Physiological Monitoring in Deep Brain Stimulation: Toward Closed-Loop Neuromodulation Therapies

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Abstract Deep brain stimulation (DBS) is a widely used, efficacious neurosurgical treatment for neurological movement disorders. For example, electrical stimulation in the ventral intermediate thalamic nucleus drastically reduces tremor in patients with essential tremor. Likewise, stimulation in the subthalamic nucleus or the internal globus pallidus significantly attenuates tremor, rigidity, bradykinesia, and gait complications of Parkinson's disease. Its application is now rapidly expanding to a wide variety of conditions including epilepsy, neuropsychiatric disorders, Tourette syndrome, Alzheimer's disease, and intractable pain. However, the exact underlying therapeutic mechanisms of action of DBS remain unclear. Despite this lack of understanding, clinical utility of DBS cannot be underappreciated, and there is a great need for studies that can elucidate patient-specific optimization of DBS parameters and targets. This chapter explores recent approaches for studying the

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underlying mechanisms of action of DBS. Additionally, it discusses the limitations of current open-loop approaches to DBS and accentuates the importance of developing a smart closed-loop DBS system that can optimize therapeutic parameters in real time to individual patients and symptoms.

1 Introduction

As recently as 30 years ago, surgical techniques for treating many neurologic disorders involved ablative procedures, potentially resulting in significant and sometimes generalized damage to the brain [26, 110]. The advent of thermal and cryogenic lesioning brought forth greater spatial selectivity during surgery; however, these procedures are irreversible and cannot be modulated if the treatment needs change [4, 10, 13]. In the early 1990's, deep brain stimulation (DBS) became a reversible alternative to lesioning procedures for the treatment of movement disorders such as Parkinson disease and essential tremor [8, 9, 87]. Since then, the use of DBS has become more widespread for the effective treatment of other neurologic disorders such as dystonia [55, 64, 87, 96], Tourette syndrome [24, 46, 87, 104, 108], epilepsy [27, 52, 103], depression [25, 37, 72, 74], neuropathic pain [31, 48, 64, 87], and obsessive-compulsive disorder (OCD) [1, 33]. Additionally, DBS offers promising outcomes for the treatment of other neurological conditions ranging from bipolar disorder [45] and Alzheimer's disease [58] to addiction [65], cerebral palsy [69, 107], and hyperphagic obesity [103] (Table 1). However, the underlying therapeutic mechanisms of DBS remain unknown despite years of research and successful clinical application.

The predominant hypothesis suggests that DBS modulates pathological activity via excitation of axonal fibers of passage and inhibition of local cell bodies [28, 73]. However, the integration of spatially and temporally distant signals suggests that the neural mechanisms underlying DBS efficacy may be far more complex [43]. Therefore, further advancement of DBS technology will require a greater understanding of the response to DBS on the molecular, biochemical, cellular, and circuitry levels. For example, the brain is a highly complex organ, with innumerable neural signals transmitted via distinct neurotransmitters capable of modulating neural activity across both local and global neural circuitry [40]. Thus, DBS may induce complex changes in synaptic plasticity that reorganize neural circuits and rectify neuropathological changes associated with neurological disorders. These changes could help explain the different timescales in therapeutic efficacy observed across different disorders. For example, DBS patients with Parkinson's disease who experience immediate symptomatic relief, and patients with major depression who require longer intervals before symptomatic improvement can be observed [42].

Table 1 Neurologic disorders and deep brain stimulation targets

Neurologic Disorders	Targets	References
Addiction	NAc, STN	[32]
Alzheimer's disease	NBM, fornix	[59]
Depression	Cg25, ALIC, NAc	[14, 25, 49, 63, 67, 72], Schlepper et al. (2008)
Dystonia	GPi, (STN)	[50, 57, 81, 107]
Epilepsy	ATN, (cerebellum, CN, STN, hippocampus, CM, CC, LoC, MB)	[12, 27]
Essential Tremor	Vim, (STN)	[8, 16, 54, 61, 84, 101, 117]
Neuropathic Pain	PAG, VPL/VPM	[86]
Hyperphagic obesity	VMH, LH	[38, 112]
Obsessive-compulsive disorder	VC/VS, (ALIC, NAc, STN, ITP)	[21, 36, 66]
Parkinson's disease	GPi, STN, (PPN)	Deep Brain Stimulation for Parkinson's Disease Study Group (2001), Schuepbach et al. (2013), [22, 23, 29, 76, 78, 98, 111, 113]
Tourette syndrome	CM thalamus, GPi, ALIC, NAc	[109]

List of neurologic disorders and deep brain stimulation targets. Targets listed in parentheses are non-validated potential targets. Anterior limb of the internal capsule: ALIC, Anterior thalamic nucleus: ATN, Cingulate area 25 or subgenus cingulate: Cg25, Centromedian nucleus of the thalamus: CM, Caudate nucleus: CN, Globus pallidus internus: GPi, Interior thalamic peduncle: ITP, Lateral hypothalamus: LH. Locus coeruleus: LoC, Mammillary bodies: MB, Nucleus accumbens: NAc, Nucleus basalis of Meynert: NBM, Periaqueductal gray: PAG, Pedunculopontine nucleus: PPN, Subthalamic nucleus; STN, Ventral capsule/ventral striatum: VC/VS, Ventral intermediate uncles of the thalamus: Vim, Ventral intermediate nucleus of the thalamus: VMH, Ventral posterolateral thalamus: VPL, Ventral posteromedial thalamus: VPM, Ventral segmental area: VTA

2 Monitoring of Neural Activity

Numerous techniques are being utilized in clinical and preclinical studies to unravel the mechanisms of action of DBS and assist in target selection as well as optimization of stimulation parameters [35, 42]. These techniques allow examination of the neural responses to DBS at local and network-levels with high spatio-temporal resolutions. The most commonly utilized techniques include electrophysiological measurement of compound neural activity, electrochemical measurement of neurotransmitter signaling, and functional imaging techniques.

2.1 Electrophysiological Monitoring

Electrophysiological analysis has played an instrumental role in unraveling the function of the central nervous system (CNS) since the early 1950s, when Hodgkin and Huxley demonstrated the electrical nature of the action potential [44]. Since then, electrophysiological analysis techniques have evolved to enable the analysis of a broad range of neurological activity, from patch-clamp techniques that allowed the study of single ion channels, to single-unit recordings and global field potentials via multiunit recording arrays [75]. This technological diversity permits comprehensive evaluation of neurological activity from the subcellular to circuitry levels [35]. For example, electrophysiological techniques have been utilized to investigate the physiological mechanisms underlying DBS efficacy in the treatment of Tourette syndrome [47]. In this study, local field potential (LFP) recording electrodes were implanted into the thalamus, globus pallidus pars internal (GPi), or nucleus accumbens to analyze neural activity before, during, and after stimulation. Results from this study suggest that the pathophysiology of Tourette syndrome is related to dysfunctional synaptic transmission within deep brain nuclei, producing oscillations of inappropriate frequency and amplitude, and preventing the effective inhibition of stereotypical behaviors and tics such as blinking, head jerking, sniffing, throat clearing, and other vocalizations [2]. Similarly, excitatory postsynaptic potentials (EPSPs) evoked by high and low frequency stimulation of neurons within the subthalamic nucleus (STN) of 6-hydroxydopamine (6-OHDA)-lesioned rats revealed that high frequency stimulation produced significant EPSP depression in dopamine-depleted rats [115]. Similarly, low frequency stimulation resulted in EPSP augmentation in dopamine-intact rats [115].

2.2 Neurochemical Monitoring

Preclinical studies have demonstrated that neurotransmitter release is evoked by high frequency stimulation, and thus may be associated with the effects of DBS [60]. Fixed potential amperometry is a technique for measuring neurotransmitters and other analytes such as Glutamate, and involves the application of a constant voltage through a carbon fiber microelectrode implanted within the target of interest (Gale et al. 2013; Tye et al. 2013). Carbon fiber microelectrodes are coated with specific enzymes that react with non-electroactive analytes of interest, resulting in electroactive products that can be electrically measured [53]. The signals detected are caused by oxidative reactions between the applied voltage and the molecules of analyte within the extracellular space (Van Gompel et al. 2010). Unfortunately, the continuous enzyme delivery required to detect the neurotransmitter of interest makes this technique impractical for chronic in vivo detection of neurochemicals (Jacobs et al. 2010). Fast scan cyclic voltammetry (FSCV) is an alternative electroanalytical technique capable of real-time detection of electroactive

neurotransmitters, hormones, and other metabolites [34, 51]. Previous studies have demonstrated that FSCV can effectively detect serotonin, norepinephrine, epinephrine, dopamine, and adenosine, as well as changes in oxygen and pH [41, 88, 106]. FSCV relies on the delivery of rapid voltage oscillations to allow oxidation and reduction of electrically active compounds of interest, resulting in the generation of unique electrical voltage versus current signatures specific for each analyte [88, 92]. By taking advantage of FSCV and a Wireless Instantaneous Neurotransmitter Concentration Sensing (WINCS) system designed to wirelessly measure neurochemical responses during DBS, Chang and colleagues showed that the immediate symptomatic relief induced by implantation of the DBS lead, also known as the microthalamotomy effect (Tasker 1998) was accompanied by a neurochemical signature resembling that of adenosine release [18, 19] (Fig. 1). Previous preclinical animal studies have demonstrated that administration of

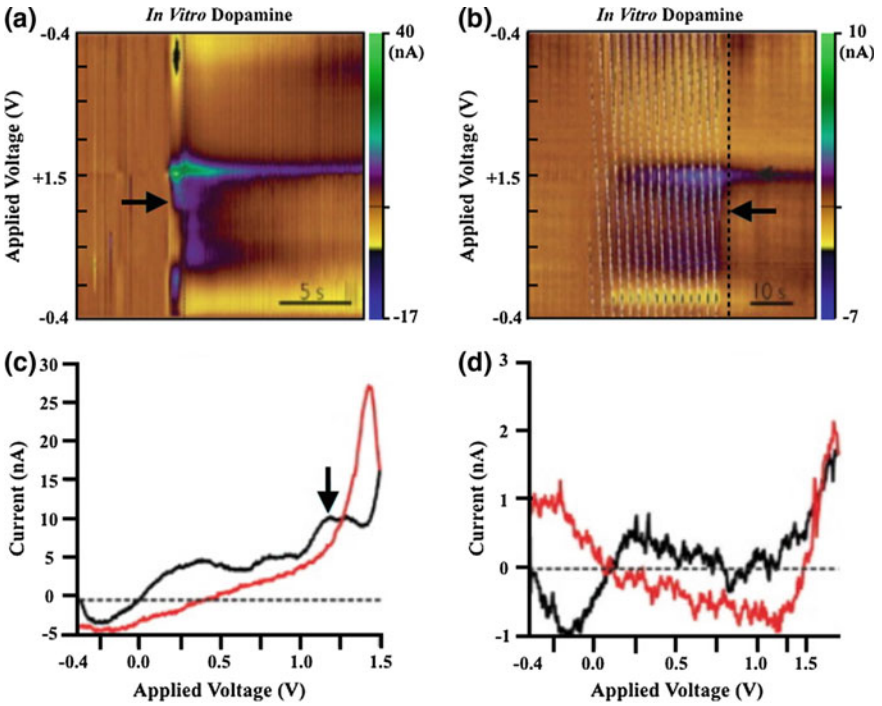

Fig. 1 Fast scan cyclic voltammetry recording during DBS electrode implantation into the VIM of the thalamus. **a** Pseudocolor plot collected from an awake patient. The plot depicts oxidation currents immediately on DBS electrode insertion. Black arrow indicates a second oxidation current peak. **b** Pseudocolor plot collected during electrical stimulation (130 Hz, 60 μsec pulse width, 2 V) through DBS electrode (in 4 out of 7 awake patients; no significant oxidation currents were not observed in the other 3 patients). The *plot* indicates oxidation current at a switching potential (1.5 V). Black arrow points to a much smaller second oxidation current. **c**, **d** Cyclic voltammograms (current versus voltage) at *black dotted lines* from A and B. Modified from [18]

adenosine A_1 agonists alleviates tremor symptoms in mice models of harmaline-induced essential tremor [7]. Therefore, it is possible that enhancement of adenosine signaling induced by the microthalamotomy effect, or by the administration of adenosine agonists, inhibits the maladaptive excitatory signaling producing uncontrolled movement in patients with essential tremor. However, the CNS contains multiple receptors for adenosine that operate through a variety of G-proteins, including G_s, G_q, and G_i. Variable effects in synaptic transmission are observed based on their localization on presynaptic, postsynaptic, or astrocytic membranes and the subsequent downstream signaling from the G-protein coupled receptor [79].

2.3 Functional Imaging

Functional magnetic resonance imaging (fMRI) is an MRI technique that measures changes in blood flow [62]. The utility of this technique for characterizing the effects of DBS is based upon the principle that the magnitude of cerebral blood flow and oxygen consumption is proportional to the relative activity of individual brain regions due to differential energy requirements during periods of neural activity [105]. Specifically, the blood-oxygen-level dependent (BOLD) signal measures changes in the magnetization of hemoglobin following deoxygenation of blood within the CNS [77]. This enables the generation of an oxyhemoglobin/deoxyhemoglobin heat map based upon changes in oxygen consumption resulting from modulation of neural activity [94].

To this end, fMRI has been recently used to characterize the effects of high (130 Hz) and low (10 Hz) frequency stimulation on neural activity in a swine model of DBS [82]. In this study, modulation of activity in the sensorimotor cortex, basal ganglia, and cerebellum was observed as a function of the stimulus voltage applied to the ventrolateral (VL) thalamus. Specifically, Paek and colleagues showed that high frequency stimulation produced a negative BOLD response in the motor cortex, while low frequency stimulation produced a positive BOLD response. Additionally, they showed that by increasing the amplitude of the applied voltage, both the change in BOLD signal as well as the size of the affected brain region increased, correlating with an increase of neural activity (Fig. 2). This suggests that differences in BOLD response can be used to analyze brain responses to electrical stimulation and characterize these responses as a function of stimulation parameters.

In addition to characterization of the neural response to DBS, functional imaging may be also effectively utilized to facilitate identification of optimal DBS targets [87]. In this context, fMRI and positron emission tomography (PET) have already demonstrated clinical utility in the treatment of treatment-resistant depression. For

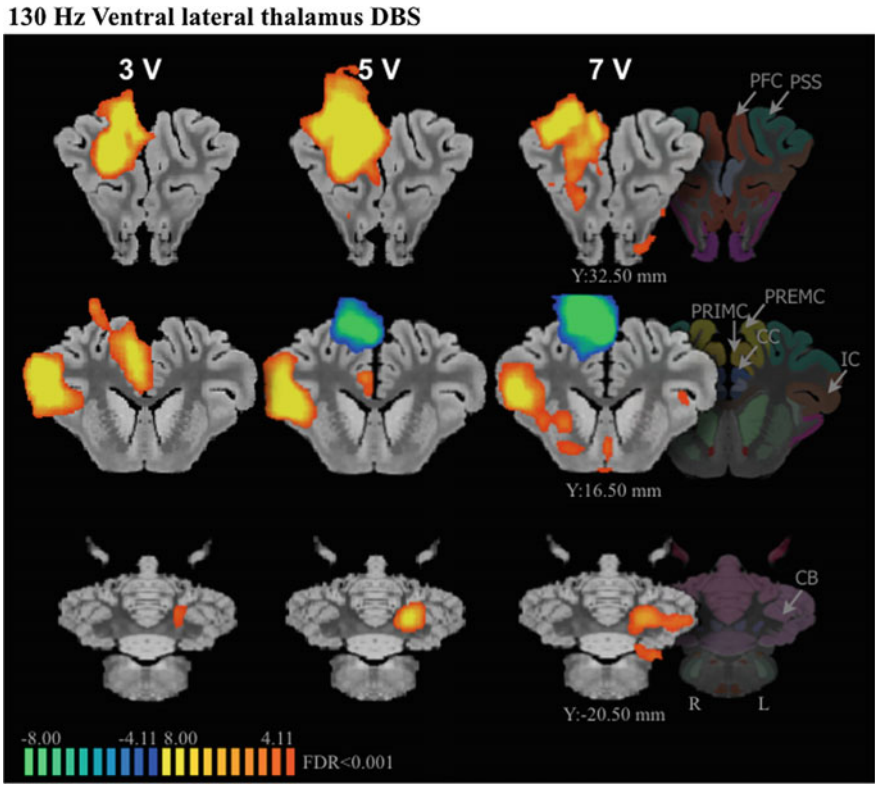

Fig. 2 Ventral lateral thalamus stimulation with different voltage intensities (3, 5, and 7 V). All voltages evoked increased BOLD signals in the ipsilateral prefrontal, primary somatosensory, insular cortices, and contralateral cerebellum. Also all voltages evoked decreased BOLD signal in the ipsilateral primary motor and premotor cortices. Abbreviations: BOLD, blood-oxygen-level dependent; CB, cerebellum; CC, cingulate cortex; DBS, deep brain stimulation; FDR, false discovery rate; IC, insular cortex; PFC, prefrontal cortex; PRIMC, primary motor cortex; PREMC, premotor cortex; V, voltage. Modified from [82]

example, an overactive subgenual cingulate cortex (Brodmann area 25) observed with PET has been shown in patients with acute sadness [71]. This overactivity has subsequently decreased in clinical responders following antidepressant treatments [25, 70, 71]. In 2005, Mayberg and colleagues used PET to show that chronic stimulation of the cingulate cortex in patients with treatment-resistant depression normalized metabolic hyperactivity and produced clinical benefits [72]. In that study, remission was accomplished in four out of six patients, with decreases in cerebral blood flow to subgenual cingulate, orbital frontal cortex, hypothalamus, anterior insula, and medial frontal cortex. At the same time, their results showed increases in cerebral blood flow within the dorsolateral prefrontal, dorsal anterior, posterior cingulate, premotor, and parietal regions.

3 Novel Stimulation Paradigms

While DBS has been used effectively to treat multiple disorders such as essential tremor and Parkinson disease, DBS technology must be further developed in order to improve patient care. For example, the existing DBS paradigm requires patients to return to the clinic for periodic adjustment of their stimulation parameters as their disease progresses [23, 35, 72]. Switching the existing DBS paradigm from an open-loop strategy where stimulation parameters are fixed, to an adaptive paradigm that relies on biological feedback to adjust stimulation parameters will be crucial for developing the next generation of DBS systems. Thus, closed-loop DBS systems equipped with electrophysiological, biochemical, and inertial sensors that monitor the molecular, cellular, and behavioral responses to DBS may allow for automated titration of stimulation parameters for sustained therapeutic benefits in the face of a changing environment. Developing a greater understanding of the cellular and molecular mechanisms of DBS by leveraging functional imaging in conjunction with neurochemical and electrophysiological techniques may also assist in optimizing DBS targets and stimulation parameters for specific disorders and individual patients [35]. Ultimately, adaptive, closed-loop DBS systems will extend battery life, reduce required hospital visits and associated healthcare costs [30].

Several key factors need to be investigated before automated adjustment of stimulation parameters can be clinically implemented. First, the complex relationships between clinical behavior and neural activity need to be elucidated. The advancement of electrochemical, electrophysiological, and functional imaging techniques from preclinical to clinical settings will be essential for the development of next-generation smart DBS systems. For example, optimal locations for recording of neural activity should be identified for specific disorders and specific patients. Furthermore, neurotransmitters critical for pathological activity and therapeutic response will need to be identified (Fitzgerald 2014). Additionally, specific neurotransmitter concentrations and their role in therapeutic efficacy will need to be elucidated. Second, the type of sensors that will be used to monitor the environment in order to effectively adjust stimulation parameters must be identified. The material of these sensors must be MRI safe and biocompatible for chronic implantation. For example, efforts are underway to develop electrochemical-sensing techniques capable of extending electrode longevity by renewing the electrochemically active surface following adsorption of chemical species [102]. This is paramount, as the carbon fiber microelectrodes typically used for FSCV are subject to electrode fouling due to the charge imbalance of the waveforms required for FSCV and are thus not suitable for chronic measurements [11]. Recent efforts to overcome this limitation have been focused on the use of boron-doped diamond microelectrodes that can be used over longer periods of time [15, 17, 39, 68, 83, 85, 93, 97, 99, 114, 116, 118]. Third, correlation of multimodal electrophysiological and neurochemical activity may provide new insight into the cellular and molecular mechanisms of therapeutic neuromodulation. Therefore, efforts should be directed toward

developing smart DBS controllers that rely on the relationships between neural activity and the clinical effects of DBS to replace the trial-and-error process currently used for clinical DBS programming [35, 91, 100]. The versatility and adaptability of such controllers will allow optimization of DBS therapies to individual patients and symptoms. In turn, this will likely improve clinical outcomes, reduce the time and frequency of patient visits, and decrease overall health care costs.

4 Conclusion

Despite its clinical efficacy, limitations in existing DBS technology make optimization of therapeutic benefits a difficult and expensive endeavor. However, combination of multimodal electrophysiological and neurochemical sensing with functional imaging techniques may provide new insight into the cellular and molecular mechanisms of therapeutic DBS. By focusing on these techniques that further the efforts in understanding the underlying therapeutic mechanisms of DBS, we may be able to tailor application of DBS to individual patients and symptoms. Furthermore, the development of closed-loop DBS strategies will likely lead to the improvement of therapeutic outcomes.

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