

PARKINSON'S DISEASE: CIRCUIT-LEVEL PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

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Abstract

Parkinson's disease is a progressive neurodegenerative disorder characterized by core motor symptoms: bradykinesia, resting tremor, rigidity, and postural instability. The primary pathophysiological cause is the degeneration of dopaminergic neurons in the substantia nigra pars compacta, depleting striatal dopamine and disrupting the balance between direct and indirect basal ganglia pathways. This leads to excessive output inhibition, abnormal beta-band synchronization, and suppressed thalamocortical drive. At the cellular level, the disease is marked by α -synuclein accumulation (Lewy pathology), mitochondrial dysfunction, oxidative stress, and neuroinflammation. While dopamine replacement and deep brain stimulation targeting the subthalamic nucleus or globus pallidus effectively treat classic motor features, axial symptoms often persist due to non-dopaminergic neurodegeneration. Elucidating these circuit mechanisms remains vital for advancing disease-modifying therapies.

Keywords: Parkinson's disease; basal ganglia; substantia nigra; dopamine; motor symptoms; neurodegeneration; pathophysiology.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide, affecting approximately 1% of the population over the age of 60 (Poewe et al., 2017; Bloem et al., 2021). Clinically, PD is defined by its cardinal motor features: bradykinesia (slowness of movement execution with progressive decrement in amplitude or speed), muscle rigidity, resting tremor, and, in advanced stages, postural instability and gait disturbances (Postuma et al., 2015). Although non-motor symptoms—ranging from cognitive decline and autonomic dysfunction to sleep disorders are increasingly recognized as major drivers of disability (Schapira et al., 2017), the motor syndrome remains the core requirement for clinical diagnosis (Postuma et al., 2015; Tolosa et al., 2021).

The neurochemical cornerstone of PD motor pathology is the loss of dopaminergic projection neurons originating in the substantia nigra pars compacta (SNpc) and innervating the striatum (Kalia & Lang, 2015). The resulting striatal dopamine deficiency disrupts the complex subcortical loop involving the basal ganglia, thalamus, and cerebral cortex (DeLong, 1990; McGregor & Nelson, 2019). The basal ganglia function as an integrative processing hub that gates voluntary motor programs, regulates movement scale, and facilitates smooth motor transitions (Wichmann, 2019). Loss of dopaminergic modulation alters basal ganglia neuronal firing rates and patterns, inducing pathological oscillations across corticostriatal circuits (Little & Brown, 2014).

This review provides a narrative synthesis of the neuroanatomical organization of the basal ganglia, the cellular mechanisms responsible for nigrostriatal neurodegeneration, the circuit-level pathophysiology underlying specific motor manifestations, and the clinical implications for current pharmacological and neuromodulatory interventions.

2. Neuroanatomical Organization of the Basal Ganglia

The basal ganglia comprise a collection of interconnected subcortical nuclei located at the base of the forebrain and upper brainstem. The main components relevant to motor control include the striatum (caudate nucleus and putamen), the globus pallidus (divided into external [GPe] and internal [GPi] segments), the substantia nigra (divided into pars compacta [SNpc] and pars reticulata [SNpr]), and the subthalamic nucleus (STN) (DeLong, 1990; Wichmann, 2019).

The striatum acts as the primary receptive structure of the basal ganglia, receiving dense excitatory glutamatergic projections from sensorimotor, premotor, and association cortices. The vast majority (approximately 95%) of striatal neurons are GABAergic medium spiny neurons (MSNs), which are divided into two distinct subpopulations based on their receptor expression and projection targets (DeLong, 1990; McGregor & Nelson, 2019).

First, the Direct Pathway is formed by MSNs expressing dopamine D1 receptors, which co-express substance P and dynorphin. Direct pathway MSNs project directly to the primary basal ganglia output nuclei, the GPi and SNpr. Activation of D1 receptors by dopamine exerts an excitatory effect, stimulating this GABAergic projection to inhibit the GPi/SNpr. Because GPi/SNpr neurons continuously send tonic inhibitory signals to the motor thalamus (ventrolateral and ventroanterior nuclei), activation of the direct pathway disinhibits the thalamus, facilitating thalamocortical drive and promoting voluntary movement (DeLong, 1990).

Second, the Indirect Pathway is formed by MSNs expressing dopamine D2 receptors, which co-express enkephalin. Indirect pathway MSNs project to the GPe, which in turn sends inhibitory projections to the STN. The STN provides excitatory glutamatergic drive back to the GPi/SNpr. Dopamine binding to D2 receptors exerts an inhibitory effect on these MSNs. When activated in the absence of dopamine, the indirect pathway disinhibits the STN, increasing excitatory drive onto the GPi/SNpr. This enhances tonic thalamic inhibition, thereby suppressing unwanted motor activity (DeLong, 1990; Wichmann, 2019). Additionally, the Hyperdirect Pathway provides a direct cortico-subthalamic glutamatergic projection that delivers rapid excitation to the STN, bypassing the striatum entirely to execute immediate motor suppression (Wichmann, 2019).

Dopamine released from SNpc terminals into the striatum acts as a key neuromodulator, concurrently activating D1-expressing direct pathway MSNs and inhibiting D2-expressing indirect pathway MSNs. This dual action facilitates intended motor acts while suppressing competing motor programs. Loss of this dopaminergic tone disrupts this equilibrium, shifting basal ganglia network dynamics toward excess inhibition of the thalamocortical circuit (Galvan & Wichmann, 2008; McGregor & Nelson, 2019).

3. Neurodegenerative Pathology

The neurodegenerative cascade in PD predominantly targets dopaminergic neurons in the ventrolateral tier of the SNpc, projecting primarily to the caudal putamen (Surmeier et al., 2017). Motor symptoms typically manifest clinically after a loss of approximately 50–70% of SNpc dopaminergic neurons and an 80% depletion of striatal dopamine (Kalia & Lang, 2015; Poewe et al., 2017).

The pathophysiological cascade initiates through primary cellular stressors, including misfolded α -synuclein aggregation, mitochondrial dysfunction, and proteostasis failure. These cellular events drive the degeneration of ventrolateral SNpc neurons, resulting in profound striatal dopamine depletion. Consequently, pathway imbalance occurs as underactivity of the D1 direct pathway combines with overactivity of the D2 indirect pathway. This imbalance alters network output through hyperactivity of STN and GPi/SNpr output, producing excessive beta-band (13–30 Hz) synchronization. The final clinical outcome is tonic inhibition of the thalamocortical loop, leading to bradykinesia, rigidity, and execution deficits.

At the pathological level, PD is characterized by intracellular proteinaceous inclusions containing misfolded α -synuclein, termed Lewy bodies (located in neuronal cell bodies) and Lewy neurites (located in neuronal processes) (Spillantini et al., 1997; Henderson et al., 2019). According to the staging model proposed by Braak et al. (2003), Lewy pathology exhibits a characteristic spatiotemporal distribution, initiating in lower brainstem structures (e.g., dorsal motor nucleus of the vagus nerve) and the anterior olfactory nucleus (Stages 1–2), ascending to the midbrain and basal forebrain (Stages 3–4, coinciding with motor onset), and ultimately spreading to neocortical areas in advanced stages (Stages 5–6).

Multiple interrelated cellular mechanisms contribute to selective neuronal vulnerability in the SNpc. Selective neuronal vulnerability arises because SNpc dopaminergic neurons possess long, highly branched, unmyelinated axons with enormous metabolic demands. Their reliance on L-type $\text{Ca}_v1.3$ calcium channels for autonomous pacemaker activity elevates cytosolic calcium levels, exposing cells to sustained basal metabolic stress (Surmeier et al., 2017).

Furthermore, mitochondrial dysfunction and oxidative stress play a crucial role, as Complex I inhibition in the mitochondrial electron transport chain causes excessive production of reactive oxygen species (ROS). Dopamine metabolism itself generates toxic reactive metabolites, including dopamine quinones and hydrogen peroxide, overwhelming cellular antioxidant defenses (Blesa et al., 2015). Impaired proteostasis also contributes, as failure of the ubiquitin-proteasome system (UPS) and autophagy-lysosomal pathway (ALP) prevents the clearance of damaged organelles and toxic α -synuclein oligomers, propagating cytosolic stress (Lees et al., 2009; Henderson et al., 2019). Finally, neuroinflammation accelerates non-cell-autonomous neurodegeneration, where extracellular α -synuclein oligomers trigger persistent microglial activation through Toll-like receptors, releasing pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6) and reactive nitrogen species (Tansey et al., 2022).

4. Pathophysiological Basis of Motor Symptoms

Dopamine depletion within the sensorimotor striatum disrupts basal ganglia circuit processing through two main alterations: shifts in overall firing rates and changes in temporal firing patterns and synchronization (Galvan & Wichmann, 2008; Little & Brown, 2014). The classical rate model predicts that loss of striatal dopamine leads to hypoactivity of the D1 direct pathway and hyperactive output from the D2 indirect pathway (DeLong, 1990). The resulting overactivity of the STN drives excessive excitatory output to the GPi/SNpr, causing tonic hyperinhibition of thalamocortical relay neurons and reduced cortical motor excitability (Galvan & Wichmann, 2008; McGregor & Nelson, 2019).

In addition to rate changes, local field potential (LFP) recordings confirm the presence of pathological beta-band (13–30 Hz) oscillations throughout the STN-GPi-cortical loop in dopamine-depleted states (Little & Brown, 2014; Wichmann, 2019). These exaggerated, hypersynchronous beta bursts correlate with motor impairment and are suppressed by levodopa administration or therapeutic deep brain stimulation (DBS) (Little & Brown, 2014; Lozano et al., 2019).

Regarding corticostriatal circuit interactions, cortical input projects directly to both the striatum (via direct and indirect pathways) and the STN (via the hyperdirect pathway). Striatal modulation then proceeds through the D1 direct pathway directly inhibiting the GPi/SNpr, while the D2 indirect pathway inhibits the GPe, which disinhibits the STN and subsequently excites the GPi/SNpr. Under dopamine-depleted conditions, the basal ganglia output structures (GPi/SNpr) deliver hyper-inhibitory GABAergic output to the motor thalamus.

5. Manifestations

Bradykinesia, akinesia (poverty of movement), and hypokinesia (reduced movement amplitude) result directly from excessive tonic inhibition of the motor thalamus and associated motor cortices (supplementary motor area [SMA] and primary motor cortex [M1]) (DeLong, 1990). Pathological beta-band synchronization prevents dynamic desynchronization—a physiological process required to prepare and execute voluntary motor programs (Little & Brown, 2014). Consequently, patients exhibit a loss of dynamic signal-to-noise ratio in corticospinal output, leading to delayed movement initiation, failure to recruit adequate burst amplitude in primary agonist muscles, and progressive fatiguing during repetitive movements (McGregor & Nelson, 2019).

Parkinsonian rigidity—characterized by "lead-pipe" or "cogwheel" resistance throughout the passive range of motion—arises from hyper-excitability of spinal motor circuits secondary to altered descending reticulospinal and vestibulospinal outputs (Galvan & Wichmann, 2008). Abnormal GPi/SNpr output alters brainstem structures, particularly the pedunculopontine nucleus (PPN) and midbrain locomotion centers. This causes loss of central inhibitory modulation over spinal stretch reflexes, leading to increased tonic muscle contraction, shortened reflex latency, and continuous co-contraction of agonist and antagonist muscle groups (Galvan & Wichmann, 2008; Bloem et al., 2021).

Unlike bradykinesia and rigidity, classical parkinsonian resting tremor (4–6 Hz) is not explained by the rate model alone. Current models point to a dynamic interaction between two distinct networks: the basal ganglia (which acts as a "trigger") and the cerebellothalamocortical circuit (which acts as an "oscillator")—known as the "dimmer-switch model" (Helmich et al., 2012). Dopamine depletion in the putamen produces transient, rhythmic signal bursts in the STN that trigger tremor onset. These signals drive the cerebellothalamocortical loop (ventrolateral thalamus, motor cortex, and cerebellum), maintaining and amplifying sustained tremor oscillations at the periphery (Helmich et al., 2012; Bloem et al., 2021).

Postural instability and freezing of gait (FOG) reflect advanced neurodegeneration extending beyond the dopaminergic striatum into non-dopaminergic subcortical networks (Nonnekes et al., 2015; Bloem et al., 2021). Destruction of cholinergic neurons in the PPN and nucleus basalis of Meynert, along with noradrenergic loss in the locus coeruleus, impairs automatic postural adjustments and gait rhythmicity (Nonnekes et al., 2015). FOG involves abnormal inhibitory output from the GPi to the PPN and mesencephalic locomotor region (MLR), disrupting automatic motor control during locomotion tasks, such as turning or navigating narrow spaces (Nonnekes et al., 2015).

6. Clinical Neuroanatomical Correlations

The motor features of PD correspond directly to disrupted signal processing in specific basal ganglia pathways.

Bradykinesia and akinesia originate in the sensorimotor putamen, SNpc, and supplementary motor area (SMA), driven by striatal dopamine depletion leading to indirect pathway overactivity, beta synchronization, and subsequent thalamocortical suppression (DeLong, 1990; Little & Brown, 2014). Rigidity involves the striatal-GPi-brainstem axis and spinal interneurons, caused by exaggerated tonic stretch reflexes secondary to a loss of descending inhibitory tone from brainstem reticulospinal tracts (Galvan & Wichmann, 2008). Classical 4–6 Hz resting tremor arises from interactions between the STN-GPi circuit and the cerebellothalamocortical loop, where a basal ganglia trigger drives persistent oscillations within the cerebellothalamocortical network according to the dimmer-switch model (Helmich et al., 2012).

Bulbar symptoms such as hypomimia and hypophonia involve corticobulbar circuits and the facial or ambiguous nuclei, manifesting as motor hypometria due to inadequate cortical drive and loss of movement scaling (Postuma et al., 2015). Micrographia maps to putamen-SMA automaticity circuits, reflecting impaired motor automaticity and an inability to maintain motor unit recruitment without conscious cortical compensation (Bloem et al., 2021). Finally, freezing of gait (FOG) stems from pathological changes in the pedunculopontine nucleus (PPN) and mesencephalic locomotor region (MLR), caused by inhibitory hyper-drive from the GPi to brainstem locomotion centers coupled with executive circuit dysfunction (Nonnekes et al., 2015).

Loss of striatal dopamine impairs motor automaticity—the ability to perform habitual, learned motor skills without continuous conscious attention (Bloem et al., 2021). Under physiological conditions, automatic motor programs are mediated by the sensorimotor putamen. When dopamine in the dorsolateral putamen is depleted, patients must recruit prefrontal and associative cortical networks to consciously plan each step or movement. This recruitment explains why external cueing (visual stripes or auditory metronomes) can transiently bypass striatal circuits to improve gait, whereas dual-tasking demands divert prefrontal attention and worsen symptoms such as freezing or micrographia (Nonnekes et al., 2015; Bloem et al., 2021).

7. Progression and Therapeutic Implications

The clinical trajectory of PD reflects progressive topographically mapped loss of dopaminergic neurons, followed by degeneration of non-dopaminergic ascending pathways (Braak et al., 2003; Armstrong & Okun, 2020). Initial degeneration in the caudal putamen primarily impairs motor control of the contralateral upper limb, causing asymmetric symptom onset (Kalia & Lang, 2015). As degeneration spreads rostrally within the striatum and bilaterally throughout the brainstem, symptoms broaden and become symmetric (Armstrong & Okun, 2020).

During early disease, degeneration is confined to the caudal putamen and ventrolateral SNpc, causing asymmetric resting tremor and distal limb bradykinesia. In mid-stage disease, bilateral putaminal depletion and extranigral ascending pathology result in symmetric motor deficits, motor fluctuations, and dyskinesias. In late-stage disease, widespread non-dopaminergic loss involving the PPN as well as cholinergic and noradrenergic systems leads to L-Dopa-resistant axial symptoms, freezing of gait, and postural instability.

Therapeutic strategies target specific steps in this pathophysiological cascade (Jankovic & Tan, 2020). First, dopaminergic pharmacotherapy utilizes levodopa (L-DOPA), the metabolic precursor to dopamine, as the most effective symptomatic treatment. It is converted into dopamine by aromatic L-amino acid decarboxylase in surviving presynaptic terminals, restoring D1 and D2 receptor signaling (Armstrong & Okun, 2020; Jankovic & Tan, 2020). Dopamine agonists (e.g., pramipexole, ropinirole) directly stimulate post-synaptic striatal D2/D3 receptors, while monoamine oxidase-B (MAO-B) inhibitors (e.g., rasagiline, selegiline) slow enzymatic breakdown of endogenous and exogenous dopamine (Jankovic & Tan, 2020).

Second, clinical responses differ between dopamine-responsive and dopamine-resistant manifestations. Early motor features such as bradykinesia and rigidity usually respond well to L-DOPA. In contrast, late-stage axial symptoms, including postural instability, swallowing difficulties, and freezing of gait, respond poorly, as they are driven by non-dopaminergic degeneration in cholinergic, noradrenergic, and serotonergic nuclei (Obeso et al., 2017; Balestrino & Schapira, 2020).

Third, surgical neuromodulation via Deep Brain Stimulation (DBS) is employed when motor fluctuations and L-DOPA-induced dyskinesias develop due to pulsatile dopamine stimulation (Lozano et al., 2019). Chronically stimulating the STN or GPi suppresses local pathological beta-band synchronization, disrupts hyperactive output signals, and normalizes thalamocortical information flow (Little & Brown, 2014; Lozano et al., 2019).

8. Conclusion

Despite advances in symptomatic therapies, critical questions regarding PD pathogenesis remain unresolved (Tolosa et al., 2021). Key research areas include understanding the mechanisms behind trans-synaptic propagation of misfolded α -synuclein (whether operating via "prion-like" templating), identifying factors driving selective cell death, and defining the role of peripheral inflammation and gut-brain interactions in disease initiation (Surmeier et al., 2017; Henderson et al., 2019; Tansey et al., 2022). Developing validated prodromal biomarkers (such as seed amplification assays for α -synuclein in cerebrospinal fluid and skin biopsies) remains essential for initiating neuroprotective therapies before irreversible nigrostriatal loss occurs (Tolosa et al., 2021).

Thus, the motor manifestations of Parkinson's disease stem from a defined pathophysiological sequence:

Substantia nigra degeneration → Striatal dopamine depletion → Basal ganglia circuit imbalance → Thalamocortical suppression → Motor deficit expression

Understanding these interactions across the cellular, circuit, and clinical levels remains essential for advancing target-specific neuroprotective strategies and optimizing functional neuromodulation.

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