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Current Opinion in Behavioral Sciences

Cellular mechanisms of deep brain stimulation: activity-dependent focal circuit reprogramming?

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Deep brain stimulation (DBS) is a well-established treatment modality for movement disorders. As more behavioral disorders are becoming understood as specific disruptions in neural circuitry, the therapeutic realm of DBS is broadening to encompass a wider range of domains, including disorders of compulsion, affect, and memory, but current understanding of the cellular mechanisms of DBS remains limited. We review progress made during the last decade focusing in particular on how recent methods for targeted circuit manipulations, imaging and reconstruction are fostering preclinical and translational advances that improve our neurobiological understanding of DBS's action in psychiatric disorders.

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Current Opinion in Behavioral Sciences 2015, **4**:48–55

This review comes from a themed issue on **Cognitive enhancement**

Edited by **Barbara Sahakian** and **Arthur Kramer**

doi:10.1016/j.cobeha.2015.02.004

Introduction

There is increasing awareness that 'circuitopathies', dysfunctions in brain circuits characterized by abnormal patterns of electrical activity and oscillations, are responsible for the signs and symptoms of neurological and psychiatric disorders. This has coincided with a rapid shift in the conceptualization of novel treatment strategies, away from brain-wide interventions based on pharmacology, and toward an upcoming generation of pathway-focused and device-based therapeutics or 'electroceuticals' [1]. These approaches aim to reprogram faulty circuits by capitalizing on our greater understanding of the brain's cellular architecture and the mechanisms of activity-dependent neuroplasticity. Deep brain stimulation (DBS) has been the prototype and is currently the most clinically advanced of such approaches. This technique, which emerged in the 1980s, has arguably served as one of the triggers for the aforementioned shift. DBS refers to the process of delivering an electrical current to a precise location in the brain using surgically implanted chronic electrodes [2,3].

The use of DBS in Parkinson's disease (PD) and other neurological disorders has thus far been the main application of this technology. Chronic high-frequency DBS for treatment of movement disorders was pioneered in the early 1990s [2,4], and stimulation of the subthalamic nucleus (STN), globus pallidus (GPi), and ventral intermediate nucleus (VIM) are now common procedures for treatment-resistant PD and essential tremor [3,5]. Nearly 100,000 patients have been implanted with DBS devices in the US [3] and this number is growing at a rate of 8000–10,000 patients per year [6].

In the early 2000s, the success of DBS for movement disorders coupled with an increasing understanding of the circuitry underlying mental disorders spurred initial investigations into the efficacy of DBS in psychiatry. This review will provide an overview of the principles of DBS action in this context, summarize the progress made during the last decade in this area and discuss the emerging understanding of the circuit, cellular and molecular mechanisms underlying its therapeutic activity.

General principles of DBS action: still many open questions

A. Stimulatory versus inhibitory effects on cell firing at the site of stimulation

DBS stimulates a spherical volume of tissue around the electrode [7], and the effects of this stimulation can vary regionally depending on the molecular characteristics of local neurons or glial cells, which determine their passive membrane properties and compositions of voltage-sensitive ion channels [2]. Accordingly, the response of individual cell bodies in the stimulated region is typically phase-locked to stimulation but varies with regard to the proportion of cells increasing and decreasing their firing rate [2,3,8]. Potential mechanisms for DBS-induced inhibition of cell bodies include depolarization block, inactivation of Na^+ channels, presynaptic depression or depletion of excitatory afferents, and stimulation of inhibitory afferents [3].

B. Modulation of cell bodies and dendrites versus axons

Because the chronaxie of a myelinated axon is typically orders of magnitude lower than for cell bodies or dendrites (making the former more excitable), DBS may

exert its effects predominantly by modulating axons that are afferent to, efferent from, or passing through the site of stimulation [2,9]. Accordingly, preclinical studies using optogenetics to dissect the action of DBS have shown that direct optical stimulation or inhibition of neuronal cell bodies at the site of electrode may not reproduce therapeutic effect of DBS, while direct optical stimulation of afferent axons to this region does so [10••]. This axonal mode of action explains the paradoxical finding that cell bodies in a stimulated nucleus can be inhibited by DBS, while output from this nucleus increases in projection areas [7]. Accordingly, DBS still maintains its therapeutic activity in certain preclinical models in the presence of lesions that ablate all cell bodies at the site of stimulation, but spare fibers of passage [11].

C. Local versus distal effects

DBS-induced changes outside the area of stimulation are relatively less well-studied. Electrophysiological and imaging studies have revealed that DBS simultaneously modulates blood flow and electrical oscillations across many brain regions distal to the site of stimulation, through both orthodromic and antidromic transmission [3]. For example, in PD, STN stimulation can reverse pathological low-frequency (~9 Hz) single-unit oscillations in the globus pallidus external (GPe) and substantia nigra reticulata (SNr) by entraining neurons in the circuit to the stimulation frequency [12], and can modify the firing probability of cortical neurons through antidromic frequency jamming, reducing pathological cortical beta rhythms [13].

The normalization of aberrant patterns of electrical and metabolic activity in connected regions by DBS may reflect at least in part an effect on neurotransmitter release. For example, NAc DBS has been shown to drive striatal dopamine release in patients and animals [14], and D2 receptor antagonism abolished the effect of NAc DBS on compulsive feeding behaviors in obese mice [15]. Similarly, in depression models, preclinical studies have shown that vmPFC DBS drives hippocampal serotonin (5-HT) release [11], and that serotonin depletion abrogates the antidepressant-like effect of DBS [11,16].

D. Neurons versus glia

In addition to neurons, glia may play an important role in the response to DBS. Two main types of glial cells have been implicated: astrocytes and microglia. Astrocytes are prime candidates as they propagate calcium waves and form a tripartite synapse together with neuronal synapses. Gliotransmitters and growth factors released from astrocytes are thus likely to mediate, at least in part, the activity of DBS in psychiatric illness. Astrocyte-derived adenosine released during DBS and acting at A1 receptors on neurons was found necessary and sufficient for the effect of thalamic DBS on essential tremor [17••] and preliminary evidence suggests a similar mode of action in preclinical models of depression [18]. Not only can astrocytes respond to the electrical changes induced by DBS, but the microlesions resulting from the implantation of the stimulating electrode also produce inflammation and reactive gliosis [19••], a known source of induced multipotent stem cells in the injured brain. The presence of these cells may contribute to neurotrophic responses and circuit reorganization [20]. Furthermore, cytokines produced by microglia at the site of implantation also appear to participate in the therapeutic action of DBS through effects on endothelial cells. Interestingly, postmortem tissue from PD patients treated with STN DBS showed lower densities of activated microglia and increased microvasculature in the STN compared to control PD patients [21].

F. Acute versus chronic effects

Most mechanistic studies to date have focused on the effects of acute DBS (Figure 1a). Although this approach has validity in the context of PD, where effects on motor deficits are observed immediately, DBS is always applied chronically in clinical settings, and long-term effects on connected networks are beginning to be uncovered in most clinical applications (Figure 1b). For example, in PD, a longitudinal case study comparing brain structural and functional connectivity after 5 months of DBS showed localized structural changes in sensory-motor, prefrontal/limbic, and olfactory brain regions and an increased nodal efficiency [22].

Disease-specific mechanisms of DBS in psychiatric disorders

A. Obsessive compulsive disorders (OCD)

OCD was the first non-motor disorder treated with DBS. It is a serious neuropsychiatric disorder characterized by persistent intrusive anxious thoughts (obsessions) and unwanted repetitive ritualistic behaviors (compulsions) that often have devastating effects on a patient's life. A quarter of all patients remain resistant to first line treatments (cognitive-behavioral therapy and pharmacotherapy with serotonin reuptake inhibitors). The application of DBS in OCD was pioneered by Bart Nuttin and colleagues in 1999 as a reversible alternative to capsulotomy, a last-resort surgical intervention which permanently disconnects the cingulate cortex by severing the fiber tracts running from the thalamus to the frontal lobe [23].

The current 'habit hypothesis' of OCD places emphasis on the pathophysiological role of cortico-striato-thalamo-cortical (CSTC) loops implicated in the acquisition of automatic behaviors [24,25]. To date, most clinical trials of DBS for OCD have focused on stimulation of the anterior limb of the internal capsule in the ventral striatum (VC/VS) [26], the adjacent nucleus accumbens (NAc) [27], and the STN [28], which are three nodes in the CSTC 'habit' circuit [29••]. Although DBS at these sites clearly improves anxiety and compulsions, it does so