Review | CIRCUITS AND CIRCUIT DISORDERS

Basal Ganglia Circuits as Targets for Neuromodulation in Parkinson Disease

Mahlon R. DeLong, MD; Thomas Wichmann, MD

IMPORTANCE The revival of stereotactic surgery for Parkinson disease (PD) in the 1990s, with pallidotomy and then with high-frequency deep brain stimulation (DBS), has led to a renaissance in functional surgery for movement and other neuropsychiatric disorders.

OBJECTIVE To examine the scientific foundations and rationale for the use of ablation and DBS for treatment of neurologic and psychiatric diseases, using PD as the primary example.

EVIDENCE REVIEW A summary of the large body of relevant literature is presented on anatomy, physiology, pathophysiology, and functional surgery for PD and other basal ganglia disorders.

FINDINGS The signs and symptoms of movement disorders appear to result largely from signature abnormalities in one of several parallel and largely segregated basal ganglia thalamocortical circuits (ie, the motor circuit). The available evidence suggests that the varied movement disorders resulting from dysfunction of this circuit result from propagated disruption of downstream network activity in the thalamus, cortex, and brainstem. Ablation and DBS act to free downstream networks to function more normally. The basal ganglia thalamocortical circuit may play a key role in the expression of disordered movement, and the basal ganglia–brainstem projections may play roles in akinesia and disturbances of gait. Efforts are under way to target circuit dysfunction in brain areas outside of the traditionally implicated basal ganglia thalamocortical system, in particular, the pedunculopontine nucleus, to address gait disorders that respond poorly to levodopa and conventional DBS targets.

CONCLUSIONS AND RELEVANCE Deep brain stimulation is now the treatment of choice for many patients with advanced PD and other movement disorders. The success of DBS and other forms of neuromodulation for neuropsychiatric disorders is the result of the ability to modulate circuit activity in discrete functional domains within the basal ganglia circuitry with highly focused interventions, which spare uninvolved areas that are often disrupted with drugs.

JAMA Neurol. 2015;72(11):1354-1360. doi:10.1001/jamaneurol.2015.2397
Published online September 26, 2015.

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Section Editor: David E. Pleasure, MD.

The 1950s and 1960s were a remarkable era for ablative stereotactic surgery for movement disorders and followed the earlier development of the stereotactic frame and methods of targeting of the basal ganglia and thalamus for treatment of Parkinson disease (PD), dystonia, and tremor. This era came to an end in the early 1970s after the introduction of levodopa for the treatment of PD in the mid-1960s and the negative public response to the excesses of psychosurgery in that period. However, the use of stereotactic surgery returned in the early 1990s. Functional surgery is once again a standard treatment for movement disorders. Critical for the revival of the procedure was the growing understanding of the functional organization of the basal ganglia circuitry and the pathophysiology of movement disorders (specifically parkinsonism), as well as the demonstration of the reversal of parkinsonism by lesioning the subthalamic nucleus (STN) in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primate model of PD.[1,2] Although these results demonstrated the value of targeted surgical interventions in the treatment of PD and identified the STN as a potential new target, lesioning of the STN was initially believed to be too risky for humans. Surgeons, also motivated by the report of Laitinen et al[3] on the significant benefits of pallidotomy for both parkinsonism and levodopa motor compilations and using the posteroventral target of the internal pallidum (GPi) of Leksell, returned to pallidotomy.

Toward the end of the 1980s, Benabid et al[4] made the important discovery that electrical high-frequency stimulation (deep brain stimulation [DBS]) of the thalamus is as effective as thalamotomy for the treatment of essential tremor. Soon thereafter, the use of DBS at the newly identified STN target for PD was explored. Studies found STN DBS to be a highly effective antiparkinsonian treatment, both

in the primate model of PD[5] and in humans with PD.[6] Since that time, the use of STN DBS has become the standard of care for patients with advanced PD, in particular those who experience drug-induced complications or treatment-resistant tremor. Following the success of STN DBS for PD, DBS has also been used successfully in patients with dystonia as a primary disorder and with dystonia as a manifestation of PD, targeting primarily the GPi.[7,8]

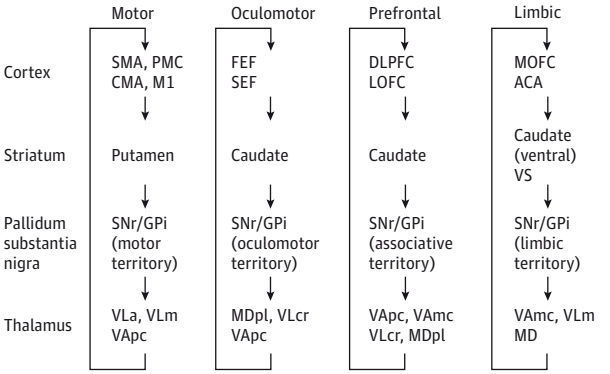
Deep brain stimulation has now virtually replaced ablative approaches because of its reversibility, adjustability, and less invasive nature. The use of DBS to treat other neuropsychiatric disorders, such as Tourette syndrome, epilepsy, Alzheimer disease, and psychiatric disorders (eg, obsessive-compulsive disorder or treatment-resistant depression), is remarkable. More than 40 brain sites have been explored with DBS for 30 clinical disorders.[9] Apart from its therapeutic benefits, DBS proved to be a highly valuable tool for research, providing a minimally invasive probe for stimulation and recording of electrical signals from the implanted targets in patients with a variety of diseases. This research has provided new insights into brain network function and dysfunction in neurologic and psychiatric disorders.

Ablation and DBS are different forms of neuromodulation that address dysfunction in cortical and subcortical networks involving the basal ganglia, cerebellum, brainstem, thalamus, and cerebral cortex. Disturbances propagated throughout specific basal ganglia circuits result in movement disorders, such as PD, dystonia, and chorea, as well as psychiatric disorders, such as obsessive-compulsive disorder and depression, which we now recognize as circuit disorders. It is surprising that, in most cases, ablation and DBS achieve similar results. Also surprising is the fact that these procedures, although remarkably effective in relieving the signs and symptoms of movement disorders, do not seem to significantly impair voluntary movement, a phenomenon referred to as the "paradox of stereotactic surgery." In the present review, we focus on aspects of basal ganglia circuit dysfunction in movement disorders, using PD as the example, that provide the understanding and rationale for use of functional neurosurgery in the treatment of these conditions. We also comment on the possible functions of the basal ganglia and their relationship to the paradox.

Functional Organization of Basal Ganglia Circuits

The basal ganglia are components of a family of parallel and largely closed circuits (**Figure 1**)[10] that originate in the cerebral cortex, traverse the basal ganglia and thalamus, and return to their individual sites of origin in the frontal lobe.[11,12] The circuits have been grouped and designated as *motor*, *oculomotor*, *prefrontal*, and *limbic*, reflecting the perceived functions of the cortical areas from which they originate. The segregated organization of the circuits provides for parallel processing of cortical inputs through the networks, presumably by processes that are similar across the different circuits. The spatial separation of these circuits provides an explanation for the remarkable fact that it is possible to surgically target network components to treat specific signs and symptoms of these diseases without disturbing other functions. The separation of functional domains is particularly obvious in the case of GPi and allows DBS to be domain specific in this nucleus. Interventions targeting the STN are perhaps less specific because of the smaller size of the nucleus, the resulting tighter arrangement of functional subdivisions, the presence of broad dendritic fields, and the apparent overlap between neighboring terminal fields of corticosubthalamic projections.[13]

Figure 1. Anatomy of Cortex–Basal Ganglia–Thalamocortical Circuits

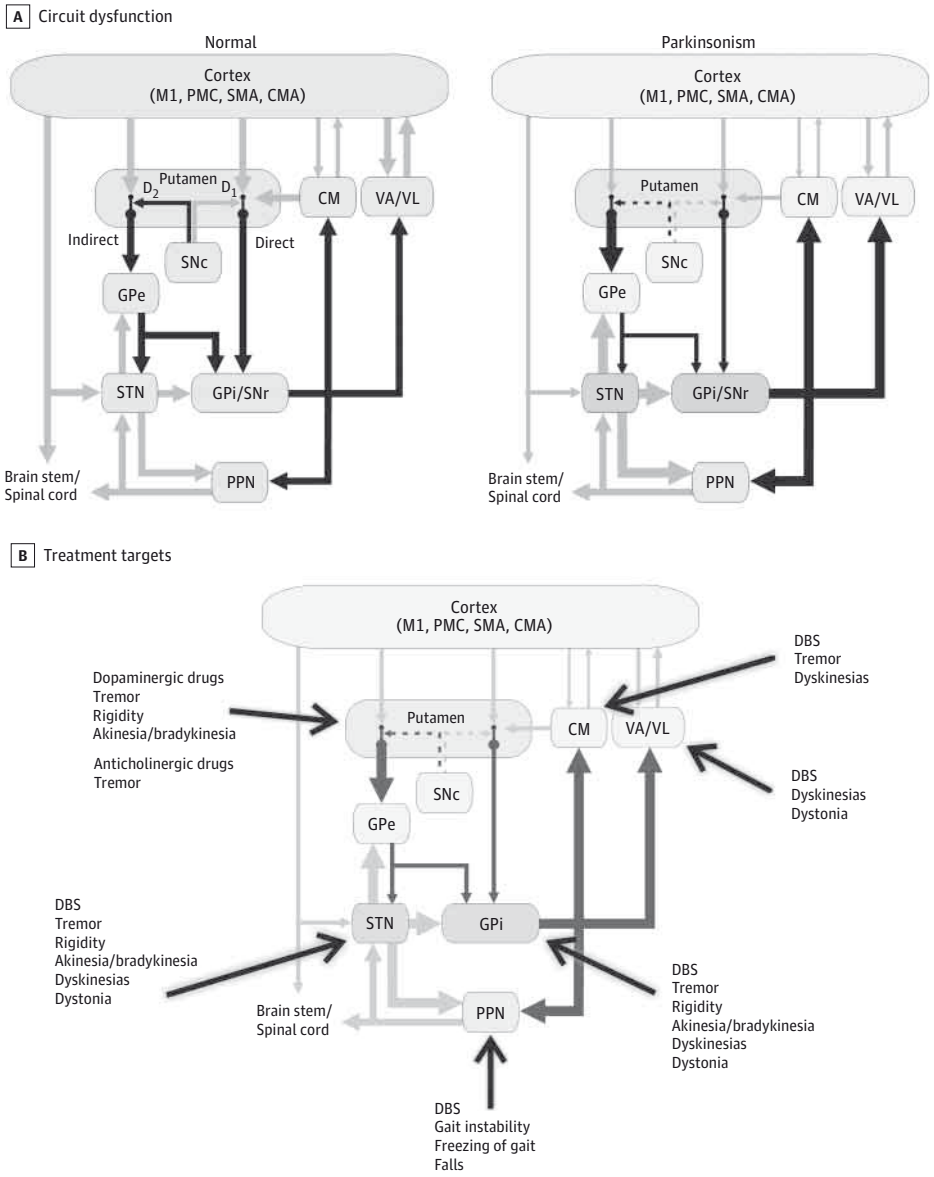


ACA indicates anterior cingulate area; CMA, cingulate motor area; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields; LOFC, lateral orbitofrontal cortex; M1, primary motor cortex; MD, mediodorsal; MDpl, mediodorsal nucleus of thalamus, pars lateralis; MOFC, medial orbitofrontal cortex; PMC, premotor cortex; SEF, supplementary eye field; SMA, supplementary motor area; SNr, substantia nigra pars reticulata; VAmc, ventral anterior nucleus of thalamus, pars magnocellularis; VApc, ventral anterior nucleus of thalamus, pars parvocellularis; VLa, anterior ventrolateral nucleus of the thalamus; VLcr, ventrolateral nucleus of thalamus, pars caudalis, rostral division; VLm, ventrolateral nucleus of thalamus, pars medialis; and VS, ventral striatum. Reprinted with permission from Elsevier Limited.[10]

The signs and symptoms of movement disorders result from dysfunction within the motor circuit (**Figure 2**A).[14] The motor circuit originates and terminates in cortical precentral and postcentral motor areas, including the motor cortex, premotor cortex, cingulate motor area, and supplementary motor area. The cortical areas of origin project in a highly topographic manner to the motor portion of the striatum, putamen, and postcommissural caudate nucleus, as well as to the motor area of the STN.[11] The preserved somatotopy and specificity of neuronal responses found at each node of the motor circuit reflects the topographic and parallel organization of connections within the motor circuit from the cortex through the basal ganglia and thalamus.

As the first leg of the motor circuit, corticostriatal projections terminate on dendrites of striatal medium spiny projection neurons. Separate families of γ-aminobutyric acid–ergic (GABAergic) topographic projections link the striatal motor areas to the external segment of the globus pallidus and to GPi and substantia nigra pars reticulate (SNr). The GPi and SNr are the major output nuclei of the basal ganglia and project to the thalamus and brainstem. The striatal projections to the GPi and SNr are divided into "direct" and "indirect" pathways. The direct pathway arises from medium spiny neurons that project monosynaptically to the GPi and SNr. These medium spiny neurons preferentially express dopamine D_1-like receptors. The indirect pathway arises from medium spiny neurons that project to the external segment of the globus pallidus and express dopamine D_2-like receptors. The indirect pathway encompasses subsequent projections from the external segment of the globus pallidus to the GPi, both directly and via the STN.

Figure 2. Parkinsonism-Related Activity Changes in the Basal Ganglia–Thalamocortical Motor Circuit and Targets of Medical and Surgical and Interventions



A, Parkinsonism-related changes in overall activity in the basal ganglia–thalamocortical motor circuit. Black arrows indicate inhibitory connections; gray arrows, excitatory connections. The thickness of the arrows corresponds to their presumed activity. B, Potential and actual targets of antiparkinsonian therapeutic interventions and signs and symptoms addressed with each target (arrows with open arrowheads). Deep brain stimulation (DBS) is approved by the US Food and Drug Administration only at the subthalamic nucleus (STN), internal pallidal segment (GPi), and nucleus ventralis intermedius targets for the treatment of Parkinson disease. CM indicates centromedian nucleus; D_1 and D_2, dopamine receptor subtypes; GPe, external segment of the globus pallidus; PPN, pedunculopontine nucleus; SNc, substantia nigra pars compacta; VA, ventral anterior nucleus of the thalamus; and VL, ventrolateral nucleus of the thalamus. For other abbreviations, see the legend to Figure 1. Reprinted with permission from Elsevier Limited.[14]

Another cortical input to the basal ganglia, the hyperdirect pathway, links frontal cortical areas to the STN.[15] It remains unclear whether the corticosubthalamic projection consists of collaterals of corticobulbar and corticospinal pathways or arises from separate cortical neurons. The corticosubthalamic pathway, together with the STN GPi connection (which is presumably shared with the indirect pathway) constitutes the hyperdirect pathway. This pathway may allow cortical inputs to reach the GPi and SNr with relatively shorter latencies than via the striatum. Similar to the other basal ganglia nuclei, the STN is divided into motor, oculomotor, associative, and limbic domains based on anatomical and physiologic studies. As mentioned above, cortical inputs to the STN may converge and be integrated to some extent.[13]

Projections from the motor circuit portions of the GPi terminate in portions of the anterior ventrolateral thalamic nucleus, whereas projections from the associative circuit (mostly from the

SNr) terminate in the ventral anterior thalamic nucleus. The primary projections to the different frontal cortical motor fields arise from thalamic neurons in the anterior ventrolateral thalamic nucleus and the ventral anterior thalamic nucleus and close the motor circuit. Considerable evidence indicates that the motor circuit is composed of multiple nonoverlapping parallel subcircuits centered on these separate motor fields.[16]

Collaterals from the main pallidofugal and nigrofugal projections to the ventral lateral thalamus are directed to the intralaminar nuclei of the thalamus: the centromedian and parafascicular nuclei. In primates, the centromedian nucleus receives input from motor areas in the GPi and SNr and projects to the motor portions of the putamen and STN, whereas parafascicular nucleus input and output are components of the associative and limbic circuits.[17] Unlike the cortical projections of the ventral anterior thalamic nucleus and the anterior ventrolateral thalamic nucleus system, projections from the centromedian and parafascicular nuclei to the cerebral cortex are sparse.

Another target of GPi and SNr axon collaterals is the brainstem, in particular, the pedunculopontine nucleus[18] and the superior colliculus. The pedunculopontine nucleus is a heterogeneous nucleus that gives rise to cholinergic projections to the thalamus, cerebellum, and other areas; noncholinergic projections to the substantia nigra pars compacta, STN, and globus pallidus; and descending projections to the pons, medulla, and spinal cord.[18] The pedunculopontine nucleus is a component of the brainstem locomotor region,[19] but it may also have other functions. For instance, lesions of the pedunculopontine nucleus in primates lead to a general reduction of movement.[20]

There is also growing evidence[21] for subcortical anatomical connections and physiologic interactions between the basal ganglia and the cerebellum across multiple functional domains. Thus, dysfunction in either cerebellar or basal ganglia networks may be directly propagated to the other. In movement disorders, there is evidence[22] that rest tremor in PD and some types of dystonia involve such subcortical circuit interactions. In light of these subcortical interactions between the cerebellar and basal ganglia networks, it is likely that pure basal ganglia or cerebellar disorders may not exist.

Interactions Between Direct, Indirect, and Hyperdirect Pathways in the Motor Circuit

A fundamental fact and starting point for all models of basal ganglia circuitry and function is that the output from the GPi and SNr consists of highly active GABAergic (inhibitory) neurons that continuously inhibit thalamic and brainstem targets. It is widely believed that activity in the motor circuit over the direct and indirect pathways facilitates or inhibits movements, respectively, and that this involves a modulation of GPi and SNr activity. Cortical phasic activation of medium spiny neurons of the direct pathway act to eventually reduce basal ganglia output with subsequent disinhibition of related thalamocortical neurons and facilitation of intended movement.[23,24] By contrast, activation of medium spiny neurons of the indirect pathway may lead to increased basal ganglia output and to suppression or prevention of movement. The balance between direct and indirect pathway activity may regulate the amplitude or speed or limit the extent or duration of ongoing movements.[22,23]

Activity over the hyperdirect pathway is proposed to play a role in preventing a premature, reflexive response by increasing inhibitory output to the thalamocortical targets, thus allowing time for the selection of the most appropriate response. This mechanism may be relevant in behavioral situations in which a switch from automatic or habitual control to voluntary control is desirable.[25]

The modulatory effect of dopamine on basal ganglia transmission (particularly in the striatum) is fundamental to basal ganglia physiology. Dopamine release facilitates corticostriatal transmission over the direct pathway while inhibiting corticostriatal transmission over the indirect pathway.[26] Given the proposed functions of the direct and indirect pathways, the net effect of striatal dopamine release therefore appears to be a reduction of basal ganglia output. Applied to the function of the motor circuit, this reduction would translate into a release of movement inhibition. In addition to its actions in the striatum, dopamine acts directly on receptors in the STN, pallidum thalamus, and cortex to influence discharge patterns and rates in these structures.[27] The behavioral effects of dopamine release at these sites are not well understood.

Phasic activation of dopamine receptors on medium spiny neurons also shapes the strength of glutamatergic (corticostriatal) transmission in the striatum, likely through modulation of long-term potentiation and depression, and may play a prominent role in reinforcement learning.[28] Based on inactivation and neuroimaging studies, the associative (prefrontal) circuit plays a prominent role in the initial learning of a motor task, and the motor circuit may contribute more to the execution of learned motor sequences.[29] It is not clear whether dopamine release in other basal ganglia locations and the cerebral cortex has similar functions in learning and plasticity. It also remains unclear how the apparent role of dopamine in the shaping of basal ganglia activity patterns intersects with the more concrete concepts of the regulation of basal ganglia output through the direct, indirect, or hyperdirect pathways.

Pathophysiology of Parkinsonism

The defining features of parkinsonism (ie, akinesia and bradykinesia, tremor at rest, and muscular rigidity) are the clinically most troublesome initial aspects for patients with PD. Parkinsonism is believed to result from decreased dopaminergic transmission in the motor portions of the basal ganglia, in particular, in the motor territory of the striatum (ie, the putamen), owing to progressive loss of innervation from dopaminergic neurons in the dorsolateral substantia nigra pars compacta. Parkinsonism is readily reversed by administration of levodopa, the precursor of dopamine. Unfortunately, the gradual emergence of levodopa-induced dyskinesias and motor fluctuations, as well as the development of dopamine-unresponsive features of gait and balance difficulties and freezing of gait, lead to increasing incapacitation, falls, and decreased quality of life.

Neuronal Activity Changes in Parkinsonism

Selective dopamine depletion can be achieved through exposure of the animals to toxins, such as 6-hydroxy-dopamine or MPTP. Studies in these models, as well as more recent studies in optogenetic models, have strengthened the view that firing rate changes in the direct and indirect pathways may contribute to parkinsonism (the so-called rate model of parkinsonism).[30] These studies showed a

reduction of neuronal discharge in the external segment of the globus pallidus and increased activity in the STN, GPi, and SNr. These changes may be a consequence of striatal dopamine depletion and may lead to increased inhibition of the external segment of the globus pallidus neurons via striatal output neurons of the indirect pathway, which, in turn, results in disinhibition of the STN, GPi, and SNr. The increased inhibitory basal ganglia output from the GPi and SNr to the thalamus may excessively inhibit thalamocortical interactions, which may then lead to slowness or absence of movement.

Changes in discharge patterns in the basal ganglia, thalamus, and cortex are now considered to be of equal or greater importance in the pathophysiology of parkinsonism than are the aforementioned rate changes.[30] One of the most discussed changes in the electrical activity of the basal ganglia of individuals with parkinsonian symptoms is the development of oscillatory fluctuations of neuronal spiking (particularly at frequencies <30 Hz) in the GPi, SNr, and STN as well as in brain areas that receive basal ganglia output, including the thalamus, pyramidal tract neurons of the motor cortex, and possibly also brain stem areas, such as the pedunculopontine nucleus. Other parkinsonism-related abnormalities are the emergence of abnormal synchrony between neurons and a tendency of neurons in the STN, GPi, SNr, and motor thalamus to discharge in oscillatory or nonoscillatory bursts. Oscillatory burst discharge patterns can occur with or without concomitant tremor.

Changes in Local Field Potentials

Oscillations can also be identified with local field potentials recorded from DBS electrodes in the basal ganglia. Such oscillations reflect synchronous membrane potential fluctuations in neuronal assemblies. Recordings demonstrate[31] the presence of oscillations in the 10- to 25-Hz range in the STN, GPi, and cortex in the unmedicated parkinsonian state and in the 60- to 80-Hz range when patients receive levodopa. More recently, abnormal coupling of the amplitude of γ-band oscillations and the phase of β-band oscillations have been described in cortical local field potentials.[32] Because the amplitude of local field potential oscillations correlates to some extent with the severity of aspects of parkinsonism, efforts are under way to use these signals in a closed-loop manner to control the delivery of DBS.[33]

Other Changes Contributing to Motor Disturbances in PD

Most of the extrastriatal portions of the basal ganglia, as well as the thalamus and cerebral cortex, receive dopaminergic innervation, and parkinsonism is associated with substantial loss of input in all of these areas. Local dopamine loss in the STN, GPi, and SNr has been shown[27] to lead to abnormal firing patterns in these nuclei and may be involved in the beneficial effects and adverse effects of dopaminergic medications.

Other structures and feedback loops, such as those involving the pedunculopontine nucleus and centromedian nucleus of the thalamus, likely also contribute to parkinsonism. Several studies[34] have shown that DBS of the centromedian nucleus of the thalamus area can ameliorate tremor and transiently reduce akinesia and bradykinesia. The projection from the centromedian nucleus of the thalamus to the striatum is also known to degenerate in patients with PD as well as in experimental animals with parkinsonism.[35,36] Reduced activity in the pedunculopontine nucleus has been linked to poverty of movement, and increasing pedunculopontine nucleus activity in parkinsonian animals ameliorates parkinsonism.[20] Furthermore, several studies[37] have shown that the cholinergic neurons of the pedunculopontine nucleus degenerate in PD, indicating that this degeneration may be crucial in the development of gait and balance disorders.

Many reports[38] have indicated parkinsonism-associated morphologic and functional plasticity of glutamatergic synapses and recipient dendritic spines in the striatum in dopamine-depleted animals and in patients with PD. Several studies have demonstrated that morphologic and functional changes also occur in the glutamatergic pathways terminating in the STN (including those from the cortex, thalamus, and pedunculopontine nucleus). Thus, *N*-methyl-D-aspartate glutamate receptor antagonists are known to ameliorate experimental parkinsonism, presumably by blocking transmission at terminals of the projections from cortex, thalamus or pedunctulopontine nucleus to the STN.[39,40] In addition evidence is emerging that the parkinsonian state is associated with profound plasticity at glutamatergic synapses in the STN,[41] which may secondarily affect GABAergic transmission at this site.[42] Similar to the findings in the striatum, it is not clear whether these changes are causative or maladaptive.

Changes in cerebellar circuits and in interactions between the cerebellum and basal ganglia may also be important in the pathophysiology of PD. Cerebellar involvement is most clearly recognized as contributing to parkinsonian tremor. Parkinsonian tremor appears to be strongly related to abnormal oscillatory activity in the cerebellar-receiving territory of the thalamus (nucleus ventralis intermedius), and DBS or lesions of this area are among the most effective treatments of isolated parkinsonian tremor. Tremor also clearly responds in many patients to dopaminergic therapy, although often only to high doses of these treatments, and it is not clear how dopamine loss is linked to tremor.[22] The degree of striatal dopamine loss does not correlate with the severity of tremor although the amount of dopamine loss in the GPi and the retrorubral area does correlate with tremor.[22]

Targeting Neurologic Signs and Symptoms Through Neuromodulation

The fact that virtually all movement disorders of basal ganglia origin appear to result from motor circuit dysfunction allows for selective interventions with ablation or DBS (Figure 2B), specifically in the STN and the GPi, which is highly effective for the cardinal features of PD as well as dystonia and drug-induced motor fluctuations and dyskinesias. Although the external segment of the globus pallidus is not currently targeted, it has been shown[43] that DBS of this region may also be effective for PD.

Unfortunately, interventions at the conventional surgical targets (STN or GPi) are generally not effective against levodopa-unresponsive gait and balance disturbances and freezing of gait. As mentioned above, degeneration of cholinergic pedunculopontine nucleus neurons is implicated in the gait and balance disturbances. In fact, low-frequency stimulation in this area, presumably by activating remaining neurons and their axons, may improve parkinsonian gait problems.[44]

Thalamic targets have also been used for DBS or ablative procedures in the treatment of PD. Ablation or DBS of the cerebellar re-

cipient portions of the thalamus is effective for treatment of tremor, including the rest tremor in PD,[45] but has little effect on akinesia and bradykinesia. Ablation or DBS of the pallidal-receiving area of the thalamus has been found[46] to be effective for drug-induced dyskinesias and some forms of dystonia but seems to have little effect on bradykinesia or akinesia, suggesting that the basal ganglia thalamocortical pathway may be more involved in the expression of abnormal movements rather than akinesia and bradykinesia. Abnormal and excessive GPi output to the pedunculopontine nucleus may disrupt and inhibit activity in this nucleus and may play a greater role in akinesia than is usually assumed.[20]

Targeting of the motor circuit portions of the STN, GPi, and thalamus for ablative or stimulation approaches is surprisingly effective for a diverse group of movement disorders, suggesting that the surgical interventions do not target specific pathophysiologic abnormalities. Instead, they appear to eliminate disruptive basal ganglia output regardless of its specific character. This finding is most easily understood in the case of pallidotomy or subthalamotomy, which directly interrupts abnormal outflow from the basal ganglia. Although the actions of DBS are complex and controversial, they may be viewed in part as acting in a fashion similar to ablation. In this case, an "informational lesion" may be achieved by overriding and blocking transmission of abnormal activity.[47] Ablative or functional lesions of basal ganglia output may subsequently allow the relatively intact portions of the motor system downstream from the basal ganglia to resume more normal functions. It would thus appear that the signs and symptoms of movement disorders that result from disordered basal ganglia activity simply reflect the disturbance induced by the altered activity in brain networks that are targeted by the abnormality and do not represent or reflect the absence of the normal functions of the basal ganglia.

The Paradox of Stereotactic Surgery

An important aspect and major element of the rationale for surgical ablation and DBS is the fact that the interventions are highly successful in ameliorating the signs and symptoms of these disorders but do not cause obvious or significant impairment of voluntary movement. This is the paradox of stereotactic surgery discussed in a well-known article by Marsden and Obeso.[48] These authors speculated that "the motor circuits of the basal ganglia are part of a distributed motor system which can operate, albeit imperfectly, in the absence of striato-pallido-thalamo-cortical feedback. There may, however, be subtle defects in motor performance after thalamic and pallidal lesions which have escaped attention."[48(p877)]

As mentioned above, numerous proposals for the general function of the basal ganglia have been advanced, but, as argued elsewhere,[49] these functions are not solidly established and are difficult to reconcile with the outcomes of both animal studies and stereotactic surgery. The dramatic and immediate effects of ablation and DBS and the absence of intervention-related motor impairments in patients with PD argue against an essential role of the basal ganglia in the basic control of movement (through processes such as response inhibition or action selection) and favor the view that the basal ganglia motor circuit primarily serves higher-order functions, such as reinforcement learning and the regulation of global movement "vigor."[50] Even if deficits exist, it may be very difficult to detect those resulting from interference with such functions in patients who have preexisting significant, widespread disturbances.

Conclusions

During the past 2 decades, there has been remarkable progress in understanding the pathophysiologic basis of movement disorders such as PD, clarifying the effects of, and rationale for, current surgical procedures and developing novel surgical targets. Deep brain stimulation has also proved to be a useful tool for exploring and studying function and dysfunction in movement disorders as well as other neuropsychiatric disorders.

To progress further and to develop more effective treatment strategies for patients with movement disorders, we need a clearer understanding of the network structure and function and of the nature of the signature network disturbances in neurologic and psychiatric disorders, in particular regarding the contribution of disturbed interactions between the hyperdirect, direct, and indirect circuits as well as the contribution of interactions between the basal ganglia, cerebellar, and brainstem networks. Also much needed is a clearer understanding of the mechanisms of action of DBS and the development of novel targets and stimulation paradigms. Finally, there remains a need to identify better ways of addressing both drug-resistant motor and nonmotor symptoms of PD.

ARTICLE INFORMATION

Accepted for Publication: July 28, 2015.

Published Online: September 26, 2015. doi:10.1001/jamaneurol.2015.2397.

Author Contributions: Drs DeLong and Wichmann had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Administrative, technical, or material support: All authors.

Conflict of Interest Disclosures: None reported.

Funding/Support: The writing of this article was supported by grant P50-NS071669 from the National Institutes of Health/National Institute of Neurological Disorders and Stroke and grant P51-OD011132 from the National Institutes of Health/Office of Research Infrastructure Programs to the Yerkes Center.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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