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Review

Understanding the dopaminergic deficits in Parkinson's disease: Insights into disease heterogeneity

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ABSTRACT

Parkinson's disease is a common condition with a broad clinical diversity suggesting the existence of distinct subgroups of patients. This paper describes how dopaminergic disruption within basal ganglia circuitry accounts for some of the major features of the disease and examines how the limited repertoire of the output nuclei within these pathways could allow for an element of "cross-talk" between competing inputs. It is proposed that such conditions could lead to an excessive inhibition of the thalamus and pedunculopontine nucleus and account for many of the familiar patterns of clinical phenotype. It is further postulated that this phenomenon may be acting via increased synchronization within the basal ganglia circuitry.

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative condition where patients typically experience difficulties with slowness of movements (bradykinesia), stiffness of the muscles (rigidity), tremor and balance disturbances. In addition to this, PD is known to have profound affects on both cognition and mood. Furthermore, quality of life is impacted on by a range of other complaints including pain, bowel dysfunction and disturbances of sleep.[1]

Although symptomatic treatments are very helpful, particularly in the early stages of the disease, not all patients respond significantly. Additionally, improvements are often selective across differing symptoms within an individual, such as the relative alleviation of bradykinesia and rigidity but not tremor. Treatment of those patients with advanced disease can be very difficult, where management is frequently complicated by drug induced dyskinesias and motor fluctuations.[2] Disease progression is also correlated with features that appear less responsive to common therapeutic strategies. Deterioration of gait and the phenomenon of freezing of gait (FOG), along with a decline in postural righting reflexes are notoriously resistant to therapy. Such disease features commonly result in patients becoming at higher risk of falls[3] and being consequently more likely to require nursing home admission.[4]

The specific pathophysiology underlying all of the symptoms observed in PD is not well understood but the severe depletion of dopamine within the striatum resulting from nigrostriatal degeneration is acknowledged as the predominant histological feature. Neuronal loss across differing populations including cholinergic, serotonergic and noradrenergic structures is also well recognised[5] and doubtless contributes to several disease features including cognitive autonomic and affective disturbances. In healthy subjects the control of physical movements and cognitive and limbic processes are contingent, in part, on functional connections between regions of the cerebral cortex and the basal ganglia through a series of parallel corticostriatal pathways.[6] Dopamine plays a key role in the regulation of these circuits and the loss of this neurotransmitter in PD is likely to account for many of the disease features experienced by these patients. Identifying the underlying pathophysiological basis of these symptoms is of great clinical significance. In particular, it may facilitate the introduction of novel targeted therapies such as cellular transplants and/or delivery of specific growth factors, as well as the management of patients with advanced disease in whom there is a complex loss of dopaminergic tone, which exerts influence across different regions of the brain where often only limited amelioration is achieved.[7]

2. Disease heterogeneity

Although PD is characterised by its cardinal symptoms, individual patients vary significantly in their pattern of disease.

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This concept of differing clinical phenotypes in PD is well represented in the literature regarding disease heterogeneity[8–10] and is usually ascribed to specific spatial topographical patterns of neuronal loss.[11–13] As such, previous work has attempted to demonstrate clinicopathological correlations for various disease features including akinesia, tremor and cognitive decline.[13,14] Moreover, studies have demonstrated the concurrence of clinical features suggesting the existence of differing subgroups of patients under the "umbrella" of PD. For example, patients with cognitive and psychiatric deficits are more likely to suffer predominant symptoms of bradykinesia and rigidity, rather than tremor.[8,10] Similarly, previous work has identified a correlation between the initially dominant symptom experienced by PD patients and their subsequent risk of developing FOG. Indeed those patients who go on to develop FOG are more likely to have had initial symptoms of gait disturbance and rigidity, rather than tremor.[15,16]

Although many disease features are clearly not directly related to pathology in the nigrostriatal tract, a central core of common traits with a dopaminergic basis does exist. Given the major effects of dopamine on corticostriatal pathways, these observations suggest that disease heterogeneity may at least in part relate to a specific clinicopathological correlation that operates predominantly through disruptions in basal ganglia circuitry. In such a model of disease heterogeneity, differing patterns of central disturbance within basal ganglia networks may interact differentially with extra-striatal pathology to result in the varied phenotypic presentations of disease. Moreover, this variety of clinical phenotypes may be further influenced by as yet to be defined predisposing genetic polymorphisms operating in this system.

3. Basal ganglia circuitry

As stated above, the disturbances in basal ganglia circuitry play a central role in the pathology of PD. Coordinated neural activities are dependent on a series of parallel neuronal networks passing through the basal ganglia that connect and integrate functions between the basal ganglia nuclei, various regions of the cerebral cortex, the thalamus and brainstem.[6] Through their anatomical convergence and functional integration these segregated circuits allow processing of diverse inputs within, rather than between, each of the identified circuits. However, more recent work, showing the dense arborisation of connections between basal ganglia nuclei would challenge this model as simplistic (for a review, see Parent et al.[17]). Nevertheless, it remains likely that dopamine integrates the complex spatiotemporal sequence of neural events that ensures the flow of cortical information through the basal ganglia. This conservative solution permits tight regulation in the broad domains of motor, cognitive and limbic function. To attain this complex level of control the anatomical substrates for these pathways or loops demonstrate connections between distinct regions of the cerebral cortex and the basal ganglia nuclei (Fig. 1). Each pathway operates through an organised network with specific neurotransmitter connections to facilitate a highly regulated functional output. The best characterised of these pathways is the motor loop. In this pathway, circuits that originate from the motor and premotor cortical areas project in a somatotopic pattern to the posterolateral putamen, where they synapse through excitatory glutamatergic neurons onto the medium spiny striatal neurons. These striatal neurons use gamma-aminobutyric acid (GABA) as their primary neurotransmitter and substance P or enkephalin as co-transmitters, and are organised into two pathways: the "direct" and the "indirect pathway" (Fig. 2a). Both of these pathways converge on the internal segment of the globus pallidus (GPi) and the substantia nigra *pars* reticulata (SNr), which represent the major output nuclei of the basal ganglia. The dynamic balance of dopaminergic stimulation exerted via these competing, yet complementary, pathways regulates the amount of movement undertaken (for a review, see DeLong and Wichmann[18]).

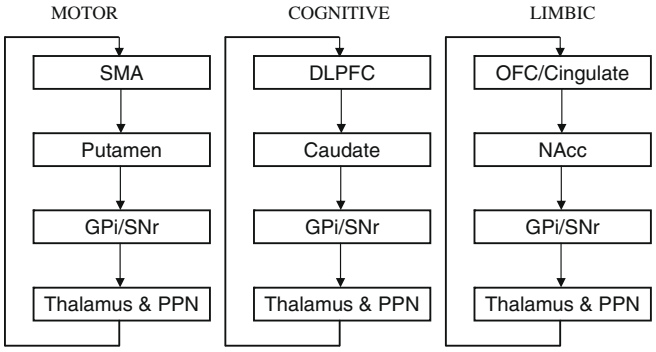

Fig. 1. The basal ganglia circuits are arranged in a parallel series of segregated pathways that coordinate the motor, cognitive and limbic functions (oculomotor pathway not included for simplicity). This arrangement allows the functional integration of information from a diverse range of inputs and modulates appropriate responses. Cingulate, cingulate cortex; DLPFC, dorsolateral prefrontal cortex; GPi, globus pallidus, internal segment; NAcc, nucleus accumbens; OFC, orbitofrontal cortex; SMA, supplementary motor area; SNr, substantia nigra *pars* reticulata; PPN, pedunculopontine nucleus.

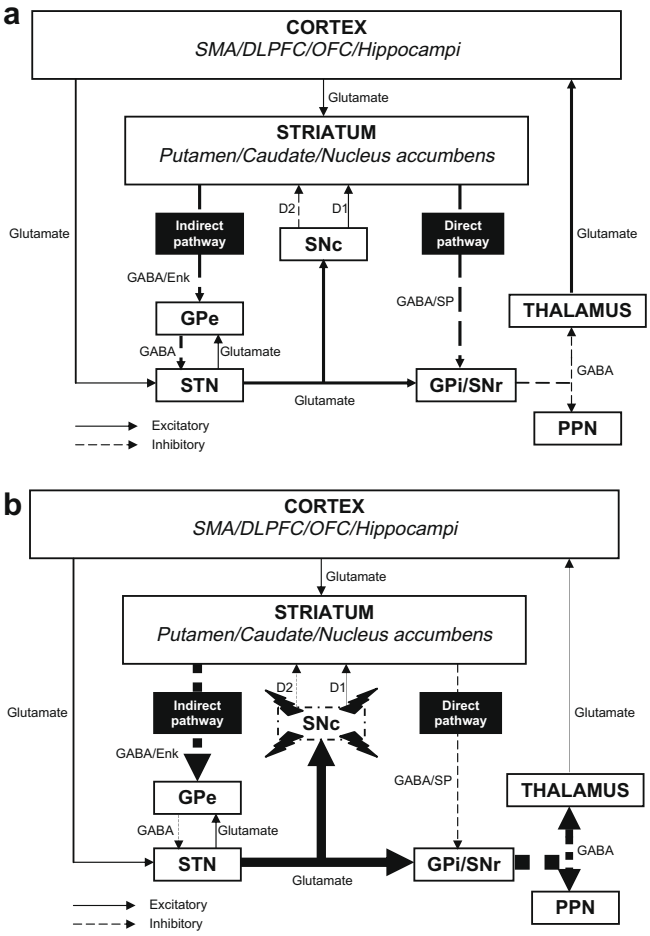

Fig. 2. (a) In normal brain, parallel neuronal networks of the striatum connect and integrate functions between the basal ganglia nuclei, various regions of the cerebral cortex, thalamus and the pedunculopontine nucleus (PPN). See text for detail (Section 3, *Basal ganglia circuitry*). (b) In Parkinson's disease, the natural balance of the basal ganglia circuitry is lost owing to the depletion of dopamine in the striatum. See text for detail (Section 4, *The motor loop in PD*).

Within the motor loop, the direct pathway connects the striatum to the GPi and the SNr. The GPi and SNr project inhibitory GABAergic neurons to both the thalamus and the pedunculopontine nucleus (PPN) within the brainstem. Thalamic output is excitatory through glutamatergic fibres and projects to the prefrontal and motor cortices. The PPN is the major brainstem nucleus implicated in the processes of locomotion and is the likely site of the proposed mesencephalic locomotor region (MLR), which is believed to activate central pattern generators (CPGs) within the spinal cord.[19]

The indirect pathway (Fig. 2a) also connects the striatum to the output nuclei of the basal ganglia (GPi and SNr) but in this circuit, inhibitory fibres first pass through synaptic connections in the external segment of the globus pallidus (GPe). The GPe exerts an inhibitory tone via GABAergic connections on the subthalamic nucleus (STN). The final stage of the indirect pathway operates via excitatory glutamatergic fibres from the STN to the output nuclei of the GPi/SNr.

Classically it is thought that these complex pathways retain functional integration by means of signalling occurring through the dopaminergic receptors on the striatal neurons. Activation of the striatum is modulated via the dopaminergic projection from the substantia nigra *pars* compacta (SNc). The striatal neurons of the direct pathway bear predominantly D1 dopamine receptors whereas the indirect pathway contains D2 receptors. Thus, simplistically the stimulation of D1 receptors in the striatal neurons of the direct pathway leads to increased inhibition of the GPi, which thus reduces the inhibitory tone on the thalamus and PPN. This in turn facilitates excitation of the cortex and CPGs and thus movement. Alternatively, stimulation of D2 receptors in the striatal neurons of the indirect pathway leads to a reduced inhibition of the GPe. Consequently there is greater inhibition of the STN, leading to less activation of the GPi. Reduced GPi activity allows greater activation of the thalamus, again facilitating movement. Thus dopamine release in the striatum operates through both direct and indirect pathways to facilitate movement, and it is believed that the regulation of this dopamine release "fine-tunes" the motoric action performed.

4. The motor loop in PD

In PD, the natural balance within the motor loop is lost owing to the depletion of dopamine in the striatum (Fig. 2b). This loss of dopaminergic stimulation results in an over-activation of the GPi/SNr output nuclei causing a profound inhibition on both the thalamus and PPN. More specifically in the direct pathway, the loss of D1 stimulation on striatal neurons reduces the degree of inhibition exerted at the level of the GPi, leading to its over-activation. Likewise, the loss of inhibitory D2 stimulation of the striatal fibres in the indirect pathway leads to over-activation of the STN and consequent over-activation of the output nuclei of the basal ganglia. This unregulated activation of the GPi/SNr leads to an inhibition of the thalamus and PPN, which in turn impairs both ascending and descending pathways, resulting in the reduction of motor activity.

Thus, this model of the motor loop in the basal ganglia networks allows a pathophysiological explanation of the akinetic features of disease and is well supported by evidence from biochemical, electrophysiological, functional imaging and clinical studies.[20–24] Indeed recent work investigating the role of the PPN may allow this model to be further extended toward the explanation of specific elements of gait disturbance in PD. Clinicopathological studies undertaken in PD patients have identified that non-dopaminergic cellular loss within the PPN can be correlated with gait disturbance.[19,25,26] This finding suggests that cellular degeneration in this region may act independently from nigrostriatal cell loss to explain aspects of gait failure in the disease, and also might explain the relative resistance of such symptoms to respond to dopaminergic amelioration.

5. Cognitive and limbic pathways

As described above most progress has been made in our understanding of the role of dopamine in regulating the basal ganglia circuitry with regards to motoric function but it is becoming increasingly clear that similar pathways are fundamentally important in both cognitive and limbic function. Frank dementia occurs in 15% to 20% of patients[27] and is felt most likely to be correlated with the diffuse accumulation of Lewy body pathology.[28] Subtle deficits are more common even within patients in the earlier clinical stages of disease[10,29] and are characterised as having a pattern similar to that seen in individuals who have experienced a frontal lobe injury.[30,31] This pattern of deficits has the most significant impact on executive processes such as working memory, planning and attentional set shifting.[32–34]

Several cognitive deficits seen in PD may be the result of dopaminergic depletion in both the mesocortical and nigrostriatal projections. In the mesocortical projection, ascending dopaminergic fibres run from the ventral tegmental area of the brainstem to the pre-frontal cortex. This pathway is likely to play a role in tasks that require less cognitive planning and appears to bypass striatal input,[35] focussing neural cortical activity. In PD patients, where the pathway is impaired, greater cortical activation is seen in functional neuroimaging studies during the performance of such cognitive tasks. It is unclear as to whether this increased cortical activation represents the recruitment of compensatory mechanisms[36,37] or a reduced efficiency within the cortex.[38–40]

Evidence provided by clinicopathological,[13,41] animal[42] and neuroimaging studies[43–45] suggests that the nigrostriatal dopaminergic fibres supporting cognitive function project to the caudate nucleus. Dopaminergic depletion of the striatum leads to cortical inactivation via increased inhibitory output of the basal ganglia to the thalamus (for a review, see Albin et al.[46] (Fig. 1)). This view is indeed supported by the finding of improved cognitive function in PD patients treated with L-dopa.[47–49]

However, not all cognitive deficits are improved by dopamine replacement. Indeed deterioration in performance has been noted on some tasks, such as probabilistic reversal learning,[50] a neural process that has a more ventral striatal basis.[51] Neuronal loss in the nigrostriatal tract is most severe in the region of the posterolateral putamen with relative sparing of the ventral striatum. As such, dopamine replacement may result in some circuits becoming "overdosed" by treatment, leading to the observed deterioration in performance.[50]

In addition to the differential pattern of dopamine loss across the striatum, genetic polymorphisms that modulate cortical dopamine levels influence cognitive performance in PD.[52] Cortical levels of dopamine are determined by the activity of the enzyme catechol-O-methyltransferase (COMT), which is dependent on the COMT Val158Met genotype. Patients with the low activity COMT genotype show inferior performance on tasks known to operate through the dorsolateral prefrontal cortex and this may be attributable to a state of mismatched dopaminergic activity between the cortex and striatum.[52] Furthermore, recent functional neuroimaging studies have confirmed that the COMT Val158Met genotype can influence frontoparietal activity during planning and attentional control in PD patients.[53,54]

Therefore, dopaminergic cognitive deficits in PD would appear to represent a complex interplay between striatal and cortical pathology that is further impacted upon by genetic polymorphisms

and medications. Thus, the performance of any individual cognitive process will depend on how these specific interactions affect the neural circuitry required to successfully perform the task.

The role of deep brain stimulation (DBS) in PD is generally targeted towards the improvement of motoric symptoms and as such most research looking at the cognitive outcomes are limited. Clearly surgical intervention in these cases is subject to strict inclusion criteria, which usually excludes those patients with any significant cognitive deficits. Most evaluations have been focussed on determining whether surgery has resulted in any negative impact on cognitive performance. While most studies suggest that DBS is a relatively benign procedure (for a review, see Voon et al.[55]), significant cognitive decline has been noted occasionally.[56] A few studies have systematically examined the role of DBS on specific cognitive functions. Stimulation of the STN has been correlated with selective improvements in various executive tasks such as working memory, planning, problem solving and processing speed.[57–59] Furthermore, in accordance with the findings of L-dopa amelioration studies where there is an inferior performance on some tasks, STN stimulation has also been associated with a worsening of certain processes, such as conditional associative learning.[58]

The limbic loop of the basal ganglia circuitry is responsible for the regulation and control of behaviours underlying motivation, decision-making and goal-directed reward. Afferent projections from a wide range of cortical areas (including the orbitofrontal, cingulate and hippocampal formations) and subcortical structures (amygdala and ventral tegmental area) target the ventral striatum, which is composed of the ventromedial part of the caudate nucleus and putamen along with the nucleus accumbens (NAcc) and olfactory tubercle. Within the NAcc these inputs are integrated under the modulatory influence of dopamine (for a review, see Grace et al.[60]). Efferent projections from this structure again target the major output nuclei (GPi/SNr) of the basal ganglia and this close integration of circuitry serving differing functional modalities permits the translation of limbic "drives" into motoric actions (Fig. 1).

Limbic dysfunction is evident in a proportion of PD patients manifesting in clinical features such as abulia,[61] paranoia[62] obsessionality[63] and occasionally risk-taking behaviours such as compulsive gambling.[64] Previous electrophysiological,[65] microdialysis,[66] psychopharmacological[67] and animal lesioning studies[68] have demonstrated the critical role of the ventral striatum in a wide range of limbic functions. In addition to these observations the role of dopamine within this limbic loop is emerging from recent neuroimaging experiments. For example, using functional MRI in healthy controls, dopamine release within the NAcc in response to reward anticipation has been correlated with local blood oxygen level dependent (BOLD) signal.[69] Furthermore, studies in PD patients have specifically identified activation within the NAcc as not only being central in limbic tasks but also as being sensitive to dopaminergic amelioration.[51]

Assessments of limbic function following DBS in PD patients have demonstrated that although postoperative behavioural disturbances can occur in individual patients, it is generally a safe procedure associated with modest improvements.[70–72] In keeping with effects of DBS on cognitive function some aspects of limbic function appear to deteriorate following this intervention, notably apathy[73] and the ability to recognise facial expression of fear.[74]

6. The role of basal ganglia circuitry in disease heterogeneity

In healthy subjects the basal ganglia circuits operate through a series of parallel pathways that can integrate information from a wide range of diverse inputs and coordinate an efficient functional output. Disturbances in this tightly regulated system have been proposed as the cause of several clinical conditions including PD, Huntington's disease and schizophrenia. As discussed above, individual disease features in PD can be attributed to specific dopaminergic influences in the motor, cognitive and limbic pathways. Furthermore, despite a highly preserved spatial topography within these segregated neural circuits, the limited repertoire of the output nuclei within these pathways could allow for an element of "cross-talk" between competing inputs (Fig. 1).

Such a model might be one possible explanation for why certain disease features correlate within specific subgroups of patients. For example, PD patients with predominant motoric features of bradykinesia and rigidity along with more severe cognitive deficits are likely to have a more profound depletion of striatal dopamine levels. Where these dopaminergic levels are critically reduced there may be only sufficient "reserve" of neurotransmitter to accomplish limited tasks. In a simplified scenario, severe dopaminergic depletion in the region of the putamen would compromise the activation within the direct, and the de-activation of the indirect, pathways. This would compromise the level of inactivation of the GPi/SNr resulting in a motoric performance characterised by profound bradykinesia and rigidity. Disruption of the basal ganglia circuitry in these patients would be further exacerbated by the additional demands of performing a cognitive task. The depleted nigrostriatal delivery of dopamine in the region of the caudate would lead to a further underactivation of the direct and an over-activation of the indirect pathways. This would result in the increased overactivity of the GPi/SNr and paroxysmal excessive inhibition of the thalamus, leading to an inactivation of the cortex that significantly impacts on cognitive performance. Thus the link between motor phenotype and cognitive performance may be explained by dopaminergic disruptions within the basal ganglia circuitry due to the limited repertoire of its output nuclei. Clearly, these deficits may be further impacted on by extra-striatal mechanisms.

As discussed above, the limbic pathway operating through dopaminergic modulation also targets the GPi/SNr outflow nuclei of the basal ganglia. Therefore, the model proposed would again suggest a mechanism that could relate limbic disturbances to other disease features. Cognitive and limbic processes can have an impact on motoric function. For example, patients experience an increased tendency towards freezing when they are required to deal simultaneously with an increased cognitive or limbic load and such an explanation could also account for the problems with multi-tasking and "motor set" that have long been recognised in PD.[75] In all of these scenarios, disease phenotypes would appear to occur as a consequence of the specific spatial topography of the underlying pathology and its interaction with extra-striatal circuitry. However, what determines these differential pathological patterns in the first instance remains unknown.

7. The role of basal ganglia synchronisation in disease heterogeneity

Over recent years rodent, primate and latterly human DBS studies in PD patients have begun to reveal the underlying pathological electrophysiology present in the diseased basal ganglia circuitry (for a review, see Gatev et al.[76]). The major findings of these studies report that while under normal conditions neighbouring cell populations and basal ganglia nuclei very rarely demonstrate any synchronous discharge activity, by comparison significant synchrony is observed in the dopamine-depleted state. These synchronous discharges or oscillations have been typically recorded at a frequency of between 8 Hz and 30 Hz (known as the "broad beta frequency band") as local field potentials (LFPs) in patients who have undergone DBS implantation.[76] Treatment with dopaminergic drugs and DBS reduces such synchrony and this can be

further correlated with the alleviation of bradykinesia and rigidity in these patients.[77] The role of synchronisation in motoric function is further highlighted by work showing that LFP recordings of beta oscillations taken at the STN and GP are reduced in PD patients just before and during self and externally paced voluntary movements.[78] Furthermore, where PD patients are required to suppress a pre-prepared movement, as in the performance of a "go and no-go" paradigm, there is an augmentation of STN LFP activity in the beta band.[79]

In contrast to the findings for bradykinesia and rigidity, the phenomenology of resting tremor in PD is not well correlated with basal ganglia oscillations. Although tremor is recognised as being associated with excessive synchronisation in the brain, this is seen to occur at lower frequencies (4–6 Hz) than occurs in the broad beta frequency band. Furthermore, tremor symptoms are not alleviated by reductions in synchrony following dopaminergic therapy and DBS[80] and as such it is felt that the tremor of PD has probably evolved as a downstream compensatory mechanism.[81]

It is clear that levels of synchronisation within the basal ganglia may be markedly different between those patients who have a tremor dominant phenotype and those characterised by features of bradykinesia and rigidity. Specific studies investigating the relationships between cognition and limbic function on synchronisation have not been reported. However, these processes might enhance synchronisation and this would presumably have more impact in those individuals with a non-tremor dominant phenotype. This proposed model would be supported by the finding that those patients with predominant motor features of bradykinesia and rigidity are more commonly affected by cognitive and limbic deficits.[9,10,82] It is not known whether the level of synchronisation within the basal ganglia circuitry represents a linear function of the striatal dopamine level because at some critical point, the number of synchronous neurons in the basal ganglia network could increase exponentially.[80] It is therefore possible that in patients with a non-tremor dominant phenotype, the performance of cognitive and limbic processes could result in a non-sustained period of increased synchronicity leading to a performance failure. This impairment would be further exacerbated by disease features outside the basal ganglia circuitry such as high cortical Lewy body load, COMT genotype and non-dopaminergic pathology.

8. Conclusions

Dopaminergic loss in the nigrostriatal tract accounts for many of the clinical features of PD. Motor, cognitive and limbic functions require integrated processing across the basal ganglia circuitry, which is modulated by striatal dopamine. The convergence of these "competing" pathways on the common output nuclei of the basal ganglia circuitry in the absence of sufficient dopamine levels may result in functional deficits. In this model the specific topographical pattern of dopamine loss and its effects on task selection and circuit activation may result in the concurrence of disease features, thereby accounting for some of the heterogeneity observed in PD. Greater understanding of such deficits may make them more amenable to directed therapies, such as targeted DBS or novel restorative agents.

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