Neurobiology of Disease 38 (2010) 329–337

Contents lists available at ScienceDirect

Neurobiology of Disease

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

Review

Network perspectives on the mechanisms of deep brain stimulation

Cameron C. McIntyre *, Philip J. Hahn

Department of Biomedical Engineering, Cleveland Clinic Foundation, 9500 Euclid Ave, ND20, Cleveland, OH 44195, USA

ARTICLE INFO

Article history:
Received 30 January 2009
Revised 21 September 2009
Accepted 27 September 2009
Available online 3 October 2009

Keywords:
Neuromodulation
Neurostimulation
Parkinson's Disease
Essential Tremor
Dystonia
Epilepsy
Tourette's Syndrome
Obsessive Compulsive Disorder
Depression

ABSTRACT

Deep brain stimulation (DBS) is an established medical therapy for the treatment of movement disorders and shows great promise for several other neurological disorders. However, after decades of clinical utility the underlying therapeutic mechanisms remain undefined. Early attempts to explain the mechanisms of DBS focused on hypotheses that mimicked an ablative lesion to the stimulated brain region. More recent scientific efforts have explored the wide-spread changes in neural activity generated throughout the stimulated brain network. In turn, new theories on the mechanisms of DBS have taken a systems-level approach to begin to decipher the network activity. This review provides an introduction to some of the network based theories on the function and pathophysiology of the cortico-basal-ganglia-thalamo-cortical loops commonly targeted by DBS. We then analyze some recent results on the effects of DBS on these networks, with a focus on subthalamic DBS for the treatment of Parkinson's disease. Finally we attempt to summarize how DBS could be achieving its therapeutic effects by overriding pathological network activity.

Contents

Introduction

Deep brain stimulation (DBS) is a powerful clinical therapy for the treatment of numerous neurological and psychiatric disorders. The origins of clinical DBS date back to neurosurgical pioneers such as Hassler et al. (1960) and Cooper et al. (1980), and the advent of modern day DBS was principally spearheaded by Benabid et al. (1987). While decades have passed since the inception of DBS, and its clinical utility has grown exponentially, the underlying therapeutic mechanisms of chronic high frequency (~100 Hz) brain stimulation remain mysterious and controversial. This review attempts to explore the mechanisms of DBS from a network perspective, relying on the concept that disorders treated with DBS are fundamentally disorders of a specific brain network, as opposed to a specific neuron type, ion channel, or molecule (Llinás et al., 1999; DeLong and Wichmann, 2007). Our working hypothesis is that DBS interacts with the diseased network to eliminate or subdue the underlying pathological neural activity. This general hypothesis was actually the original proposition of Benabid et al. (1991), which later became known as "jamming" (Benabid et al., 1996). However, following years saw much of the

* Corresponding author. Fax: +1 216 444 9198.
E-mail address: mcintyc@ccf.org (C.C. McIntyre).
Available online on ScienceDirect (www.sciencedirect.com).

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doi:10.1016/j.nbd.2009.09.022

scientific investigation on DBS mechanisms transition away from a systems-level perspective to focus on the cellular effects of stimulation near the electrode, with contentious debate over whether high frequency stimulation induced neural activation or inhibition (Lozano et al., 2002; McIntyre et al., 2004c). While that interesting question continues to be explored, we propose that it may not be the fundamental issue underlying the therapeutic mechanisms of DBS. Recent results suggest that changes in the underlying dynamics of the stimulated brain networks may represent the core mechanisms of DBS and that those basic dynamical changes can be achieved via activation, inhibition, or lesion. In turn, the goal of this review is to summarize some of the latest findings on DBS induced network activity in a quest to create a scientific definition for the term "jamming."

Cortico-basal-ganglia-thalamo-cortical network

Currently, the most common form of clinical DBS is stimulation of the subthalamic region for the treatment of Parkinson's disease (PD). As such, this review will focus on subthalamic nucleus (STN) DBS and the basal ganglia (BG). However, we believe that the general concepts discussed in this review are applicable to all forms of DBS and that while subtle details may differ the fundamental mechanisms of DBS are consistent across all therapeutic applications. We propose that the first step in unlocking the mechanisms of DBS is to understand the brain circuits that are being stimulated (Fig. 1).

The BG consists of four interconnected nuclei: the striatum (caudate nucleus and putamen), globus pallidus (internus and externus), substantia nigra (pars compacta and pars reticulata) and subthalamic nucleus (Parent and Hazrati, 1995a,b). Traditional theories propose that two main pathways are present through the BG, the direct and indirect. Cortical information is transmitted through the direct and indirect pathways to the basal ganglia output nuclei, the globus pallidus pars interna (GPi) and the substantia nigra pars reticulata (SNr). Neurons from GPi and SNr project to the ventral motor and intralaminar nuclei of the thalamus, which project back to the frontal cortex and striatum, respectively (Fig. 1).

While we prefer to think of the network as a series of continuous loops that interact with each other (Fig. 1B), the striatum is commonly considered the main input structure of the basal ganglia sub-circuit. Glutamatergic projections from virtually all cortical areas converge onto striatal spiny projection neurons. The striatum also receives an important dopaminergic input from the substantia nigra pars compacta (SNc). The output of the striatum is transmitted by subpopulations of spiny neurons that project either directly to the output nuclei (GPi and SNr), or convey their information to the output nuclei via an indirect route. The striatal neurons that give rise to the indirect pathway project to the globus pallidus pars externa (GPe), which, in turn, project to the STN and then to the output nuclei of the BG (GPi and SNr).

A simplified explanation of BG function is commonly provided by the rate theory which laid much of the original groundwork for the network analysis of movement disorders (Albin et al., 1989; Alexander et al., 1990). The rate theory proposes that by virtue of the neurotransmitters and base line activity of the neurons in the cortico-basal-ganglia-thalamo-cortical network, modulation of the direct and indirect pathways produces functionally opposite effects in the thalamic neurons receiving BG output. Corticostriatal neurons, thalamocortical neurons and neurons of the STN are excitatory, utilizing glutamate as a neurotransmitter. All other neurons in the network are inhibitory using GABA as their main neurotransmitter. Under resting conditions, the activity of the output neurons of the striatum is low compared to that of tonically active neurons in the GPe and STN. Activation of the corticostriatal pathway leads to increased firing of striatal projection neurons. Increased activity of the direct pathway (striatum → GPi/SNr) leads to inhibition of the output nuclei (GPi and SNr). A reduction in tonic activity of the neurons in GPi/SNr leads to a reduction in the inhibition of neurons in the thalamus. In contrast, activation of the traditional indirect pathway (striatum → GPe → STN → GPi/SNr) leads to the opposite functional effect on the thalamus. Increased activity of the striatal output neurons inhibits the tonically active neurons in the GPe. Inhibition of the neurons in GPe disinhibits neurons in the STN. Increased activity of the excitatory neurons of the STN leads to increased firing of neurons in GPi and SNr. An increase in the tonic activity of the neurons in GPi and SNr leads to an increase in the inhibition of neurons in the thalamus. It should be noted that this is a highly simplified view of the workings of the BG, ignoring numerous additional pathways (e.g. hyperdirect pathway–direct cortical input to STN), nuclei (e.g. peduncluopontine nucleus), and synaptic interactions (Parent and Hazrati, 1995a,b; Smith et al., 1998; Pahapill and Lozano, 2000; Nambu, 2004) (Fig. 1C). However, the general framework described above does provide a good starting point and conceptual guide to preliminary network analysis.

Functional imaging

Research modalities such as functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) represent excellent tools to investigate brain networks. However, when interpreting the results from functional imaging experiments it is important to remember that the brain activity changes are not direct measures of neural activity and that the activated regions are most indicative of changes in afferent input to that region, not necessarily efferent output (Logothetis et al., 2001; Lin et al., 2008). Nonetheless, functional imaging does provide a unique opportunity to observe systems-level changes in the network activity of human subjects implanted with DBS devices.

Functional imaging experiments performed during DBS has shown that therapeutic stimulation, in all forms tested, generates metabolic and blood flow changes throughout the brain (Perlmutter and Mink, 2006). The first functional imaging investigation of DBS was performed by Limousin et al. (1998) to compare subthalamic DBS and globus pallidus DBS for the treatment of PD. They and many subsequent others, have shown changes in both cortical and subcortical brain regions during DBS. Recently, PET studies from the Eidelberg laboratory have shown that suppression of their Parkinson's disease related spatial covariance patterns are a common feature of dopaminergic therapy, STN lesioning, and STN DBS (Trost et al., 2006; Asanuma et al., 2006). Several PET studies of STN DBS have also concluded that therapeutic stimulation drives STN output, inducing metabolic activation of the STN region and pallidum (Hilker et al., 2008); thereby increasing regional cerebral blood flow (rCBF) in thalamus and midbrain while decreasing rCBF in frontal cortical areas (Hershey et al., 2003; Payoux et al., 2004; Grafton et al., 2006; Karimi et al., 2008). Similarly, PET studies of DBS for neuropsychiatric disorders show network wide changes in the cortico-striato-thalamo-cortical circuit, albeit through limbic and prefrontal territories (Rauch et al., 2006; Mayberg et al., 2005).

In general, fMRI has higher spatial and temporal resolution than PET. Additionally, fMRI is more easily integrated with other MRI datasets such as diffusion tensor imaging and high-resolution anatomic imaging of lead placement. Consequently, fMRI is ideally suited to individual subject analysis, and direct comparison of experimental data with patient-specific DBS computer models (McIntyre et al., 2008). However, due to safety concerns the number of DBS fMRI studies has been limited (Rezai et al., 1999; Jech et al., 2001; Stefurak et al., 2003; Arantes et al., 2006; Phillips et al., 2006). The general consensus from the available fMRI studies is that STN DBS generates activation throughout the network, with activation of the globus pallidus and thalamus being common across most patients.