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Anatomy and Physiology of the Basal Ganglia: Implications for Deep Brain Stimulation for Parkinson's Disease

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Abstract: Central to surgical management of movement disorders is an understanding of the anatomy and physiology of the basal ganglia. The basal ganglia have been a target for neuromodulation surgery since Russell Meyers' pioneering works in the late 1930s. With the development of deep brain stimulation as the gold standard of surgical intervention for movement disorders, there has been a concomitant evolution in the understanding of the role the basal ganglia plays in the genesis of normal and abnormal motor behaviors. The fundamental concept of the cortico–striato–pallido–thalamocortical loop will be explored in the context of deep brain stimulation. The current targets for deep brain stimulation for Parkinson's disease, the subthalamic nucleus, the globus pallidus internus, and the ventral intermediate nucleus, will be discussed in the framework of the current physiological and anatomical models of Parkinson's disease (PD). Finally, the current understandings of the mechanisms underpinning the beneficial effects of deep brain stimulation for PD will be discussed. © 2006 Movement Disorder Society

Key words: basal ganglia; deep brain stimulation; Parkinson's disease

Contemporary movement disorder neurosurgery evolved from empirical observations in patients with movement disorders undergoing lesions placed in various regions of the neuraxis. The basal ganglia have been a target for neuromodulation surgery since Russell Meyers' pioneering works in the late 1930s. Under the hypothesis that abnormal movements were mediated by the neopallidum, Meyers extirpated the anterior two-thirds of the head of the caudate through an anterior transventricular approach. The idea to excise the caudate head reportedly arose from a chance observation by Browder, who during a frontal lobectomy carried the extirpation far into the caudate nucleus in a patient with parkinsonian features. When the patient awoke, Browder observed that the shaking had stopped.[1]

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Irving Cooper's serendipitous observation in 1952 of the virtual disappearance of tremor and rigidity without the loss of motor strength in a parkinsonian patient on whom he ligated the anterior choroidal artery further implicated the role of the basal ganglia and the thalamus in movement disorder physiology/surgery. Spiegel and Wycis brought the tool of stereotaxis to movement disorder surgery in the basal ganglia in 1947, and Hassler similarly pioneered stereotactic surgery in the ventrolateral (VL) thalamus.

It was not until the 1980s that an a priori rationale for targeting the basal ganglia for movement disorders was developed by Albin and colleagues.[2] Similar to Hughlings Jackson's observation that localizing damage and localizing function are two different things, it is argued that observations of the effect of lesions in the basal ganglia on motor function have offered very little insight into the actual functions of the basal ganglia. Nevertheless, stereotactic lesions for Parkinson's disease continued to be utilized despite the near cessation in movement disorder surgery caused by the application of levodopa to the treatment of Parkinson's disease (PD) patients by

Hornykiewicz and Birkmeyer in 1961 as complications associated with medical therapy became apparent over time. The modern stereotactic lesion targets in use are the ventral intermediate nucleus (Vim) thalamus, first described by Hassler, the ventrolateral globus pallidus internus (GPi), reintroduced by Laitinen in the early 1990s, and, more recently, the subthalamic nucleus (STN).[3,4]

A major development in movement disorder surgery has been the application of electrical stimulation, in the form of deep brain stimulation (DBS), to stereotactic surgery for PD. The application of this new technology stemmed from the observations that bilateral thalamic or pallidal lesions were associated with a high incidence of side effects and the empiric observation during lesion surgery that high-frequency (>100 Hz) stimulation in candidate lesion targets often produced amelioration of movement disorder symptoms.[5–7] Today, DBS has become the gold standard for the surgical treatment of Parkinson's disease. This has occurred in part because the side effects associated with stimulation therapy are reversible and one can change stimulation parameters to optimize clinical benefit.

The current targets of DBS for Parkinson's disease are the Vim (VLp) thalamus,[8] the ventrolateral globus pallidus pars internus (GPi),[9] and the subthalamic nucleus of Luys (Vim).[10] The indications for Vim DBS are confined largely to tremor, while the other two targets are being used to address all the cardinal motor symptoms of PD as well as levodopa-induced dyskinesias and motor fluctuations. Although the vast majority of centers currently target the STN for the treatment of PD, the relative advantage of GPi vs. STN as a target for DBS in PD is still a matter of investigation and debate. Despite the proven and durable benefits of DBS for PD, the exact mechanism underlying its beneficial effect also remains a matter of debate. Early hypotheses that DBS acts like a lesion stemmed from the observation that stereotactic lesions and DBS have similar clinical results. However, more recent studies have suggested stimulation may actually mediate its beneficial effects by increasing output from the stimulated structure, not suppressing it.[11] Just as new insights into basal ganglia physiology led to the resurgence of lesioning therapy for PD, new and improved applications of DBS will continue to evolve as we improve our understanding of the pathophysiology of disease and the mechanism(s) underlying DBS.

ANATOMICAL CONSIDERATIONS

The essence of any neurosurgical procedure, even one that inherently seeks to alter physiology, is an understanding of anatomy. The anatomical relationships of basal ganglia–thalamocortical circuits provide the framework by which DBS may be applied to the treatment of neurological disease. Much of what is currently known about the anatomy of these structures stems from Albin, Alexander, and Delong's work in the mid-1980s.[2,12] The hallmark of their work involves the description of a network of basal ganglia–thalamocortical circuits subserving different functions. These cortico–striato–pallido–thalamocortical loops (CSPTC) are viewed as largely segregated networks that involve projections from specific cortical areas to separate areas within subcortical structures that project recurrently in a closed-loop manner to the same areas of cortex through specific thalamic relay nuclei.[13] In this scheme, the striatal structures of the caudate and putamen serve as the input stage, while the GPi and the substantia nigra pars reticularis (SNr) serve as the output stage.[14]

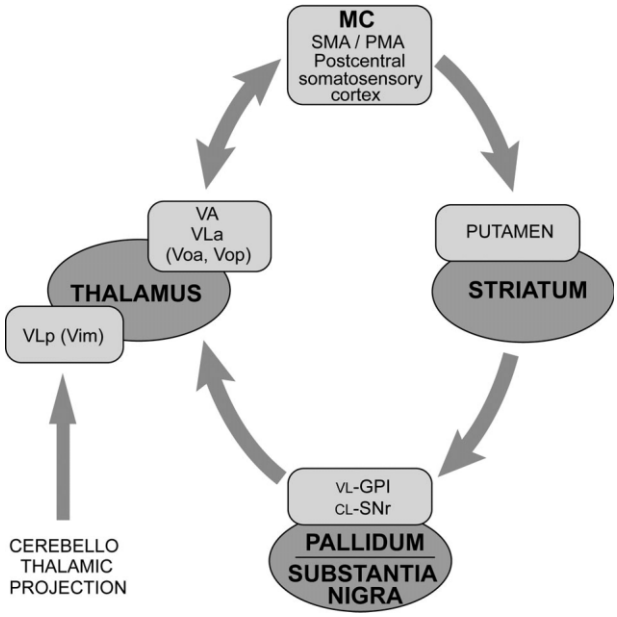

FIG. 1. General Delong overview of the various CSPTC loops. MC, primary motor cortex; SMA, supplementary motor area; PMA, premotor area; vl-GPi, ventrolateral portion of globus pallidus pars interna; cl-SNr, caudolateral portion of substantia nigra pars reticulata; VLp, posterior portion of ventral lateral thalamic nucleus (Vim–ventralis intermedius in the Hassler terminology); VLa, anterior portion of the ventral lateral thalamic nucleus (Voa–ventralis oralis anterior Vop–ventralis oralis posterior in the Hassler terminology); VA, ventral anterior thalamic nucleus.

The most relevant of these loops in the genesis of Parkinson's disease and the application of DBS surgery is the motor circuit (Fig. 1). The motor circuit involves precentral motor (especially Brodmann areas 4 and 6) and postcentral somatosensory projections to the putamen. The putamen in turn projects to the output structures of the ventrolateral GPi and the caudolateral SNr. These structures project largely to the thalamic relay

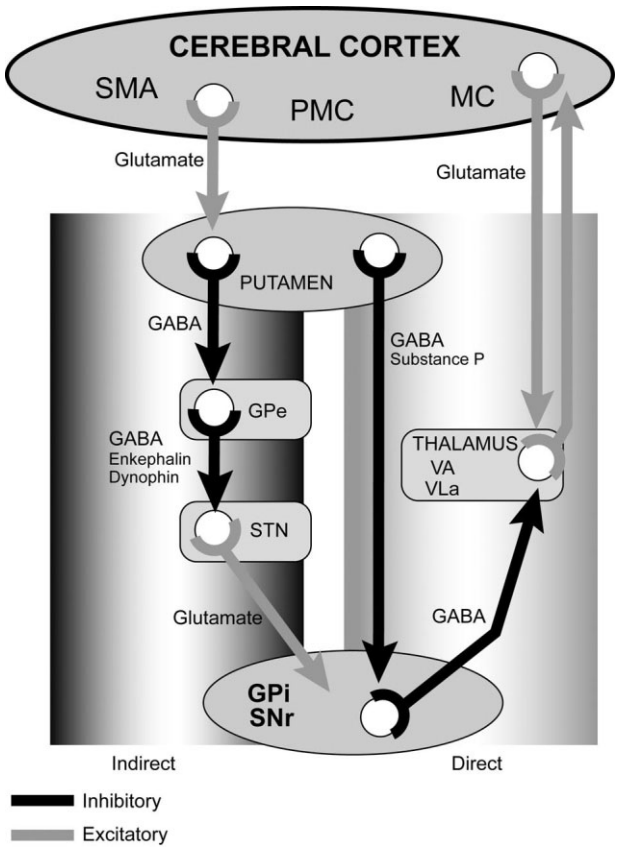

FIG. 2. Original Alexander and Delong model of the direct and indirect pathways. PMC, premotor cortex; GPe, globus pallidus pars externa; GABA, gamma amino butyric acid.

nuclei VA and VLa in the Hirai and Jones terminology, roughly corresponding to the Voa and Vop thalamic nuclei in the Hassler terminology.[15] The segregation of these output structures to the different thalamic targets may represent specialization in function with the predominant GPi projections to the VLa involved with sequencing and execution of movements and the SNr projections to VA involved in the planning of movement.[16] The VLp thalamic nucleus, corresponding to the Vim in the Hassler terminology, is largely a cerebellar receiving area. It is believed to be important in the genesis of tremor (as opposed to the other cardinal symptoms of PD) whether in PD, essential tremor, or outflow tremor as seen in multiple sclerosis or posttraumatic tremor.

Within the motor loop itself, there exist two main pathways to the output structures of the basal ganglia: GPi and SNr, the indirect and the direct pathways (Fig. 2). In the indirect pathway, information flows from the putamen in a polysynaptic fashion to the globus pallidus pars externus (GPe), the STN, and then ultimately to the GPi/SNR. In the direct pathway, the activity projects largely monosynaptically from the putamen to the GPi/SNr. Another key difference between the direct and the indirect pathways is that source neurons in the direct pathway contain the neuropeptide substance P, while the indirect pathway neurons carry the neuropeptides enkephalin and dynophin.[13]

Within these two pathways, all but one intrinsic and output projections are inhibitory, mediated by the neurotransmitter GABA. The exception to this is the projection of the STN to GPi/SNr that is mediated by glutamate and excitatory in nature. Projections from the cortex to basal ganglionic structures and the reciprocal thalamocortical projections are likewise excitatory and glutamatergic.

More recently, there have been other projections within this network that have important implications to the mechanisms underlying DBS in PD (Fig. 3). The STN has a direct connection to SNc and has a reciprocal projection to the GPe[17] and CM/Pf,[18] while the GPe has been found to have direct projections to the GPi, SNr, and the reticularis nucleus of the thalamus (NRT).[17] A direct cortical projection, from primary motor cortex,

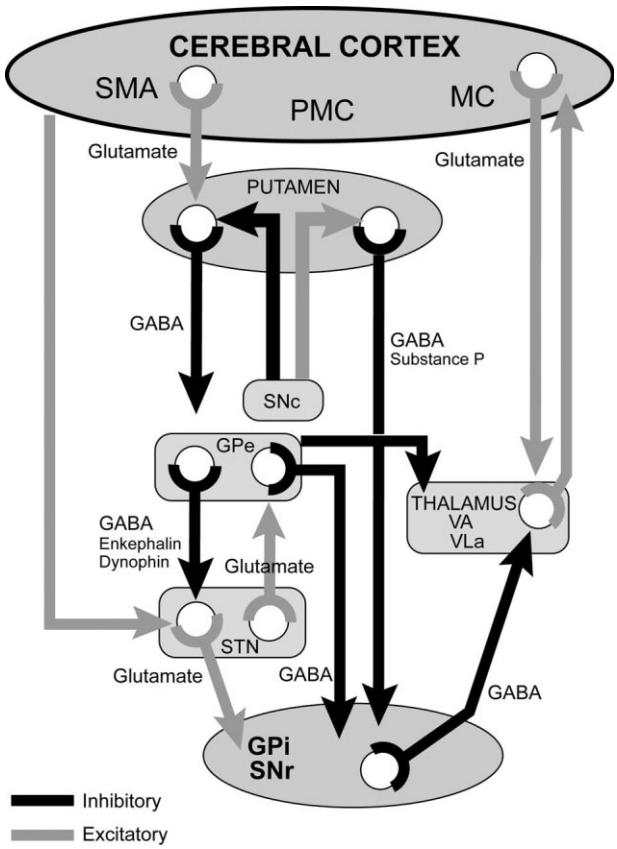

FIG. 3. Indirect and direct pathways + added STN and globus pallidus pars externa (GPe) connections. SNc, substantia nigra pars compacta.

SMA, and PMA to the STN, has been described and may be important in relaying sensory input to the basal ganglia[18–20] and synchronizing oscillatory activity in the cortex, STN, and pallidum.[21]

One of the most powerful modulators of this network is the neurotransmitter dopamine. Dopaminergic input to this network comes from the substantia nigra pars compacta (SNc) and predominately impacts neurons in the putamen, in the case of the motor subcortical circuits, but may also affect GPi and thalamic neurons directly given observations of dopaminergic receptors in these nuclei.[22] Dopamine can have either an inhibitory or excitatory effect on striatal neurons depending on the receptor subtype. D1 receptors result in an excitatory effect while D2 receptors result in an inhibitory effect. The net effect of dopaminergic input to the striatum is to reduce basal ganglia output and subsequently disinhibit thalamocortical activity. Furthermore, while this remains a matter of debate, dopaminergic activity also has the net effect of facilitating activity through the direct pathway over the indirect pathway.[23]

There are other networks outside the basal ganglia network described above that play important roles in the genesis of PD symptoms (Fig. 4). These structures may ultimately be targets for DBS therapy for PD symptoms that are not well addressed by STN or GPi stimulation, such as balance and gait difficulties. They may also explain why DBS in currently used targets may influence nonmotor aspects of PD, such as behavioral reinforcement, attention, and sleep via direct spread of stimulation to these sites as well as propagation of stimulus trains via adjacent fiber pathways.[24,25] These networks serve to integrate cortical, thalamic, basal ganglionic, and spinal activity. Besides the direct projections to striatum described above, cortical projections may reach the striatum via the CM/Pf thalamic complex. The output structures of the basal ganglia GPi/SNr give rise indirectly to descending pathways to the brainstem and spinal cord as well as the direct ascending thalamocortical projections. Two significant receiving areas are the pedunculopontine nucleus (PPN) and the midbrain extrapyramidal area (MEA). These regions via excitatory cholinergic and glutamatergic projections may influence both ascending and descending projections. The reciprocal ascending pathways target the CM/Pf and reticular thalamus as well as the STN. The descending influences project onto spinal motor neuronal pools.

PHYSIOLOGICAL CONSIDERATIONS

Dopamine exerts a powerful influence on the flow of activity through the basal ganglia circuits described above. The loss of dopaminergic input to the striatum results in the characteristic symptoms in PD of tremor, bradykinesia, and rigidity. The hallmark physiological change that results from this dopamine loss is, according to the most-accepted models of PD, the net increase of information flow through the indirect over the direct pathway.[26] This would in turn result in the net hyperactivity of GPi/SNr and subsequent inhibition or "braking" of target thalamocortical activities.

A review of functional imaging studies in PD corroborates aspects of this model. Many different cortical and subcortical areas have been implicated in the genesis of PD symptoms by virtue of their metabolic and blood flow–related changes during the untreated and treated disease states. Two prevailing findings have been most consistent. The first is a relative increase in pallidal metabolism in PD patients.[27,28] The second is the near-universal finding of decreased metabolism and blood flow in SMA and prefrontal motor cortices that reverses with dopaminergic therapy.[29–31] Both of these findings are consistent with excessive activity in the STN and GPi neurons.

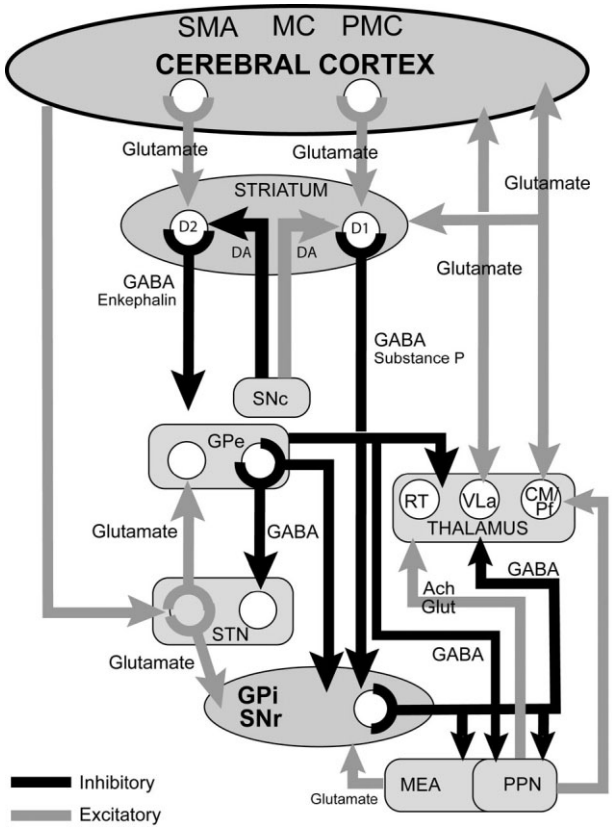

FIG. 4. Indirect and direct pathways + added STN and GPe connections + midbrain and other thalamic structures. RT, nucleus reticularis thalami; CM/Pf, centromedian/parafasicularis thalamic nucleus; PPN, pedunculopontine nucleus; MEA, midbrain extrapyramidal area; Ach, acetylcholine; DA, dopamine; glut, glutamate.

Two prevailing models have been hypothesized to explain what specific changes are occurring in neuronal activity as a result of dopaminergic depletion: a rate model and a pattern model. Until recently, the rate model has been the most accepted model. The rate model of PD is a literal interpretation of the effect of dopaminergic depletion on the anatomical model illustrated above. Hypokinetic disorders such as PD are the result of an increase in activity in the GPi as a result of increased STN excitatory input. Hyperkinetic disorders such as dystonia, hemiballismus, and drug-induced dyskinesias conversely are the result of decreased GPi neuronal activity due to changes in both the direct and the indirect pathways. Consistent with the predictions of the rate model, microelectrode recording in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–treated monkeys (the primate model of PD) and PD patients undergoing stereotactic movement disorder surgery have reported decreased mean discharge rates in GPe and VLa and increased mean discharge rates in the STN and GPi.[25,32–35]

The finding of alterations in rate of pallidal, STN, and thalamic nuclei involved in PD in both primates and humans appears to hold that these rate changes underlie the pathophysiology in PD. Yet, if one explores the experience with stereotactic lesion surgery for movement disorders, the concept of rate as the sole pathognomonic change in PD becomes tenuous. The fact that lesions along the circuit described above can ameliorate PD symptoms reveals a paradox in the rate model of PD.[36] According to the rate model, ultimately it is the decreased rate in VLa that gives rise to PD symptoms; it would predict that a further decrease in rate would exacerbate symptoms. Yet stereotactic lesions made in the motor thalamus ameliorate PD symptoms. Furthermore, it would be expected that pallidal and subthalamic nucleus lesions would lead to a disinhibition of the thalamus and promote increased unwanted motor activity such as drug-induced dyskinesias.[37] Yet the opposite is found with pallidotomy for the treatment of such hyperkinetic disorders as dystonia and hemiballismus.[38] Clearly, rate alone cannot explain the manifestation of PD symptoms. In addition to rate, however, other changes have been observed in the anatomical areas involved in the PD model. There appears a consistent alteration of patterns of activity in neuronal pools within the STN, GPi, and VLa with a greater tendency to discharge in bursts and a higher degree of synchronized oscillatory activity among neighboring neurons.[14] The direct connections between the cortex and STN as well as the basal ganglia and thalamus described above may serve to predispose the circuit to synchronized oscillatory activity. It is well known that thalamic neurons fire in distinct patterns depending on their resting membrane potentials.[39] These neurons change from a largely tonic pattern of activity to an oscillatory/bursting pattern when they are either hyperinhibited or disfacilitated. With dopamine depletion, thalamic targets of pallidal projections receive more inhibitory influence than in the normal state; these cells tend to fire in bursting patterns that would then be reflected at the cortical level. Furthermore, bursting activity in the STN and GPi may be transmitted to thalamic neurons, as such recurrent bursting projections from cortex to striatum and STN would serve to further entrain these basal ganglia neurons to fire in a bursty oscillatory fashion. Projections from GPe to the NRT as well as GPi projections to PPN could in turn further amplify the tendency of other neuronal pools to fire in a synchronous and oscillatory fashion by virtue of their widespread connections to other thalamic subnuclei and cortical regions. Thus, the circuit modeled above not only would be expected to have rate-related changes due to dopaminergic depletion, but substantial changes in bursting and synchrony indexes. An additional observation that may also contribute to the changes in motor function in patients with PD and in the MPTP animal model of PD is the abnormally widened receptive fields of neurons in the basal ganglia and thalamus. Microelectrode recording (MER) data in STN, GPi, and thalamus have shown a lack of specificity and increased responses of these neurons to passive limb manipulations in PD compared to the normal state.[30,40–42]

Widespread oscillatory activity has been implicated in several models of PD. One hypothesis regarding basal ganglia function holds that these networks act to compare efferent iterations of motor programs with peripheral sensory input. It is possible that certain phasic oscillatory activity would erroneously mimic excessive sensory feedback of velocity, amplitude, or acceleration of movement. This, in turn, could lead to a slowing or premature arrest of ongoing motor behaviors.[14] Another model has proposed that the abnormal motor behaviors seen in movement disorders is the result of aberrations in lateral inhibition of competing motor programs surrounding the locus of normal motor behavior. Each type of movement disorder in turn has a specific pattern of aberration of this lateral inhibition.[43]

In 1999, Llinas and colleagues[44] proposed the concept of thalamocortical dysrhythmia (TCD). This model proposed that the fundamental pathophysiology that results in the symptoms of PD is an increase in power of thalamocortical oscillatory activity in the theta band (4–8 Hz). This coherent theta activity, the result of a resonant interaction between thalamus and cortex, is due

to the generation of low-threshold calcium spike bursts by thalamic cells. The presence of these bursts is directly related to thalamic cell hyperpolarization, brought about by either disfacilitation or excess inhibition (such as the increased GPi activity found in intraoperative MER data and primate models of PD). Such oscillation, by activating return corticothalamic pathways entrains, through the reticular thalamic nucleus and through direct thalamic activation, the intralaminar thalamic system. The result via the widespread connections of the intralaminar thalamus to cortical layer I is the promotion of large-scale low-frequency oscillatory coherence. At the cortical level, the reduction of lateral inhibition due to these areas entrained by low-frequency oscillation promotes a surrounding area of coherent gamma band frequency oscillation and thus positive symptoms such as tremor and rigidity.[44] Magnin and colleagues[45] have tailored surgical approaches in order to disrupt this synchronized oscillatory activity. In 2001, they reported the results of pallidothalamic tractotomy in 21 patients. Given the predominance of GABAergic projections from the pallidum to the thalamus in this region, such a lesion would be expected to reduce the hyperpolarization of thalamic neurons. While the initial results seem positive, the study itself was open-label and awaits replication by other centers.

DBS MECHANISMS IN LIGHT OF ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

The exact mechanisms of how DBS modulates neuronal network function resulting in the amelioration of the symptoms of PD remain under debate. Initial hypothesis concerning DBS mechanism of action was based on the observation that stereotactic lesions and high-frequency electrical stimulation have similar clinical results when applied to the same target. The initial interpretation of this clinical similarity was that DBS functioned by depressing neural function at the target site of stimulation, i.e., a "functional lesion."[46] There are several problems with this explanation. This concept of a functional lesion still suffers from the logistical fallacy of the Marsden paradox in much the same way as stereotactic lesions, in which lesions in a supposedly already "hyperinhibited" motor thalamus do not further impair voluntary movement.[47] Electrical stimulation can affect multiple regions of the neuron: dendrite, soma, axon hillock, and axon. In 2003, Shen and colleagues[48] found multiple effects of high-frequency stimulation (HFS) on synaptic function, inhibitory and facilitatory, further adding to the complexity of the effects of electrical stimulation in a neural network. Depending on the extent of what portions of the neuron is being affected by HFS, experimental data exist to support excitation, inhibition, and changes in network synchrony as mechanisms underlying DBS function.

In support of inhibition, both historical and recent evidence have implicated synaptic failure as a consequence of HFS. In 2002, Urbano and colleagues[49] performed a series of experiments looking at the effects of HFS in the thalamus, similar to clinical DBS parameters, on cortical projections. The axons themselves were demonstrated to be able to follow high-frequency stimulation trains as high as 120 Hz. In contrast, the cortical responses began to decrement starting at frequencies of 60 Hz and higher. Inhibition has also been demonstrated to play a role at the level of the soma in neurons exposed to extracellular HFS. Several studies have shown the suppression of STN neuronal activity during STN HFS.[50,51] Based on this observation, the effect of this net inhibition would be to remove the effect of increased and abnormal patterns of neuronal activity emanating from the nuclear area being stimulated.

Contrary to the above observations, HFS has also been shown to excite neural elements. Historical data based on chronaxie experiments have shown that the most sensitive element in gray and white matter undergoing extracellular HFS equivalent to DBS parameters is the axon and that stimulation drives the activity of this structure.[52,53] More recent data have corroborated this finding in primate models of DBS. Hashimoto and colleagues[54] have shown that DBS in the STN had the net effect of increasing the mean firing rate of GPi neurons, implying the activation of glutamatergic subthalamo–pallidal projections. A similar effect was seen with GPi stimulation with reduction in firing rates in the VL thalamus secondary to excitation of inhibitory pallidothalamic GABAergic projections.[55] Looking at concentrations of neurotransmitters downstream from implanted STN electrodes, Windels and colleagues[56] found a significant increase in glutamate in GPi and SNr and a significant increase in GABA in SNr following trains of high-frequency stimulation. In 2000, Montgomery and Baker[57] expanded on this excitatory effect of DBS in their model of DBS mechanisms. This excitation effect may also be fundamental to facilitating a proposed model of DBS mechanism utilizing the concept of stochastic resonance in which a subthreshold normal signal, lost in the noise of a deranged neural network, is amplified by the addition of a regular noise (in this case HFS) by a constructive interference paradigm.

Besides simple excitation and inhibition effects of HFS, there is a growing body of evidence that DBS produces alterations in oscillatory behavior in the networks undergoing HFS. Hashimoto and colleagues[54]

showed a time-locked alteration of firing patterns in GPi neurons receiving projections of STN neurons influenced by DBS. Devos and colleagues[58] have shown that this effect on oscillatory activity is reflected at the cortical level in patients undergoing STN DBS for PD. This effect can be explained by taking into account the data above demonstrating the excitatory nature of HFS on axonal projections combined with the orthodromic and antidromic anatomical connections of STN to the cortex.

The growing body of functional imaging data appears to corroborate the excitatory influence of DBS on neural networks. PET and fMRI studies have consistently demonstrated increased metabolism/BOLD signal changes in various structures along the subcortical network described above with STN and GPi DBS such as the putamen, pallidum, subthalamic nucleus, and thalamus.[29,59,60] As these increases reflect local changes in synaptic activity,[61] this corroborates the presumed driving effect of DBS on axonal elements. Furthermore, this increase in local synaptic activity has also been demonstrated at cortical areas directly connected to this subcortical network, especially SMA in the case of STN DBS and primary motor cortex in the case of Vim DBS.[28] Inhibition of local metabolic and, by implication, synaptic activity has also been demonstrated in the context of Vim DBS for tremor.[62]

Thus, there are apparent conflicting data in the literature regarding the inhibitory or excitatory effects of DBS. Certainly, inherent differences in experimental paradigms may explain some contradictions.[5] However, the beneficial effects of DBS may involve all of these apparently contradictory mechanisms. McIntyre and Grill[63] have demonstrated the variable effect on extracellular HFS on neural elements. The effective current density decreases along the radial distance from a DBS electrode. The gradient of current density could explain the apparent contradictions presented above. Very close to the epicenter of the area of effect of a DBS electrode would be an area of higher current density. In this region, stimulation may indeed be above the level of somatic activation and could lead to a depolarization block of somatic elements. In addition, the axons themselves could fire at a 1:1 ratio between stimulus and axonal spike and result in the ultimate synaptic failure of synapses downstream at frequencies greater than 100 Hz.[45] Further away from this epicenter, the current density would decrease. The simulation current could be below the chronaxie of somatic effect while still activating axonal elements, both of passage and emerging from the target nucleus. These axonal elements, due to the lower current density, may fire at ratios less than 1:1 and be below the frequency that would lead to synaptic failure. The net result could indeed be the overall alteration of patterns of activity to a more regular pattern that is better tolerated by the system and manifested by improved motor behavior. Further refinement of the waveforms of the electrical stimulus, beyond the rectified square wave currently used in DBS, may allow a highly selective activation of different components of the neuron.[64]

CONCLUSIONS

Understanding the anatomy and physiology of Parkinson's disease is an evolving process. Surgical intervention is by definition an anatomically based endeavor. Improved understanding of the functional organization of basal ganglia–thalamocortical circuits in the MPTP primate model of PD led to the renaissance of movement disorder surgery in the 1990s. The insights gained by the new wave of stereotactic lesion procedures led to refinements in surgical technique, and with the advent of DBS in the field of movement disorder surgery, a nonablative means was developed to treat patients with movement disorders. An additional benefit of DBS has been to provide insight into the pathophysiology of PD and to generate alternative models of PD. Further exploration of the anatomical and physiological basis underlying the development of movement disorders and the mechanisms by which DBS improves motor function will lead to refinement of current applications of DBS for the treatment of PD and the development of new applications for DBS surgery.

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