Proceedings of the 2nd International Conference on Biological Engineering and Medical Science (ICBioMed 2022), Part II
DOI: 10.54254/2753-8818/4/20220541

Effects Of Deep Brain Stimulation on Parkinson's Disease as Viewed From The Basal Ganglia Network

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Abstract. This article focuses on the resolution strategy of deep brain stimulation to improve Parkinson's disease symptoms by correcting pathological concussions of the basal ganglia network. Years of clinical practice have shown that Subthalamic nucleus (STN) and Internal globus pallidus (GPI) are two effective sites for DBS intervention in Parkinson's disease. Through the observation of animal experiments and drug intervention, the characteristics of pathological oscillations of basal ganglia network and spontaneous oscillations among various nuclei were sorted out. Based on the functional system hypothesis of cortical-basal ganglia-thalamo-cortical loops, the pathological oscillation pattern of the β-band is analyzed, and how electrical impulse stimulation changes the generation pattern of action potentials at the cellular level, thereby effectively changing pathological oscillations at the network level; This paper analyzes the improvement of symptoms such as tremor, rigidity, and frozen gait with DBS, and looks forward to a composite treatment strategy.

Keywords: Parkinson's Disease, Deep Brain Stimulation , Beta Oscillation , Reversible Lesion Hypothesis

1. Introduction

Parkinson's disease (PD) is a long-term neurodegenerative disease caused by the death of substantia nigra dopaminergic neurons, which mainly affects the motor function and central motor nervous system in middle-aged and elderly people. Due to impaired cortical-basal ganglia-thalamo-cortical ring function, patients present with four main motor symptoms: tremor, slow movement (bradykinesia), rigidity, and postural instability. As one of the main means to deal with Parkinson's disease, deep brain stimulation (DBS) is a surgery to change the behavior of neurons in a specific area by implanting electrodes. There are three hypotheses about the mechanism of deep brain stimulation: the inhibition hypothesis, the local The neuron activation hypothesis and the interruption hypothesis; all three hypotheses may be true under different conditions[1].This review discusses the change of pathological oscillations of the cortical-basal ganglia-thalamo-cortical circuit by deep brain stimulation; and combined with existing computational models and organoid culture experiments, analyzes the frequency-selective effects of electrical pulse stimulation Classes of neuronal activity and synaptic plasticity, in turn, provide an explanation for symptom relief.

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2. Reversible lesion hypothesis and dyskinesia

A popular model of basal ganglia function holds that the cortex-basal ganglia-thalamo-cortical loop is divided into direct and indirect pathways. The direct pathway consists of cortex-striatum-GPi/SNr-thalamus, responsible for the initiation and execution of voluntary movements. The indirect pathway is composed of cortical-striatal-pallidal exosomes, and its function is to prevent unnecessary muscle contractions from competing with voluntary movements; the GPe-STN-GPi/SNr-thalamic pathway functions to inhibit movement. In this model, in addition to the motor system, there are multiple parallel subsystems that are considered part of the oculomotor, limbic, and associative functions. In recent years, other functionally important pathways have been recognized. The hyperdirect pathway consists of direct excitatory input from the cortex to the STN and is thought to play a role in conflict-related response inhibition[2].

Phase reversal of the cumulant density estimates suggests that the activity of the GPi and STN is generated locally rather than via bulk conduction from a more distant source. In mature cortical-striatal-STN-GPe organoid cultures, neurons in the STN and GPe spontaneously generated synchronized oscillatory pulses of 0.4, 0.8, and 1.8 Hz. Neuronal death and cortical lesions in the globus pallidus altered this oscillatory pattern, causing the cultured organoids to burst in a predominantly 0.8 Hz pattern. In addition, signal projections from the striatum, thalamus, and peduntopontine nucleus may further alter this innate oscillation pattern.

Mean neuronal firing rates did not change after onset of Parkinson's disease in mouse models, although disturbances in firing patterns (i.e., neuronal entropy) were significantly increased in the globus pallidus and substantia nigra reticulum. This increase in neuronal entropy was reversed by symptomatic DBS. While an increase in signal entropy usually indicates a similar increase in information transmission, there is an estimated 70 percent decrease in directional information through the globus pallidus and substantia nigra reticulum after the onset of Parkinson's disease; Pulse stimulation partially reversed this reduction in telematic projection. Taken together, these results suggest that the basal ganglia system in Parkinson's disease is unable to carry out the original efficient information transmission due to the additional entropic activity. There is also experimental evidence that DBS restores effective information dissemination under normal conditions by reducing the entropy noise floor. In this view, Parkinson's symptoms may be more like the default mode of the direct pathway, overridden in healthy individuals by information from the indirect pathway that functions normally. When the indirect pathway produces pathophysiological changes, it exhibits typical Parkinson's disease symptoms such as symptoms of impaired motor function[3].

Partial neuronal populations within the globus pallidus and STN form a functional network whose resonance is most pronounced at approximately 70 Hz in the presence of an intact dopaminergic drive in healthy individuals. In clinical observations using levodopamine, this rhythm is important for the efficient organization of voluntary movements in patients, and this implication for deep brain stimulation therapy is that by using frequencies that may induce resonance within this network, at or near 70 Hz or The use of electrical pulse stimulation at the fundamental frequency of its second harmonic may bring about anti-Parkinsonian effects, but this still requires a more microscopic and systematic understanding of the functional network of the basal ganglia[4]. Figure 1 showed the diagram of this model.

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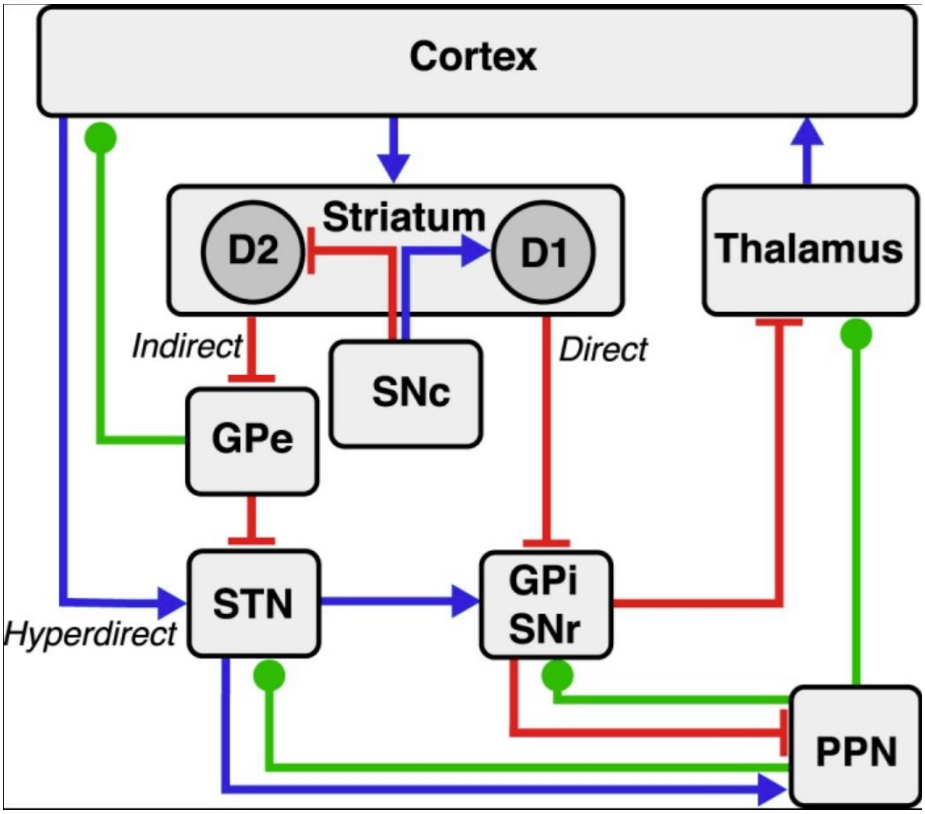


Figure 1. Cortico-basal-ganglia-thalamo-cortical circuitry including the direct, indirect, and hyperdirect pathways. (Adapted from Todd et al., 2016) [5].

3. How DBS selectively affects neuronal activity

DBS creates an electric field outside the cell through electrical pulses of less than 100 microseconds, thereby activating the cell membrane voltage sensor and manipulating the opening and closing of sodium ion channels. With the Tsodyks-Markram neuron behavior model, three types of synapses can be defined as inhibitory, facilitative, or pseudolinear, depending on the choice of parameter settings. Different synapses exhibited different excitatory postsynaptic potential properties in exogenous 20HZ and 130HZ control stimulation. In inhibitory synapses, no matter under the stimulation of 20HZ or 130HZ electrical pulses, a strong excitatory postsynaptic potential signal is generated at the beginning of the electrical pulse, and it decays rapidly with time and finally reaches slightly higher than the resting state. The stable value of ; this is due to the reduction in the amount of transport transmitter resource x specified in the model. In the facilitative synapse, under the stimulation of the 20HZ electrical pulse, the weak excitatory postsynaptic potential at the beginning gradually increases with time, so that the potential spike of the neuron is finally stable at a higher position. In this case, the transmission transmitter resource x is not exhausted; in contrast, under the stimulation of 130 Hz, the transmission transmitter resource x is also depleted in the facilitative synapse, and the excitatory synapse is also depleted. The post-haptic potential slowly rises to the highest point at the beginning, and then maintains a lower constant peak value after decaying with time. It is worth noting that this constant state is higher than that of the inhibitory synaptic constant state at 130 Hz[6]. The results of the computational model provide an idea of implanting electrodes to stimulate deep nuclei and selectively affect different types of neurons, which also suggests that the choice of an effective electrical pulse stimulation mode in the clinic needs to be based on the composition of the movement. On the understanding of the general properties of various neuronal cells of the system.

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4. Effects of DBS on synaptic plasticity

DBS can intervene within hours or days of axial symptoms, possibly due to the anatomical changes that DBS brings about due to synaptic plasticity. Thirty minutes and sixty minutes after transcranial magnetic stimulation of the subthalamic nucleus in a Parkinson's patient group and a healthy control group by examining the action evoked potential and paired correlation stimulation of the abductor pollicis brevis muscle Enhancement of motor evoked potentials in the abductor pollicis brevis muscle was observed in both the human control group and in the Parkinson's group receiving levodopamine and deep brain stimulation of the subthalamic nucleus, while the other groups within the Parkinson's group (levodopamine alone, No significant enhancement of motor evoked potentials in the abductor pollicis brevis muscle was observed in the subthalamic nucleus deep brain stimulation group or neither. Subsequently, paired-related stimuli prolonged cortical silence periods in healthy controls, and no significant changes in cortical silence periods were found in all groups of Parkinson's patients. In addition, studies have also made a molecular biological explanation for the striatum, which is part of the cortex-basal ganglia-thalamo-cortical loop, and glutamatergic high-frequency stimulation of glutamatergic input from the cortex to the striatum at high magnesium ion concentrations. produced long-term inhibition at low magnesium ion concentrations and exhibited long-term enhancement at low magnesium ion concentrations. The striatum also receives dopaminergic input from the substantia nigra. The dopamine receptors D1 and D2 act in the opposite direction to adenylyl cyclase. D1 promotes adenylyl cyclase activity, while D2 inhibits adenylyl cyclase. Glyxidyl cyclase activity thus also plays an opposite role in inducing long term depression in striatal neurons. It may be inferred that the plasticity of the cortico-basal ganglia-thalamo-cortical loop is presented at multiple scales, and the good effect of deep brain stimulation combined with levodopamine also predicts that there will be more ways to exploit plasticity in the future[7].

5. The effect of DBS on symptoms of various movement disorders

As shown in figure 2. In the treatment of movement disorders and psychiatric disorders, different symptomatic responses to DBS have different time courses. Subthalamic nucleus (STN) DBS for PD provides tremor relief in seconds, relief of less severe and frequently occurring axial symptoms is delayed by hours or days; symptom response to therapy on significantly different time scales suggests DBS works through several different mechanisms. According to the finite element simulation model of computational neuroscience, the local stimulation of DBS has an opposite effect on the cell body and axon, which is manifested as inhibiting the action potential of the cell body and promoting the activation of the axon. Therefore, the stimulation effect is derived from its local dendritic membrane. rather than the cell body itself. This was also observed in tissue experiments, where neuronal activity in the stimulated area was suppressed and the input received by neurons in the projected area was increased, which is consistent with the calculated results. Neuronal responses to DBS depend primarily on the position and orientation of axons relative to electrodes and on stimulation parameters, further illustrating the need for fine-tuning via DBS[8, 9].

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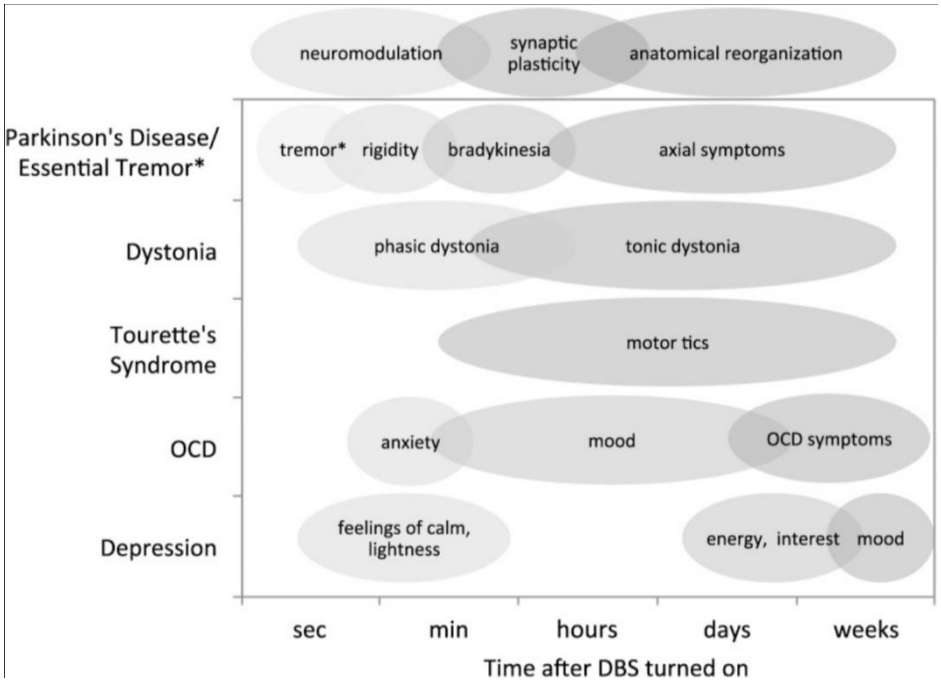


Figure 2. Deep brain stimulation (DBS) may be used to treat a variety of illness symptoms with different reaction time. (Adapted from Todd et al., 2016) [5].

In a clinical study of the combination of deep brain stimulation and levodopamine, the combination of deep brain stimulation and levodopamine scored better than either alone on the Unified Parkinson's Disease Rating Scale. It is worth noting, however, that the behavioral parameter of body stability in the resting state, which is not often analyzed in research, has also been explored in depth in recent years; in this study, the body stability in the resting state was Interpreted as orientation characteristics of postural instability, foot pressure center trajectories on the two-dimensional plane, and assessment of postural asymmetry. The results were most pronounced in tests of foot pressure center trajectories, where deep brain stimulation alone was superior to levodopamine alone or both; more critically, levodopamine alone was even more effective than neither. Difference. Due to the mechanism of action of deep brain stimulation, we can know that electrical impulses do not only act on dopaminergic neurons. At the system level, this shows that deep brain stimulation can affect both dopaminergic and non-dopaminergic systems. Further research may require More understanding of the role of GABAergic or glutamatergic neurons in the cortico-basal ganglia-thalamo-cortical loop may explain this trajectory in postural instability, especially in the foot pressure center difference[10].

In clinical practice, pulsed stimulation at 5-10 Hz exacerbates symptoms of bradykinesia, which has also been demonstrated in the MPTP primate model; stimulation at 30-100 Hz is infrequently used, but there is also evidence that 60 to 100 Hz Stimulation at 70 Hz is effective in treating focal and generalized dystonia; high-frequency pulsed stimulation at 130-200 Hz is the most effective and most commonly used for symptoms of bradykinesia. For freezing gait, the association between high βSTN oscillations and cortical-STN projections suggests that this oscillatory activity may interfere with the frontal cortex-basal ganglia network to participate in pathological responses in freezing gait symptoms. Conversely, artificial actuation of the human STN at low frequencies causes or exacerbates Parkinson's disease; this suggests that spontaneous synchronization at low frequencies may contribute to the abnormal motor patterns in Parkinson's disease. In conclusion, in many studies, abnormal beta oscillations are considered to be closely related to the above typical symptoms. Therefore, beta-band oscillations may be a promising target for rhythmic DBS-based intervention strategies[5].

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6. Conclusion

In the practice of deep brain stimulation with dyskinesia, different symptoms have different time courses in response to DBS; By sorting out the conclusions of previous experiments, this article discusses the electrical impulse stimulation on neuronal activity and the synaptic plasticity of the Subthalamic nucleus and internal globus pallidus at different levels, and explains the reasons for improvement of Parkinson's symptoms from seconds to days. Also, not only analyzes patient data and animal experimental conclusions, but also combines the conclusions of organoid models and computational models. There is much evidence of abnormal oscillations in the β abnormal oscillations associated with the Subthalamic nucleus-globus pallidus-related network in Parkinson's patients, as well as effective interventions for deep brain stimulation, which can reduce the patient's symptoms and reduce the β abnormal oscillations by high-frequency pulse stimulation at 130-200 Hz; It is still worth a lot of research to effectively reduce the symptoms of Parkinson's disease in the longer term through the selection of stimulation patterns and sites.

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