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REVIEW

Deep Brain Stimulation for Movement Disorders of Basal Ganglia Origin: Restoring Function or Functionality?

Thomas Wichmann[1,2] · **Mahlon R. DeLong**[1]

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Abstract Deep brain stimulation (DBS) is highly effective for both hypo- and hyperkinetic movement disorders of basal ganglia origin. The clinical use of DBS is, in part, empiric, based on the experience with prior surgical ablative therapies for these disorders, and, in part, driven by scientific discoveries made decades ago. In this review, we consider anatomical and functional concepts of the basal ganglia relevant to our understanding of DBS mechanisms, as well as our current understanding of the pathophysiology of two of the most commonly DBS-treated conditions, Parkinson's disease and dystonia. Finally, we discuss the proposed mechanism(s) of action of DBS in restoring function in patients with movement disorders. The signs and symptoms of the various disorders appear to result from signature disordered activity in the basal ganglia output, which disrupts the activity in thalamocortical and brainstem networks. The available evidence suggests that the effects of DBS are strongly dependent on targeting sensorimotor portions of specific nodes of the basal ganglia-thalamocortical motor circuit, that is, the subthalamic nucleus and the internal segment of the globus pallidus. There is little evidence to suggest that DBS in patients with movement disorders restores normal basal ganglia functions (e.g., their role in movement or reinforcement learning). Instead, it appears that high-frequency DBS replaces the abnormal basal ganglia output with a more tolerable pattern, which helps to restore the functionality of downstream networks.

Keywords Parkinson's disease · Dystonia · Deep brain stimulation · Oscillation · Synchrony · Pathophysiology · Basal ganglia circuits

Introduction

Neurosurgeons first targeted the basal ganglia for movement disorders in the 1930s, using ablative procedures, with emerging evidence that pathology in the basal ganglia was associated with movement abnormalities and a growing understanding of the anatomy of the basal ganglia and subcortical structures [1]. By the 1950s and 1960s, lesioning of the globus pallidus (pallidotomy) and the thalamus (thalamotomy) were widely performed for treating Parkinson's disease (PD), dystonia, and various forms of tremor. The successful introduction of levodopa for PD in the mid-1960s, however, spelled the nearly complete demise of functional stereotaxic surgery, other than thalamotomy for medically intractable tremor.

The revival in the early 1990s of pallidotomy as a treatment for PD resulted, in part, from the need for a more effective treatment for the unforeseen, and often disabling, levodopa-induced motor complications (severe motor fluctuations and dyskinesias). Other factors were the growing understanding of the pathophysiology of basal ganglia disorders, including the development of circuit models of basal ganglia function and circuit dysfunction in movement disorders and studies in the newly introduced 1-methyl-1,2,3,6-phenyl-tetrahydropyridine (MPTP) primate model of parkinsonism [2]. Collectively, these advances provided a clear rationale and impetus for the revival of ablative procedures. The report by Laitinen et al. [3] in the early 1990s, of significant benefits of pallidotomy for

✉ Thomas Wichmann
twichma@emory.edu

[1] Department of Neurology, Emory University School of Medicine, Atlanta, GA, USA

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

both parkinsonism and levodopa-induced side effects, contributed greatly to the renewed use of this approach.

The return to ablative procedures was short-lived, however. Beginning in the late 1990s, the lesioning strategies were increasingly replaced by high-frequency deep brain stimulation (DBS), a reversible and adjustable form of neuromodulation that was perceived to be less invasive yet equally effective [4]. The use of DBS stems from the seminal publication by Benabid et al. [5], reporting that DBS of the thalamus was an effective treatment for tremor, which led to a replacement of thalamotomy. The successful application of DBS to the subthalamic nucleus (STN), following the report of reversal of parkinsonism with STN ablation in the MPTP primate model of parkinsonism [6], led to its widespread use for the treatment of PD and, later, dystonia. DBS is currently approved by the US Food and Drug Administration for use in patients with tremor, PD, dystonia, and obsessive compulsive disorder. DBS has also been explored for many other neurologic and neuropsychiatric disorders, including epilepsy, Alzheimer's disease, Tourette syndrome, and treatment-resistant depression [7].

The introduction of DBS and the use of electrophysiologic techniques to guide the placement of DBS electrodes also provided a unique opportunity to learn more about the pathophysiology of the disorders, as well as the mechanism of action of DBS. In this review, we first consider relevant anatomical and functional concepts of basal ganglia circuits and circuit dysfunction, and then discuss the current understanding of the pathophysiology of the two basal ganglia movement disorders most frequently being treated with DBS, PD and dystonia, and the proposed mechanism of action of DBS in treating these and related disorders.

Functional/Anatomic Considerations of the Basal Ganglia Circuits

The basal ganglia are key components of a family of largely segregated parallel cortical-subcortical circuits, which involve the cerebral cortex, basal ganglia, and the ventral thalamus [8, 9]. The circuits have been grouped and designated broadly as "motor", "oculomotor", "prefrontal", and "limbic", reflecting the perceived functions of the frontal cortical areas from which they originate and to which they return. Dysfunction within these circuits is generally associated with signs and symptoms that broadly reflect the functions of the cortical areas they serve. We will limit ourselves here to a description of the connectivity of the nodes of the motor circuit (without discussion of interneuronal processing), since their dysfunction, when propagated to downstream targets in the brainstem and thalamus, leads to the signs and symptoms of movement disorders, both hypokinetic (e.g., PD) and hyperkinetic (e.g., dystonia, chorea, ballismus, or motor tics).

Throughout its subcortical course, the motor circuit (included in Fig. 1) maintains its somatotopic organization and neuronal specificity, reflecting highly topographic projections [8, 10]. This circuit originates in multiple pre- and postcentral sensorimotor areas, including the motor cortex (MC), premotor cortex, cingulate motor area, and the supplementary motor area. These areas project primarily to the putamen, the sensorimotor portion of the striatum [8, 10], terminating on two distinct populations of striatal medium spiny projection neurons (MSNs), which, in turn, send projections either to the external segment of the globus pallidus (GPe), or to the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr), the two output nuclei of the basal ganglia. The monosynaptic striatal projection to GPi/SNr is called the *direct* pathway, while the projection linking the striatum to the GPi/SNr by way of GPe and the STN is called the *indirect* pathway (see Fig. 1). All connections of the basal ganglia are inhibitory except for those from the STN. Another cortical input to the basal ganglia, the "hyperdirect" pathway, links frontal cortical areas directly to the GPi/SNR via topographic projections to the corresponding functional domains of the STN (Fig. 1) [11, 12].

Projections from the output nuclei, GPi/SNr, are sent to portions of the thalamus, terminating in the anterior ventrolateral thalamic nucleus (VLa) and the magnocellular portion of the ventral anterior nucleus, as well as the caudal intralaminar nuclei, that is, the centromedian and parafascicular nuclei (CM/Pf). While CM/Pf projections are mostly part of a pallido–CM/Pf–striatal feedback system (see below), cortical projections from VLa close the motor loop, sending efferents to respective precentral motor fields, the MC, SMA, premotor cortex, and cingulate motor area. The same GPi and SNr neurons that send their axons to the thalamus also project to the brainstem, terminating predominately in the pedunculopontine nucleus and tectum.

A major feature of basal ganglia output is that the γ-aminobutyric acid (GABA)ergic neurons in GPi and SNr are tonically active and inhibitory upon their projection targets in thalamus and brainstem. The basal ganglia motor circuit is thus viewed as holding the thalamic and brainstem networks in check [13–16], and the level of tonic and phasic inhibition is determined by the interplay of direct, indirect, and hyperdirect pathways at the level of GPi/SNr.

The arrangement of the intrinsic basal ganglia pathways into direct/indirect and hyperdirect pathways is incorporated into several interpretations of basal ganglia function, including the hypothesis that these pathways may play a role in action selection [e.g., 15, 17–19], the scaling of movement parameters [20], and, in a more general sense, "motor motivation", or action "vigor" [21], and cost/benefit aspects of actions [21, 22].

The role of the basal ganglia in action selection has been long considered to be one of the fundamental roles of these

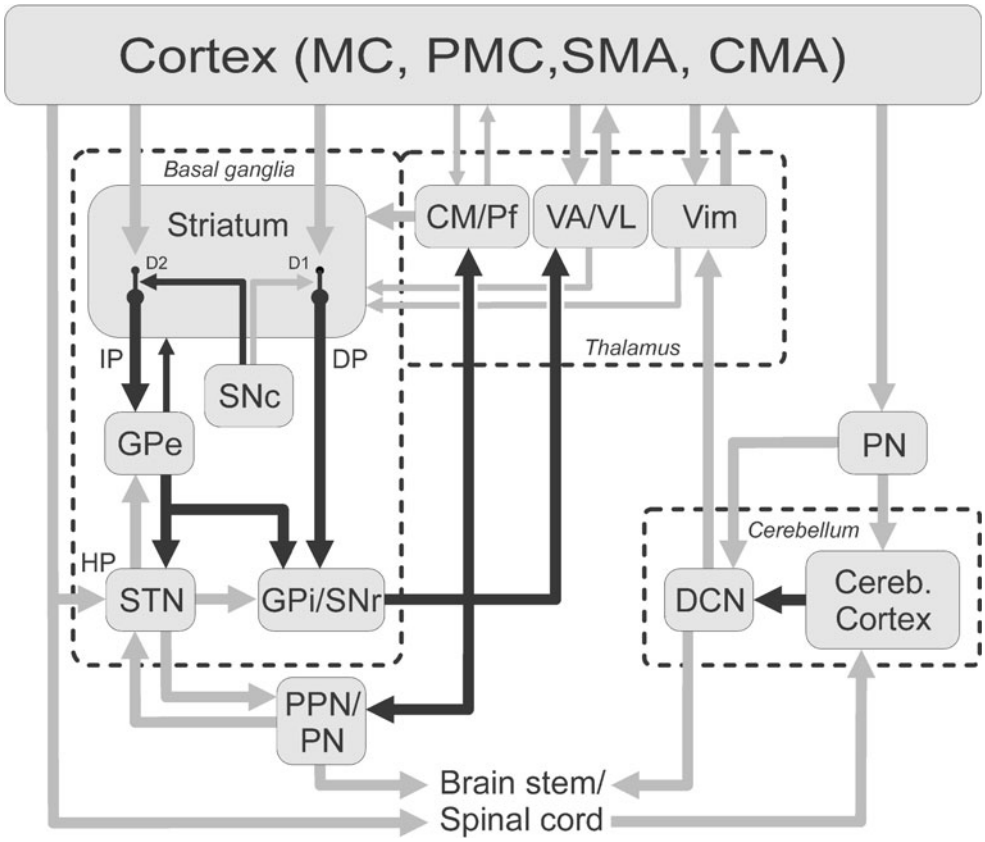

Fig. 1 Corticosubcortical motor circuits. Black arrows indicate inhibitory connections; gray arrows indicate excitatory connections. Basal ganglia, thalamus, and cerebellum are marked. CM/Pf = centromedian and parafascicular nuclei of the thalamus; Cereb. Cortex = cerebellar cortex; CMA = cingulate motor area; DCN = deep cerebellar nuclei; DP = direct pathway; D1 = D1-like dopamine receptor subtype; D2 = D2-like dopamine receptor subtype; GPe = external segment of the globus pallidus; GPi = internal segment of the globus pallidus; HP = hyperdirect pathway; IP = indirect pathway; MC = motor cortex; PMC = premotor cortex; PN = pontine nuclei; PPN = pedunculopontine nucleus; SMA = supplementary motor area; SNc = substantia nigra pars compacta; SNr = substantia nigra pars reticulata; STN = subthalamic nucleus; VA/VL = ventral anterior and ventral lateral nuclei of the thalamus. Figure from Wichmann 2015 [339]

nuclei [23]. It is most often used in the sense that the basal ganglia play a role in making the most appropriate action for a given situation by selecting the optimal response and blocking competing ones [24]. The general concept that activation of the direct pathway facilitates movement, while activation of the indirect pathway reduces movement, is supported by recent optogenetic studies [25–27]. This general framework may have pathophysiologic relevance (see below), in that hypokinetic diseases such as PD are associated with increased basal ganglia output, while hyperkinetic diseases (such as dystonia or chorea) are associated with abnormally low basal ganglia output [15, 16].

In addition to influencing the direct and indirect pathways, the cerebral cortex can also influence basal ganglia output via the hyperdirect corticosubthalamic pathway. While much sparser than the indirect pathway, the hyperdirect projection has received increasing attention. By circumventing the striatum, it may provide a mechanism for cortical inputs to influence GPi and SNr output with shorter latencies and thereby assist in situations that require rapid "stop" responses to external and internal triggers [17, 19, 28–41].

It is important to point out that some of the aforementioned hypotheses for the motor functions of the basal ganglia, in particular, a role of the basal ganglia in the initiation of movement, are difficult to reconcile with much of the available data. Combined single-cell/behavioral studies in primates have found highly specific changes in neuronal activity in relation to (trained) limb movements throughout the nodes of the motor circuit, particularly in relation to movement amplitude/velocity, However, the observed changes in discharge lag behind activity changes in the MC [42–45], and the activation of (antidromically identified) corticoputaminal neurons lags that of nearby corticofugal projections to brainstem and spinal cord [46, 47]. Moreover, lesions interrupting the output of the motor circuit in the sensorimotor territory of GPi in normal primates and individuals with PD or dystonia [48], following pallidotomy, have little or no effect on reaction times, although a slowing of movement is a consistent finding [49–52]. Of course, it could be argued that the basal ganglia might play a more direct role in the initiation of internally generated movements. The lack of obvious deficits in humans undergoing pallidotomy or animals following large bilateral lesions of GPi, however, does not

support this. Collectively, these findings argue against a role of the motor circuit in the initiation and selection of movement and support a more general effect on speed and amplitude of movement or motor vigor.

It is likely that the projections of the motor circuit portions of GPi to the pallidal receiving areas of the thalamus and to the brainstem serve different functions. Studies of lesioning in the primate have found that pharmacologic (transient) inactivation of the basal ganglia receiving territory of the ventral motor thalamus resulted in a reduced number of internally or externally triggered movements and an increased reaction time (depending on the injection site), with no obvious effect on spontaneous movements outside the task [53]. Large bilateral permanent lesions interrupting the basal ganglia receiving areas and sparing the cerebellar receiving areas resulted in impaired motor learning without a significant effect on spontaneous movements, providing evidence for a role of the basal ganglia–thalamocortical components of the motor circuit in motor learning [54]. In contrast, interventions at the PPN level in primates seem to have more overt effects on spontaneous behavior, resulting in akinesia/bradykinesia [55]. The effects of functional surgery targeting the VLa and PPN in patients are mentioned below.

As stated above, collaterals from the pallido- and nigrofugal projections are also directed in a topographically specific manner to the intralaminar nuclei of the thalamus, that is, the CM/Pf (see Fig. 1). The CM/Pf–striatal system is seen as providing sensory and salience information to the basal ganglia, which may assist in procedural and reinforcement learning and action selection (see below) [56, 57]. Lesions of CM, the motor portions of CM/Pf, have little or no effect in relieving akinesia/bradykinesia in the MPTP-treated primate [58], although DBS of CM in patients with PD has been reported to be beneficial for dyskinesias in limited studies [59].

Collaterals from the basal ganglia output projections to that thalamus also reach the PPN (Fig. 1) [60–73]. The STN sends a more modest glutamatergic projection to PPN [74–76]. The PPN is a very heterogeneous structure, consisting of a caudolateral pars compacta (PPNc) and an anteromedial pars dissipata. Cholinergic cells predominate in PPNc, but PPNc and anteromedial pars dissipata also contain large populations of GABAergic or glutamatergic neurons [77–79]. The input and output relationships of the various neuron groups in the PPN have not been precisely determined, but it is known that the nucleus gives rise to projections to the basal ganglia, thalamus, basal forebrain, reticular formation, and spinal cord [69, 74, 80–93], thus being, at the same time, part of the extended basal ganglia family of nuclei [74], and a conduit of descending basal ganglia outputs. The function(s) of this nucleus are poorly understood, although portions of the (primate) PPN are implicated in the control of gait and balance because of overlap with the physiologically identified mesencephalic locomotor region and possibly other motor functions (see below).

Although it has long been believed that basal ganglia and cerebellar subcortical networks are segregated, there is growing evidence for highly specific anatomical connections and physiologic interactions between the basal ganglia and the cerebellum ([94]; see Fig. 1). Thus, it appears that both the basal ganglia and cerebellum participate and interact under normal conductions in motor and nonmotor functions, and that they share pathologic activity in certain movement disorders, such as parkinsonian tremor and some types of dystonia [95–98].

Basal ganglia networks are influenced by several neuromodulators. Among these, the effects of dopamine on striatal transmission play a central role in all models of basal ganglia function and in the proposed pathophysiologic mechanisms in both PD and dystonia. Dopamine is released in the striatum and other nodes of the motor circuit from terminals of projections from the substantia nigra pars compacta, and regulates the activity of the basal ganglia output neurons by facilitating corticostriatal transmission upon MSNs of the direct pathway and inhibiting corticostriatal transmission upon MSNs of the indirect pathway ([99–102]; Fig. 1). The net effect of striatal dopamine release appears to be to reduce basal ganglia output to the thalamus and other targets. According to the classic circuit model, this will result in increased overall movement. By contrast, a decrease in striatal dopamine release, as is seen in PD, leads to a decrease in movement. Dopamine also has effects in all other nodes of the basal ganglia–thalamocortical network. The specific effects of dopamine at sites outside of the striatum are poorly understood [103].

Striatal dopamine release also plays a role in procedural and reinforcement learning [e.g., 104–108], owing to synaptic plasticity and remodeling. In terms of procedural learning, the "associative" portions of the caudate nucleus appear to be involved in early phases of learning, while the "motor" putamen is more prominently engaged when animals execute previously learned movement sequences [109–118]. Hypotheses about the role of dopamine in reinforcement learning are closely tied to the finding that dopamine neurons fire in relation to (positive) prediction errors in rewarded tasks [119–125]. Substantia nigra pars compacta neurons also receive information about negative prediction errors, through connections that originate in the lateral habenula [126–131].

Pathophysiology of Parkinsonism and Dystonia

Parkinsonism

PD is a progressive multisystem neurodegenerative disorder that affects many regions of the central and peripheral nervous systems [132], and leads to a plethora of motor and nonmotor signs and symptoms. However, the cardinal motor features of PD, constituting what is termed parkinsonism (including akinesia/bradykinesia, tremor, and muscular rigidity), are the

most prominent aspects of the disease during the initial phases. They arise from dopamine loss in the basal ganglia, in particular the sensorimotor portions of the putamen. During later phases of the disease, other signs and symptoms emerge, specifically gait and balance problems, and cognitive impairments. It is widely believed that balance problems are the result of degeneration in the portion of the PPN that belongs to the mesencephalic locomotor region and/or degeneration of cholinergic cell groups [e.g., 90, 133–139]. Cognitive impairments are likely caused by a combination of factors, including the extension of significant dopamine loss to nonmotor portions of the basal ganglia, and the spread of pathology to prefrontal cortical regions [132].

Parkinsonism (as defined above) is highly responsive to the administration of levodopa, the precursor of dopamine. As mentioned, the long-term use of dopaminergic replacement therapies can have substantial side effects, especially the emergence of highly disruptive dyskinesias and unpredictable "off times" and motor fluctuations. These problems, together with medication-refractory tremor, are the major factors for the use of DBS in PD.

Early studies of primates in (nondyskinetic) MPTP-treated monkeys emphasized the importance of changes in the overall activity of striatopallidal pathways. Metabolic studies suggested [140, 141], and microelectrode recording studies demonstrated, a reduction of neuronal discharge in GPe, and increased activity in the STN, leading to increased excitatory drive upon the basal ganglia output nuclei, GPi, and SNr [142–145], all strongly implicating increased activity over the indirect pathway in the pathophysiology of PD. Based on this evidence, models were developed positing that akinesia/bradykinesia results from excessive inhibitory output from GPi [13, 15, 16], and emphasizing the role of increased GPi output in hypokinetic and decreased output in hyperkinetic disorders.

It was later recognized, however, that changes in the patterning of activity in the basal ganglia are likely to be at least as important as rate changes for the development of parkinsonian motor signs [146]. Among these, abnormal bursting and oscillatory fluctuations of neuronal discharge are particularly noticeable [147–152]. Oscillatory activity can be identified in electrophysiological recordings of the activity of single neurons in GPi, SNr, STN, and MC in animals and patients with PD [153]. The proportion of cells in STN and GPi that discharge in bursts is also greatly increased in parkinsonism [143, 144, 152, 154, 155]. Finally, a highly important parkinsonism-related change in spontaneous discharge is the abnormal level of synchrony between neighboring neurons [144, 152]. It is not specifically known how changes such as burst discharges, oscillatory discharge, or abnormal synchrony develop in parkinsonism, although altered striatal output to the extrastriatal basal ganglia, changes in collateral inhibition in the external pallidum [156], or changes in the strength and morphology of synapses within the subthalamopallidal network of connections (see below and [157, 158]) may contribute to correlated oscillatory activity in the output nuclei of the basal ganglia [152, 159, 160] .

It is clear that the synchronous oscillatory activity in populations of neurons in the nodes of the corticobasal ganglia motor circuit contributes to the finding of power spectral changes in recordings of local field potentials (LFPs) in patients with PD, as well as in animal models of the disorder [161]. LFP signals reflect membrane potential fluctuations, both subthreshold (synaptic potentials) and suprathreshold (spiking-related). The realization that the amplitude of LFPs depends on the degree of temporal alignment of the electrical activities of the neural tissue from which they originate has rendered the recording and analysis of LFP signals an important tool for the exploration of circuit-level synchrony.

The fact that implanted DBS electrodes can also be used to record electrical signals in patients with these conditions has been one of the major scientific benefits of the introduction of DBS technology and had a major impact on our thinking about the pathophysiology of parkinsonism and other neuropsychiatric disorders. LFP recordings in patients with PD, particularly in the dorsolateral motor regions of the STN and GPi, have demonstrated oscillations in the 10–25 Hz (beta) range in the unmedicated state, and in the 60–80 Hz (gamma) range in the levodopa-treated state [152, 162]. It is thought that the overly strong beta-band LFP oscillation indicates that desynchronization processes of neurons within the circuitry fail in PD, which may contribute to the hypokinetic features of the disease. This has led to the proposal that beta-band LFP oscillations are antikinetic and strongly correlated with rigidity and bradykinesia [163], while gamma-band oscillations (a sign of desynchronization) are thought to be prokinetic [162]. Beta oscillations are viewed as normal for the resting or "idling" state; their reduction with movement onset may play a role in allowing movement to take place. Conceivably increased or persistent beta-band oscillations could disrupt movement initiation and execution, or may reflect the underlying impairment of movement initiation or even be a compensatory mechanism [164].

There is no evidence that LFP oscillations per se influence motor performance. The finding of LFP signals with greater amplitude in patients with PD may simply reflect the fact that the system is in a state of increased synchrony [152]. A similar caveat applies to the recently described finding of increased coupling between the amplitude of gamma-band oscillations and the phase of beta-band activity at the same location [165]. This finding likely corresponds to synchronized bursts of single cell activity (accounting for the broadband gamma-band peak) whose timing reflects an underlying beta-rhythm (accounting for the apparent entrainment of activity in the beta-band range).

Although it is tempting to attribute signs and symptoms to specific abnormalities in neuronal activity or LFPs in PD, the

(causal) importance of any of the multiple changes in basal ganglia activity for the development of parkinsonism remains uncertain because they are not always found in animal models of parkinsonism, or in humans with PD, and, if they occur, tend to occur late in the development of parkinsonian signs in animal models, well after their onset [158–161].

Changes in the basal ganglia other than dopamine loss (but likely related to it) may also contribute to activity changes in the basal ganglia. These include a growing list of chronic morphological changes in the basal ganglia, affecting glutamatergic and GABAergic transmission in these structures. For instance, plasticity at glutamatergic synapses has been demonstrated in animal models of parkinsonism and in patients with PD, affecting the corticostriatal, thalamostriatal, and corticosubthalamic pathways [166–173]. Recent studies have suggested additional plasticity of the GABAergic collaterals within the GPe, as well as the pallidosubthalamic projection, the latter perhaps related to heterosynaptic homeostatic modulations, driven by *N*-methyl-D-aspartate receptor activation at corticosubthalamic synapses [157, 158, 174]. The fact that many of these changes can be identified in dopamine depletion models strongly suggests that they are a late consequence of dopamine loss, affecting brain areas rich in dopamine (like the striatum), as well as those with little direct dopamine input (e.g., the STN or the thalamus). It is not known whether these late morphologic changes are reversible.

The role of brain structures outside of the basal ganglia in the motor manifestations of PD remains uncertain. Traditional explanations focus on the transmission of abnormal patterns of activity via the basal ganglia-thalamocortical projections. However, as mentioned above, the available evidence suggests a more important role of the projections of GPi to the thalamus in motor learning than in movement execution. In contrast, interventions directed at the PPN have revealed significant motoric effects in animal experiments [55]. Thus, PPN inactivation in normal primates reduces body movements of arms, trunk, and legs [142–146], and PPN injection of a GABA-A receptor antagonist, or low-frequency stimulation of PPN, alleviates experimental akinesia in monkeys, presumably by increasing PPN activity [146–156]. This constellation of findings suggests the possibility that the descending basal ganglia projections to the brainstem may play a greater role in the pathophysiology of akinesia/bradykinesia and movement than is commonly assumed. A particular role of the PPN in the axial control of gait and balance, and in abnormalities of these functions in patients with movement disorders, is suggested by the fact that portions of the PPN are part of the brainstem locomotor region [90, 137, 138], and the finding that PPN neurons in this region degenerate in PD [133–136].

Finally, the cerebellar outflow pathways also seem to be involved in aspects of the pathophysiology of PD, specifically tremor [95, 175, 176], as suggested by imaging studies [177], and by the finding that, unlike other signs of the disease, parkinsonian tremor is effectively treated with surgical interventions targeting the cerebellar-receiving portions of the thalamus [178, 179]. While dopamine loss is, in some way, related to the expression of tremor, this parkinsonian sign is often less sensitive to dopamine replacement therapy than the other parkinsonian signs, and not strongly related to beta-band power in LFP signals recorded in the basal ganglia [163].

Dystonia

Dystonia is a heterogeneous hyperkinetic movement disorder "characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements, postures, or both. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation" [180]. Co-contraction of agonist and antagonist muscles is common. Dystonia can be classified by the presence or absence of associated clinical manifestations, differentiating "isolated dystonia" from "combined dystonia", where dystonia appears as a component of other disorders, such as PD. In adults, focal forms of dystonia are common, whereas in children and young adults, generalized inherited forms of dystonia are more common, such as idiopathic torsion dystonia [DYT1; 181].

Physiologic studies in isolated generalized and focal hand dystonia have demonstrated evidence of a widespread loss of GABAergic inhibition, involving cortex, brainstem and spinal cord, evidence of abnormal sensorimotor integration, and abnormalities of synaptic plasticity [182]. Some forms of dystonia are clearly associated with basal ganglia dysfunction. For instance, dystonia may result from disturbances in dopaminergic transmission assumed to affect strongly basal ganglia activity [183]. Thus, dystonia may develop either acutely or delayed (tardive dystonia), in normal individuals treated with dopamine-receptor blocking agents, or can be a sign of other diseases with disturbed dopamine metabolism, such as PD, levodopa-responsive dystonia, or DYT1 [184–189]. Transient dystonia has also been observed in monkeys treated with the dopaminergic neurotoxin MPTP [190–192].

Studies in primate models have shown that dystonia is associated with a reduction of activity along the putamen–GPe connection, and increased inhibition of STN and GPi by GPe efferents [193, 194]. Based on pharmacologic studies, there seems to be a relative increase in the activity of striatal neurons of the direct pathway over those that give rise to the indirect pathway in dystonia [195, 196], and single-cell recording studies in patients undergoing functional neurosurgical treatments have demonstrated low discharge rates in both GPe and GPi [197–202], in distinction to the aforementioned changes in PD where GPi discharge rates are generally increased. The presence of low-frequency discharge in the GPi in patients with dystonia is similar to that in other hyperkinetic disorders, including chorea/ballismus and motor tics [197, 203, 204]. Other studies have shown the emergence of low-frequency oscillations in single-

cell and LFP activities in the basal ganglia or thalamus [200, 201, 205–207], comparable with those found in PD. Electrocorticographic recordings over the MC in patients with isolated dystonia showed less coupling between the phase of beta-band oscillations and the amplitude of gamma-band oscillations than found in patients with PD [208].

In some types of dystonia, the cerebellum may also be involved, either alone or in conjunction with basal ganglia abnormalities [96, 98, 209, 210]. For instance, gene carriers of the autosomal dominant DYT1 and DYT6 dystonias show *functional* disturbances of cerebellar connections. DYT1 has a relatively low penetrance (about 30 %) that may result from an additional abnormality in thalamocortical projections, which may be protective in these cases [97, 211–213]. Subtle *structural* cerebellar pathology is suspected to occur in some forms of dystonia [214]. Interplay between the cerebellar and basal ganglia circuits in the development of dystonias is suggested by experiments aimed at replicating the pathophysiology of the genetically inherited rapid-onset dystonia parkinsonism [RDP; 210].

DBS

Implantation and Programming

Candidates for DBS therapy with PD or dystonia undergo placement of stimulating leads into the STN or GPi, guided by neuroimaging followed by electrical macrostimulation to assess clinical responses and sensory and motor thresholds. Microelectrode recording and mapping of the targeted area is used by some groups, prior to placement and testing of the DBS lead, since correct placement is critical to the success of DBS. An internal pulse generator (IPG), which is similar to a cardiac pacemaker, is simultaneously or subsequently implanted, usually in the subclavicular region, and connected to the electrode [215]. The currently available electrodes contain 4 separate contacts, spaced either 0.5 or 1.5 mm apart. Programming of the IPG is typically carried out 2–4 weeks after implantation of the electrodes, using a telemetric system by which the clinician can remotely select specific electrode contacts used for stimulation, their configuration for mono- or bipolar stimulation, and parameters, including frequency, pulse width, and amplitude of the stimuli. Several groups are currently working on improvements to the design of electrodes and pulse generators. Some of these efforts are mentioned below.

Use of DBS in PD

DBS is currently used to treat patients with PD for whom the signs and symptoms cannot be satisfactorily controlled by medications due to the development of side effects. Stimulation of the sensorimotor STN or GPi between 30 and 100 Hz is relatively ineffective for parkinsonian features, while benefit is seen around 100 Hz and above, using stimulation amplitudes of 2–4 V and pulse widths of 60–90 μs. The available data indicate that both STN and GPi DBS in patients with PD relieve tremor, rigidity, and bradykinesia [216–221], and may improve gait and postural control in some patients [222].

Although the STN is most commonly targeted for PD, both GPi and STN DBS have comparable benefits for the cardinal features of PD. The pros and cons of STN *versus* GPi targeting are debated [223], and the relative incidence of side effects and complications of either of these procedures have been the focus of considerable discussion [215, 224]. Differences between these procedures are, in part, explainable by anatomical differences between the STN and GPi. As illustrated in Fig. 2, the STN is surrounded by major fiber systems and receives direct input from the cortex via the hyperdirect pathway. The STN is much smaller than the GPi, making inadvertent activation of nonmotor areas and extrinsic fiber systems and side effects more

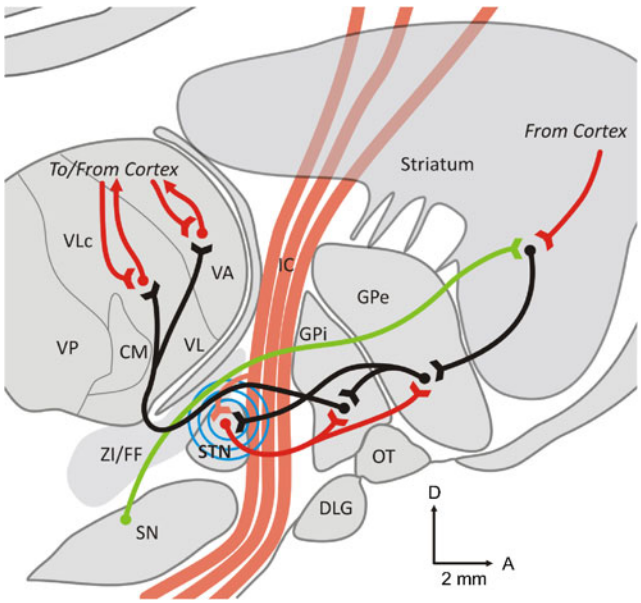

Fig. 2 Major anatomical pathways that are affected by subthalamic nucleus (STN) stimulation, and may contribute to the generation of cortical evoked potentials. Excitatory (glutamatergic) pathways are shown as red lines, inhibitory (γ-aminobutyric acid-ergic) connections are shown as black lines, and modulatory dopaminergic fibers as green lines. The blue circles symbolize the spread of the electrical stimulation of the STN. CM = centromedian nucleus of the thalamus; DLG = lateral geniculate body; FF = Fields of Forel; IC = internal capsule; GPe = external pallidal segment; GPi = internal pallidal segment; OT = optic tract; Put = putamen; SN = substantia nigra; VA = ventral anterior nucleus of the thalamus; VL = ventrolateral nucleus of the thalamus; ZI = zona incerta. Figure from Devergnas and Wichmann 2011 [298], used with permission

likely. The greater proximity and potential overlap of motor, associative, and limbic territories in this nucleus (compared with the larger GPi) contributes to the fact that DBS at this location is more likely to produce nonmotor effects than GPi DBS [225]. Another (unexplained) difference between these procedures is that the levodopa dose can usually be reduced in patients treated with STN DBS but not with GPi DBS.

Several other targets have been used to treat patients with PD. There is a general consensus among neurosurgeons that DBS of the ventral intermediate nucleus of the thalamus (Vim) is highly effective for tremor (but not other parkinsonian signs). Vim receives strong inputs from the cerebellum, and the effectiveness of tremor control with DBS at this location is a strong argument in favor of cerebellar involvement in the pathophysiology of tremor. PPN DBS [226–239], alone or in combination with STN or GPi DBS, is currently under study for patients with advanced PD who develop levodopa-unresponsive freezing of gait, balance impairments, and falls. DBS of the PPN has been shown to be most effective at low stimulation frequencies [240]. However, the location of effective PPN stimulation sites remains debated [e.g., 231, 241]. Other groups have targeted the zona incerta and CM in patients with PD [7, 59], particularly for tremor or dyskinesias.

Use of DBS for Dystonia

There is strong evidence supporting the use of GPi DBS for the treatment of isolated generalized or segmental dystonia, as well as for patients with cervical dystonia [242, 243]. The stimulation parameters are typically the same as for PD, although some patients may also respond to lower frequencies. There is growing evidence supporting the use of GPi DBS for the treatment of tardive dystonia or myoclonus dystonia [244–254]. Lesser and inconsistent benefit is seen in dystonia secondary to structural brain damage [255]. DBS at other locations, particularly the STN, has also been found in pilot studies to be effective for isolated dystonia [256–262]. Compared with GPi DBS, STN DBS may offer the advantage of more rapid improvement for dystonia and reduced stimulation parameters [257]. While there is a prior history of thalamotomy for generalized dystonia, thalamic DBS has not been utilized for this indication, perhaps because of the success with GPi and STN DBS, although thalamic DBS (targeting Vim, or the thalamic ventralis oralis nucleus) is being explored for focal forms of dystonia, such as writer's cramp [263–265].

Time Course of Responses

The signs and symptoms of basal ganglia disorders respond to DBS with different time courses [266]. It seems intuitively clear that signs and symptoms that respond rapidly to DBS must be mediated by modulation of ongoing network activity, whereas signs and symptom that respond after longer delays may be the result of synaptic plasticity with gradual reshaping of synaptic activity or morphology. Most striking are the very short (seconds) latencies needed to treat essential tremor with thalamic DBS and rest tremor of PD with DBS in the STN. The response of appendicular rigidity and bradykinesia in PD with DBS delivered to the STN or GPi is likewise rapid.

At the other end of the time spectrum, the effects of GPi DBS for generalized dystonia may take days to begin and months to reach maximum effect, suggesting that short- and long-term plasticity may play a role [261]. Movement-induced limb dystonia responds more rapidly than fixed postural dystonia. It is also noteworthy that delayed temporal responses are the norm for both pallidotomy and DBS for dystonia, strongly suggesting that the mechanism of action may, in both cases, involves long-term plastic remodeling of cortical and brainstem mechanisms. The return of symptoms once DBS is turned off generally mirrors the time course of the onset times [267, 268].

DBS Mechanism of Action

Considering the complex anatomical connectivity and the relatively widespread effects of electrical stimulation with current DBS electrodes within the nodes of the basal ganglia motor circuit and beyond, it is no surprise that the mechanisms of action of DBS remain controversial. The early finding that DBS of the STN or GPi results in clinical benefits that are strikingly similar to those of lesioning at these sites for tremor and PD, respectively, suggested initially that DBS may act by inhibiting neurons in the area of stimulation [269–271]. This view was supported by the demonstration that some neurons in the vicinity of the stimulation site in STN and GPi in experimental animals and in patients with PD are, indeed, inhibited [272–275], perhaps by depolarization block or the release of GABA from terminals of afferents to the stimulated area [276–280].

Later electrophysiologic recording studies in primates and patients demonstrated that DBS has, in fact, multiple actions that may differ with the distance from the stimulation site and the spatial orientation of electrodes and neural elements studied [276, 277]. Axons are known to be more sensitive to stimulation than cell bodies [276, 277, 281–283], so that high-frequency DBS may alter the activity of axons emerging from a given area (this was specifically shown for STN and GPe DBS [283, 284]), thus leading to a functional blockade of transmission of information, whether pathological or normal, through the stimulated area, but without silencing of the tissue. This effect is summarized in the term "informational lesion" [285]. The concept that DBS produces an informational lesion provided an explanation for the fact that DBS is equally effective for a variety of hypo- and hyperkinetic disorders.

Support for the idea that DBS produces an informational lesion comes from studies of evoked responses of GPi neurons to electrical stimulation of the MC [279]. In intact animals, such stimulation triggers triphasic response patterns in some GPi neurons, which are thought to be mediated via the sequential actions of the hyperdirect, direct, and indirect pathways [286]. GPi DBS was found to inhibit such stimulation-induced responses due to GABAergic inhibition of cell bodies [279].

Recent studies in awake behaving primates, however, have provided some evidence that physiologic sensorimotor-related discharge in the basal ganglia output nucleus (GPi) may be at least partially maintained during STN or pallidal DBS [266, 287]. These studies have suggested that DBS may act as a "selective filter" that permits some sensorimotor-related modulation of the activity of neurons in the stimulated area, while eliminating transmission of pathological low-frequency neuronal activity patterns.

The conclusion that DBS does not completely disrupt basal ganglia activities is also supported by the (limited) literature on the effects of DBS on motor learning. Contrary to the expectation that DBS of the STN or GPi would disrupt this important basal ganglia function, GPi DBS and STN DBS were, in fact, shown to improve performance in a motor sequence learning task or rewarded decision learning tasks [288–291]. Concomitant positron emission tomography studies suggested that the improvement after DBS was related to an enhancement of the activity of prefrontal or frontal corticobasal ganglia–thalamocortical loops [288, 291].

Yet another mechanism of action of DBS may be that it disrupts synchrony of neuronal discharge. This is suggested by studies in MPTP-treated monkeys [292]. Recent reports have provided additional evidence that pathological low-frequency oscillations are reduced or decoupled between nodes of the basal ganglia thalamocortical circuits at clinically effective high-stimulation frequencies [293, 294]. Thus, it has been found in the MPTP-treated monkey that therapeutically effective STN DBS alters the pattern and power of oscillatory activity of neuronal activity in the motor thalamus, resulting in more regular firing patterns and significant changes in bursting activities [295]. Other recent studies in such animals have shown that clinically effective levels of GPi DBS also affected the firing rates and rhythmicity of cortical neurons [296, 297].

As is shown in Fig. 2, STN DBS, because of its location and proximity to nearby structures and fiber systems, could produce effects through a variety of mechanisms. Thus, STN DBS, with use of the contacts in the sensorimotor region of the nucleus, may stimulate nearby pallidal–thalamic fibers and cerebellar–thalamic fibers in the zona incerta, and may antidromically activate afferents from GPe, which send (inhibitory) collaterals to GPi. STN DBS may also directly activate the nigrostriatal tract [298], but this is unlikely to be relevant in the treatment of PD because of the degeneration of this pathway in PD. Spread of stimulation from the STN stimulation site may also activate nearby corticospinal or corticobulbar fibers. STN stimulation has also been found to influence directly cortical neurons via antidromic activation of the corticosubthalamic pathway [298–301]. In fact, optogenetic studies in rodents have suggested that the antidromic activation of motor cortical input may be responsible for the clinical effects of STN DBS [299, 302]. While antidromic stimulation of cortex has also been shown in nonhuman primates and in patients, based on short-latency cortical-evoked potentials [298, 301, 303–305], it is not clear what role they play in the overall behavioral response to STN DBS in patients with movement disorders. Antidromic effects are not likely to play a prominent role in the case of GPi DBS [297, 298], which achieves the same motor result as STN DBS. Finally, a recent rodent study of STN DBS showed that STN DBS may also engage cerebellar activity to improve parkinsonian motor symptoms [306].

DBS has been shown to alter some of the electrophysiologic abnormalities observed in patients with movement disorders. For instance, STN DBS in patients with PD suppresses beta-band oscillations in the basal ganglia and reduces the aforementioned pathological coupling between beta-band phase and gamma-band amplitudes in MC [307–310]. GPi DBS also reduces beta-band oscillations in GPi and MC [297, 311]. These findings suggest that DBS may exert some of its effects by disrupting abnormal cortical synchronization. The fact that the clinical DBS effects are reflected in changes to electrophysiologic markers of disease severity may become practically relevant, as it may permit dynamic adjustment of DBS using closed-loop control designs (see below).

Based on animal studies, DBS may have effects on the release of growth factors (e.g., brain-derived neurotrophic factor), which may, in turn, promote neuroplasticity, neurogenesis, or neuroprotection [312–316]. At the present time there is no strong evidence from the human literature for a disease-modifying effect of DBS, although a recent study suggests that such effects may occur [317].

Discussion

The use of DBS has proven to be a major clinical advance for movement disorders and other neurologic conditions, and has already helped more than 150,000 patients to achieve better control of the signs and symptoms of their disease, and to improve their quality of life. However, despite intense research, the use of DBS remains largely empiric. Here, we make several general points about the lessons learned regarding the clinical effects and possible mechanisms of action of DBS.

The Removal of Abnormal Basal Ganglia Output is Sufficient to Treat Signs and Symptoms of Movement Disorders of Basal Ganglia Origin

The experience with ablation and functional inactivation of the basal ganglia motor circuit in STN or GPi has shown that interruption of pathologic output can efficiently restore functionality for PD and dystonia and other hyperkinetic disorders. While DBS clearly has diverse effects on the stimulated brain areas, it is clear that the clinical benefits of DBS are not the result of a DBS-induced restoration of normal basal ganglia or brain function. Whether by inducing an "information lesion" or by acting as a "selective filter", DBS appears to override the impact of pathologic basal ganglia activity on downstream targets. The DBS-induced activities in the basal ganglia thalamocortical network are perhaps more stable, allowing normal short- and long-term plasticity to take place downstream from the site of DBS.

The fact that GPi or STN DBS is effective for both hypokinetic and hyperkinetic disorders is similar to the clinical experience with pallidotomy for these disorders. This reinforces the impression that the actual effects of the intervention (lesion or DBS) may not matter so much, as long as the activity of downstream areas of the brain are released from pathologic basal ganglia output, and are allowed to reach a new equilibrium that is conducive to an improved clinical state.

The Basal Ganglia Assist (or Disturb) the Activities of Other Brain Regions

A corollary of the preceding discussion is that the signs and symptoms of movement disorders do not necessarily represent or reflect the normal motor functions of the basal ganglia, but rather the dysfunction of the targeted thalamocortical and brainstem networks resulting from pathologic basal ganglia output in the motor circuit. In fact, the striking variety of clinical abnormalities of movement in clinical disorders of the basal ganglia seems to give a greatly exaggerated and distorted picture of the role and extent of basal ganglia participation in normal motor function as discussed earlier.

The finding that interruption of basal ganglia output by pallidotomy or thalamotomy (or DBS of basal ganglia or thalamus) relieves signs and symptoms of movement disorders, with modest effects on movement in patients and experimental animals, has been called the "paradox of stereotaxic surgery" [318]. The clinically identifiable impairments of pallidotomy appear to be only a small degree of bradykinesia and a minor disruption of reinforcement learning [51, 318–320]. As mentioned above, the available evidence suggests that GPi DBS or STN DBS does not disrupt procedural learning, and may even improve it [288–291]. The absence of overt motor impairments with surgical disruption of basal ganglia output in patients with movement disorders does not negate a more significant function of the basal ganglia under normal conditions. The fact that the basal ganglia can be identified at the earliest stages in vertebrate evolution and that the evolutionary expansion of these structures mirrors that of the cerebral cortex is indirect evidence for their biological importance [23, 321]. However, the "paradox" suggests that the contribution of the basal ganglia to movement may be largely assistive rather than essential, and that its loss can be compensated for by the system as a whole with little deficit. The impression that it is "paradoxical" that the basal ganglia can be lesioned without major functional consequences may simply belie our failure to recognize that the clinical features of basal ganglia disorders do not represent or reflect the actual functions of the basal ganglia but dysfunction of the downstream networks resulting from propagated abnormal basal ganglia activity.

Abnormal Levels of Synchrony may be a Fundamental Electrophysiologic Abnormality Resulting in Akinesia/Bradykinesia and Dystonia

The use of DBS electrodes for recording purposes in humans, and in a large number of animal studies [44, 152, 322–326], has emphasized that many of the identified electrical disease markers (e.g., oscillatory bursting or phase-amplitude coupling) can be explained by an abnormal level of synchronous neuronal discharge that may ultimately result in increased beta-band oscillations throughout the corticobasal ganglia circuits. Studies in the normal basal ganglia have shown that neighboring neurons tend to fire independently (e.g., [44, 45]), perhaps continuing at the cellular level what is readily apparent as circuit segregation at the macroanatomic level [8, 10]. The finding of increased cross-correlation of single-cell discharge in many basal ganglia regions in animal models and patients with PD and increased LFP amplitudes in specific power spectral ranges indicates that the normal level of independence of discharge is substantially reduced in the parkinsonian state [44, 322, 323, 325, 326]. Effective antiparkinsonian therapies, including levodopa replacement and DBS reduce the LFP amplitudes to more normal levels, and reduce the abnormal synchrony of neurons in at least some brain regions [see, e.g., 152, 297, 327].

Studies in animal models of parkinsonism and in patients with PD have shown that parkinsonism is associated with peaks in power spectra of LFP signals. The location of these spectral peaks appears to differ between species, ranging from the theta-range of frequencies to the low gamma-range [328]. The exact spectral position of such

peaks may be less important than the fact that there is a (low-frequency) peak at all, suggesting the presence of abnormally synchronized activity patterns that may interrupt cortical and brainstem operations. Synchrony of this kind is most easily studied with spectral methods, but it is not clear whether the disruptive synchrony has to be oscillatory in nature. For future research it may be fruitful to focus less on studies of spectral LFP peaks and more on the correlation of single-cell discharge. It is also worth emphasizing that, if synchrony between neurons is an important element of parkinsonism (and dystonia), these diseases may respond favorably to DBS regimes that specifically desynchronize circuit activities (see below).

Technical Developments and Future of Neuromodulation

Current DBS technology is essentially 25 years old. Engineers have already developed IPGs that deliver constant stimulation currents (rather than the conventional constant stimulation voltages) and are now developing pulse generators that will allow the use of more flexibly programmable stimulation regimes, allowing, for example, patterned stimulation instead of the currently available constant-frequency stimulation [329, 330]. Greater flexibility is desirable because it has been shown that intermittent or irregular stimulation may be as effective or even more effective than continuous stimulation [329, 331], and may help to preserve the battery life of the implanted devices. A related effort is that of developing stimulators that would allow the use of stimulation parameters that may desynchronize circuit activities [e.g., 332, 333] by stimulating with stimulation patterns that involve (in predetermined temporal sequences) multiple contacts in the stimulated area ("coordinated reset" stimulation). With regard to the disorders mentioned in this article, this approach has been used with some success in preliminary studies in MPTP-treated monkeys and in patients with PD [333, 334]. In the patient study, coordinated reset stimulation was carried out for 2 short daily sessions over a period of 3 days. This resulted in antiparkinsonian effects that persisted for days. Over the 3-day trial periods, the patients showed a gradual decrease in beta-band power in their STN.

Device development also tries to address the fact that the signs of symptoms of basal ganglia diseases are not necessarily stable over time. While slow drifts in severity can be addressed by repeated (re-) programming of the existing devices, short-term fluctuations are not easily remedied with the current technology. The generation of closed-loop adaptive stimulation devices, a type of stimulation that dynamically adjusts the stimulation parameters according to the level of patient's disability is therefore a major development goal. The most pressing scientific and engineering issue in this effort is that reliable biomarkers for disease severity need to be found, and that the implanted device(s) must be able to detect them and adjust their output accordingly. In encouraging studies in parkinsonian primates it was shown that STN DBS triggered by the firing patterns of MC cortical neurons treated parkinsonism more effectively than conventional DBS [335], and subsequent studies in humans showed that STN DBS can be controlled by recorded LFP signals in the STN [336]. Major issues remain unsolved, including further optimization of the detection and extraction of the control signals, demonstration of the stability of the relationship between these signals and the disease signs and symptoms, and the obvious need to minimize battery consumption of the added sensing circuitry in the new devices.

The further development of new electrodes is also underway, with the goal of permitting more precise shaping and steering of the electrical field, through the use of multiple contacts along the electrode shaft [337, 338], in order to better control unintended spread and optimal shaping of current flow. Obviously, the freedom of being able to use additional electrode contacts must be balanced against the resulting more complex programming requirements.

Conclusion

The introduction of DBS had a strong impact on the treatment of movement disorders and other neuropsychiatric conditions, and has led to a better understanding of the pathophysiology of these disorders. The focus on neural networks and the mechanism of action of DBS have opened wide areas for further exploration in the form of novel targets and forms of stimulation for a variety of neuropsychiatric disorders.

DBS, although less invasive that ablation, is, nonetheless, an invasive procedure, requiring long-term care and maintenance. Moreover, although highly effective for nonprogressive disorders such as dystonia and the dopamine-responsive features of parkinsonism, it is a purely symptomatic treatment. While substantial refinements and progress is being made with current technology, other forms of neuromodulation may become important, in particular optogenetic and chemogenetic stimulation methods. Both techniques have the benefit of being cell-specific (through the use of cell-specific promoters) and less invasive, and may, therefore, produce benefits similar to those of DBS, but with fewer side effects. Major biological hurdles remain for both of these techniques, however. While it is hoped that less invasive and more effective forms of neuromodulation will be developed, it seems clear that DBS will undergo significant improvements and it is unlikely that it will be supplanted in the near future.

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