiological characteristics of various types of epilepsy; however, these activities are different in regard to their onset and disappearing mechanisms, severity and age of people affected. Absence epilepsy, which primarily occurs in childhood and adolescence, is an idiopathic, generalized non-convulsive epilepsy that has a multiple genetic aetiology (Crunelli and Leresche 2002). Absence epilepsy seizures are characterized by disruptions in consciousness that only last for a few second, and may recur hundreds of times a day. Typical spike-and-wave discharges (SWDs)

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can be observed in electroencephalograms (EEGs) of absence epilepsy patients, with an oscillation frequency of approximately 2–4 Hz (CoCaTotILA 1989; Cheong and Shin 1828). Although the cause of absence seizures has been debated for decades, the attack mechanism has not been confirmed. Several previous studies have supported the traditional idea that SWDs primarily arise from aberrant recurrent interactions between the thalamus and cerebral cortex tissue, the combination of which forms the thalamocortical network in the brain (Timofeev and Steriade 2004; Velazquez et al. 2015). For instance, Timofeev and Steriade (2004) evaluated the detailed mechanisms during the initiation, propagation and cessation processes of epileptic seizures by performing multiple intracellular and field potential recordings in vivo; their results provided direct evidence that abnormal interactions among the thalamocortical system were major factors that led to seizures. Several additional studies on computational models, specifically on the thalamocortical mean field network model (Robinson et al. 2002; Rodrigues et al. 2006, 2009; Takeshita et al. 2007; Marten et al. 2009a, b; Wilson et al. 2006; Case and Soltesz 2011; Dadok et al. 2012; Lytton 2008; Hu et al. 2015), explored the mechanisms of epilepsy seizures. Marten et al. examined the onset and bifurcation mechanism of the classical spike and wave activity, poly-spike and wave, wave spike and lack of discernible spike-wave during an absence epilepsy seizure in a human thalamocortical mean field network model. This method provides a useful tool for distinguishing different types of absence epilepsy (Marten et al. 2009a, b). Dadok et al. (2012) developed a mean-field cortical model to explore the evolution pathways of seizures. Recently, Hu et al. (2015) observed that absence seizures in the excitatory pyramidal neurons (EPN) can be induced by excitatory pathways related to the specific relay nuclei (SRN) in the corticothalamic system; this result supports observations from several previous studies (Rodrigues et al. 2009; Marten et al. 2009a, b). In the above studies, the SWDs of the epileptic seizure were supposed to appear in the cortex. However, we know that during an epilepsy seizure, several regions of the brain exhibit synchronous oscillatory activities, especially in the basal ganglia and corticothalamic system. Therefore, it remains unclear whether the spike-and-waves of epilepsy additionally appear in other regions of the brain or shift between different regions during seizures.

The basal ganglia (BG), as a basic functional unit of the brain, are the largest subcortical structures in the human forebrain. In the anatomical structure, the BG receive inputs from both the cortex and part of the thalamus; additionally, through their major output nuclei substantia nigra pars reticulata (SNr) and GPi (globus palladium interior), the BG project to thalamic tissue. This anatomical

structure determines the primary role played by the BG in the executive function of the forebrain, especially for movement and cognitive behaviour (Graybiel 2000; Tepper et al. 2007). Multiple studies reported that the physiological activities of the BG may have a considerable effect on modulating and controlling certain neural diseases induced by the abnormal interactions in the corticothalamic system, such as epileptic seizures (Arakaki et al. 2016; Hu et al. 2017; Gey et al. 2016; Chang et al. 2016; Paz et al. 2007; Kase et al. 2012; Cheng et al. 2015; Dong et al. 2016; Rajab et al. 2015; Rektor et al. 2013; Knowlton 2015; Chen et al. 2015b). For example, using PET technology, Biraben et al. (2004) observed that the circuit in the BG and striatal dopaminergic transmission play important roles in the inhibition of epileptic seizures. Luo et al. (2012) confirmed that the BG are important modulators in the process of idiopathic generalized epilepsy seizures using resting-state fMRI analysis. Výtvarová et al. (2017) observed significant changes in the resting-state functional connectivity between the cortical and subcortical structures, which implied a key role of the BG in the generation of focal epilepsies. With respect to theoretical research, recently, Arakaki et al. (2016) determined that striatal feedforward inhibition plays a key role in the maintenance of absence seizures. Hu et al. (2017) observed that absence seizures were inhibited by modulating the activation level of the striatal neurons. The firing activities of the subthalamic nucleus (STN) (Gey et al. 2016; Chang et al. 2016) and SNr (Paz et al. 2007; Kase et al. 2012) have been reported to have a marked effect on epileptic seizures, and both have been considered to be targets for brain stimulation technology to control seizures for decades. Cheng et al. observed that a low-frequency stimulation acting on the external globus palladium (GPe) can produce an anti-epileptogenic effect in rats (Cheng et al. 2015). Recently, Chen et al. reported that modulating the activation level of GPe regulated absence seizures in a theoretical model (Chen et al. 2015b). However, regardless of its importance, the effect of the substantia nigra pars compacta (SNc) on epilepsy seizures is less studied. Moreover, it remains unclear whether the abnormal electrophysiological activities of the BG are also the direct factors that induce epileptic seizures, and there is almost no relevant theoretical research on this topic.

In this paper, inspired by the brain mean field model developed in Parkinson's disease (van Albada and Robinson 2009; van Albada et al. 2009; Holgado et al. 2010; Pavlides et al. 2012, 2015; Bogacz 2015) and epilepsy (Chen et al. 2014, 2015b) study, we proposed a new model, i.e., a basal ganglia-corticothalamic model, to determine the potential importance of the BG in the development of absence epileptiform activities. We observed that absence epileptiform activities can be directly induced by the

abnormal coupling strengths of certain pivotal pathways in the BG. These epileptiform activities can be modulated according to the coupling strengths of three major pathways projected from the thalamocortical network to the BG in this model. Supported by previous studies (Sabatino et al. 1988; Bonhaus et al. 1986; McNamara et al. 1984; Morimoto and Goddard 1987), our results implied that changing the activation level of the SNc is an effective strategy for controlling epileptiform activities. In particular, we observed that the final presentation position of the epileptic slow spike waves was not limited to the cerebral cortex and that it might additionally appear in the thalamus, striatal medium spiny neurons (MSN), striatal fast spiking interneurons (FSI), SNc, STN, SNr and GPe. Consistent

with multiple previous studies, the delay in our network is a critical factor that induces the transition between different types of absence epileptiform activities. Our model not only clearly describes the onset and control mechanisms but also introduces a new approach to study similar problems in biology and medicine.

Model description

In this section, we first describe the connection structure of our new model in Fig. 1, which contains the BG, corticothalamic system and brainstem tissue. In the SNc, degeneration of dopaminergic neurons, which is the major

Fig. 1 Schematic diagram of the model. Neural populations are denoted as follows, e = excitatory pyramidal neurons; i = inhibitory interneurons; r = thalamic reticular nucleus; s = specific relay nuclei; m = medium spiny neurons; f = striatal fast spiking interneuron; p₁ = substantia nigra pars reticulata; p₂ = globus pallidus external segment; ζ = subthalamic nucleus; c = substantia nigra pars compacta; b = brainstem. The arrows represent excitatory inputs

adjusted by glutamate, the solid dots indicate inhibitory projections regulated by gamma-aminobutyric acid, and the dotted line in the “TRN → SRN” pathway denotes the second messenger processes mediated by GABA_B receptors. V_s represents the sensory stimuli of specific relay nuclei projected from the brainstem, which is considered to be a constant in this model. The brainstem organization is not a critical population considered in our study

pathological mechanism leading to Parkinson's disease, sends important dopaminergic projections to the striatum. The striatum is divided into the MSN and FSI, which are primarily distinguished by their targets and sources of activity. More than 90 percent of striatal neurons are medium spiny neurons (Yelnik et al. 1991) that exert inhibitory projections to the GPe and GPi. These neurons induce an overall inhibitory effect on the thalamus via the pathways " $MSN \rightarrow GPe \rightarrow GPi$ " and " $MSN \rightarrow GPe \rightarrow STN \rightarrow GPi$ " and an overall excitatory effect through the pathway " $MSN \rightarrow SNr$ " (cf. Fig. 1). These neurons additionally exert overall excitatory effects on the cortex through two direct pathways, " $MSN \rightarrow GPe \rightarrow EPN$ " and " $MSN \rightarrow SNr \rightarrow EPN$ ", which are rarely considered in the traditional models, as well as an overall inhibitory through the indirect pathway " $MSN \rightarrow GPe \rightarrow STN \rightarrow GPe \rightarrow EPN$ ". Although FSI only account for a small part of the striatal population, they play an important role in maintaining the activity of epilepsy seizures (Arakaki et al. 2016). The SNr and GPi are both major inhibitory output sources from the BG to the thalamus, and we model them as a single structure due to their close relation with inputs and outputs, as well as their similarities in cytology and function (van Albada and Robinson 2009; van Albada et al. 2009). In this model, the GPe exerts a direct GABAergic inhibitory projection to the EPN, the existence of which has been indicated in previous experimental studies (Chen et al. 2015a; Saunders et al. 2015; Qiu et al. 2010) and recent theoretical model study (Chen et al. 2015b). The STN acts as an additional input station of the BG, which project excitatory glutamatergic inputs to the SNr and GPe. The thalamus is composed of two parts, the thalamic reticular nucleus (TRN) and specific relay nuclei (SRN). The TRN contains a large number of GABAergic neurons have strong inhibitory effects on the SRN, and the signal transmission of this inhibitory pathway is relatively slow because the $GABA_B$ receptors act via second messenger processes. Therefore, in this model, we introduce a delay τ to describe the slow synaptic kinetics of the pathway " $TRN \rightarrow SRN$ ", denoted by the dotted line in Fig. 1. The SRN exert excitatory outputs to the cortex and TRN, and they both receive excitatory projections from the cortex, which is an excitatory population in the corticothalamic system and plays a role as a signal relay between the cortex and thalamus. The effect of the thalamus on the BG is primarily via excitation of the " $SRN \rightarrow MSN$ " pathway. The cerebral cortex includes the inhibitory interneurons (IIN) and EPN in our model, and we view them as a single population in this study due to their similar intracortical connectivities (Marten et al. 2009a, b). The EPN receives excitatory signals from the SRN, and its outputs to the BG are primarily through the excitatory pathways " $EPN \rightarrow STN$ ", " $EPN \rightarrow MSN$ " and

" $EPN \rightarrow FSI$ ". The brainstem predominantly receives excitatory projections from the EPN and projects sensory stimuli to the SRN, which is considered to be a constant input V_s in our model. It should be noted that the brainstem is not a critical population considered in our study. To facilitate the following description, all of the populations are abbreviated as follows: $e = EPN$; $i = IIN$; $r = TRN$; $s = SRN$; $m = MSN$; $f = FSI$; $p_1 = SNr$; $p_2 = GPe$; $\zeta = STN$; $b =$ brainstem; and $c = Snc$. The arrows represent excitatory inputs adjusted by glutamate, the solid dots indicate inhibitory projections regulated by gamma-aminobutyric acid (GABA), and the dotted line in the pathway " $TRN \rightarrow SRN$ " denotes the second messenger processes mediated by $GABA_B$ receptors.

To evaluate the dynamic behaviour of the network shown in Fig. 1, we need to know the mean firing rate Q_a , the potential V_a and propagation effect of the pulsed field ϕ_a for each population "a" ($a = e, i, r, s, m, f, c, p_1, p_2, \zeta$). In the following study, we use the mean field theory to evaluate these physical quantities (van Albada and Robinson 2009; van Albada et al. 2009). First, the Q_a represents the mean firing rate of the nerve nuclei "a" and is a sigmoid function of its potential V_a ,

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

Q_a^{max} is the maximum firing rate (MFR) of "a"; here, the shape feature of sigmoid function assures that the firing rate of each population cannot increase infinitely but can be infinitely close to Q_a^{max} . θ_a represents the mean threshold potential (MTP) of the population, which implies that the neural population will fire if and only if the membrane potential V_a exceeds θ_a . σ is the standard deviation of the firing thresholds obtained by statistical analysis and is considered to be a constant in this paper.

The evolution of the cell-body potential V_a is described by the following differential equations,

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

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

$D_{\alpha\beta}$ is a differential operator representing axon and dendritic integrals of input pulse signals. α and β are considered to be constants that represent the attenuation and rising rate of the membrane potential V_a , respectively. v_{ab} is the coupling strength on the pathway " $b \rightarrow a$ ". A is a set that contains all of the populations that project to "a". When the projection from "b" to "a" is excitatory, $S(v_{ab})=1$; otherwise, $S(v_{ab}) = -1$. The signal transmission delay on each pathway is omitted for simplicity, except for the " $TRN \rightarrow SRN$ " pathway, which will be discussed in

detail in “Controlling absence epileptiform activities via three major pathways projected from the thalamocortical circuit to the BG” section.

The propagation effect of the pulsed field ϕ_a is depicted by the following damped wave equation,

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

where $\gamma_a = v_a/r_a$ is the damping rate, v_a is the velocity of pulse propagation, and r_a is the characteristic axonal range. In this model, we suppose that the axons of all populations, except the EPN are too short to support obvious pulse propagations; thus, $\phi_P = F(V_P)$ ($P = i, r, s, m, f, c, p_1, p_2, \zeta$), as in multiple previous studies (Marten et al. 2009a; Hu et al. 2017; van Albada and Robinson 2009; van Albada et al. 2009). The pulse spreading effect of the EPN is described individually as follows,

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

Finally, for the purpose of numerical calculations, we rewrite Eqs. (1)–(5) in the first-order form via the transformation method of ordinary differential equations,

$$\frac{d\phi_e(t)}{dt} = \dot{\phi}_e(t) \quad (6)$$

$$\frac{d\dot{\phi}_e(t)}{dt} = \gamma_e^2 [-\phi_e(t) + F(V_e(t))] - 2\gamma_e \dot{\phi}_e(t) \quad (7)$$

$$\frac{dX(t)}{dt} = \dot{X}(t), X(t) = [V_e(t), V_m(t), V_f(t), V_{p_1}(t), V_{p_2}(t), V_\zeta(t), V_r(t), V_s(t), V_c(t)]^T \quad (8)$$

$$\begin{aligned} \frac{d\dot{V}_e(t)}{dt} = & \alpha\beta(v_{ee}\phi_e + v_{ei}F(V_e) + v_{es}F(V_s) + v_{ep_1}F(V_{p_1}) \\ & + v_{ep_2}F(V_{p_2}) - V_e(t)) - (\alpha + \beta)\dot{V}_e(t) \end{aligned} \quad (9)$$

$$\begin{aligned} \frac{d\dot{V}_m(t)}{dt} = & \alpha\beta(v_{me}\phi_e + v_{mm}F(V_m) + v_{mf}F(V_f) + v_{ms}F(V_s) \\ & + v_{mc}F(V_c) - V_m(t)) - (\alpha + \beta)\dot{V}_m(t) \end{aligned} \quad (10)$$

$$\frac{d\dot{V}_f(t)}{dt} = \alpha\beta(v_{fe}\phi_e + v_{fc}F(V_c) - V_f(t)) - (\alpha + \beta)\dot{V}_f(t) \quad (11)$$

$$\begin{aligned} \frac{d\dot{V}_{p_1}(t)}{dt} = & \alpha\beta(v_{p_1m}F(V_m) + v_{p_1p_2}F(V_{p_2}) + v_{p_1\zeta}F(V_\zeta) \\ & + v_{p_1p_1}F(V_{p_1}) - V_{p_1}(t)) - (\alpha + \beta)\dot{V}_{p_1}(t) \end{aligned} \quad (12)$$

$$\begin{aligned} \frac{d\dot{V}_{p_2}(t)}{dt} = & \alpha\beta(v_{p_2m}F(V_m) + v_{p_2p_2}F(V_{p_2}) + v_{p_2\zeta}F(V_\zeta) \\ & - V_{p_2}(t)) - (\alpha + \beta)\dot{V}_{p_2}(t) \end{aligned} \quad (13)$$

$$\frac{d\dot{V}_\zeta(t)}{dt} = \alpha\beta(v_{\zeta e}\phi_e + v_{\zeta p_2}F(V_{p_2}) - V_\zeta(t)) - (\alpha + \beta)\dot{V}_\zeta(t) \quad (14)$$

$$\begin{aligned} \frac{d\dot{V}_r(t)}{dt} = & \alpha\beta(v_{re}\phi_e + v_{rp_1}F(V_{p_1}) + v_{rs}F(V_s) \\ & - V_r(t)) - (\alpha + \beta)\dot{V}_r(t) \end{aligned} \quad (15)$$

$$\begin{aligned} \frac{d\dot{V}_s(t)}{dt} = & \alpha\beta(v_{se}\phi_e + v_{sp_1}F(V_{p_1}) + v_{sr}^A F(V_r) \\ & + v_{sr}^B F(V_r(t - \tau)) - V_s(t) + V_s) - (\alpha + \beta)\dot{V}_s(t) \end{aligned} \quad (16)$$

$$\frac{d\dot{V}_c(t)}{dt} = \alpha\beta(-V_c(t)) - (\alpha + \beta)\dot{V}_c(t) \quad (17)$$

which are delay differential equations and we only consider the term τ in Eq. (16).

Methods

We consider state changes of the EPN based on the bifurcation analysis. The one-dimensional bifurcation graph of ϕ_e is obtained by considering the stable local minimum and maximum values of the EPN axonal fields over changes for each parameter, as shown in Fig. 2a. In Fig. 2a, with each fixed coupling strength value $-v_{rp_1}$, one extreme point represents the low firing state (NS) (Chen et al. 2014) of the brain and four extreme points indicate the SWDs. Similarly, a two-dimensional state bifurcation diagram can be derived, as presented in Fig. 2c. To verify the type of epilepsy that appears in the model, we perform power spectral analysis on the time series of ϕ_e via fast Fourier transform and consider the maximum peak frequency to be the dominant frequency of the EPN. Figure 2d indicates that the seizure frequency nearly falls into the range of 2–4 Hz, which is the absence seizure frequency range. To facilitate our understanding of the onset and control mechanism of epileptiform activities that appear in the model, we simulated the mean discharge rates (MDFs) of certain critical populations, which were obtained by meaning the time series (such as ϕ_e) and represented the firing activation level of populations. The numerical calculation was performed via the standard fourth-order Runge–Kutta method using MATLAB software, with an iteration step of $\Delta t = 0.05$ ms. All of the parameter values used in the numerical calculations are derived and estimated from real experimental data, which are listed in the appendix.

Fig. 2 Absence epileptiform activities induced by the strength of $-v_{rp1}$ and $-v_{sp1}$, which are two projection strengths from the SNr to the TRN and SRN, respectively. **a** A bifurcation diagram of ϕ_e with a variation in $-v_{rp1}$, which pushes the EPN from the low firing state (NS) to the absence epileptiform activity state; $-v_{sp1}$ is set as 0.01 mV s. **b** A bifurcation diagram of ϕ_e with an increase in $-v_{sp1}$, which pushes the EPN from the absence epileptiform activity state to the NS, and here, $-v_{sp1}$ is considered to be 0.15 mV s. **c** The state bifurcation diagram of ϕ_e in the two-dimensional parametric plane ($-v_{rp1}$, $-v_{sp1}$) derived from **a** and **b**. With change in $-v_{rp1}$ and $-v_{sp1}$, the EPN has two states: the NS and absence epileptiform activity

state, which are distinguished by two different colours. **d** The dominant frequency analysis corresponds to **c**, and the epileptic area is denoted by “SWD”. We observe that the epileptiform activity frequency nearly falls in the range of 2–4 Hz and is clearer in **e**, which was obtained by setting $-v_{sp1} = 0.01$ mV s. **f–i** Four specific time series diagrams obtained by setting $-v_{sp1} = 4.8$ mV s, $-v_{rp1} = 0.18$ mV s in **f**; $-v_{sp1} = 0.06$ mV s, $-v_{rp1} = 0.15$ mV s in **g**; $-v_{sp1} = 0.02$ mV s, $-v_{rp1} = 0.175$ mV s in **h**; $-v_{sp1} = 0.01$ mV s, $-v_{rp1} = 0.16$ mV s in **i**; respectively. Here, **f** represents the NS and **g–i** represent the epileptiform activity state. (Color figure online)

The absence epileptiform activities induced by certain critical pathways in the BG

“ $SNr \rightarrow SRN$ ” and “ $SNr \rightarrow TRN$ ” are two major direct inhibitory output pathways from the BG to the thalamus, the coupling strengths of which are denoted by $-v_{sp1}$ and $-v_{rp1}$, respectively. Figure 2 describes the state bifurcation of the EPN with changes in $-v_{sp1}$ and $-v_{rp1}$. Figure 2a presents the state transferred from the NS to the SWDs, an increase in $-v_{rp1}$. The model in Fig. 1 indicates that $-v_{rp1}$ affects the activation level of the EPN primarily through the pathway “ $SNr \rightarrow TRN \rightarrow SRN \rightarrow EPN$ ” and that

$-v_{rp1}$, overall, exerts excitatory effects on the EPN. Therefore, the enhancement of $-v_{rp1}$ pushes the EPN from the NS into the SWDs. On the other hand, $-v_{sp1}$ can affect the state of the EPN via two different pathways: (I) the direct pathway “ $SNr \rightarrow SRN \rightarrow EPN$ ”, which has overall inhibitory effects on the EPN; (II) the indirect pathway “ $SNr \rightarrow SRN \rightarrow TRN \rightarrow SRN \rightarrow EPN$ ” relayed at the TRN, which in contrast, exerts overall excitatory effects on the EPN. However, generally, the effect of the direct pathway (I) plays a major role. Thus, enhancing of $-v_{sp1}$ pushes the EPN from the absence epileptiform activity state into the NS, as depicted in Fig. 2b. Figure 2c presents

the state bifurcation diagram of ϕ_e in the two-dimensional parametric plane $(-v_{rp1}, -v_{sp1})$, derived directly from Fig. 2a and b. We used two different colours to distinguish the states “NS” and “SWD”. Figure 2d shows the dominant frequency analysis results of EPN shocks, whose parameter range is shown in Fig. 2c. The epileptic area denoted by “SWD” demonstrates that the seizure frequency nearly falls in the range of 2–4 Hz, which indicates that the epileptiform activity appearing in this model is due to absence epilepsy. To clearly observe the frequency characteristics of the epileptiform activities, we present a specific frequency diagram in Fig. 2e, which was obtained by setting $-v_{sp1} = 0.01$ mV s in Fig. 2d, illustrating that the frequencies are nearly proximal to the range of 2–4 Hz. Figure 2f–i show four specific time series diagrams that were obtained by setting $-v_{sp1} = 4.8$ mV s, $-v_{rp1} = 0.18$ mV s (Fig. 2f); $-v_{sp1} = 0.06$ mV s, $-v_{rp1} = 0.15$ mV s (Fig. 2g); $-v_{sp1} = 0.02$ mV s, $-v_{rp1} = 0.175$ mV s (Fig. 2h); $-v_{sp1} = 0.01$ mV s, $-v_{rp1} = 0.16$ mV s (Fig. 2i). Figure 2f represents the NS, which is the low frequency oscillation phenomenon with a constant. Figure 2g shows a typical absence epileptiform activity time sequence diagram with two-pair extreme points in one period. Figure 2h and i are periodic oscillations with multiple extreme points in a period; although they were rarely observed in previous studies, they may represent the absence epileptiform activity type as well.

In addition to “ $SNr \rightarrow SRN$ ” and “ $SNr \rightarrow TRN$ ”, we determined that the other pathways in the BG may be additional key factors for generating absence epileptiform activities, as shown in Fig. 3. We attempt to explain certain onset mechanisms from the model presented in Fig. 1 as follows: (1) Figure 3a shows that the state is transferred from “SWD” to “NS”, with an increase of the coupling strength on the pathway “ $GPe \rightarrow SNr$ ”, which can further affect the firing activity of the EPN via the competition mechanism between “ $SNr \rightarrow SRN$ ” and “ $SNr \rightarrow TRN$ ”. We infer that, in this case, the effects of “ $SNr \rightarrow SRN$ ” occupy the dominant position because the transition process is similar to that shown in Fig. 2b. Similar generation mechanisms may be suitable for Fig. 3c, e and h. (2) “ $GPe \rightarrow EPN$ ” and “ $SNr \rightarrow EPN$ ” are two direct inhibitory pathways that project to the cortex; therefore, with increases in $-v_{ep1}$ and $-v_{ep2}$, the state is transferred from “SWD” to “NS”, as presented in Fig. 3b and f. (3) An increase in the self-feedback coupling strength of the GPe, i.e., $-v_{p2p2}$, will reduce the inhibitory coupling strength on the pathway “ $GPe \rightarrow EPN$ ”. In other words, $-v_{p2p2}$ can enhance the activation level of the EPN. Thus, the state is transferred from “NS” to “SWD” with the enhancement of $-v_{p2p2}$. (4) The effect of the inhibitory self-feedback coupling strength of the MSN is weak in this model, as shown in Fig. 3g. (5) The model indicates that $-v_{p2m}$ affects the activation level of the EPN via the competition mechanism between the direct

pathway “ $MSN \rightarrow GPe \rightarrow EPN$ ” and other indirect pathways relayed at the SNr and STN. Moreover, the effect of the direct pathway “ $MSN \rightarrow GPe \rightarrow EPN$ ” is important. Thus, the onset mechanism shown in Fig. 3i is similar to that shown in Fig. 3d. Additionally, $v_{p2\zeta}$ may primarily affect the EPN via the direct pathway “ $STN \rightarrow GPe \rightarrow EPN$ ”; however, the mechanism shown in Fig. 3m is different than those shown in Fig. 3d and i because $v_{p2\zeta}$ is the excitatory coupling weight. (6) Figure 3j, k indicates that increases in $-v_{mf}$ and v_{fc} can push the EPN from “SWD” to “NS”. By contrast, v_{mc} promotes the occurrence of epilepsy, as shown in Fig. 3l. However, these mechanisms can-not be easily explained by the model itself due to its complicated network connection structure. (7) $v_{p1\zeta}$ acts through four pathways to change the physiological activities of the EPN: (a) the overall effects of the “ $STN \rightarrow SNr \rightarrow EPN$ ” and “ $STN \rightarrow SNr \rightarrow SRN \rightarrow EPN$ ” pathways are inhibitory; (b) the overall effects of the “ $STN \rightarrow SNr \rightarrow SRN \rightarrow TRN \rightarrow SRN \rightarrow EPN$ ” and “ $STN \rightarrow SNr \rightarrow TRN \rightarrow SRN \rightarrow EPN$ ” pathways are excitatory. Therefore, (a) and (b) form competitive mechanisms to modulate the activation level of the EPN. When $v_{p1\zeta}$ is relatively small, the effect of (b) is dominant; thus, the state is transferred from “NS” to “SWD”. However, after $v_{p1\zeta}$ is increased to a sufficiently large value (> 1 mV s), the effect of (a) occupies the dominant position, and thus, the EPN reverts to the NS.

To improve our understanding of these onset mechanisms, especially for Fig. 3j, k, we calculated the MDFs of the EPN corresponding to Fig. 3a–n in Fig. 4 and determined that the changing tendency of the MDFs were consistent with each state bifurcation diagrams shown in Fig. 3.

Controlling absence epileptiform activities via three major pathways projected from the thalamocortical circuit to the BG

“ $EPN \rightarrow STN$ ”, “ $EPN \rightarrow MSN$ ” and “ $SRN \rightarrow MSN$ ” are the three major pathways projected from the thalamocortical circuit to the BG and may greatly influence the physiological activity in the BG loop as well as the absence epileptiform activities generated in the model. We confirmed this hypothesis in Fig. 5. “ $SNr \rightarrow TRN$ ” and “ $SNr \rightarrow SRN$ ” are the two major output pathways from the BG to the thalamocortical system, and the connection from the SNr to the thalamus is uncertain. The “ $SNr \rightarrow TRN$ ” pathway is often omitted in previous theoretical studies (van Albada and Robinson 2009; van Albada et al. 2009) due to the lack of experimental data. Here, we introduced a scale factor k to represent the size relation of the projection intensities between the “ $SNr \rightarrow TRN$ ” and “ $SNr \rightarrow SRN$ ”

Fig. 3 State transition diagram of the EPN induced by several pathways related to the BG. In all of the simulations, we set $-v_{rp1} = 0.135 \text{ mV s}$ (a), $-v_{rp1} = 0.12 \text{ mV s}$ (b), $-v_{rp1} = 0.12 \text{ mV s}$ (c), $-v_{rp1} = 0.075 \text{ mV s}$ (d), $-v_{rp1} = 0.135 \text{ mV s}$ (e), $-v_{rp1} = 0.12 \text{ mV s}$ (f), $-v_{rp1} = 0.108 \text{ mV s}$ (g), $-v_{rp1} = 0.12 \text{ mV s}$ (h),

$-v_{rp1} = 0.108 \text{ mV s}$ (i), $-v_{rp1} = 0.108 \text{ mV s}$ (j), $-v_{rp1} = 0.111 \text{ mV s}$ (k), $-v_{rp1} = 0.09 \text{ mV s}$ (l), $-v_{rp1} = 0.105 \text{ mV s}$ (m) and $-v_{rp1} = 0.12 \text{ mV s}$ (n), respectively

pathways, i.e., $-v_{rp1} = -kv_{sp1}$ (Chen et al. 2014) to study the control effect of the above three pathways on the absence epileptiform activity. In Fig. 5, we observed that changing the coupling strength of these pathways may affect the firing activity on the EPN. Figure 5a–c are three state regional bifurcation diagrams on the two-dimensional parametric plane $(k, v_{\zeta e})$, (k, v_{ms}) and (k, v_{me}) , respectively. They depict that the epileptic activity may be effectively inhibited in certain suitable parameter ranges, as indicated by the arrows in Fig. 5a–c. The related control mechanisms are difficult to explain from the model itself due to the complex interactions among all populations. To better understand the control mechanism, we simulated the MDFs of all of the populations in Fig. 6. Fig. 6a–c were obtained

by setting $k = 3.5$ (Fig. 5a), $k = 3.35$ (Fig. 5b) and $k = 3$ (Fig. 5c), respectively. We observed that the general trend of the MDFs is consistent with that in the EPN. As shown in Fig. 6a, with a change in $v_{\zeta e}$, the MDFs of the model first increase and then decrease, which might explain the inhibited effect indicated by the bidirectional arrow in Fig. 5a.

Several previous experimental and theoretical studies have implied that the STN (Feng et al. 2014; Polosan et al. 2016), SNr (Hu et al. 2015; Guo et al. 2014; Shi et al. 2006; Moussawi et al. 2016; Hu and Wang 2015), cortex (Hu and Wang 2015; Morrell 2011; Sprengers et al. 2017), thalamus (Möttönen et al. 2015; Lehtimäki et al. 2016; Lee et al. 2017), GPe (Chen et al. 2015b) and striatum (Arakaki

Fig. 4 The MDFs of the EPN varied with various coupling strengths, corresponding to Fig. 3

et al. 2016; Hu et al. 2017; Kubu et al. 2013; Kwon et al. 2015) can be considered to be effective deep brain stimulation (DBS) targets to control the absence epileptic seizure slow wave. However, the SNc is involved to a lesser extent. As presented in Fig. 3k and l, we know that changes in v_{fc} and v_{mc} can markedly influence the firing activity in the EPN, which may induce an epileptiform activity. These are two major coupling strengths projected from the SNc to the striatum, the intensity of which is considerably affected by the activation level of the SNc. Therefore, we infer that the discharge activation level of the SNc may participate in mediating the epilepsy epileptiform activity state of the brain. To verify this hypothesis, we employed an external stimulus voltage on the SNc. Figure 5d is the state bifurcation diagram in the plane (k, V). V is the external voltage that acts on the SNc. The epileptiform activities disappeared upon reducing the voltage strength, as indicated by the downward arrow, when k falls into a suitable range ($2 < k < 4$). Figure 5e and f are the specific state bifurcation diagram and time series bifurcation diagram, respectively, both of which were obtained by setting $k = 3.5$ in Fig. 5d.

They represent the obvious process change between the NS and SWDs with the increase in V . Figure 6d aids in explaining this complicated mechanism, which represents the changing of the MDFs of all of the populations and is obtained by setting $k = 3$ in Fig. 5d. With an increase in V , the MDFs of the EPN are enhanced gradually, as well as other populations considered in the model; thus, the state of the EPN is pushed from “NS” to “SWD”.

Noteworthy open questions

In addition to the origin of epilepsy, the precise seizure location is unclear and controversial. It is usually considered that the typical SWDs of epilepsy appear in the cortex of the brain. Multiple EEGs of patients (Crunelli and Leresche 2002; CoCaTotILA 1989; Cheong and Shin 1828) and theoretical studies (Robinson et al. 2002; Rodrigues et al. 2006, 2009; Takeshita et al. 2007; Marten et al. 2009a, b; Wilson et al. 2006; Case and Soltesz 2011; Dadok et al. 2012; Hu et al. 2015, 2017; Chen et al.

Fig. 5 The controlling effect of epileptiform activities. **a–c** State regional bifurcation diagrams on the two-dimensional parametric plane (k, v_{ze}) , (k, v_{ms}) and (k, v_{me}) , respectively. k is a scale factor defined as $-v_{rp1} = -kv_{sp1} \cdot v_{ze}, v_{ms}$ and v_{me} are three major pathways projected from the corticothalamic system to the BG. The SWDs can be inhibited by altering v_{ze} , v_{ms} and v_{me} within a suitable range, as

indicated by arrows in **a** to **c**. **d** The state bifurcation diagram in the plane (k, V) . V is an external voltage exerted on the SNc. It is demonstrated that the epileptiform activities disappeared by reducing the voltage strength. **e, f** The state bifurcation diagram and time series bifurcation diagram obtained by setting $k = 3.5$

2015b) support this viewpoint. Previously, certain studies indicated that the SWDs may additionally appear in the thalamus (Gibbs and Gibbs 1951; Pinault et al. 1998) and STN (Dinner et al. 2002). In this study, we observed that the SWDs can additionally appear in other populations, such as the SRN, TRN, STN, MSN, GPe and SNr, as depicted in Fig. 7. Therefore, we inferred that the absence epileptiform activities might coexist in multiple brain regions of the patients or shift between different regions; however, further experiments are required to confirm this theory. The model in Fig. 1 provides a unified framework for such studies. Figure 7g represents the saturated state of the brain, Fig. 7h represents the epileptiform activity, Fig. 7i depicts the simple oscillation (usually considered to be a transition state between the NS and the epileptiform activity) and Fig. 7j indicates the NS with a low frequency. The figures obtained by setting $-v_{sr} = 0.2$ mV s, $-v_{sr} =$

0.8 mV s, $-v_{sr} = 1$ mV s and $-v_{sr} = 1.8$ mV s in Fig. 7f, respectively.

It should be noted that we have omitted the delay for all of the pathways in the model, except for the “TRN $\rightarrow$ SRN” pathway, for the purpose of simplicity. We considered the effect of delays on the epileptiform activities in Fig. 8. Figure 8a1–a3 are three discharge time sequence diagrams of the TRN, which were obtained by setting $\tau = 0.04$ s, $\tau = 0.095$ s and $\tau = 0.11$ s, respectively. They indicate that the number of extreme points in one period increases with the enhancement of delays. A similar effect may exist in other populations, such as the GPe, as presented in Fig. 8b1–b3. Moreover, Fig. 8a4 and b4 indicate that the dominant frequency of these seizures approximately falls in the range of 2–4 Hz; thus, they may also represent absence epileptiform activities. Consistent with previous studies (Rodrigues et al. 2009; Marten et al. 2009a, b), we inferred that the delay may be a key

Fig. 6 MDFs of all of the populations from Fig. 5a–d, which were obtained by setting $k = 3.5$ (Fig. 5a), $k = 3.35$ (Fig. 5b), $k = 3$ (Fig. 5c) and $k = 3$ (Fig. 5e), respectively

parameter to distinguish different types of absence epileptiform activities, which are different in the number of extreme points in one period.

Conclusion

By employing our new BG-thalamocortical-brainstem mean-field network model, which is described in Fig. 1, we revealed the effects of the BG in the development of absence epileptiform activities. We observed that several pivotal GPe-related pathways, SNr-related pathways, MSN-related pathways, FSI-related pathways, STN-related pathways and SNc-related pathways can induce typical absence epileptiform activity slow waves over specific ranges of coupling strengths. The data used in the

numerical computation approximately fall in the meaningful physiological range, which was reported in multiple previous studies. In addition to the corticothalamic system, these results provide the theoretical basis for the participation of the BG in the initiation of absence epileptiform activities directly through abnormal interactions among different populations and that the BG assists the onset of epilepsy. Therefore, we infer that the neurons in the BG and corticothalamic network might work together and exhibit a functional complementation for onset or termination of absence epilepsy. Several experimental and theoretical studies have implied that the STN (Feng et al. 2014; Polosan et al. 2016), SNr (Hu et al. 2015; Guo et al. 2014; Shi et al. 2006; Moussawi et al. 2016; Hu and Wang 2015), cortex (Hu and Wang 2015; Morrell 2011; Sprengers et al. 2017), thalamus (Möttönen et al. 2015;

Fig. 7 **a–f** State bifurcation diagrams of the population SRN, TRN, STN, MSN, GPe and GPi. $-v_{sr}$ is the changing parameter considered here. **g–j** Four specific time sequence diagrams corresponding to **f**, which were obtained by setting $-v_{sr} = 0.2$ mV s, $-v_{sr} =$

0.8 mV s, $-v_{sr} = 1$ mV s and $-v_{sr} = 1.8$ mV s, respectively. They represent the saturated state, epileptic state, simple oscillation state and low frequency firing state of the brain

Lehtimäki et al. 2016; Lee et al. 2017), GPe (Chen et al. 2015b) and striatum (Arakaki et al. 2016; Hu et al. 2017; Kubu et al. 2013; Kwon et al. 2015) can be considered to be effective DBS targets for inhibiting the absence epileptiform activity slow wave. In this model, we additionally determined that absence epileptiform activities can be controlled by adding an external stimuli on the SNc, which might serve as an alternative DBS therapeutic target for treating absence epilepsy. In addition to the initiation problem of absence epilepsy, the attack position remains unclear and rarely studied. In “Controlling absence epileptiform activities via three major pathways projected from the thalamocortical circuit to the BG” section, certain open questions are raised regarding the attack position of absence epilepsy. We observed that, in addition to the EPN, the typical absence epileptiform activity slow wave might appear in other populations in the model. Consistent with previous studies, the delay is additionally the key

parameter to distinguish different types of absence epilepsy. Although these theoretical results still require further experiments for validation, it is an interesting research topic from theoretical and computational perspectives, and our new model presented in this paper provides a unified framework for exploring this problem.

Although the model developed in this paper illustrates that abnormal interactions in the BG directly contribute to the onset of absence epileptiform activities, we should note that the mean field model is a class of simplified mathematical models that can effectively describe the qualitative dynamic properties of nerve nuclei but may miss certain detailed mechanisms regarding the positions of different BG, concentration of ion channels and other complex physiological environments involved in the development of epilepsy. In addition to epilepsy, the activity of the BG is closely related to other neurological diseases involving motor dysfunction, such as Parkinson’s disease.

Fig. 8 Multipole attack phenomenon on the TRN and GPe induced by delay. In all of the simulations, we set $-v_{sf} = 1$ mV s in **a1–a4** and $-v_{sf} = 0.9$ mV s in **b1–b4**

Degeneration of dopaminergic neurons in the SNc leads to abnormal interactions in the BG, specifically, among the STN, GPe, GPi and SNr, which are major physiological characteristics of Parkinson's disease. Therefore, more detailed pathological mechanisms of the BG involving in nervous system diseases, such as epilepsy and Parkinson's disease, deserve further investigation. All of these research topics are related to the spiking neuron model in the future.

The advantage of the mean field equation is easy to handle in mathematical calculations, however, the results of which are qualitative, which should resort to the spiking model and experiments to verify in the future. Therefore, we listed the following points to further consider in the future study: (1) In this model, we supposed that the time constant for all synaptic transfers are equal to simplify

analysis. However, in the real physiological environment, time constants between different types of synapses are different. (2) We mainly explored the possible regulation and control roles of the BG in the development of absence epileptiform activities in this model. We found that epileptiform activities may be induced by changing coupling strengths of many critical pathways related to the BG, as shown in Fig. 3. We think that the importance of these factors are different for different patients. However, which pathways are most essential are difficult to reflect in this mean-field model. (3) The simple periodic oscillation shown in Fig. 7i may represent a state different from the SWDs. However, whether it represents the normal state remains to be confirmed in the future. Because when the oscillation amplitude is too large may also indicate an

abnormal state in the brain. (4) It is noted that the population transfers from the stable state to the SWDs may be induced by a bifurcation, however, specific bifurcation types are unclear, which is worthy of further research. (5) In addition to the typical SWDs, in this model, we also observed polyspike waves as shown in Fig. 2h and i. As reported in previous studies (Marten et al. 2009a), polyspike waves were mainly induced by the delay. In Fig. 2, we found that they might also be induced by coupling strengths, which was little involved in previous studies. The number of extreme points in one period is also more than that in previous studies (Marten et al. 2009a). As shown in Fig. 2e, the DF of polyspike waves falls in 1–6 Hz (when v_{rp1} approximately larger than 0.15). Therefore, we hope that the results can provide a new idea for future study. (6) It is noted that we added a voltage V on the SNc to study its control effect on epileptiform activities, which implies that the SNc may be an effective target to relieve epileptiform activities. However, the DBS is pulsed in clinical and experiment, and the frequency of which has great effects on treatment. The mechanism of the pulsed DBS is difficult to explain in this model, but should be further considered in the spiking model and experiments. (7) In addition to the EPN, we found that typical epileptiform activities can also appear in other populations in this model, as shown in Fig. 7. However, we admit that whether these epileptiform activities originated from these populations or the EPN was leading is difficult to answer in this model. At least, we know that the BG directly participate in regulating epileptiform activities in this model. The related theoretical results were rarely reported in previous studies, which should be verified in spiking model and experiment. We hope that they can provide a new research method for reference in the future. (8) Most of the data employed in numerical simulations were derived from experiments, we have listed the sources of them as detailed as possible in the “Appendix”. A few data were estimated in the reasonable physiological range to generate stable dynamic behaviors in this model. Similar mean field models in previous studies were proven to be effective to study and evaluate the mechanisms of epilepsy disease, such as Robinson et al. (2002), Rodrigues et al. (2006, 2009), Takeshita et al. (2007), Marten et al. (2009a, b), Arakaki et al. (2016), Chen et al. (2014, 2015b), Breakspear et al. (2005). However, we admit that the results obtained in the model are difficult to be directly validated in experiments at this stage. We hope that the model and method can inspire further research in the spiking model and experiment in the future.

In summary, we performed a systematic calculation study using the new model to elucidate the effects of the BG on regulating absence epileptiform activity slow

waves. Our results implied that abnormal firing activity of the BG neurons might be the key pathological factor that directly induces epileptiform activities in addition to the thalamocortical system and that the SNc might serve as an effective therapeutic target for treating absence epilepsy. The emergent position of the typical SWDs is not limited to the EPN, and it may additionally appear in other populations in the model. Direct experimental evidence is required to validate the above theoretical results, and our theoretical results are expected to form a basis for further experimental studies.

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Appendix

Unless otherwise noted, we used the following values for numerical simulations:

Parameter	Meaning of parameter	Unit	Values	References
Q_e^{max}, Q_i^{max}	The MFR of the cortex	Hz	250	Robinson et al. (2002), Marten et al. (2009a), Chen et al. (2014, 2015b), Breakspear et al. (2005)
Q_m^{max}	The MFR of the MSN	Hz	65	van Albada and Robinson (2009), van Albada et al. (2009), Chen et al. (2014, 2015b)
Q_f^{max}	The MFR of the FSI	Hz	70	van Albada and Robinson (2009); van Albada et al. (2009), Chen et al. (2014, 2015b)
Q_{p1}^{max}	The MFR of the SNr	Hz	250	van Albada and Robinson (2009); van Albada et al. (2009), Chen et al. (2014, 2015b)

Parameter	Meaning of parameter	Unit	Values	References	Parameter	Meaning of parameter	Unit	Values	References
$Q_{p_2}^{max}$	The MFR of the GPe	Hz	300	van Albada and Robinson (2009); van Albada et al. (2009), Chen et al. (2014, 2015b)	θ_{ζ}	The MTP of the STN	mV	10	van Albada and Robinson 2009; van Albada et al. 2009, Chen et al. (2014, 2015b)
Q_c^{max}	The MFR of the SNc	Hz	300	Estimated	θ_r	The MTP of the TRN	mV	15	Robinson et al. (2002), Marten et al. (2009a), Chen et al. (2014, 2015b), Breakspear et al. (2005), Robinson et al. (2004)
Q_s^{max}	The MFR of the SRN	Hz	250	Robinson et al. (2002), Marten et al. (2009a), Chen et al. (2014, 2015b), Breakspear et al. (2005)	θ_s	The MTP of the SRN	mV	15	Robinson et al. (2002), Marten et al. (2009a), Chen et al. (2014, 2015b), Breakspear et al. (2005), Robinson et al. (2004)
Q_{ζ}^{max}	The MFR of the STN	Hz	500	van Albada and Robinson (2009); van Albada et al. (2009), Chen et al. (2014, 2015b)	θ_c	The MTP of the SNc	mV	10	Estimated
Q_r^{max}	The MFR of the TRN	Hz	250	Robinson et al. (2002), Marten et al. (2009a), Chen et al. (2014, 2015b), Breakspear et al. (2005)	γ_e	Cortical damping rate	Hz	100	Robinson et al. (2002), Marten et al. (2009a), Chen et al. (2014, 2015b), Breakspear et al. (2005)
θ_e, θ_i	The MTP of the cortex	mV	15	Robinson et al. (2002), Marten et al. (2009a), Chen et al. (2014, 2015b), Breakspear et al. (2005), Robinson et al. (2004)	τ	The delay	ms	55	Marten et al. (2009a), Chen et al. (2014, 2015b)
θ_m	The MTP of the MSN	mV	19	van Albada and Robinson (2009); van Albada et al. (2009), Chen et al. (2014, 2015b)	α	Synaptodendritic decay time	s^{-1}	50	Robinson et al. (2002), Marten et al. (2009a), Chen et al. (2014, 2015b), Breakspear et al. (2005), Robinson et al. (2004)
θ_f	The MTP of the FSI	mV	10	van Albada and Robinson (2009); van Albada et al. (2009), Chen et al. (2014, 2015b)	σ	Standard deviation of firing thresholds	mV	6	Robinson et al. (2002), Chen et al. (2014, 2015b), Breakspear et al. (2005), Robinson et al. (2004)
θ_{p_2}	The MTP of the GPe	mV	9	van Albada and Robinson (2009); van Albada et al. (2009), Chen et al. (2014, 2015b)	β	Synaptodendritic rise time	s^{-1}	200	Robinson et al. (2002), Marten et al. (2009a), Chen et al. (2014, 2015b), Breakspear et al. (2005), Robinson et al. (2004)
θ_{p_1}	The MTP of the SNr	mV	10	van Albada and Robinson (2009); van Albada et al. (2009), Chen et al. (2014, 2015b)	V_s	The sensory stimuli constant	mV s	2.1	Estimated

Coupling strength	The output nuclei	The receiving nuclei	Values (mV s)	References	Coupling strength	The output nuclei	The receiving nuclei	Values (mV s)	References
v_{ei}	IIN	EPN	− 1.6	Marten et al. (2009a), Chen et al. (2014, 2015b), Breakspear et al. (2005)	$v_{p_1\zeta}$	STN	SNr	0.32	van Albada and Robinson (2009), van Albada et al. (2009), Chen et al. (2014, 2015b)
v_{ee}	EPN	EPN	1.1	Marten et al. (2009a), Chen et al. (2014, 2015b), Breakspear et al. (2005)	v_{p_2m}	MSN	GPe	− 0.31	van Albada and Robinson (2009), van Albada et al. (2009), Chen et al. (2014, 2015b)
v_{rs}	SRN	TRN	0.51	Robinson et al. (2002), Marten et al. (2009a), Chen et al. (2014, 2015b)	$v_{p_2p_2}$	GPe	GPe	− 0.07	van Albada and Robinson (2009), van Albada et al. (2009), Chen et al. (2014, 2015b)
v_{re}	EPN	TRN	0.052	Robinson et al. (2002), Marten et al. (2009a), Chen et al. (2014, 2015b)	$v_{p_1p_1}$	SNr	SNr	− 0.006	van Albada and Robinson (2009), van Albada et al. (2009), Chen et al. (2014, 2015b)
$v_{sr}^{A,B}$	TRN	SRN	− 2.3	Robinson et al. (2002), Chen et al. (2014, 2015b), Robinson et al. (2004)	$v_{p_2\zeta}$	STN	GPe	0.47	van Albada and Robinson (2009), van Albada et al. (2009), Chen et al. (2014, 2015b)
v_{me}	EPN	MSN	1.1	van Albada and Robinson (2009), van Albada et al. (2009), Chen et al. (2014, 2015b)	$v_{\zeta p_2}$	GPe	STN	− 0.042	van Albada and Robinson (2009), van Albada et al. (2009), Chen et al. (2014, 2015b)
v_{mm}	MSN	MSN	− 0.22	van Albada and Robinson (2009), van Albada et al. (2009), Chen et al. (2014, 2015b)	v_{es}	SRN	EPN	1.9	Robinson et al. (2002), Marten et al. (2009a), Chen et al. (2014, 2015b)
v_{ms}	SRN	MSN	0.12	van Albada and Robinson (2009), van Albada et al. (2009), Chen et al. (2014, 2015b)	v_{se}	EPN	SRN	2.1	Robinson et al. (2002), Chen et al. (2014, 2015b)
v_{fe}	EPN	FSI	0.72	van Albada and Robinson (2009), van Albada et al. (2009), Chen et al. (2014, 2015b)	v_{sp_1}	SNr	SRN	− 0.03	van Albada and Robinson (2009), van Albada et al. (2009), Chen et al. (2014, 2015b)
v_{fc}	SNC	FSI	0.35	Estimated	$v_{\zeta e}$	EPN	STN	0.15	van Albada and Robinson (2009), van Albada et al. (2009), Chen et al. (2014, 2015b)
v_{mc}	SNC	MSN	0.35	Estimated	v_{p_1}	SNr	TRN	− 0.03	Chen et al. (2014, 2015b)
v_{p_1m}	MSN	SNr	− 0.08	van Albada and Robinson (2009), van Albada et al. (2009), Chen et al. (2014, 2015b)	v_{ep_2}	GPe	EPN	− 0.04	Chen et al. (2015b)
$v_{p_1p_2}$	GPe	SNr	− 0.031	van Albada and Robinson (2009), van Albada et al. (2009), Chen et al. (2014, 2015b)	v_{ep_1}	SNr	EPN	− 0.04	Estimated
					v_{mf}	FSI	MSN	− 0.3	van Albada and Robinson (2009), van Albada et al. (2009), Chen et al. (2014, 2015b)

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