Experimental Neurology 247 (2013) 296–302

Contents lists available at SciVerse ScienceDirect

Experimental Neurology

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

Commentary

The temporal pattern of stimulation may be important to the mechanism of deep brain stimulation

Christopher W. Hess[a], David E. Vaillancourt[b], Michael S. Okun[c,*]

[a] Center for Parkinson's Disease and Other Movement Disorders, Columbia University Medical Center, New York, NY, USA
[b] Laboratory for Rehabilitation Neuroscience, University of Florida, Gainesville, FL, USA
[c] University of Florida Center for Movement Disorders & Neurorestoration, Gainesville, FL, USA

ARTICLE INFO

Article history:
Received 20 December 2012
Revised 30 January 2013
Accepted 1 February 2013
Available online 8 February 2013

Keywords:
Deep brain stimulation
Frequency
Non-regular
Temporal pattern

ABSTRACT

Deep brain stimulation (DBS) has emerged as an important and potentially powerful treatment option for the management of carefully selected patients with advanced Parkinson's disease (PD) who are not adequately controlled by standard medication therapy. Though considerable advances have been made, the mechanisms underlying the therapeutic effects of DBS remain unclear despite its clinical efficacy. It is now widely held that both excitation and inhibition can occur secondary to stimulation, and it is suspected that abnormal synchronized oscillations may also be important in the mechanism of DBS. Other potentially important processes, including blood flow changes, local and upstream neurogenesis, and the modulation of neurotransmitters through stimulation of bordering astrocytes are also being investigated. Recent research has suggested that the temporal pattern of DBS stimulation is also an important variable in DBS neuromodulation, yet the extent of its influence on DBS efficacy has yet to be determined. As high stimulation frequency alone does not appear to be sufficient for optimal symptom suppression, attention to stimulation pattern might lead to more effective symptom control and reduced side effects, possibly at a lower frequency. Stimulation pattern may be potentially amenable to therapeutic modulation and its role in the clinical efficacy of DBS should be addressed through further focus and research.

Introduction

In 1987, a report of successful tremor reduction achieved through high frequency thalamic stimulation (Benabid et al., 1987) ushered in a new era of chronic deep brain stimulation (DBS), and a renewed interest in the surgical treatment of movement disorders. DBS has since become an invaluable tool in the management of advanced levodopa-responsive Parkinson's disease (PD) in patients who are not adequately controlled by medication, and who are appropriately screened by interdisciplinary teams (Okun, 2012). Despite the efficacy of DBS as a therapy, our understanding of the therapeutic mechanism of stimulation remains to be completely elucidated. The reason for this discrepancy is multifaceted (Montgomery, 2012), yet it is clear that new approaches will be required to refine the clinical benefit provided by DBS and to minimize potential side effects. In this issue of *Experimental Neurology*, Brocker and colleagues (Brocker et al., 2012) explore the influence of temporal pattern regularity on high frequency stimulation (HFS), both clinically in patients with previously implanted DBS and in computational basal ganglia models. We review the state of current thinking regarding the role of frequency and temporal pattern in DBS mechanism, and discuss the study by Brocker and colleagues and other related works. We emphasize the implications of these studies on current theories of DBS mechanisms and future approaches in DBS treatment.

DBS mechanisms and theories of basal ganglia dysfunction

Initial theories regarding the therapeutic mechanism of DBS were based upon the classical theory of basal ganglia function known widely as the "rate model", and the similarity between the clinical effect of DBS and surgical lesioning (Albin et al., 1989). However most experts now believe that there are significant problems associated with this approach. In the classic model of basal ganglia functioning (Fig. 1), the caudate nucleus and putamen (functionally known as the striatum) act as the primary input to the basal ganglia, and receive both glutaminergic excitatory cortical and thalamic input as well as neuromodulatory dopaminergic input from substantia nigra pars compacta (SNc). The internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr) act as the major output nuclei of the basal ganglia, ultimately projecting through the thalamus to the cerebral cortex. The classical model of basal ganglia emphasized two parallel pathways in motor processing: a "direct" pathway that promoted movement

* Corresponding author at: UF Center for Movement Disorders & Neurorestoration, 3450 Hull Road, Gainesville, FL 32607, USA. Fax: +1 352 294 5010.
E-mail address: okun@neurology.ufl.edu (M.S. Okun).

0014-4886/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.expneurol.2013.02.001

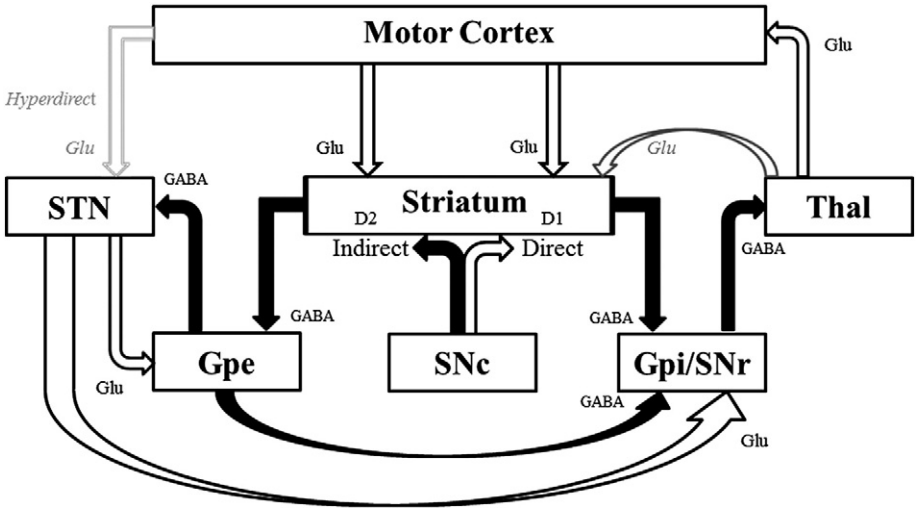

Fig. 1. Schematic of the classical model of the direct and indirect pathways in basal ganglia circuitry. Unfilled arrows are excitatory connections. Filled arrows are inhibitory connections. Grey and italics indicate updates to the classical model. D1 = D1 dopaminergic receptors; D2 = D2 dopaminergic receptors; GABA = γ-aminobutyric acid (GABA)-ergic; Glu = glutaminergic; GPe = external segment of the globus pallidus; GPi = internal segment of the globus pallidus; SNc = substantia nigra pars compacta; SNr = substantia nigra pars reticulata; STN = subthalamic nucleus; Thal = thalamus.

(the gas pedal) and an "indirect" pathway that inhibited movement (the brake) (Albin et al., 1989; Alexander et al., 1986). In both pathways dopaminergic modulation favors movement, and is mediated by the number of inhibitory connections within the circuit and also partially by the respective dopamine receptor type represented within each pathway. In hypokinetic movement disorders such as PD, the "balanced" activity of the direct and indirect pathways was thought to be disrupted, resulting in an increase in the tonic activity of the neurons in the STN and the GPi/SNr. This disruption was thought to further contribute to increased basal ganglia inhibition of neurons in the thalamus, which in turn have excitatory connections to the cortex. Similar to the proposed mechanism of action of surgical lesioning, it was theorized that HFS acted as a "virtual lesion", suppressing neuronal activity in the electrode target (Benabid et al., 1998), perhaps by local depolarization blockade, depression of synaptic transmission, or activation of local inhibitory terminals (Dorval et al., 2010).

While the classical rate model of basal ganglia functioning has been invaluable in framing theories of pathophysiology, our understanding of basal ganglia function has matured and expanded since it was first put forth, and the limitations of the model have been highlighted. The study of electrophysiologic recordings of local field potentials (LFPs) obtained during and after DBS surgery in humans and experimental lesioning in animals, as well as sophisticated computational models of basal ganglia networks, has suggested that dysfunctional firing patterns, rather than just absolute increases or decreases in firing rates, are occurring within the basal ganglia network (McIntyre and Hahn, 2010). In both animal models and in PD patients off of their dopaminergic medications, basal ganglia and thalamic neurons in the parkinsonian state seem to exhibit complex changes in discharge patterns, with increased bursting and beta band (13–35 Hz) oscillations, as well as a greater tendency toward hyper-synchronization (Birdno and Grill, 2008; Nambu, 2008; Wichmann et al., 2011). Abnormal beta synchronization has been reported in LFPs in the striatum, STN, and GPi, as well as in single unit recordings, with reports of suppression of beta power in LFPs by levodopa and associated improvements in bradykinesia and rigidity (Eusebio et al., 2012). The spatial extent of beta band phase synchronization in the region of the STN has been shown to correlate with rigidity and bradykinesia (Pogosyan et al., 2010). However, beta activity in LFPs has not been consistently shown to correlate with motor UPDRS in the off state, nor is beta always present (Priori et al., 2013; Weinberger et al., 2006). Recently studies have investigated whether abnormal synchronized oscillations could also be demonstrated in the sensorimotor cortex in patients with movement disorders (Air et al., 2012; Crowell et al., 2012), and whether this oscillatory activity could distinguish between different diseases. Similar to the techniques commonly used in epilepsy patients, concomitant subdural electrode recordings placed in patients undergoing DBS surgery (Crowell et al., 2012) for PD, dystonia, or essential tremor (ET) showed that patients with PD had increased broadband gamma frequency spectral power in M1, and a relatively higher alpha–beta range median peak frequency on spectral analysis compared to non-PD movement disorders (dystonia and ET). In addition, PD patients had an increase in high beta band (20–30 Hz) power relative to dystonia and ET, but only during the stop phase of a stop/start movement task. These results support the notion that dysfunctional beta oscillatory activity is reaching the cortex and altering sensorimotor cortical activity in movement disorders.

Similar to the progress in mechanistic theories of basal ganglia dysfunction, current notions of how DBS improves symptoms in movement disorders have evolved beyond the idea of a "virtual lesion" to recognize that the effects of DBS are likely more complicated than simple inhibition or excitation. Early theories held that DBS worked by inhibition or by "jamming the circuit" (Benabid et al., 1998). This sparked a transoceanic debate about the roles of inhibition versus excitation in the mechanism of the underlying DBS efficacy (Grill et al., 2004; Miocinovic et al., 2006). However, recent studies have shown that DBS can act both to inhibit and to excite; there is common inhibition of neuronal cell bodies immediately surrounding the electrode, but excitation of efferent projections and resultant activation of complex neural networks (Eusebio et al., 2012; Montgomery and Gale, 2008; Vitek et al., 2012). Beyond direct effects of excitation and inhibition, proposed therapeutic mechanisms of DBS include the masking of pathological activity with innocuous regularity, direct suppression of local pathological neuronal activity, and interactions with reentrant non-linear oscillations occurring in the basal ganglia–thalamocortical network (Johnson et al., 2008; Montgomery and Gale, 2008; Obeso et al., 2008). The degree to