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Basal Ganglia, Movement Disorders and Deep Brain Stimulation: Advances Made Through Non-Human Primate Research

Thomas Wichmann[1,2], **Hagai Bergman**[3,4], and **Mahlon R. DeLong**[1]

[1]Dept. of Neurology, Emory University, Atlanta, GA

[2]Yerkes National Primate Research Center at Emory University, Atlanta, GA

[3]Department of Medical Neurobiology (Physiology), Institute of Medical Research – Israel-Canada (IMRIC), and The Edmond and Lily Safra Center for Brain Research (ELSC), The Hebrew University, Jerusalem, Israel

[4]Department of Neurosurgery, Hadassah Medical Center, Jerusalem, Israel

Abstract

Studies in non-human primates (NHP) have led to major advances in our understanding of the function of the basal ganglia and of the pathophysiologic mechanisms of hypokinetic movement disorders such as Parkinson's disease and hyperkinetic disorders such as chorea and dystonia. Since the brains of NHPs are anatomically very close to those of humans, disease states and the effects of medical and surgical approaches, such as deep brain stimulation (DBS), can be more faithfully modeled in NHPs than in other species. According to the current model of the basal ganglia circuitry, which was strongly influenced by studies in NHPs, the basal ganglia are viewed as components of segregated networks that emanate from specific cortical areas, traverse the basal ganglia, and ventral thalamus, and return to the frontal cortex. Based on the presumed functional domains of the different cortical areas involved, these networks are designated as 'motor', 'oculomotor', 'associative' and 'limbic' circuits. The functions of these networks are strongly modulated by the release of dopamine in the striatum. Striatal dopamine release alters the activity of striatal projection neurons which, in turn, influences the (inhibitory) basal ganglia output. In parkinsonism, the loss of striatal dopamine results in the emergence of oscillatory burst patterns of firing of basal ganglia output neurons, increased synchrony of the discharge of neighboring basal ganglia neurons, and an overall increase in basal ganglia output. The relevance of these findings is supported by the demonstration, in NHP models of parkinsonism, of the antiparkinsonian effects of inactivation of the motor circuit at the level of the subthalamic nucleus, one of the major components of the basal ganglia. This finding also contributed strongly to the revival of the use of surgical interventions to treat patients with Parkinson's disease. While ablative procedures were first used first for this purpose, they have now been largely replaced by DBS of the subthalamic nucleus or internal pallidal segment. These procedures are not only effective in the treatment of parkinsonism, but also in the treatment of hyperkinetic conditions (such as chorea or dystonia) which result from pathophysiologic changes different from those underlying Parkinson's disease. Thus, these interventions probably do not counteract specific aspects of the pathophysiology of movement disorders, but non-specifically remove the influence of the different types of disruptive basal ganglia output from the relatively intact portions of the motor circuitry downstream from the basal ganglia. Knowledge gained from studies in NHPs remains critical for our understanding of

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the pathophysiology of movement disorders, of the effects of DBS on brain network activity, and the development of better treatments for patients with movement disorders and other neurologic or psychiatric conditions.

Introduction

Deep brain stimulation (DBS) of specific brain targets and neural networks, introduced over 3 decades ago, is now widely used as a treatment for a growing number of neurologic and psychiatric disorders. The development and clinical use of DBS for the treatment of Parkinson's disease (PD) and other movement disorders is one of the major success stories in Neurology and Neurosurgery. Non-human primate (NHP) research has been instrumental for the resurgence of ablative brain surgery and the development of DBS for movement and other neuropsychiatric disorders. The major contribution of studies in NHPs in this field is the development of circuit models of movement disorders (specifically, PD) and the demonstration that surgical interventions targeting specific nodes of the basal ganglia networks are highly effective in treating the motor signs and symptoms of these disorders. NHP research has also proven to be highly relevant for exploring the mechanisms of action of DBS, for the identification of new brain targets, and for the development and testing of novel DBS treatment strategies. In the following, we review the role and importance of NHP research in the development of circuit models of basal ganglia function and dysfunction and the recognition of the key involvement of the subthalamic nucleus (STN) in the pathophysiology of both hyper- and hypokinetic disorders, which led to the identification of this nucleus as a major target for neurosurgical interventions, specifically for the treatment of PD.

Development of models of the functional anatomy of basal ganglia circuits

Views of the network organization and functions of the basal ganglia went through a rapid transformation in the 1980s and 1990s. These subcortical nuclei were long viewed as playing a major role in action selection by acting upon and "funneling" influences from diverse portions of the cerebral cortex to motor cortical areas (Kemp and Powell 1971). Early studies in behaving primates demonstrated, however, a segregation of motor and non-motor areas throughout the basal ganglia and a maintained somatotopic organization and specificity to somatosensory inputs and limb movements from input to output nuclei of the basal ganglia (e.g., DeLong 1971; DeLong 1972; DeLong et al. 1983; Delong et al. 1984). These findings and the available anatomical studies showing strong topographic relations throughout the basal ganglia, resulted in the development of the now established 'segregated circuit' model of the basal ganglia (Alexander et al. 1990; Alexander et al. 1986; DeLong et al. 1986; Delong et al. 1984). This model posits that the basal ganglia interact with the cerebral cortex and thalamus via segregated circuits which are focused on the different functional domains in the frontal lobe from which they originate, and are thus designated as 'motor', 'oculomotor', 'associative' and 'limbic' circuits. Available evidence suggests that these circuits are at least partially closed. Each of the larger circuits is similarly comprised of multiple subcircuits (Hoover and Strick 1993; Strick et al. 1995; Turner et al. 2003; Turner et al. 1998). Details as to the degree of segregation of the larger circuits and their sub-elements remain debated, however (Haber et al. 2000; Joel and Weiner 1994).

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The concept of a discrete motor circuitry that is anatomically separate from other cortico-basal ganglia-thalamo-cortical circuits strongly supports the use of focal surgical interventions such as ablation and DBS to treat the signs and symptoms of movement disorders. Such focal surgical interventions provide motoric benefits by removing abnormal movements with (relatively) few motor and non-motor side effects. A similar argument can, of course, also be made with regard to the use of DBS targeting of non-motor circuits to treat psychiatric disorders such as obsessive compulsive disorder or depression.

Description of indirect and direct pathways

Tract-tracing studies in animals demonstrated that the striatum, the major target of cortical basal ganglia projections, is linked to the basal ganglia output structures, the internal pallidal segment (GPi) and the substantia nigra pars reticulata (SNr), via two pathways that emanate from different striatal projection neuron classes (Albin et al. 1989; Alexander and Crutcher 1990; DeLong 1990). The ‘direct’ pathway is a monosynaptic connection between dopamine D1-receptor expressing medium spiny neurons and GPi/SNr target neurons. The ‘indirect’ pathway originates from D2-receptor expressing neurons, and engages the external pallidal segment (GPe) and the STN before reaching the GPi/SNr (Albin et al. 1989; Alexander and Crutcher 1990; DeLong 1990; Gerfen et al. 1990). In terms of the polarity of this connection (and the function of the entire circuitry), it was crucial that studies in rats (Chang et al. 1984; Hammond et al. 1978; Kita and Kitai 1987; Kitai and Kita 1987), and NHPs (Smith and Parent 1988) found that the STN was glutamatergic, in contrast to all other inter-nuclear intrinsic connections of the basal ganglia which are GABAergic.

Activity along the direct and indirect pathways is influenced differentially by dopamine, released in the striatum from terminals of the nigrostriatal projection. Dopamine acting at D1 receptors increases transmission at corticostriatal synapses onto striatal neurons of the direct pathway, while actions on D2 receptors reduces transmission at corticostriatal synapses onto striatal neurons of the indirect pathway. Given the polarity of connections within the basal ganglia, release of dopamine in the striatum leads to inhibition/reduced facilitation in the GPi/SNr. Because basal ganglia output to the thalamus and brainstem is GABAergic and inhibitory (Chevalier and Deniau 1990), reduced basal ganglia output was thought to lead to increased thalamic and cortical activity under these circumstances, leading to overall increased movement. Conversely, reduced dopamine release in the striatum (as seen in parkinsonism) would lead to an increase of GPi/SNr activity and inhibition of thalamocortical transmission (Albin et al. 1989; Alexander and Crutcher 1990; Chevalier and Deniau 1990), and an overall reduction of movement. The description of these two striatal output pathways was an important step towards our understanding of the pathophysiology of hypo- and hyperkinetic movement disorders.

Discovery that lesions of the subthalamic nucleus (STN) lead to hyperkinetic movement disorders

An important early finding regarding our understanding of the pathophysiology of hyperkinetic movement disorders, was the discovery, first in humans (e.g., see review by (Moersch and Kernohan 1939)) and then in NHPs (Carpenter et al. 1950; Whittier and Mettler 1949), that hemiballism, a rare, but dramatic, movement disorder, can result from

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lesions confined to the STN. In the NHP, discrete electrolytic lesioning of the STN were shown to result in contralateral chorea if at least 20% of the STN was destroyed, while surrounding brain areas (such as the fields of Forel and the zona incerta) were left intact (Carpenter et al. 1950; Whittier and Mettler 1949). In partial contrast to previous studies in humans with discrete strokes within the STN (Juba and Rakonitz 1937; Martin 1927; von Santha 1932), the extent or location of the electrolytic STN lesions in NHPs in these early studies was not correlated with the overall severity or duration of chorea (Carpenter et al. 1950). Subsequent studies, in the 1980s and 1990s demonstrated that transient or permanent fiber-sparing inactivation of the STN in primates has the same effect as permanent lesioning (Baron et al. 2002; Crossman et al. 1984; Hamada and DeLong 1992b), thus showing that inactivation of neurons in this nucleus is sufficient for hemiballism to occur. The finding of reduced discharge rates of GPi neurons, following STN lesioning (Hamada and DeLong 1992a), further supported the view that involuntary movements are associated with decreased inhibitory output from GPi to the thalamus. Previous electrophysiologic studies had demonstrated a detailed somatotopy of the primate STN (DeLong et al. 1985), as had already been suggested earlier for the human STN (see above) (Mettler and Stern 1962), based on studies correlating the clinical characteristics of hemiballism with the location of small strokes or other lesions within the STN.

The use of NHPs has been critical for elucidating the functional organization of the STN and its role in hemiballism because NHPs and humans share a high degree of topographic specificity of anatomical connections between the STN and other basal ganglia nuclei and the cerebral cortex (see, e.g., (Hartmann-von Monakow et al. 1978; Haynes and Haber 2013; Lambert et al. 2012; Nambu et al. 1996)). The demonstration that dysfunction of discrete regions of the STN may be responsible for involuntary limb movements has, in fact, no direct equivalent in lower species. Surprisingly, in rodents, inactivation of the STN produces either no effect (Carvalho and Nikkhah 2001; Gradinaru et al. 2009; Phillips et al. 1998; Yoon et al. 2014), or behavioral abnormalities (Baunez and Robbins 1999; Phillips and Brown 2000; Scheel-Kruger and Magelund 1981; Scheel-Kruger et al. 1981a; Scheel-Kruger et al. 1981b).

Together with the concept of the existence of direct and indirect pathways, the finding that decreased activity in the motor portions of the STN is responsible for the development of hemiballism was one of the foundations for the subsequent development of unifying models of basal ganglia dysfunction in movement disorders. These models, in turn, helped to develop current targeting strategies for DBS and continue to inform models of DBS effects (see below).

Studies of the pathophysiology of parkinsonism

Studies in parkinsonian NHPs in the 1980s and 1990s contributed to the development of DBS, by providing important insights into the motor circuit abnormalities that underlie parkinsonism. These studies were done in monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin that had previously been shown to produce parkinsonism in humans, clinically indistinguishable from that seen in idiopathic Parkinson’s disease (Davis et al. 1979; Langston et al. 1983; Langston and Ballard 1983).

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The MPTP-treated NHP remains the phenotypically most faithful animal model of parkinsonism (Burns et al. 1983; Langston et al. 1984). MPTP-treated NHPs exhibit a highly selective loss of neurons in the substantia nigra pars compacta, leading to dopamine depletion in the striatum. It is now known that the MPTP-treated NHP is not only a model of the dopamine depletion in PD, but that it also manifests many of the other anatomic/pathologic features found in the brains of parkinsonian patients. These include loss of catecholaminergic brain stem neurons, loss of neurons in the centromedian and parafascicular nucleus of the thalamus, and plasticity of glutamatergic synapses in striatum, cortex and STN (Alexander et al. 1992; Elsworth et al. 1990; Masilamoni et al. 2011; Mathai et al. 2015; Pifl et al. 1990; Pifl et al. 2013; Pifl et al. 1991; Pifl et al. 1992; Smith et al. 2009; Villalba et al. 2015; Zeng et al. 2010).

Together with studies in rodent models of dopamine depletion (Albin et al. 1989), studies of metabolic (Crossman et al. 1985) and electrophysiologic abnormalities in the MPTP NHP model (Filion et al. 1988; Miller and DeLong 1987) contributed to the development of a circuit model of the pathophysiology of parkinsonism (Albin et al. 1989) whereby dopamine loss in the striatum leads to reduced activation of D1- and D2-receptors in the striatum, and subsequent reduction of activity along the direct (D1) pathway, and increase of activity along the indirect (D2) pathway, leading to an overall increase of activity in GPi, which, in turn, leads to a decrease and slowing of movement (akinesia and bradykinesia, respectively).

The model is consistent with the results of studies in MPTP-treated NHPs which demonstrated a decrease in the average discharge rate of GPe neurons and an increase in the discharge rate of GPi neurons (Filion and Tremblay 1991; Miller and DeLong 1987) as well as in the discharge rate of STN neurons (Bergman et al. 1994; Miller and DeLong 1987). Studies in parkinsonian patients suggested regional differences in the firing rate changes, demonstrating higher firing rates in the ventral (motor) GPi than in the dorsal GPi (Hutchison et al. 1994). Further supporting the ‘rate model’ of PD, *decreases* of GPi discharge rates in response to dopamine replacement therapy were reported in human patients (Hutchinson et al. 1997; Lee et al. 2007; Levy et al. 2001; Merello et al. 1999) and NHPs (Filion and Tremblay 1991; Heimer et al. 2006; Papa et al. 1999). Recent optogenetic studies in rodents also support the basic finding that activation of direct pathway neurons leads to increased movement, while activation of indirect pathway neurons reduces movement (Kravitz et al. 2010a; Kravitz et al. 2010b).

However, clinical and other observations indicate that the “rate” model of movement disorders is too simplistic. For example, the model would predict that pallidal lesions would produce chorea, while thalamic lesions would produce parkinsonism. Neither of these predictions is true, suggesting that abnormalities of discharge other than rate changes are pathophysiologically relevant. Current models of the pathophysiology of parkinsonism emphasize changes in firing patterns (e.g., the emergence or abnormal coupling of oscillations, burst patterns, and abnormal neuronal synchronization). Many of these revisions were also the results of discoveries in NHPs (e.g., (Bergman et al. 1994; Leblois et al. 2007; Nini et al. 1995; Raz et al. 2000; Wichmann and Soares 2006)). Of these, low frequency oscillations in single cell and network activities have been most intensely studied (starting with the seminal paper by Brown et al. 2001). As described below, the first attempts to

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utilize electrophysiologic signals for online adjustments of DBS in parkinsonian individuals have utilized the power of these low frequency signals (Little et al. 2013; Rosin et al. 2011).

Effects of STN lesions in parkinsonian NHPs

Another pre-DBS era discovery in NHPs that contributed greatly to the introduction of DBS therapy into the clinic as a treatment for PD was the observation that STN lesions have powerful antiparkinsonian effects. The motivation for the experimental use of STN lesions came from the ‘rate model’ of PD (see above). Based on this model, reduction (normalization) of the pathologically increased activity along the indirect pathway in the parkinsonian state would be expected to lead to an amelioration of parkinsonism, in particular akinesia/bradykinesia. It was clear that the most effective target for testing the model would be to lesion the motor portion of the STN. Reducing STN activity in the parkinsonian state should reduce the excessive glutamatergic drive from STN onto the basal ganglia output nuclei, GPi and SNr. This would, in turn, reduce the excessive pallidal inhibition of basal ganglia-receiving portions of the ventral thalamus.

This idea was first examined in parkinsonian NHPs (Aziz et al. 1992; Aziz et al. 1991; Bergman et al. 1990; Guridi et al. 1996; Wichmann et al. 1994). The experiments showed that transient inactivation or permanent lesioning of the STN had almost immediate and strong antiparkinsonian effects with substantial reduction of akinesia/bradykinesia, tremor and rigidity. The appearance of mild transient hemi-chorea was also observed, as expected. Confirming the earlier NHP studies, later studies of the effects of radiofrequency lesioning of the motor area of the STN in PD patients demonstrated substantial sustained antiparkinsonian benefits as well as, generally transient, hemi-chorea. (Alvarez et al. 2001; Alvarez et al. 2005; Gill and Heywood 1998; Patel et al. 2003)

The beneficial effects of ablation are now considered to reflect not only rate changes, as initially assumed, but also a reduction in abnormal firing patterns and neuronal synchronization throughout downstream networks (Galvan and Wichmann 2008). The practical importance of the STN inactivation studies was that they provided a clear rationale for the surgical treatment of parkinsonism and other movement disorders (such as dystonia), and identified the motor circuit portion of the STN as a novel and effective target for treatment of patients with PD.

Role of NHPs for the development of DBS

Modern era of functional surgery and the development of DBS

In the absence of effective pharmacologic treatments, empirically developed ablative neurosurgical procedures such as pallidotomy and thalamotomy were frequently used in the 1950s and ‘60s for treatment of parkinsonism (Laitinen et al. 1992b; Svennilson et al. 1960). The use of these procedures eventually diminished, mostly because of the introduction of levodopa for PD. Shortly thereafter, however, physicians realized that not all symptoms and signs of PD respond to levodopa therapy (e.g. tremor often responds relatively poorly to this medication), and that long-term levodopa treatment in patients with PD can be complicated by significant adverse effects, such as motor fluctuations or the emergence of involuntary

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movements. As discussed above, studies in NHPs resulted in new insights into the pathophysiology of parkinsonism and the effects of basal ganglia lesioning in the late 1980s, generating renewed interest in, and a strong rationale for, focal surgical procedures targeting the motor circuit of the basal ganglia to treat the motor signs and symptoms of PD. While encouraged by the (then recently described) antiparkinsonian effects of STN lesioning in NHPs (see above), surgeons did not initially move to the STN as a target for surgical interventions, because of deep- seated concerns that STN lesioning might lead to the development of intractable hemiballism or chorea in patients. Instead, many initially returned to posterolateral pallidotomy (Laitinen et al. 1992a), which was found to be effective for parkinsonism, as well as levodopa-induced motor fluctuations and dyskinesias.

The resurgence of pallidotomy was short-lived, however, because implantable stimulation devices had become available which made chronic brain stimulation, subsequently referred to as ‘DBS’, possible. The French neurosurgeon, Alim Benabid, found, serendipitously, while performing a thalamotomy for tremor, that high-frequency DBS of the ventral intermedius nucleus (Vim) of the thalamus was a highly effective treatment for intractable tremor (Benabid et al. 1991; Benabid et al. 1987). The initial belief that DBS acted like a lesion, together with the fact that it is reversible and less invasive than lesioning, subsequently encouraged efforts to use DBS at the newly discovered STN target for the treatment of PD. This was explored in parkinsonian NHPs (Benazzouz et al. 1996; Benazzouz et al. 1993; Gao et al. 1999) and shortly thereafter in patients with PD (Pollak et al. 1993).

DBS of the STN was found to be highly effective in treating parkinsonism, and making it possible to reduce the requirements for levodopa replacement. STN DBS was also found to be effective for drug-induced motor fluctuations and dyskinesias, similarly to patients undergoing pallidotomy. DBS of the GPi, at the traditional pallidotomy site, was found to be similarly effective, although GPi-DBS treated patients are usually not able to reduce their dopaminergic medications (Bronstein et al. 2010; Siegfried and Lippitz 1994a; Siegfried and Lippitz 1994b; Vitek 2002; Weaver et al. 2012). STN- and GPi-DBS are now FDA-approved therapies for advanced cases of PD (and dystonia), and have been used in more than 100,000 patients worldwide.

The current DBS strategies do not treat all motor signs and symptoms of PD equally well. While akinesia/bradykinesia, rigidity and tremor respond favorably to STN- or GPi-DBS, problems with freezing of gait, postural instability and speech are poorly responsive to current DBS strategies (Aldridge et al. 2016; Schlenstedt et al. 2017). In the search for more effective DBS treatment strategies for these axial problems, DBS has been explored in other brain targets, e.g., the pedunculopontine nucleus, PPN (Golestanirad et al. 2016; Hamani et al. 2016a; Hamani et al. 2016b; Yousif et al. 2016) and at the STN-SNr border (Weiss et al. 2011; Weiss et al. 2013). Studies of the effects of DBS and pharmacologic interventions at the level of the PPN have, indeed, demonstrated antiparkinsonian effects in patients as well as NHP models of PD (Gomez-Gallego et al. 2007; Grabli et al. 2013; Jenkinson et al. 2004; Jenkinson et al. 2006; Kojima et al. 1997; Nandi et al. 2008; Zhang et al. 2012), rendering NHPs a good model for future exploration of the effects of PPN DBS in parkinsonism.

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Role of NHPs in elucidating the mechanisms of action of DBS

In this section we cannot comprehensively review the voluminous literature on DBS effects, but will provide information on studies of this topic in primates. As mentioned, the fact that lesioning and DBS produce similar clinical effects suggested initially that DBS may act to inhibit the circuitry it is applied to, perhaps by producing depolarization block or by "jamming" transmission (Benabid et al. 2001). However, experiments in NHPs did not confirm this. These studies were the first to show that stimulation of the STN does not simply mimic lesion effects, but strongly alters firing patterns in GPi neurons, with prominent temporal entrainment of the discharge of pallidal neurons to the stimuli applied to the GPi (Bar-Gad et al. 2004; Hashimoto et al. 2003). Subsequent modeling of these results *in silico* showed that the observed DBS effects may be explainable by the combined actions of the stimulation on cell bodies and fiber tracts, both afferent and efferent (McIntyre et al. 2004). Given the stimulation parameters used for DBS, most of the relevant effects of DBS are now considered to be mediated by activation of fibers rather than cell bodies (Brocker and Grill 2013).

DBS in the basal ganglia has numerous electrophysiologic effects on the basal ganglia and related brain structures. Many of the observed phenomena are probably epiphenomenal, and it has been a challenge to firmly link excitation of one or more of the presumably involved fiber tracts to the symptom relief afforded by DBS therapy. For instance, it remains debated whether the complex excitatory effects of STN-DBS on GPi activity (e.g., Hahn et al. 2008; Hashimoto et al. 2003), the reductions of STN firing rates, oscillations and the level of synchronization seen after STN-DBS in NHPs (Meissner et al. 2005), or the inhibitory effects of GPi-DBS on STN activity that were described in recordings in human dystonia patients (Liu et al. 2012), selectively counteract the pathophysiologic abnormalities in diseases like PD (see above) or dystonia, while allowing relevant information to be processed. Alternatively, some or all of these may simply block the transfer of all information, normal or pathologic (Agnesi et al. 2013; Chiken and Nambu 2013; Dorval et al. 2008; Grill et al. 2004). Ortho- or antidromic DBS effects on passing fiber systems are also to be considered. Thus, STN stimulation likely affects nearby pallidothalamic fibers in the zona incerta and antidromically activates corticofugal fibers (Devergnas and Wichmann 2011; Gradinaru et al. 2009; Li et al. 2007). Recent studies in animals, including NHPs, have shown that orthodromically mediated effects of DBS in STN or GPi also alters firing rates and patterns in the associated thalamocortical circuitry (Anderson et al. 2003; Guo et al. 2008; Kammermeier et al. 2016; Muralidharan et al. 2017), and may act to normalize intracortical inhibition (Cunic et al. 2002; Tisch et al. 2007).

Future use of NHPs in DBS development

The role of NHPs in the development of new stimulation paradigms

Current DBS protocols utilize continuous high-frequency stimulation for the treatment of movement disorders such as PD or dystonia. The stimulation parameters often require adjustments ('programming') by physicians to maintain the beneficial effects, especially for tremor. While effective in most patients, this mode of stimulation for PD comes with the potential for substantial expenditure of battery life of the implanted pulse generator device,

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and creates a significant need for programming services by medical professionals which may not always be available. In theory, it may only be necessary to stimulate when tremor or parkinsonism is manifest, thus saving battery life and reducing or obviating the need for physician-directed programming (an important considerations in many medically underserved areas of the world). Such closed-loop stimulation may be most easily attainable with disturbances that rapidly respond to stimulation (such as tremor), while the development of self-adjusting stimulation will be more difficult for treatment of disorders that slowly respond to DBS, such as dystonia.

A principal problem for the closed-loop control of stimulation is the fact that reliable control signals are needed. Research in NHPs has strongly contributed to the discovery of potential control signals for the use of DBS in PD patients. The most promising signals for parkinsonism remain the prominent beta-band oscillatory activity which was found to be present in the neuronal discharge in the STN of parkinsonian animals (Bergman et al. 1994). Similar oscillations have also been identified in many other parts of the basal ganglia-thalamocortical circuitry (Galvan and Wichmann 2008), even leading to the idea of parkinsonism as an ‘oscillopathy’ (Nimmrich et al. 2015). They have also been detected in patients and, because they are part of synchronized oscillatory network activity patterns, can be monitored as oscillations in local field potential recordings (Brown et al. 2001; Gatev et al. 2006; Hammond et al. 2007)

In encouraging studies in parkinsonian NHPs it was shown that ‘closed-loop’ GPi DBS, controlled by the presence of oscillatory firing patterns of neurons in the primary motor cortex, is equally as effective to continuous DBS (Rosin et al. 2011). This study provided proof-of-concept information for the idea that dysfunctional basal ganglia motor networks can indeed be controlled via a closed-loop mechanism. A successful first attempt at the development of a system allowing closed-loop controlled DBS in parkinsonian patients demonstrated that STN-DBS for parkinsonism can be controlled by local field potential signals recorded from the implanted DBS electrode in the STN (Little et al. 2013; Little et al. 2014; Little et al. 2016; Tinkhauser et al. 2017). Similar effects have also been studied in monkeys (Johnson et al. 2016).

The recent development of ‘sensing stimulators,’, i.e., stimulators with built-in amplifiers, digitizers, and a digital processing unit, could simplify the task of using electrical brain signals to control DBS parameters of stimulation (Connolly et al. 2015; Houston et al. 2015). The present iteration of sensing stimulators remains fairly simple; in the future, machine learning algorithms could be incorporated into these systems to enable multiple-level sensing and processing that may integrate assessments of electrical brain signals, quantitative assessment of clinical symptoms (such as accelerometry measurements of the intensity of tremor, see, e.g. (Malekmohammadi et al. 2016)), and may even allow input of the patient’s (and care giver’s) assessment of the quality of life.

It would be difficult to depend exclusively on human experimentation in the development of such higher level stimulation paradigms. It is also difficult to see how new stimulation techniques such as coordinated reset stimulation (Adamchic et al. 2014; Popovych and Tass 2012; Tass et al. 2012; Wang et al. 2016) or on-demand stimulation could be meaningfully

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developed without the use of pathologically and phenotypically convincing animal models, such as the MPTP-treated NHP model of parkinsonism (Tass et al. 2012; Wang et al. 2016).

Surgical development, programming

The surgical approaches and indications for DBS are also under revision, with the exploration of new DBS targets, and simplification of the intraoperative procedures through the increased use of intraoperative imaging and automated recording devices to assist neurosurgeons with lead placement. While some of these new developments are best done directly in human patients (such as the use of new device programming techniques, or the development of new imaging protocols), others will continue to benefit from the use of NHPs.

The search for new targets for DBS is best guided by a clearer understanding of the brain networks that are influenced by DBS, and the mechanisms of action of DBS. In a more general sense, it will be important to have more complete knowledge of the pathophysiology of movement disorders and other disease that are amenable to DBS therapy. Considerable further animal research is needed to optimize and expedite the identification of new stimulation targets and new stimulation paradigms. While research in non-primate species can help in this regard, the striking differences in the anatomic complexity of the rodent and NHP brains limits the interpretation of the results from the non-primate species, so that NHPs will remain critical for future research into the pathophysiologic concepts and the effects of DBS on brain networks in humans.

Another area of development is the creation of multi-contact electrodes that permit some degree of current steering, i.e., the shaping of the electrical stimulation field, thereby reducing side effects of the stimulation (Keane et al. 2012; Pollo et al. 2014). The first such devices have come to market, and are currently being tested in patients. Future multi-contact electrodes may enable yet more fine-grain recording of neuronal activity. Finding optimal stimulus configurations and potentially adjusting them on the fly will require considerable additional experimentation, both in terms of the engineering hardware, and the biological evaluation of stimulation effects. NHP models of movement disorders remain the model of choice for the required biological experiments.

Conclusions

While the development of DBS for the treatment of movement disorders such as the use of Vim DBS for the treatment of tremor was empiric, a better understanding of the pathophysiology of movement disorders and, most importantly, the identification of the STN as a novel target for lesioning in the NHP model of PD, contributed substantially to the revival of surgical approaches to treating PD, first with pallidotomy and then with the introduction of STN DBS. NHP research has also helped to elucidate some of the mechanisms that underlie DBS effects. Studies in NHPs continue to be important for the identification of new brain targets for DBS, and for tests of the effects of new stimulation paradigms. In this field of research, the use of NHPs has a fundamental advantage over the use of non-primate species, i.e., the fact that anatomic and behavioral complexities of the human brain are more faithfully represented in NHPs than in any other species. These

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features, including, among others, the highly complex organization of the primate neocortex, the segregation and specialization of networks involving cortex, basal ganglia and thalamus, and important details of the cellular and biochemical composition of nodes of the basal ganglia-thalamocortical circuitry, are discussed in detail in other articles in this issue (XXX).

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