Journal of Theoretical Biology 370 (2015) 157–170

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Improving desynchronization of parkinsonian neuronal network via triplet-structure coordinated reset stimulation

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HIGHLIGHTS

- We propose a new triplet-structure coordinated reset stimulation (CRS) paradigm.
- CRS can significantly desynchronize the neuronal network of Parkinson's disease.
- Synaptic plasticity can greatly enhance the CRS-induced desynchronization.
- The closed-loop CRS can improve desynchronization and reliability.

ARTICLE INFO

Article history:
Received 2 August 2014
Received in revised form
7 December 2014
Accepted 28 January 2015
Available online 7 February 2015

Keywords:
Desynchronization control
Stimulation paradigms
Synaptic plasticity

ABSTRACT

We investigate how the triplet-structure coordinated reset stimulations (CRS), which acts on the GPe, STN and GPi within the basal ganglia-thalamocortical motor circuit, can destabilize the strong synchronous state and improve the reliability of thalamic relay in the parkinsonian network. It is shown that compared with the permanent (1:0 ON–OFF) CRS or the classic deep brain stimulation paradigm, the periodic m:n ON–OFF CRS (i.e., m ON-cycles stimulation followed by n OFF-cycles stimulation) can significantly desynchronize the neuronal network of Parkinson's disease, and evidently improve the fidelity of thalamic relay. In addition, the CRS-induced desynchronization can be greatly enhanced when the STN subpopulation within the pathologic network is subjected to the synaptic plasticity. Furthermore, the desynchronization and reliability can also be further improved as the closed-loop CRS strategy is introduced. The obtained results can be helpful for us to understand the pathophysiology mechanism of Parkinson's disease, even though the feasibility of CRS still needs to be explored in clinic.

1. Introduction

Even though the mechanism of neurological disorder such as Parkinson's disease or essential tremor remains unclear, experimental results have indicated that these motor disorders can be characterized by the excessively strong pathological synchronization (Nini et al., 1995; Brown et al., 2001; Levy et al., 2002; Timmermann et al., 2002; Hammond et al., 2007; Smirnov et al., 2008). Therefore, desynchronizing neuronal activity can be a desirable way to suppress the pathological synchronization and restore the normal brain function. For a clinical purpose, several desynchronizing techniques have been developed by means of nonlinear dynamics (Dovzhenok et al., 2013; Tass, 2003a), which are based upon either the feedback loop (Dovzhenok et al., 2013) or the phase resetting principle (Tass, 2003b), e.g., coordinated reset stimulation.

It is well known that several deep brain stimulation (DBS) techniques including classic open-loop DBS (Rubin and Terman, 2004; Kühn et al., 2008; Meissner et al., 2005) or closed-loop DBS (Feng et al., 2007a; Little et al., 2013; Rosin et al., 2011) have been designed to deliver the stimulation signal to the subcortical basal ganglia (BG) via implanted electrodes. This can clinically improve the hypokinetic motor symptoms of patients with idiopathic Parkinson's disease (PD) or essential tremor and animal models of PD. However, because of its continuous strong stimuli or fixed stimulation target, standard DBS cannot sufficiently restore the motor function of brain, and can lead to some prominent side effect, e.g., damaging the brain tissue or worsening the motor ability as the delivery of stimulation signals ends up. Resultantly, new DBS strategy must be further developed to obtain maximal control effects.

Coordinated reset stimulation (CRS) is a very promisingly desynchronizing stimulation method, where brief high-frequency (HF) pulse trains (i.e., bursts) are delivered via different sites rather than continuously on a fixed site. Recently, CRS has received much attention and appears to be the best candidate of clinical therapy

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http://dx.doi.org/10.1016/j.jtbi.2015.01.040
0022-5193/

(Hauptmann and Tass, 2009; Lysyansky et al., 2011; Popovych and Tass, 2012; Tass et al., 2012). It can be performed in both open and closed loop mode (Tass, 2003a). However, this strategy has not been implemented in PD patients. To our knowledge, it is only proposed in *ex-vivo* experiments (Tass et al., 2009) or theoretical studies (Tass and Majtanik, 2006) to counteract the pathological synchronization. In addition, most of previous studies are mainly based on the sub-network of STN or STN-GPe. Recently, some interesting works set out to focus on the study of behaviors within the global basal ganglia-thalamocortical network (Meijer et al., 2011; Guo and Rubin, 2011). Meijer et al. (2011) presented a computational model of a thalamocortical relay neuron to explore the basal ganglia-thalamocortical loop behavior in the context of Parkinson's disease and deep brain stimulation (DBS). Guo and Rubin (2011) established the basal ganglia-thalamocortical network to investigate the TC reliability as CRS is applied to STN neuron. However, it is still not fully clear that how the desynchronizing effect of CRS can globally influence the behavior of downstream thalamic neurons. To extend the previous studies, we will propose a new CRS paradigm to explore the effect of CRS on PD network by using the network composed of the basal ganglia-thalamocortical motor circuit.

In the basal ganglia-thalamocortical motor circuit, different stimulation targets, whether the stimulation is current standard DBS or newly proposed phase resetting CRS, are used to treat the neurological disorder including PD. The DBS targets lie in the area of BG, typically in the STN, GPi or GPe (Saxena, 2011) for PD patients. As a typical case, the STN is usually a standard anatomical target for DBS. During the stimulation, the stimulation signal is usually conducted on a fixed target area or the same structure in the basal ganglia. And, the stimulation strength is always excessive and disruptive because of the characteristic of high-frequency(HF) or long-lasting procedure of DBS. For clinical application, the stimulation parameter is very crucial with the stimulation being effective enough, but not too strong for the purpose of energy-saving and avoiding side effect (e.g., caused by current spread). For this purpose, we propose a new CRS protocol, which implies that we can not use one or more electrodes on a fixed area permanently. This method will simultaneously apply three micro-electrodes into three different basal ganglia nuclei (see Fig. 1): GPe, STN and GPi, respectively. For each nucleus, a brief pulse train (i.e., bursts) is delivered via one of three electrodes.

Based on the proposed stimulation protocol, we can globally investigate the desynchronizing effect of CRS on the network of the basal ganglia-thalamocortical motor circuit. Here, we mainly consider the effect of intermittent *m*:*n* ON–OFF CRS, in which, *m* cycles ON stimulation are followed by *n* cycles OFF stimulation. In addition, we also show that how the CRS affects the relay behavior of thalamic neurons, where reliability of information transmission will be viewed as a measuring standard. Meanwhile, it is shown that both CRS with synaptic plasticity and the closed-loop can influence the desynchronizing effect and reliability performance of the network model for the basal ganglia-thalamocortical motor circuit.

The paper is organized as follows. In Section 2, we introduce the computational model of network dynamics. The simulation results of CRS on the computational network model are presented in Section 3. Finally, conclusion is made in Section 4.

2. Description of model

2.1. The network model

We use the computational model based on basal ganglia-thalamocortical motor circuit, which was initially originated in Refs. Terman et al. (2002) and Rubin and Terman (2004), and then revised by Feng et al. (2007a) for the purpose of searching for new DBS waveforms. Connection of the network model is the "sparsely connected" framework that is firstly proposed in Terman et al. (2002). Here, we will reconstruct the synaptic structure and connectivity of the network architecture as illustrated in Fig. 1, which has been developed by Feng et al. (2007a). In particular, this network consists of four parts (see Fig. 1): the spheres denote the eight GPe neurons, the cylinders are the eight STN neurons, and the cubes describe the eight GPi neurons, together with two thalamocortical relay (TC) model neurons. Each GPe neuron inhibits two STN neurons, which skips its three nearest STN neurons, as well as sends inhibitions to the two immediate neighboring GPe neurons and one GPi neuron. Each STN neuron sends excitations to the nearest single GPi neuron, and GPe neuron in the 'circle' of neurons, respectively. Each GPi neuron inhibits only one TC neuron, but each TC neuron receives synaptic inhibitions from four GPi neurons (e.g., 1st TC neuron receives inhibitory inputs from 1st, 2nd, 5th and 6th GPi neurons). In addition, GPe neurons receive striatal inhibitory inputs, and TC neurons receive excitatory sensorimotor (SM) signals (see Rubin and Terman, 2004). And, all three basal ganglia nuclei, GPe, GPi and STN, receive excitatory HF stimulation (HFS) inputs from three different micro-electrodes (see Fig. 1), respectively. All model parameters can be found in Refs. (Terman et al., 2002; Rubin and Terman, 2004; Feng, 2007a,b; Dovzhenok et al., 2013), where $g_{\mathrm{GPe}\to\mathrm{GPe}}$ and $I_{\mathrm{app}}(\mathrm{GPe})$, i.e., self-synaptic conductance within the GPe and constant input from striatum to GPe, are two essential parameters in changing the healthy state of neural systems. Physiologically and anatomically, the PD-like state of neural system can be induced by the degeneration of dopaminergic neurons within the substantia nigra pars compacta (SNc). This is because the degeneration of dopaminergic neurons can first directly decrease the release of dopamine, and further indirectly affect the downstream synaptic connections of dopaminergic modulation within the basal ganglia-thalamocortical motor circuit. On the other hand, both the $g_{\mathrm{GPe}\to\mathrm{GPe}}$ and $I_{\mathrm{app}}(\mathrm{GPe})$ are modulated by the dopamine (Dovzhenok et al., 2013). When the other parameters are fixed, tuning the values of $g_{\mathrm{GPe}\to\mathrm{GPe}}$ and $I_{\mathrm{app}}(\mathrm{GPe})$ can produce the transition between parkinsonian state and normal state (Terman et al., 2002; Feng, 2007a,b; Dovzhenok et al., 2013). Especially, the larger values of both $g_{\mathrm{GPe}\to\mathrm{GPe}}$ and $I_{\mathrm{app}}(\mathrm{GPe})$ correspond to the normal state of system, but the smaller values correspond to the parkinsonian state. Accordingly, in the numerical experiments these correspond to the random or synchronous dynamics.

2.2. Model for each neuron type

The well known Hodgkin–Huxley (HH) type equations are used to model dynamical behaviors of the STN, GPe and GPi neurons. We take the canonical form of HH equations as follows.

$$C_m V' = -\sum_k I_k^{\mathrm{ion}} - I_{\mathrm{syn}} + I_{\mathrm{app}} + I_{\mathrm{CRS}} \tag{1}$$

where V is the membrane potential, $C_m = 1\ \mu\mathrm{F\,cm^{-2}}$ is the membrane capacitance.

$$\sum_k I_k^{\mathrm{ion}} = I_L + I_K + I_{Na} + I_T + I_{\mathrm{Ca}} + I_{\mathrm{AHP}} \tag{2}$$

is the total ionic current through the membrane, where $I_L = g_L(V - V_L)$ is the leak current, $I_K = g_K n^4 (V - V_K)$ is the potassium current, $I_{Na} = g_{Na} m_\infty^3(V) h (V - V_{Na})$ is the sodium current, $I_T = g_T a_\infty^3(V) r (V - V_{\mathrm{Ca}})$ is the low-threshold T-type Ca^{2+} current, $I_{\mathrm{Ca}} = g_{\mathrm{Ca}} s_\infty^2(V)(V - V_{\mathrm{Ca}})$ is the high-threshold Ca^{2+} current and $I_{\mathrm{AHP}} = g_{\mathrm{AHP}}(V - V_K)([\mathrm{Ca}]/([\mathrm{Ca}] + k_{\mathrm{AHP}}))$ is the Ca^{2+}-activated, after-hyperpolarization K^+ current. Among these ionic currents, g_x represents the channel conductance and V_x represents the reversal potential for the ion x.