Clinical Implications of Basic Neuroscience Research

Cortical Effects of Deep Brain Stimulation
Implications for Pathogenesis and Treatment of Parkinson Disease

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High-frequency electrical stimulation that targets the subthalamic nucleus has proved to be beneficial in alleviating the motor symptoms in many patients with Parkinson disease. The mechanism of action for this paradigm of deep brain stimulation is still not fully understood, and this is, in part, attributed to the fact that there are diverse cellular elements at the stimulation site that could bring about local and distal effects. Recent studies in both human and animal models strongly suggest that the activity in the cortex, especially in the motor cortical areas, is directly altered by deep brain stimulation by signals traveling in an antidromic fashion from the subthalamic nucleus. Herein, we discuss the evidence for this proposition, as well as the mechanism by which antidromic activation desynchronizes motor cortical activity. The implications of these new findings for the pathogenesis and treatment of Parkinson disease are highlighted.

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Parkinson disease (PD) is a neurodegenerative disease for which there is no known cure. The onset of PD usually occurs after 50 years of age. As global life expectancy continues to increase, the prevalence of PD is projected to escalate in the coming decades. The immediate cause of PD is the degeneration of the dopaminergic projection from the midbrain to the striatum and other areas. The resulting depletion of dopamine apparently leads to drastic changes in multiple areas both within the basal ganglia circuitry and within other motor and nonmotor areas. All current treatments of PD aim to alleviate the debilitating symptoms that result from the gradual depletion of dopaminergic neurons. Deep brain stimulation (DBS) is a type of surgical treatment that has been recognized as effective in reducing motor symptoms. In DBS, 1 or more electrodes attached to leads are implanted in the target area (in most cases, the subthalamic nucleus [STN]). High-frequency (>120 Hz) electrical pulses are delivered to the target area. Randomized control trials confirmed the efficacy of DBS, which is also associated with less adverse effects compared with the conventional pharmacological approach (eg, levodopa treatment).

Although approved as a treatment for PD for over a decade, the underlying mechanism of DBS remains unclear. Different mechanisms have been proposed to explain the therapeutic actions of DBS. The earliest studies proposed an inhibitory action, mainly because of the similarity with the clinical outcome of STN lesioning. Functional inactivation, such as the depletion of neurotransmitters, depolarization block, or the activation of inhibitory afferents, could decrease the output from the STN. Later experimental studies in both animals and humans found that DBS could increase, rather than decrease, the output from the STN, as evidenced by the increased activity in the internal segment of the globus pallidus (GPi), the downstream nucleus of the STN. Thus, a decoupling of the activities between the soma and the axon at the stimulation target may occur. The fact that axons in the vicinity of the stimulation site can follow high-frequency stimulation led to the hypothesis that DBS interferes with the abnormal oscillatory and synchronized neuronal activities that are commonly found in the basal ganglia of patients with PD. More recently, an important role of the motor cortex, previously ignored site of action of DBS, is becoming clear, and the emerging picture has important implications for both the pathogenic process and treatment strategies for PD.

Abnormal Neuronal Activities in the Motor Cortex of Patients With PD

Functional information gathered by electrophysiological recordings provided rich information on the changes in neuronal activities of the brain in parkinsonism. The phenomena suspected of playing an important role in the etiology of PD symptoms include the presence of ß-band oscillations (10-30 Hz) and neuronal synchrony in different brain areas following dopamine depletion. However, the anatomical origin and pathogenic process of the abnormal oscillations and the synchrony are still unclear and controversial. These could involve alterations within the basal ganglia (eg, the intrinsic oscillation of the STN–GPi network and the striatal inhibitory microcircuits) or the entire motor cortex–basal ganglia–thalamus loop.

Despite the fact that the motor cortex is the major target of the basal ganglia output, the roles played by this brain area in mediating parkinsonian motor symptoms have received relatively little attention. There is evidence from noninvasive studies indicating abnormal oscillatory rhythms in the cortex of patients with PD.
Intriguingly, β-band oscillations in the basal ganglia nuclei (the STN and GPi) are coherent with electroencephalograhic and magnetoencephalographic signals recorded from the motor cortex, suggesting a tight functional connection between the cortex and these basal ganglia nuclei. Recent studies on patients with PD based on subdural electrocorticography demonstrated excessive β-phase and γ-amplitude coupling in the primary motor cortex, and the γ activity could drive the neuronal discharge of basal ganglia nuclei such as the STN. Interestingly, these PD-specific aberrant interactions could be suppressed by DBS of the STN. However, solid evidence that the abnormal oscillations in the basal ganglia cortex or cortex underlying motor impairment in PD is still lacking. Previous invasive studies that characterized the firing patterns of primary motor cortical neurons in parkinsonian animals at the single-cell level revealed increased synchronized firing among neurons, highly similar to those found in basal ganglia nuclei. Our recent experiments using multiunit and local field potential recordings confirmed that, following severe dopamine depletion, the spiking of the layer V projection neurons in the motor cortex is highly synchronized, especially during abnormal burst discharge. The synchronized activity was correlated with increased power in the β frequency. Although the origin of these changes is not known, such altered neuronal activities in the motor cortex likely contribute directly to the parkinsonian motor symptoms.

Evidence of Antidromic Activation of the Motor Cortex

In principle, DBS can directly activate different neuronal elements in the STN and nearby areas. These include STN neuronal somas and axons, passing fibers, and afferent terminals, including those from the cortex to the STN. Stimulation of STN neuronal somas or their axons would bring about orthodromic effects on its downstream target within the basal ganglia (namely, the GPi). On the other hand, stimulation of incoming fibers from the motor cortex via the so-called hyperdirect pathway could antidromically activate the cortex in a retrograde manner. Thus, DBS of the STN can potentially generate widespread and heterogeneous effects at local and distal sites.

A number of studies of both humans and animals support that STN stimulation can evoke or modulate cortical activities, and may be beneficial to PD symptoms. Evoked cortical potentials suggestive of antidromic activation were reported in patients undergoing DBS of the STN. In an anesthetized rats, the antidromic activation of cortical layer V neurons by stimulation of the STN had been demonstrated, and this action may underlie the effect of DBS of the STN in releasing dopamine antagonist-induced akinesia. Other studies also showed that the stimulation disrupted the β rhythms in the cortex in akinetic animals. These studies hinted at the importance of the antidromic activation of cortico-STN fibers, axon collaterals of the corticofugal projection (Figure), in the therapeutic effects of DBS of the STN.

To enable us to address this question directly in an animal model of PD, we made recordings of both single-unit activities and local field potentials in the motor cortex of freely moving rats with hemiparkinsonism when DBS of the STN was either on or off. During the delivery of DBS to the STN, we identified antidromic spikes in layer V projection neurons based primarily on their short, fixed latency (~1 millisecond) and also on their collision with, and therefore elimination by, a spontaneously generated spike. However, in contrast to general belief, the antidromic spikes did not follow high frequencies. In fact, as the robustness of their generation decreased dramatically at high frequencies, the maximum number of antidromic spikes was generated at around 125 Hz stimulation. Intriguingly, in these animals, stimulation at 125 Hz also produced the optimal effect in suppressing parkinsonian motor symptoms. The therapeutic effect of DBS of the STN was accompanied by a restoration of the firing rate, a reduction of abnormal burst spiking, and a breaking of the synchrony of firing in the motor cortical neurons. Field potential analysis also revealed normalization of the pathological β rhythm and reduced coherence between the spike and the local field potential at the β-frequency range.

Our identification of antidromic spikes in the rats with hemiparkinsonism matched the findings of a recent study on patients. Using a novel technique to suppress the stimulation artifact, Walker et al revealed a previously unknown ultrafast component of the cortical response to STN stimulation. Although a collision test could not be used to confirm the antidromic nature of the response, the speed of this component (~60 m/s) is too fast to be accounted for by a process involving synaptic transmission. Furthermore, the magnitude of this fast component decreased with increasing frequency, which matched our finding that the robustness of the antidromic spikes decreased in high frequencies.

Possible Mechanism of Desynchronization by DBS

Our analysis of the firing pattern of individual layer V motor cortical neurons also offers a putative mechanism by which antidromic activation helps to desynchronize their activities (Figure). We have shown that immediately after the arrival of an antidromic spike, the firing probability of the neuron undergoes a biphasic change (namely, a strong depression that lasts for about 1 millisecond followed by a period of increased excitability that lasts for about 2 milliseconds). The timing of this biphasic influence on the excitability of the neuron will depend on the time of occurrence of the antidromic spike. In relation to this, one crucial observation in our study is that, because the generation of the antidromic spike is not robust, a highly random pattern of antidromic spikes is produced, especially when the stimulation is delivered at a high frequency. It is believed that interconnections among the layer V neurons, as well as with local interneurons via axon collaterals, are important in underlying the synchrony of the motor cortical neurons. During DBS of the STN, as each layer V neuron is bombarded by a unique train of antidromic spikes, its firing probability will be modified independent of neighboring neurons. These highly desynchronized effects on the neurons could therefore serve as a powerful means to disrupt their synchronized firing and to release the motor cortex from the pathological rhythm. In other words, the breaking of the phase relationship among the neurons could be a key to this process. A simulation based on a computer model of the cortex-STN-thalamus circuitry also demonstrates the potential involvement of antidromic activation in DBS and the feasibility of our proposed mechanism (G. Kang, BE, and M. Lowery, PhD, written communication, March 2013).
There are other possible actions of the antidromic spikes that mediate the therapeutic effect of DBS of the STN. For example, antidromic spikes activated from the STN may travel down to the efferent motor targets of the cortical neurons by passing through the branching point that gives rise to the axon collaterals. In addition, the local circuitry, including the inhibitory neurons, may be affected by the invasion of the antidromic spikes into the projection neurons. Consistent with this idea, there is evidence from human studies that DBS of the STN has a direct effect on intracortical neurons, modifying the balance between excitation and inhibition.

In human PD, DBS of the GPi has also been shown to be therapeutically effective, albeit with different efficacies on different motor symptoms when compared with that of DBS of the STN. Given the known cortex-GPi projection and the reported modulation of neuronal firing in the primary motor cortex of primates with PD, it is possible that a similar antidromic action contributes to the therapeutic effect of DBS of the GPi. Alternatively, because the fibers to the STN pass through the GPi en route, DBS of the GPi might exert an action partly similar to that of DBS of the STN. This speculation is in line with studies showing that stimulation of axonal bundles or nuclei in the vicinity of the STN could be more effective than stimulation of the STN. For example, the zona incerta is innervated by collaterals of layer V pyramidal neurons of widespread cortical areas, and there is evidence that stimulation of the zona incerta is superior to DBS of the STN in treating parkinsonism.

### Implications for Pathogenesis and Treatment of PD

Being a major output station of the motor system, the motor cortex receives information relayed by the basal ganglia on motor control. As such, the motor cortex plays a critical role in the manifestation of parkinsonian motor symptoms. It has been suggested that bradykinesia and rigidity in PD are correlated with increased coherence between the spikes and the local field potential in the motor cortex, and the pathological enhancement in the β-band oscillation may contribute to degraded motor control and persistence of the status quo. Thus, in principle, directly rectifying the abnormal activities in the motor cortex could have a therapeutic effect. A powerful corroboration of this notion comes from a recent optogenetic study in which the
Although our results would lend support to the proposition that the cortex could be a therapeutic target in PD, epidural, subdural, or transcranial magnetic stimulation of the cortex in patients with PD has been a subject of debate and has only met with limited success. It appears that the efficacy of cortical stimulation will depend on the means, location, and paradigm of the stimulation. This idea is in line with our proposition that antidromic activation represents a unique mode of activation because the trains of random antidromic spikes could not be adequately mimicked by direct cortical stimulation. Nevertheless, novel strategies that aim to break the synchronized activities in the motor cortex by noninvasive means would represent a promising direction. In fact, the abnormal oscillatory activity in the motor cortex could serve as a marker of PD symptoms, as well as a target of treatment. A recent study showed that short trains of high-frequency stimulation driven by cortical activity and delivered to the GPe were more effective than continuous stimulation in alleviating parkinsonian symptoms. By means of a refined electrocorticographic technique to record local field potentials from the primary motor cortex in patients, another study showed that it is possible to detect excessive brain synchronization at the surface of the brain of patients with PD. These findings and our findings could serve as the scientific basis for the development of a next-generation deep brain stimulator.

In conclusion, the difficulties in elucidating the cause of PD symptoms and the therapeutic mechanisms of DBS are mainly due to the complex interactions among different nuclei in the basal ganglia, in the thalamus, and in the layers of the motor cortex. There is ample evidence to suggest that the mechanisms of DBS therapy and of abnormal β rhythm and synchrony are closely related, and a better understanding of this relationship will help us to optimize treatment in ways that increase safety and effectiveness. Future research on animal models driven by improved technologies that can provide a sufficient level of control and resolution in vivo would be indispensable toward this goal.

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