From symphony to cacophony: Pathophysiology of the human basal ganglia in Parkinson disease

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Abstract

Despite remarkable advances, the relationship between abnormal neuronal activity and the clinical manifestations of Parkinson disease (PD) remains unclear. Numerous hypotheses have emerged to explain the relationship between neuronal activity and symptoms such as tremor, rigidity and akinesia. Among these are the antagonist balance hypothesis wherein increased firing rates in the indirect pathway inhibits movement; the selectivity hypothesis wherein loss of neuronal selectivity leads to an inability to select or initiate movements; the firing pattern hypothesis wherein increased oscillation and synchronization contribute to tremor and disrupt information flow; and the learning hypothesis, wherein the basal ganglia are conceived as playing an important role in learning sensory-motor associations which is disrupted by the loss of dopamine. Deep brain stimulation (DBS) surgery provides a unique opportunity to assess these different ideas since neuronal activity can be directly recorded from PD patients. The emerging data suggest that the pathophysiologic changes include derangements in the overall firing rates, decreased neuronal selectivity, and increased neuronal oscillation and synchronization. Thus, elements of all hypotheses are present, emphasizing that the loss of dopamine results in a profound and multifaceted disruption of normal information flow through the basal ganglia that ultimately leads to the signs and symptoms of PD.

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1. Introduction

The basal ganglia (BG) are a group of subcortical nuclei involved in multiple-partly segregated parallel loops that modulate cortical activity (Alexander et al., 1986; Alexander and Crutcher, 1990; Alexander, 1994; Hoover and Strick, 1999). These loops share some common features in that they begin with convergent input from the cortex to the striatum (caudate and putamen) and then proceed through different pathways to the globus pallidus internus (GPi) or the substantia nigra pars reticularis (SNpr), which are the output nuclei of the basal ganglia. From there, the output nuclei project to the thalamus or other brainstem nuclei. A number of circuits have been characterized including oculomotor, prefrontal, limbic, and motor loops (Alexander and Crutcher, 1990). The nuclei involved in the motor loop include the striatum, globus pallidus, substantia nigra, subthalamic nucleus (STN), and the motor nuclei of the thalamus.

Concurrent with the tremendous increase in knowledge regarding basal ganglia structure and function, surgery for the treatment of refractory PD has undergone a dramatic evolution over the past 15 years. Laitenen’s reintroduction of pallidotomy was followed by its widespread use for about 10 years (Laitinen et al., 1992; Alkhani and Lozano, 2001). More recently, pallidotomy has been almost completely replaced by subthalamic (STN) and pallidal (GPi) deep brain stimulation (DBS) (Limousin et al., 1995; DBS Study Group, 2001; Krack et al., 2003; Rodriguez-Oroz et al., 2005). The major appeal of DBS therapy is that it is adjustable, reversible, and demonstrates therapeutic efficacy for many years (Rodriguez-Oroz et al., 2005). Consequently, in the United States, DBS therapy has almost completely replaced lesional surgery for the treatment of refractory PD (Eskandar et al., 2003).

From a scientific perspective, microelectrode recordings performed during DBS surgery provide a unique opportunity to directly record neuronal activity from the STN or GPi of human patients with PD. While recording from human subjects has limitations, it provides insights that are not available in other ways. The 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) animal model of Parkinsonism has been invaluable in advancing our understanding of PD. However, the model is not a perfect match for idiopathic PD, and primates treated with MPTP are usually unable to perform complex behavioral tasks (Raz et al., 2000). This makes it difficult to evaluate neuronal activities during complex behaviors. In contrast, human subjects can be easily trained to perform intraoperative tasks and represent the true disease state.

This review will briefly present the current models of BG function and how they account for the symptomatology of PD. It will then outline the implications of intraoperative findings for specific models of BG function. What will become apparent is that no one-model adequately describes all the features of the basal ganglia dysfunction in PD. Rather, dopamine plays a critical role in multiple facets of basal ganglia function, and the loss of dopaminergic neurons results in derangements of firing rates, neuronal selectivity, and firing patterns of BG neurons, all of which contribute to the clinically observed manifestations of the disease.

2. Principal models

2.1. The standard “antagonist balance” model

The Standard Model suggests that there are two pathways through the BG—the direct and indirect pathways. Based on the polarities of the known connections, the direct pathway is thought to facilitate movements while the indirect pathway is thought to suppress movements (Fig. 1) (Albin et al., 1989; DeLong, 1990). The model posits that the effect of dopamine is different in the two pathways due to the presence of different dopaminergic receptors in striatal neurons (Albin et al., 1989). Dopamine is hypothesized to excite D1 receptors of the direct pathway and D2 receptors of the indirect pathway.
striatal neurons and inhibit D2 receptors of indirect pathway neurons (Gerfen et al., 1990). The primary derangement in PD is a loss of dopaminergic neurons in the pars compacta of the substantia nigra (SNpc). Thus, the loss of dopamine is posited to result in derangements both pathways. Specifically, loss of dopamine causes the direct pathway to become less active and the indirect pathway to become more active resulting in increased STN activity, increased GPi, and excessive thalamic inhibition.

Thus, the overall inhibitory effect of the indirect pathway predominates, inhibiting intended movement. While the distribution of D1 and D2 receptors on striatal neurons may not be so clearly segregated (Aizman et al., 2000), there is considerable evidence that abnormal activity of the STN and GPi contribute to PD. A broad range of abnormalities of neuronal activity have been described, including increased firing rates, increased bursting, increased synchrony, and decreased selectivity (Bergman et al., 1990, 1994; Filion and Tremblay, 1991; Filion et al., 1991; Wichmann et al., 1994a, b). Some of the most compelling evidence regarding the importance of abnormal activity in these nuclei, is that surgery aimed at modulating the activity of either nucleus can lead to a significant clinical improvements (Lahtinen et al., 1992; Limousin et al., 1995; Gill and Heywood, 1997; Alkhani and Lozano, 2001; DBS Study Group, 2001). What remains to be determined is the relationship between specific abnormalities of activity and the clinical manifestations of PD, and of equal interest, the mechanisms by which DBS modifies this activity in a beneficial fashion.

The standard model has been empirically helpful in selecting targets for the surgical treatment of PD. Moreover, it has provided an extremely helpful framework for evaluating basal ganglia function. However, since the inception of the standard model, considerably more information has been discovered suggesting that the model needs to significantly revised. For example, studies in MPTP treated monkeys have failed to demonstrate the predicted changes in the spontaneous neuronal activities of the different nuclei of the basal-ganglia-thalamic-cortical pathway. Wichmann et al. (1999) failed to find any difference in the mean spontaneous spike rate, in the GPi or SNpr, between pre- and post-MPTP treated monkeys. Similarly, Raz et al. (2000) also failed to demonstrate a difference in GPi mean discharge rate, but did show a decrease in the mean rate of the globus pallidus externus (GPe) following MPTP treatment (in 1 of two monkey). In the STN, Meissner et al. (2005) found no change in mean discharge rate between pre- and post-MPTP treated monkey. The standard model predicts that the GPe and STN should all have elevated mean rates. Likewise, the primary motor cortex (Goldberg et al., 2002) and thalamus (Pessiglione et al., 2005) of the monkey also exhibited no change in mean discharge rate pre- and post-MPTP treatment. As will be discussed in subsequent sections, intraoperative DBS research has yielded addition physiologic data that is inconsistent with the “standard model”.

More recent anatomic evidence also suggests that the model needs to be revised. For example, it is now clear that in addition to the standard indirect pathway, there is an important direct projection from motor cortical areas to the STN (Kita 1994; Nambu et al., 2000; Kita et al., 2005). This cortical-STN pathway likely has a significant influence on information processing in the basal ganglia (Mink and Thach, 1993; Kita, 1994; Mink, 1996; Nambu et al., 2000; Kita et al., 2005). There are also limitations to the standard model from a clinical perspective. For example, increased activity in the indirect pathway might be expected to result in a generalized decrease in the frequency or amplitude of movements, which is in fact observed in PD. However, the model does not provide a good explanation for tremor, nor does it provide a particularly good explanation of rigidity, which arises from activation of antagonist muscle groups. Hence, other models of BG function have emerged in an effort to remedy some of these limitations. At the heart of the issue lies the question of the overall role of the BG in movement control and the nature of the interaction between the various pathways.

2.2. Center-surround model

A modification of the standard model suggests that the two pathways interact in a center-surround organization similar to that described in the visual system. In the visual system, the center-surround system is thought to enhance contrast, for example to improve edge detection. In the motor system the correlate would be movement specificity. In this model, the primary role of the BG is to focus movement control and the nature of the interaction between the various pathways.

The anatomic basis for the center-surround model is that the direct pathway’s putaminal projections to the GPi tend to be relatively discrete and to densely synapse on particular neurons. In contrast, STN projections to GPi tend to be diffuse and to synapse evenly on multiple neurons (Parent and Hazrati, 1993, 1995a, b; Mink, 1996). There is some physiologic evidence to support the model as well. Approximately 70% of arm movement-related GPi neurons increase activity and 30% decrease activity from their tonic baseline during movement (Anderson and Horak, 1985; Mitchell et al., 1987; Mink and Thach, 1991). This is consistent with the idea that the majority of GPi output is inhibitory, with a small fraction of cells decreasing their activity and thereby permitting the desired movement. The model can also be invoked to explain different movement disorders. For example, STN over-activity in PD leads to excessive inhibition of all movements, both desired and undesired, leading to akinesia and
bradykinesia. In contrast, decreased activity of the STN results in decreased suppression of undesired movements and their florid expression in the form of hemiballismus (Mink, 1996).

The center-surround model is most effective in explaining the apparent excess of activity observed in hemiballismus. However, the central idea that for any given movement there are a number of competing movement programs, while attractive, it is experimentally difficult to prove.

2.3. Abnormal firing pattern model

More recent studies have emphasized the role of neuronal oscillations and increased synchrony in PD. Studies employing microelectrode recordings from the MPTP primate model of Parkinsonism, and from PD patients, have demonstrated an increase in oscillatory and synchronized activity in GPi, GPe and STN neurons. Filion and Tremblay (1991) reported that with primates treated with MPTP, neurons of the GPi and GPe developed rhythmic bursting activity in two frequency bands, 5-8 Hz and ~15 Hz. Bergman et al. (1994) also reported increased oscillatory activity in STN and GPi neurons following MPTP treatment. The increased oscillations were seen in low frequency ranges (6.0 Hz in the GPi and 5.1 Hz in the STN), as well as in higher frequency ranges of (10.5 Hz in the GPi and 14.4 Hz in the STN). Increased oscillations and phase-locked synchronizaton were reported in the activity of simultaneously recorded GPi neurons (Nini et al., 1995). Furthermore, Raz et al. (2000) demonstrated increased synchronzation and oscillations (at 13-14 Hz) between GPe and GPi neuron following MPTP treatment.

These abnormalities may play several roles in the pathogenesis of PD. For example, the abnormal oscillations in the low frequency range 5–8 Hz may contribute to Parkinsonian tremor (Filion and Tremblay, 1991; Bergman et al., 1994; Wichmann et al., 1994b; Levy et al., 2000). Additionally, abnormal oscillation and increased synchronization in the 15–30 Hz frequency range may contribute to the normal flow of information through the basal ganglia (Brown, 2003; Hutchison et al., 2004), or be associated with a loss of neuronal selectivity and hence result in the observed impairments in movement (Boraud et al., 2002; Levy et al., 2000).

The mere presence of oscillatory activity in the BG may not in itself be abnormal. Courtemanche et al. (2003) reported the presence of widespread coherent oscillation in local field potentials (LFP) in the beta-band, of the striatum (in both the caudate nucleus and the putamen) in the normal behaving monkey. Interestingly, the power of the beta-band LFP activity decreased between the movement and reward periods of a simple saccade task. These findings in normal animals suggest that beta-band oscillatory activity may play a role in the normal function of the BG and that their attenuation may be necessary for the generation of motor behaviors. However, in PD the abnormally high power of the beta-band oscillations may act to impede or obscure normal signals, therefore slowing or preventing movements.

2.4. Learning model

There is an emerging consensus that the anterior neostriatum is involved in learning new motor tasks and that dopamine plays an important role in this process (Schultz, 1998; Bar-Gad et al., 2003). The neostriatum is characterized by a strong input from dopaminergic midbrain neurons. It has been estimated that a typical medium spiny neuron has about 10,000 cortical efferents and 100–1000 dopaminergic inputs (Freund et al., 1984; Doucet et al., 1986; Houk et al., 1995). The dopaminergic neurons have very characteristic properties. They fire most robustly to unexpected reward, and have a depression in their otherwise low tonic baseline in response to an expected but omitted reward (Schultz, 1998). However, these neurons do not signal the appetitive component of reward itself. Rather, over time, the activity becomes associated with the conditioned stimulus predicting reward in classical conditioning tasks. Hence these neurons have been viewed as conveying a signal regarding an error in the temporal prediction of reward (Schultz, 1998).

More recently it has become clear that phasic dopamine release can cause long-term potentiation or depression, depending on the state of the striatal neurons (Hernandez-Lopez et al., 1997). Studies using in vivo preparations have demonstrated that electrical stimulation of the SNpc can potentiate corticostriatal synapses for 10–20 min and dopaminergic antagonists can block this potentiation (Reynolds et al., 2001). Other studies in primates have revealed that the responses of striatal neurons depend strongly on the reward contingencies of the task. Many striatal neurons have greatly enhanced activity to various cues in behavioral tasks if there is an expectation of reward. Such responses diminish when the same tasks are performed without reward (Hollerman et al., 1998; Kawagoe et al., 1998). Both primate and human studies support the idea that the anterior neostriatum is specifically involved in learning new motor behavior. Changes in striatal activity appear to be correlated with reinforcement motor learning in animals (Jog et al., 1999; Hassani et al., 2001; Miyachi et al., 1997; Schultz, 1998; Barnes et al., 2005; Williams and Eskandar, 2006). Moreover, injections of muscimol into the caudate and anterior neostriatum of primates lead to deficits in learning new motor sequences, whereas similar injections in the posterior putamen disrupt well-learned sequences (Miyachi et al., 1997). Conversely, electrical stimulation in the caudate can lead to a selective...
enhancement in learning visual-motor associations, supporting its role in associative learning (Williams and Eskandar, 2006). Human functional imaging studies have demonstrated that the anterior neostriatum is activated during new learning, the mid-putamen during movement selection, and the posterior putamen during automatic movements (Jueptner and Weiller, 1998).

This evidence suggests that the neostriatum, and by extension the rest of the BG, play a critical role in the reward-based learning. There are several reinforcement-learning models based on such findings (Houk et al., 1995; Bar-Gad et al., 2003). In most models, phasic dopamine release selectively potentiates particular corticostriatal synapses or circuits. This is an iterative process, which progressively strengthens successful or profitable associations while it weakens unsuccessful ones. This is a particularly attractive model, as it accounts for many features of the anatomy and physiology, while explaining a number of apparent paradoxes (Bar-Gad et al., 2003). For example, lesions of the motor thalamus do not lead to hypokinetic symptoms, and lesions of the GPi do not lead to hyperkinetic movements, as would be predicted by the standard model. In further support of the role of the BG in learning, studies indicate that lesions of the globus pallidus result in selective learning impairments (Jahanshanai et al., 2002; Carr et al., 2003).

2.5. Intraoperative observations

The growing number of surgical procedures performed in patients with PD over the past several years has provided an invaluable opportunity to study neuronal activity within the basal ganglia. Such studies have provided interesting observations that can be compared to animal models of the disease. These observations can be related to more general features of the BG such as somatotopic organization and their role in motor initiation, selection and execution. In addition, these observations can be used to address specific hypothesis regarding BG function. We will first discuss observations that relate to general features of the BG and then address observations relevant to proposed models of BG function.

Many animal studies have shown that neuronal firing rates within the BG are modulated with movement, and likely play an important role in motor execution. Similarly, in human subjects, a considerable fraction of cells alter their firing rates with passive and volitional movement. Our group has shown, for example, that 45% of GPi cells exhibit increased perimovement activity and 80% of such cells are direction-selective (Williams et al., 2005). Between 32% and 51% of the STN cells also exhibit increased firing rate during arm movements and most of these cells are in the dorsolateral portion of the STN (Amirnovin et al., 2004; Williams et al., 2005). The distribution of movement-modulated cells follows a gross somatotopic representation within the STN with the oromandibular portion located medially and the arm region laterally (Abosch et al., 2002; Romanelli et al., 2004). Therefore, in agreement with animal recordings, human recordings of patients with PD suggest that activity within the STN and GPi is strongly linked with movement initiation or execution, and that there is a relatively intact somatotopic organization.

2.6. Intraoperative findings and the standard model

Consistent with findings made in MPTP treated animals, Magnin et al. (2000) observed that mean firing rates of pallidal cells in patients with PD are relatively high, and that firing rates in the GPi (91 ± 52 Hz) are higher than those of the GPe (60 ± 21 Hz). However, some of the data does not completely agree with the standard model. Tang et al. (2005) found that the mean discharge rates of GPi neurons were not significantly different between PD (81.8 ± 4.3 Hz; mean ± s.e.m) and Huntington’s disease (89.9 ± 3.0 Hz) patients. Mogilner et al. (2002) showed that the firing rates of STN neurons ipsilateral to a pallidotomy (31.5 ± 1.4 Hz) were lower than those observed in the contralateral STN (47 ± 12.3 Hz). These data suggest that PD results in a more complex interaction between the STN, GPi, and cortex than can be described using simple increases or decreases in firing rates.

Lesion data have lent support the standard model. Lesions of the STN decrease GPi activity overall, and result in an improvement in Parkinsonian symptoms in MPTP treated primates (Wichmann et al., 1994b). Numerous human reports agree with animal data, demonstrating that lesions of the human GPi and, and the STN, result in clinical improvement in PD (Laitinen et al., 1992; Alkhani and Lozano, 2001; Alvarez et al., 2001; Barlas et al., 2001; Parkin et al., 2001; Su et al., 2003). This suggests that subthalamic or pallidal lesions, by inactivating the indirect pathway, release its inhibition of motor control, leading to a facilitation of movement. Of course, such lesions in GPi would also be expected to damage the direct pathway—hence the net balance should not be altered. This is one of the many paradoxes of BG surgery (Marsden and Obeso, 1994).

The role of DBS in this process is even more uncertain, since it appears from animal studies that DBS of the STN may actually lead to increased pallidal firing (Hashimoto et al., 2003; Montgomery et al., 2003). Furthermore, GPi DBS in the human had no effect on thalamic discharge rates (Baker et al., 2001; Montgomery, 2006); while GPi stimulation in the monkey results in a decrease in thalamic discharge rates (Anderson et al., 2003). On the other hand, other human studies have suggested that GPi DBS leads to inhibition of firing in nearby neurons (Dostrovsky et al., 2000). Hence, it is important to recognize that the local effects of DBS may not be the same as the downstream effects. Namely, while the cell body of the stimulated neuron may be hyperpolarized (inhibited) by stimulation the axons may be activated (McIntyre and Grill, 1999). Thus, the question of whether DBS results in inhibition or
excitation remains unresolved. However, the range of therapeutic DBS targets supports the notion that the interactions within the BG are far more complex that what can be accounted for by a simple increase or decrease in firing rates. Rather, a more contemporary view holds that the effects of DBS are due to changing abnormal patterns of activity, rather than simple modulation of the firing rates.

2.8. Intraoperative findings on the abnormal firing pattern model

Intraoperatively, GPi (Hutchison et al., 1997; Magnin et al., 2000), GPe (Magnin et al., 2000) and STN (Levy et al., 2000) neurons, have been found to exhibit oscillatory activity. Several types of cells have been described in relation to oscillatory activity. For example, one study described three types of STN cells: tonic, phasic, and rhythmically firing cells. The tonic and rhythmic cells tend to fire at a higher mean rate (65 and 69 Hz, respectively) than the phasic cells (59 Hz) (Magarinos-Ascone et al., 2000).

Normal motor functioning may rely in part on the natural oscillatory “harmony” between neuronal activity in the cortex and deep subcortical nuclei. For example, studies employing simultaneous recordings in the STN and cortical EEG reveal coherence in the beta (15–30 Hz) and in the gamma (70–85 Hz) range (Williams et al., 2002). Such studies suggest that certain frequency bands may function to facilitate communication or synchronization of activity between the different parts of the brain. One recent study examined the LFP of the human STN in a go/no-go movement paradigm (Kühn et al., 2004). In the go-trials, they found that the oscillatory frequency in the beta range decreased prior to movement. On the other hand, in no-go trials, the beta oscillations decreased only for a short time and then reversed. These findings therefore imply that normal beta oscillatory activity within the STN may be important for inhibiting movement, and that attenuation of this frequency is associated with the facilitation of movement.

Whatever role oscillations play in normal movement, in primates, the Parkinsonian state appears to be associated with an abnormal increase in oscillatory and synchronized activity. (Filion and Tremblay, 1991; Bergman et al., 1994; Raz et al., 2000) Studies in human subjects seem to agree. For example, Levy et al. (2000) demonstrated an increase in the oscillatory and synchronized activity in the STN of patients with PD. The dopaminergic agonist apomorphine decreases the overall proportion of burst and irregular discharge patterns within both the GPi and STN cells (Levy et al., 2001). Brown et al. (2001) demonstrated that there is a strong coherence at less than 30 Hz between the local field potentials of the STN and GPi in PD patients off L-dopa. After L-dopa is given, the coherence in the low frequency range is lost and a new coherence is found at ~70 Hz. Cassidy et al. (2002) demonstrated that low-frequency coherence is lost during periods of active movement. Finally, Foffani et al. (2005) showed that adding L-dopa decreased the power of the 13–20 Hz and 20–35 Hz band oscillations in the STN of patients with PD. Together, these findings indicate the loss of dopamine is associated with an increase in the power of oscillations and the presence of bursting, and that abnormal patterns of BG oscillatory may interfere with the natural flow of information.

The source and dynamic properties of oscillations in the basal ganglia are the subject of intense interest. One study found that abnormal oscillatory activity in the STN was present whether or not patients with PD had previously undergone pallidotomies (Canavero et al., 2002). They argue that, since the STN oscillations were independent of the GPi, and highly correlated with the beta oscillations of the motor cortex at rest, that the motor cortex is likely the...
source of STN oscillation. Our group has recently observed that visually guided movements suppress STN oscillations and synchrony in the beta band, using single and multiple unit recordings (Amirnovin et al., 2004). Furthermore, as movement progressed, there was a relatively inverse linear relationship between the dynamic increase in STN firing rates and the decrease in beta oscillatory activity. This suggested that concerted cortical drive might dampen resting beta-frequency oscillations, and thus allow execution of movement. Another recent study found that DBS was associated with a decrease in beta-band oscillations in LFP’s recorded from the STN (Wingeier et al., 2006). These data suggest that the oscillations are dynamic, and that an important mechanism of DBS maybe the attenuation, or modification, of these oscillations.

2.9. Intraoperative findings and the learning model

The role of the basal ganglia in learning is becoming increasingly more appreciated (Bar-Gad et al., 2003; Frank and O’Reilly, 2006). How this relates to the pathophysiology of PD remains unclear. However, it has long been known that patients with PD have difficulty with learning and executing complex patterns of movements (Sahakian et al., 1988; Postle et al., 1997). Moreover, elevation of dopamine levels, with D2 receptor agonists, enhances cognitive function in subjects with low working memory and reduces cognitive function in subjects with high working memory (Kimberg et al., 1997; Mattay et al., 2000; Mehta et al., 2001; Frank and O’Reilly, 2006). Intraoperative studies have not yet focused on this particular aspect of basal ganglia function. However, certain predictions can be made based on the available data. For example, primate studies have demonstrated that striatal neurons can exhibit fairly rapid changes in activity and selectivity during associative learning. By extension, it is likely that pallidal and possibly STN neurons, exhibit similar changes. Hence, it is reasonable to expect that BG neurons in the dopamine-depleted state will have a blunted or slowed response during learning, and that these changes can be partially reversed by the administration of l-dopa. Alternatively, it maybe that phasic dopamine release, which is more closely associated with reward and learning-related changes, is relatively preserved. The actual effects of DBS on learning are difficult to assess. Some studies have demonstrated that DBS may result in a decline in cognitive function, particularly in older patients (Trepanier et al., 2000). This effect is presumably due to direct traumatic effects on structures that are traversed by the electrodes (cortex, white matter tracts, caudate, thalamus, STN) or to disruption of other circuits that engage the STN. On the other hand, another study of the neuropsychological effects of DBS found support for two different models of PD (Jahanshahi et al., 2000). DBS was found to increase speed on a Stroop interference task, which was is normally associated with frontal executive function. Hence, this is consistent with the idea that DBS releases the brake on the frontal lobes imposed by an overactive indirect pathway. Interestingly, this study also found that DBS resulted in worsening of associative learning, suggesting that this is an important function of the basal ganglia, and that disruption of the normal flow of information through the basal by DBS leads to impairments in learning.

3. Conclusions

The recent emergence of intraoperative single-unit recordings in humans has begun to shed light on the pathophysiology of PD. From the observations detailed above, four basic models have emerged, each accounts for some features of the clinical and physiological manifestations of this disease. Human recordings provide an extremely valuable snapshot into the workings of the BG in the actual disease. There are limitations inherent to such studies; in that there is no “normal” control comparison with normal patients. It is also difficult to demonstrate a clear “causal” relationship between observed activity and the clinical manifestations of the disease.

Nevertheless, given the unique opportunity to observe neuronal activity in subjects with PD, there are many possible directions in which such studies could proceed. It is important to examine how oscillatory and direction dependent neuronal activity in the BG changes in the context of more complex sensory-motor tasks. Simultaneous single-unit recordings from different BG nuclei may also shed further light on the dynamic interaction between these structures during movement in patients actively affected by PD. Finally, with the introduction of a growing number of indications for DBS placement within the BG for various disorders such as depression and essential tremor, valuable comparisons may be made between such patients and those with PD.

Taking the various theories discussed above into account, a general scheme emerges. The loss of dopamine in PD severely impairs the delicate balance of what is normally a well-concerted symphony of activity. This is manifested as a loss of balance between the antagonistic pathways of the BG as proposed by the standard model, by loss of contrast between wanted and unwanted actions as proposed by the center-surround model, by the introduction of noise into the system through excessive oscillations as in the abnormal firing pattern model and by impairment of the normal flow of information associated with the learning model. In essence then, the result is a cacophony of conflicting and discordant signals, which are clinically manifested as Parkinson Disease.

References


