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Optimal control of directional deep brain stimulation in the parkinsonian neuronal network

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ABSTRACT

The effect of conventional deep brain stimulation (DBS) on debilitating symptoms of Parkinson's disease can be limited because it can only yield the spherical field. And, some side effects are clearly induced with influencing their adjacent ganglia. Recent experimental evidence for patients with Parkinson's disease has shown that a novel DBS electrode with 32 independent stimulation source contacts can effectively optimize the clinical therapy by enlarging the therapeutic windows, when it is applied on the subthalamic nucleus (STN). This is due to the selective activation in clusters of various stimulation contacts which can be steered directionally and accurately on the targeted regions of interest. In addition, because of the serious damage to the neural tissues, the charge-unbalanced stimulation is not typically indicated and the real DBS utilizes charge-balanced bi-phasic (CBBP) pulses. Inspired by this, we computationally investigate the optimal control of directional CBBP-DBS from the proposed parkinsonian neuronal network of basal ganglia–thalamocortical circuit. By appropriately tuning stimulation for different neuronal populations, it can be found that directional steering CBBP-DBS paradigms are superior to the spherical case in improving parkinsonian dynamical properties including the synchronization of neuronal populations and the reliability of thalamus relaying the information from cortex, which is in a good agreement with the physiological experiments. Furthermore, it can be found that directional steering stimulations can increase the optimal stimulation intensity of desynchronization by more than 1 mA compared to the spherical case. This is consistent with the experimental result with showing that there exists at least one steering direction that can allow increasing the threshold of side effects by 1 mA. In addition, we also simulate the local field potential (LFP) and dominant frequency (DF) of the STN neuronal population induced by the activation of 32 different contacts with optimal stimulation intensity and immediately after the stimulation, respectively. These can reveal regional differences in pathological activity within STN nucleus. It is shown that in line with the experimental results directional steering stimulation can induce the low-amplitude LFP which implies the occurrence of desynchronizing regime, as well as the distribution of DF can locate at the 13–40 Hz of beta frequency range. Hopefully, the obtained results can provide theoretical evidences in exploring pathophysiologic activity of brain.

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1. Introduction

Deep brain stimulation (DBS) involves an external pulse generator that can produce high frequency stimulations (HFS) for the specific subcortical targets through the deeply implanted electrodes. Due to the restorability after stimulation and the ability to effectively alleviate the pathological symptoms of patients with neurological disorders, DBS has been gradually becoming the dominant surgical treatment for various neurodegenerative diseases including Parkinson's disease (PD) [1]. However, DBS cannot be equally effective for all the parkinsonian symptoms [2]. Also, the stimulation parameters for the DBS can still only be adopted empirically [3]. In order to achieve optimal stimulation effect, the stimulation parameters should be optimized and different stimulation therapies also should be employed for various patients with different clinical characteristics. Presently, these stimulation paradigms involve the open-loop stimulation [4], closed-loop stimulation [5,6], adaptive feedback stimulation [7], coordinated reset stimulation [8–14] and coordinated delayed feedback stimulation [15–17], and so on. Therein, feedback stimulation can be applied in the necessary amount to suppress pathological activities. Batista et al. [16,17] compared the efficiency of both the conventional high-frequency stimulation and the delayed feedback stimulation procedures, and pointed out that the delayed feedback stimulation procedure is thought to save energy when implemented by the surgical such as the implanted pacemaker [16,17]. The multi-site stimulation modality is particularly relevant for the coordinated reset of neural sub-populations which is introduced as an effectively desynchronizing stimulation technique by Tass [9]. During the coordinated reset stimulation, high-frequency but short sequences pulse trains are administered on the different sites in a coordinated manner. Many works [10–14] have highlighted the potential effects of the coordinated reset stimulation and encouraged the further development of this approach. In addition, due to the serious damage to the neural tissues, the charge-unbalanced stimulation is not typically indicated. The real surgical DBS utilizes the charge-balanced bi-phasic (CBBP) pulses (see Fig. 2). However, the mechanism underlying the effects of DBS is still enigmatic and under debate.

Parkinson's disease is the typical neurodegenerative disorder which originates from the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) [18]. The SNc is the key part of the basal ganglia–thalamocortical motor circuit that is closely correlated to the pathophysiological movement disorder [19]. The schematic of the basal ganglia thalamocortical motor circuit is shown in Fig. 1, where the basal ganglia is mainly composed of subthalamic nucleus (STN), globus pallidus pars externa (GPe) and interna (GPi), striatum, substantia nigra pars compacta (SNc) and reticulata (SNr) [19]. We can find that striatum and STN are the primary input nuclei of basal ganglia receiving information from the cortex, and as coped in [20,21] the main output nuclei GPi and SNr are considered as the single structure due to their similar connections and cytological functions. The damage of SNc (see Fig. 1(b)) first leads to the depletion of dopamine, which can further indirectly modulate the information flow received by the subcortical structures from cortex through the direct/indirect pathways consisting of the downstream synaptic connections within the basal ganglia and modulated by the dopamine D_2/D_1-receptor-bearing striatal neurons in the striatum [8,19], respectively. In addition, the loss of dopamine can eventually influence the synaptic function of GPi to thalamus (Thal), and then affect the ability of thalamus to relay the information of cerebral cortex. Continuous high-frequency deep brain stimulation (HF-DBS) has been widely used for the therapy of patients with advanced parkinsonian symptoms [5,22]. Specifically, the structures or nuclei under the cerebral cortex such as STN [23], GP (GPi and GPe) [24–26] and the ventral intermediate (VIM) [27,28] have been chosen as the stimulation targets of HF-DBS for the parkinsonian symptoms, where the STN is applied for the PD, and the GPi, GPe and VIM are applied for the essential tremor (ET) [29,30]. Particularly, relevant works have demonstrated

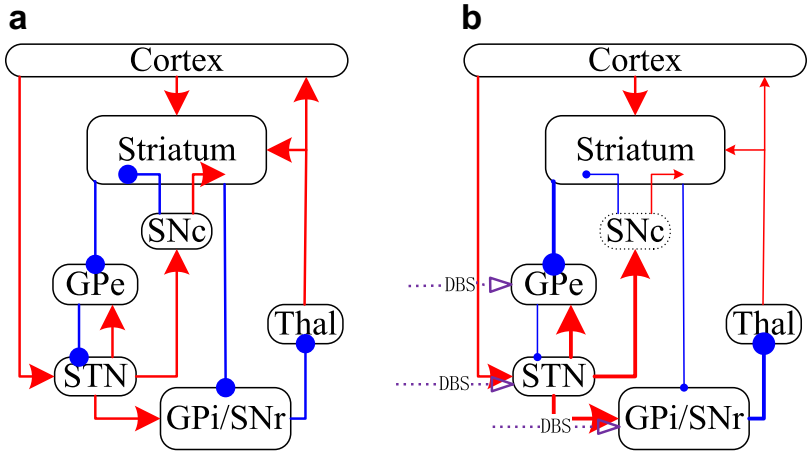

Fig. 1. Schematic of the classic basal ganglia–thalamocortical model, adapted from Obeso in [19] and composed of cerebral cortex, basal ganglia and thalamus (Thal), where basal ganglia mainly consists of substantia nigra (SN), striatum, globus pallidus pars externa (GPe), globus pallidus pars interna (GPi), substantia nigra pars reticularis (SNr) and subthalamic nucleus (STN). The healthy (a) and parkinsonian (b) states are depicted. Excitatory projections are indicated by red solid arrows. Inhibitory projections are shown in blue lines with closed circles. The dashed lines with open arrows are the external excitatory current inputs. The thickness of lines represents the degree of activation of projections. The striatum can communicate with GPi or SNr not only through the direct pathway but also the indirect pathway consisting of the GPe and STN. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)