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General Overview of Parkinson's Disease

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Abstract

Parkinson's disease is a progressive neurodegenerative disorder characterized by the degeneration of dopaminergic neurons in the Substantia Nigra Pars Compacta, located in the midbrain. Neurons in the SNc project extensively into the striatum, comprising the caudate and putamen, where dopamine regulates the activity of basal ganglia circuits involved in motor control and learning. While the cardinal motor symptoms of PD have long been attributed to dopaminergic loss, recent studies reveal that PD pathology is more complex. Understanding these mechanisms not only explains the disease's diverse symptoms but also offers novel strategies for intervention. This essay examines the multifactorial pathophysiology of PD, focusing on clinical symptoms, basal ganglia circuitry, the vulnerability of dopaminergic neurons, associated genes, and the role of other neurotransmitters. It also discusses stem cell therapies and future directions for treatment, aiming to provide a comprehensive understanding of Parkinson's disease.

Keywords

Parkinson's Disease, Basal Ganglia, Dopamine, Substantia Nigra Pars Compacta, Genes, Neurotransmitters, Motor/Non-Motor Symptoms, Stem Cells

1. Basal Ganglia Circuitry and Dopaminergic Signaling

The basal ganglia are a group of interconnected subcortical nuclei that play a central role in regulating voluntary movement and learning. They are located in the forebrain, and their core components include the dorsal striatum (including the caudate and putamen nuclei), globus pallidus (internal and external segments, GPi and GPe, respectively), and the subthalamic nucleus. The basal ganglia also include the substantia nigra (SNc and SNr); however, it is located in the midbrain, rather than the forebrain. These structures work together to receive input and send

output to the cerebral cortex and thalamus, essentially creating a motor loop, as shown in Figure 1.

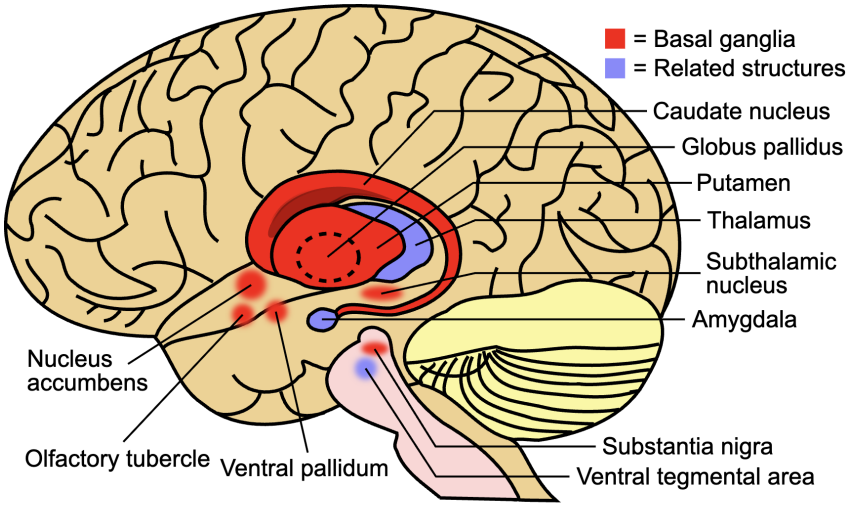

Figure 1. Diagram of basal ganglia structure (sagittal plane) [1].

It is also important to note the types of input each structure provides to its target, specifically its primary neurotransmitter. For example, the striatum's Medium Spiny Neurons (MSNs), both segments of the globus pallidus, and the SNr are all GABAergic, releasing the neurotransmitter GABA. This major inhibitory neurotransmitter promotes hyperpolarization of the postsynaptic membrane, making its target less likely to fire an action potential. On the other hand, the Subthalamic Nucleus (STN) releases glutamate, the major excitatory neurotransmitter, which promotes depolarization of the postsynaptic membrane and the subsequent firing of an action potential.

In the healthy brain, the basal ganglia modulate motor commands sent from the cortex through two fundamental pathways: the direct pathway, which facilitates movement, and the indirect pathway, which inhibits unwanted movement, as shown in Figure 2. The cortex sends glutamatergic signals to the Medium Spiny Neurons (MSNs) located in the striatum, which either express D1-type dopamine receptors, involved in the direct pathway, or D2-type dopamine receptors, involved in the indirect pathway.

In the direct pathway, glutamatergic input from the cortex stimulates D1-expressing MSNs to send GABAergic signals to the GPi/SNr, which usually exerts inhibitory input to the thalamus. This disinhibits the thalamus, allowing it to activate the motor cortex and promote movement. In contrast, the indirect pathway involves glutamatergic signals from the cortex that stimulate D2-expressing MSNs to send GABAergic signals to the GPe, which usually sends GABAergic signals to the STN. This disinhibits the STN, which typically sends glutamatergic input to the GPi/SNr. Finally, the excitation of the GPi/SNr increases thalamic inhibition, thereby suppressing movement.

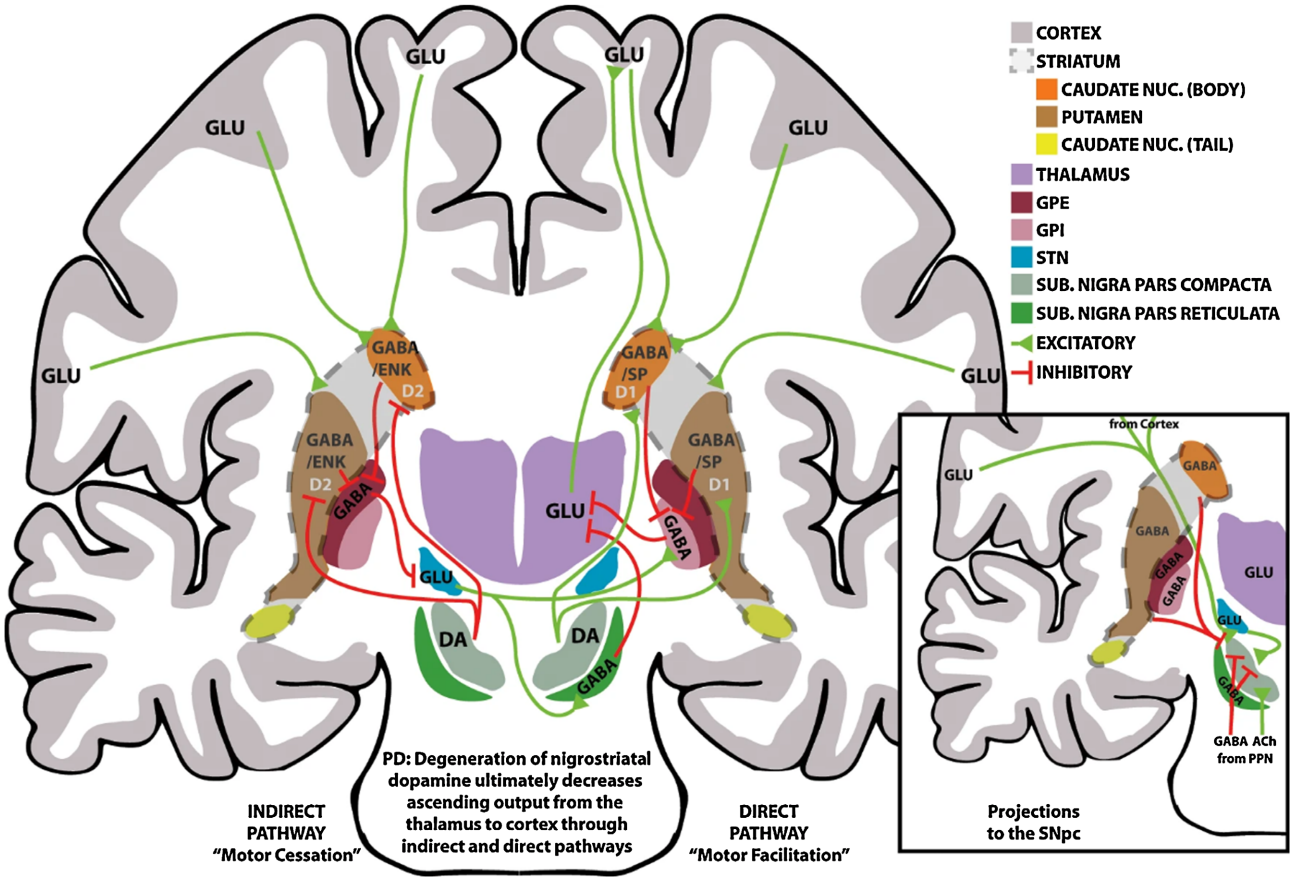

Figure 2. Diagram of basal ganglia pathways, including direct and indirect pathways, as well as inputs to the SNc (transverse plane) [2].

In both pathways, the GPi and the SNr are analogous in function, as both project tonic inhibitory input to the thalamus. While the GPi primarily projects to the thalamus, coordinating limb and axial movements, the SNr projects to the thalamus as well as to other brainstem structures, including the superior colliculus, the pedunculopontine nucleus, and brainstem motor centers. This allows the SNr to play a role in oculomotor regulation, controlling eye movements such as saccades, as well as head and neck movements and head orientation. Furthermore, these two structures differ in their source of inputs, specifically in the direct pathway. While the GPi primarily receives feedback from the putamen of the striatum, the SNr primarily receives input from the caudate nucleus of the striatum. Therefore, the putamen is involved mainly in motor control, receiving input from the motor, premotor, and somatosensory cortices. At the same time, the caudate plays a role in cognitive and ocular motor loops, receiving input from the prefrontal cortex, frontal eye fields, and association cortices.

Dopamine released from the SNc onto the striatum modulates both pathways. That is, it excites the direct pathway via D1 receptors and inhibits the indirect pathway via D2 receptors. Therefore, dopamine biases the basal ganglia circuitry towards movement initiation and execution. D1 and D2 receptors are both classes of G-Protein-Coupled Receptors (GPCRs). Further, D1 receptors are mainly ex-

pressed on MSNs in the direct pathway. When dopamine binds to D1 receptors, it activates a Gs protein (stimulatory G protein), leading to the activation of adenylyl cyclase. This increases cAMP levels and subsequent activation of downstream protein kinase A, which then phosphorylates ion channels and intracellular proteins, enhancing the excitability of these MSNs. The enhanced activity of MSNs, in turn, promotes the inhibition of the GPi/SNr, thereby disinhibiting the thalamus and facilitating movement.

In contrast, D2 receptors are predominantly expressed on MSNs of the indirect pathway. Dopamine binding to D2 receptors activates a Gi protein (an inhibitory G protein), which inhibits adenylyl cyclase and thus lowers cAMP levels. This has the opposite effect as the previously mentioned D1 receptors and decreases the excitability of indirect pathway MSNs. This reduces inhibition of the GPe, allowing it to inhibit the STN. Inhibition of the STN leads to reduced excitatory input to the GPi/SNr. This ultimately facilitates movement as well, by lowering thalamic inhibition and promoting excitatory input to the cortex [3].

In PD, reduced dopaminergic input disrupts the balance of motor circuitry, leading to excessive inhibition of thalamocortical output and resulting in motor symptoms.

Furthermore, the dopaminergic neurons of the SNc receive a wide array of inputs from multiple brain regions, helping to regulate dopaminergic firing patterns, influence motor control, and integrate cognitive, emotional, and sensory information. Firstly, the striatum's MSPs from the Caudate and Putamen, as well as the GPe, send GABAergic input to the SNc; this creates a negative feedback loop that regulates dopaminergic tone. The STN also regulates SNc neuronal activity by providing excitatory input, which controls firing patterns. Another central structure that modulates SNc activity is the Pedunculopontine Nucleus (PPN). The PPN provides cholinergic (acetylcholine) and glutamatergic input. Acetylcholine acts on nicotinic and muscarinic receptors, and glutamate acts on AMPA and NMDA receptors. Both signals promote bursting firing patterns and subsequent phasic dopamine release, which are short episodes of dopamine surges. This system is active during wakefulness, attention, and REM sleep [4].

2. Why SNc Dopamine Neurons Are Vulnerable

Despite other areas of the brain having dopaminergic neurons, particularly the ventral tegmental area (used in reward, motivation, and addiction), dopaminergic neurons in the Substantia Nigra pars compacta are particularly susceptible to degradation, as seen in PD. This vulnerability is due to a myriad of factors that create a "perfect storm", which will be discussed.

Accumulation and misfolding of *α*-synuclein:

α-synuclein is a small, soluble protein localized at presynaptic terminals. It is classified as an Intrinsically Disordered Protein (IDP). This means that, unlike conventional globular proteins, *α*-synuclein lacks a fixed secondary or tertiary structure under physiological conditions. It plays a vital role in regulating synaptic

vesicle trafficking, modulating dopamine release, and maintaining the assembly of the SNARE complex, which is essential for the release of neurotransmitters. However, this structural flexibility means that α-synuclein is particularly susceptible to misfolding and self-association under pathological conditions. These include, but are not limited to, hyperphosphorylation, oxidative stress, impaired protein clearance, or mutations in the SNCA gene, which encodes α-synuclein.

The earlier aggregation products are oligomers, which comprise small clusters of α-synuclein monomers, typically ranging in size from 2 to 30 monomers. Many oligomers exhibit high concentrations of β-sheet secondary structures, which contribute to their pathogenicity. Intuitively, this aggregation of α-synuclein abnormally binds to SNARE proteins, including VAMP2, Synaptin-1, and SNAP-25, thereby inhibiting synaptic vesicle docking and neurotransmitter release. In addition, their β-sheet-rich structure enables these oligomers to interact abnormally with lipid membranes, forming pore-like structures that disrupt calcium homeostasis and trigger oxidative stress. In addition, α-synuclein interferes directly with mitochondrial dynamics: oligomeric forms have been shown to bind to mitochondrial membranes. This includes the Voltage-Dependent Anion Channel (VDAC), which typically allows the exchange of ions and metabolites, such as ATP/ADP, pyruvate, NADH, and Ca^{2+}. The binding of α-synuclein here can block the channel partially or entirely, leading to reduced export of ATP and increased import of ADP, as well as disrupted calcium homeostasis. α-synuclein can also bind to complex I of the electron transport chain, essentially inhibiting it. This impairs oxidative phosphorylation in SNc neurons, which require a high energy demand. Lastly, oligomeric α-synuclein can bind to and inhibit proteasome subunits, as well as autophagy components, such as p62 and LC3-II, leading to the accumulation of misfolded proteins and damaged organelles, and also impairing the clearance of α-synuclein itself. These oligomeric forms of α-synuclein aggregates are considered the most neurotoxic α-synuclein species due to their solubility, mobility, and ability to spread within the cell rapidly.

As oligomers accumulate, they can further assemble into protofibrils, which then form fibrils. These fibrils are long, insoluble, linear structures composed of tightly packed β-sheets aligned perpendicular to the fibril axis. This form of intracellular aggregated α-synuclein is the core structure of Lewy bodies. In addition to misfolded and aggregated α-synuclein, Lewy bodies also contain ubiquitin and neurofilaments (neuronal cytoskeletal components). Lewy bodies can accumulate in the cell body, and when they accumulate in neuronal processes (dendrites and axons), they are called Lewy neurites. Lewy bodies physically obstruct intracellular transport, disrupt neurotransmitter release, and displace organelles, especially mitochondria. Moreover, Lewy bodies are highly immunogenic, capable of activating microglia via Toll-Like Receptors (TLRs), resulting in the production of pro-inflammatory cytokines (including TNF-α and IL-1β) and sustained inflammation. This ultimately creates a hostile extracellular environment that promotes further neuronal injury. While less immediately toxic than oligomers, fibrils are unique in

that they express prion-like propagation. That is, when *α*-synuclein fibrils break, spontaneously or due to stress, into fragments, they can be released and spread from cell to cell. Each fragment can act as a new nucleation center, inducing normal *α*-synuclein to adopt the same misfolded, aggregated structure via sequence-specific motifs.

Because *α*-synuclein functions in presynaptic terminals, it is particularly abundant in SNc neurons, due to their highly branched architecture that forms millions of synapses. This makes SNc neurons especially likely to experience toxic *α*-synuclein aggregation into oligomers and fibrils (Lewy bodies) [5]. The steps for *α*-synuclein aggregation are shown in Figure 3.

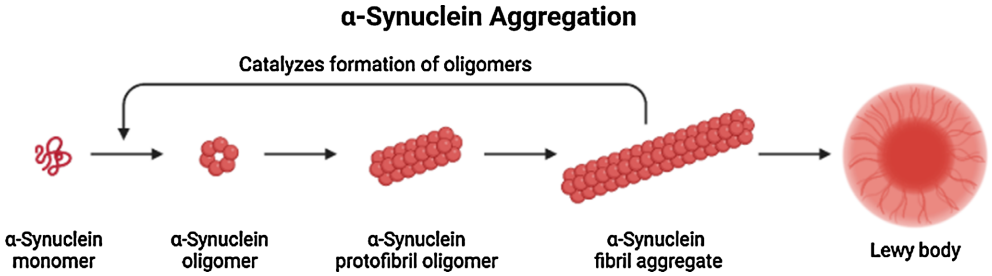

Figure 3. Progression of *α*-synuclein aggregation into Lewy Bodies [6].

High Energetic demand:

Dopaminergic neurons in the SNc are vulnerable to damage in PD due to their high metabolic demand. SNc neurons have a particularly high metabolic rate for various reasons. For example, these neurons in the SNc exhibit autonomous pacemaking activity, firing action potentials rhythmically and continuously without external synaptic stimulation via L-type voltage-gated calcium channels (allowing a steady influx of Ca^{2+}). Therefore, Ca^{2+} levels must be tightly regulated to avoid toxicity, necessitating energy-intensive buffering mechanisms, such as ATP-dependent Ca^{2+} membrane pumps as well as mitochondrial Ca^{2+} uptake. More significantly, dopaminergic neurons in the SNc project to the dorsal striatum and form up to 1 - 2 million synapses, thus exhibiting extensive axonal arborization. This process requires continuous synaptic vesicular recycling, as well as long-distance anterograde and retrograde transport, protein turnover, and ion pumping.

All these factors make SNc neurons more prone to mitochondrial dysfunction than other cells. However, this excessive mitochondrial workload leads to increased electron transport chain activity, which in turn increases the likelihood of electron leakage, thereby stimulating the production of Reactive Oxygen Species (ROS) that can overwhelm the neuron's antioxidant defenses. Indeed, in PD, the dysfunction of mitochondrial complex I (NADH: ubiquinone oxidoreductase) is consistently reported, causing impaired ATP production, increased ROS concentrations, and oxidative damage to cellular components, including proteins, lipids, and DNA, and ultimately, cell death [7].

Cytotoxicity of Dopamine:

Dopamine is an inherently unstable molecule. When cytosolic dopamine is not

packaged correctly into synaptic vesicles via VMAT2 (a protein transporter), it can undergo auto-oxidation or enzymatic metabolism by monoamine oxidase, producing hydrogen peroxide, dopamine quinones, and other free radicals. This can lead to the damage of proteins, especially mitochondrial and cytoskeletal proteins. Further, dopamine quinones can covalently modify *α*-synuclein, promoting its misfolding and aggregation into Lewy bodies [8].

Calcium Cytotoxicity:

L-type voltage-gated Ca^{2+} channels (Cav1.3 subtype) primarily mediate the autonomous pacemaking of dopaminergic neurons in the SNc, allowing the constant influx of calcium ions into the neuron. However, chronic calcium influx places stress on mitochondria, as they take up calcium ions to buffer intracellular levels. Mitochondria take up calcium ions via the mitochondrial calcium uniporter protein channel. This uptake enhances oxidative phosphorylation, which increases the generation of ROS, leading to oxidative damage to neuronal components. Further, high calcium levels in the mitochondrial matrix and ROS promote the formation of the mitochondrial Permeability Transition Pore (mPTP). This channel opens on the inner mitochondrial membrane in response to stress, leading to the loss of membrane potential and matrix swelling. If the pressure buildup inside the matrix causes the rupture of the outer membrane, it can promote the release of cytochrome c (an apoptotic factor), leading to cell death and the degeneration of dopaminergic neurons. Additionally, excessive calcium levels can activate calpain, a calcium-activated protease that cleaves cytoskeletal and mitochondrial proteins, thereby also promoting cell death [9].

Now, neurons in the ventral tegmental area are also dopaminergic, but why are they inherently more stable than SNc neurons? VTA neurons primarily project to the prefrontal cortex, amygdala, and nucleus accumbens, playing a crucial role in reward, motivation, and addiction through their dopaminergic input. However, their projections have a less branched axonal architecture, making them metabolically less taxed.

Furthermore, VTA neurons are far less dependent on L-type Ca^{2+} channels for pacing. Instead, they use HCN and T-type Ca^{2+} channels, which do not cause the same Ca^{2+} burden. They also generally have higher concentrations of Ca^{2+} binding proteins, like calbindin, to help buffer Ca^{2+} levels. This allows them to avoid the potential cytotoxicity of calcium.

VTA neurons express higher levels of antioxidant enzymes than SNc neurons, including glutathione peroxidase. In addition, dopaminergic neurons in the VTA express far lower levels of *α*-synuclein, preventing the formation of Lewy pathology.

All these factors also contribute to the ability of VTA neurons to maintain more stable mitochondria under stress, exhibiting less complex dysfunction and producing fewer ROS than SNc [10].

3. Parkinson's Associated Genes and Molecular Pathways

Multiple genes have been implicated in both familial and sporadic forms of PD,

with their protein products involved in critical cellular pathways, including mitochondrial function, proteostasis, and autophagy.

One of the most well-studied genes involved in PD is SNCA, which encodes *α*-synuclein. Dysfunction of the SNCA gene causes autosomal dominant PD. Typically, *α*-synuclein is a presynaptic neuronal protein that plays an essential role in synaptic recycling and neurotransmitter release. Under pathological conditions, however, due to point mutations, DNA duplications, or post-translational changes, *α*-synuclein misfolds into beta-sheet-rich oligomers and fibrils, leading to aggregation in Lewy bodies. These aggregates disrupt proteostasis, impair vesicle trafficking, inhibit mitochondrial activity, and interfere with autophagy and lysosomal clearance, leading to neuronal death.

Another well-studied gene is LRRK2 (leucine-rich repeat kinase 2), which is another gene linked to autosomal dominant PD. It encodes a kinase involved in vesicular trafficking, cytoskeletal dynamics, and the regulation of autophagy. Pathogenic mutations such as G2019S enhance its activity, causing abnormal phosphorylation of Rab GTPases, which are essential for endolysosomal transport and membrane recycling. This disrupts the fusion of the autophagosome and lysosome, contributing to neuronal dysfunction.

Moreover, PINK1 and Parkin are central to mitochondrial quality control via the PINK1-Parkin mitophagy pathway. Dysfunction of either of the two genes contributes to autosomal recessive PD. PINK1 encodes a mitochondrial serine/threonine kinase that accumulates on the outer membrane of damaged mitochondria and recruits Parkin, an E3 ubiquitin ligase. Parkin then ubiquitinates numerous outer mitochondrial membrane proteins, targeting the mitochondria for degradation via mitophagy. Mutations in either gene impair the clearance of dysfunctional mitochondria, leading to energy production failure, ROS accumulation, and neuronal apoptosis.

PARK7 is a gene linked to autosomal recessive PD. It encodes DJ-1, a multifunctional protein that plays a key neuroprotective role in PD by regulating oxidative stress, mitochondrial integrity, and protein homeostasis. As a redox-sensitive molecule, DJ-1 contains a highly reactive cysteine residue (Cys106) that undergoes oxidation in response to elevated ROS, allowing it to function as a redox sensor. Upon activation, DJ-1 promotes antioxidant pathways, including the activity of the transcription factor Nrf2, which upregulates the expression of enzymes that detoxify ROS, such as glutathione peroxidase and superoxide dismutase. DJ-1 also localizes to mitochondria, where it supports mitochondrial membrane potential, maintains ATP production, and limits ROS generation. Furthermore, DJ-1 exhibits chaperone-like activity, preventing the aggregation of misfolded proteins, particularly *α*-synuclein, contributing to proteostasis. Pathological mutations in PARK7, such as the pathogenic L166P variant, destabilize the DJ-1 protein, impairing its ability to buffer oxidative stress and support mitochondrial function [11].

Lastly, GBA1 encodes the lysosomal enzyme glucocerebrosidase (GCase).

While not inherited in the traditional Mendelian pattern like other PD genes, it is considered a strong genetic risk factor for PD. GCase is responsible for degrading glucosylceramide and other glycolipids in lysosomes. Mutations reduce GCase activity, resulting in the accumulation of lipids within lysosomes. This impairs autophagy and promotes the aggregation of *α*-synuclein. *α*-synuclein accumulation can then further damage lysosomes, creating a toxic cycle. Thus, GBA1 is linked directly to lysosomal degradation, lipid metabolism, and *α*-synuclein proteostasis. Mutations in both copies of the GBA1 gene cause Gaucher disease, a lysosomal storage disorder, which dramatically increases the risk of PD. On the other hand, mutations in one copy do not cause Gaucher disease, but they still increase the risk of developing PD (although not as much as when both copies are affected) [12].

SNCA	Autosomal dominant	*α*-Synuclein proteostasis/autophagy-lysosomal pathway (misfolding/aggregation; disrupted vesicle trafficking)
LRRK2	Autosomal dominant	Endolysosomal/vesicular trafficking & autophagy (hyperactive kinase → abnormal Rab GTPase phosphorylation)
PINK1	Autosomal recessive	Mitochondrial quality control; PINK1/Parkin mitophagy initiation
Parkin	Autosomal recessive	Mitochondrial quality control: E3 ubiquitin ligase in mitophagy
PARK7	Autosomal recessive	Oxidative-stress defense and mitochondrial maintenance (redox sensor; supports proteostasis)
GBA1	Genetic risk factor for PD	Lysosomal lipid metabolism/autophagy-lysosomal pathway (↓ GCase → lipid buildup → ↑ *α*-syn aggregation)

4. Braak's Hypothesis and "Single-Hit" Model

Braak's hypothesis is a model of PD progression first proposed by Heiko Braak and colleagues in 2003. By analyzing postmortem brains from individuals at various stages of PD, Braak's model suggests that neurodegeneration, via the aggregation of misfolded *α*-synuclein, begins in two peripheral entry points: the olfactory bulb, responsible for the sense of smell, and the enteric nervous system, which regulates gastrointestinal activity. This concept posits that PD pathology can be initiated by the inhalation or ingestion of environmental toxins, including certain pesticides, dry cleaning chemicals, and air pollution. Once these pathogenic agents gain access to the nervous system via the nasal or gastrointestinal mucosa, they initiate *α*-synuclein misfolding, which then propagates in a prion-like fashion upward through connected structures, leading to a predictable, stepwise spread of Lewy pathology.

Firstly, the progression affects the brainstem nuclei early on, including the locus coeruleus and raphe nuclei. The SNc eventually reaches the limbic system and cortex, causing cognitive, emotional, and behavioral disturbances. Braak's hypothesis supports the concept of a prodromal phase during which non-motor symptoms

may serve as early indicators of PD. For example, loss of sense of smell (anosmia), constipation, and REM sleep behavior disorder are non-motor symptoms that can manifest before the SNc becomes affected with Lewy pathology, and motor symptoms arise.

Brain-first/Body-first model:

In the past, Braak's model was referred to as the "dual-hit" hypothesis, suggesting that the two routes (olfactory and enteric nervous system) co-occur, converging at the brainstem and then affecting the SNc. This generally agrees with the observations that hyposmia and autonomic symptoms appear together before the onset of PD. However, recent postmortem and imaging studies have challenged the "dual-hit" concept for multiple reasons:

1) Some cases have been identified in which α-synuclein pathology presents itself in only one of the two peripheral pathways.

2) Sometimes, motor symptoms affect only one side of the patient, rather than exhibiting symmetry.

3) Some patients exhibit minimal prodromal non-motor symptoms, while others display more prominent ones.

These topics of concern led to the development of a more accurate "single-hit model," including the brain-first and body-first subtypes, also shown in **Figure 4**:

- In brain-first PD, Lewy pathology is thought to originate in the brain, particularly in one of the olfactory bulbs. From here, pathology propagates unilaterally downwards toward the amygdala, SNc, brainstem nuclei, and eventually to the peripheral nervous system. Furthermore, because Lewy pathology spreads unilaterally, it leads to asymmetric motor symptoms, such as tremor or rigidity that start in just one hand or leg. In brain-first cases, there are fewer prodromal non-motor symptoms since the SNc is reached so quickly before Lewy pathology can affect other areas. Thus, non-motor symptoms typically appear closer to or even after motor symptom onset, such as cognitive decline. Counterintuitively, early-stage loss of smell (hyposmia) is relatively rare in brain-first cases. This is because pathology typically begins in only one of the two olfactory bulbs and spreads unilaterally, initially leaving the contralateral olfactory bulb and its associated olfactory pathways unaffected. Eventually, in later stages, both hemispheres of the brain are affected.
- In body-first PD, Lewy pathology begins in the peripheral nervous system, particularly the enteric nervous system. From there, pathology ascends through the vagus nerve and then reaches the Dorsal Motor nucleus of the Vagus (DMV) in the brainstem. Then it ascends bilaterally (as opposed to unilaterally in brain-first PD) towards the SNc, and eventually reaches the cortex. This is why body-first models lead to more symmetric motor symptoms. Furthermore, because body-first pathology spreads bilaterally and affects the SNc much later, it results in widespread Lewy pathology in the CNS and PNS before motor symptoms even appear. Thus, the prodromal phase is particularly long, with non-motor symptoms preceding motor symptoms by 5 to 20 years. These

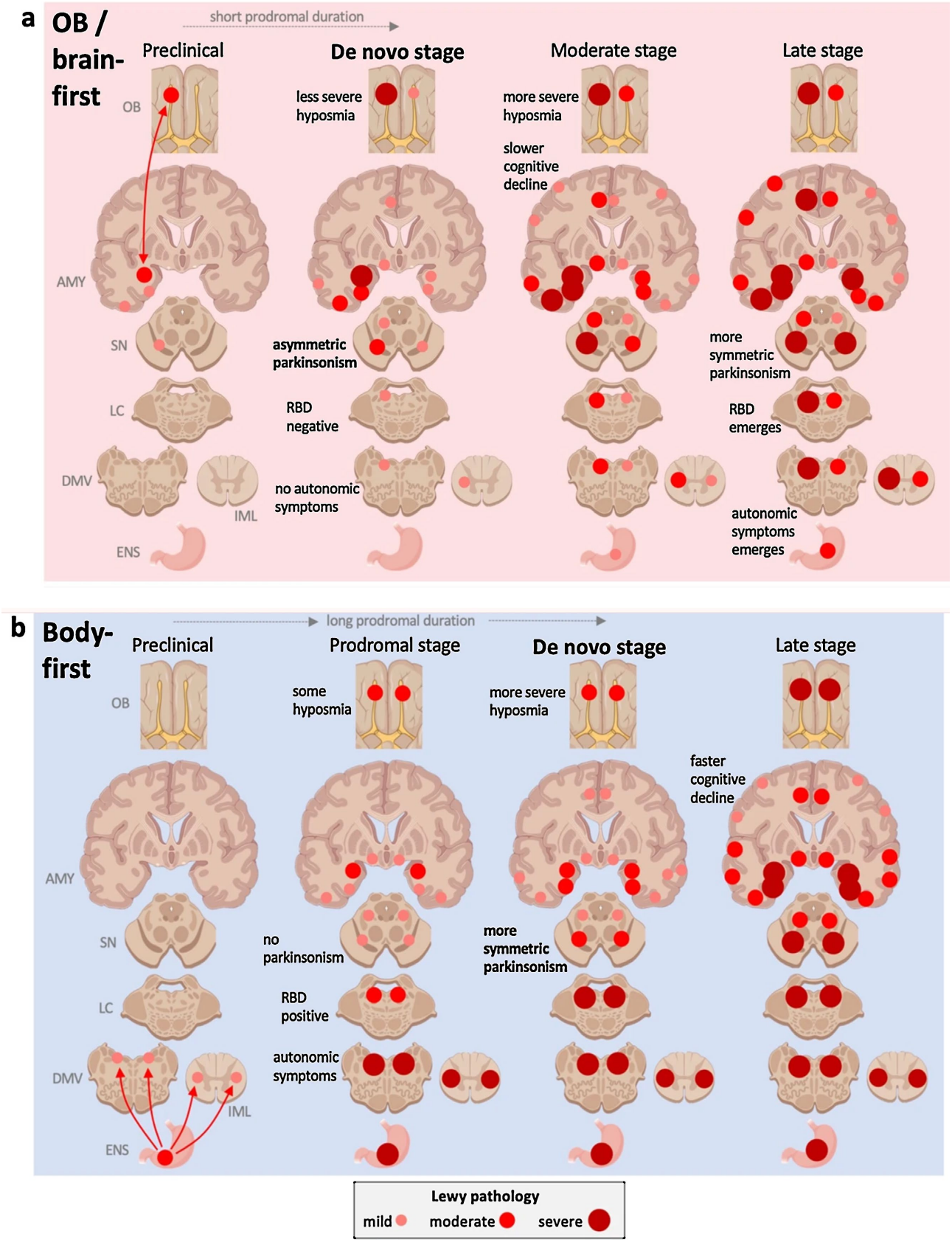

Figure 4. Progression of α-synuclein spread across the body in brain-first (top image) and body-first (bottom image) PD [14].

include autonomic symptoms like constipation, orthostatic hypotension, and urinary dysfunction; mood symptoms (like anxiety and depression); and REM Sleep Behavior Disorder. Early-stage hyposmia is also more frequently observed in body-first PD. Although the olfactory bulbs are not the initial site of pathology, bilateral spread allows it to affect both olfactory bulbs and multiple olfactory processing centers well before reaching the SNc.

In addition to this, α-synuclein can potentially originate directly in the midbrain and SNc itself—an idea not accounted for in body or brain-first PD. These individuals typically do not experience any prodromal symptoms. In this circumstance, the leading causes are the vulnerability of dopaminergic SNc neurons, genetic risk factors, and aging [13].

5. Role of Other Neurotransmitters in Parkinson's Disease

While dopamine loss is the hallmark of PD, several other neurotransmitter systems are also significantly affected and contribute to both the motor and cognitive symptoms of the disease.

Cholinergic system (acetylcholine):

In PD, acetylcholine plays a crucial and multifaceted role, particularly in the striatum, as shown in Figure 5. The striatum contains a small population of tonically active cholinergic interneurons that regulate the activity of MSNs. Acetylcholine in the striatum binds to muscarinic receptors on both D1 and D2 MSNs. It tends to have an inhibitory effect on D1 MSNs and an excitatory effect on D2 MSNs, thereby generally promoting motor suppression. Under normal conditions, dopamine exerts an inhibitory effect on these cholinergic interneurons via D2 receptors, maintaining a balanced excitatory-inhibitory tone within the striatum. However, in PD, the degeneration of SNc dopaminergic neurons disrupts

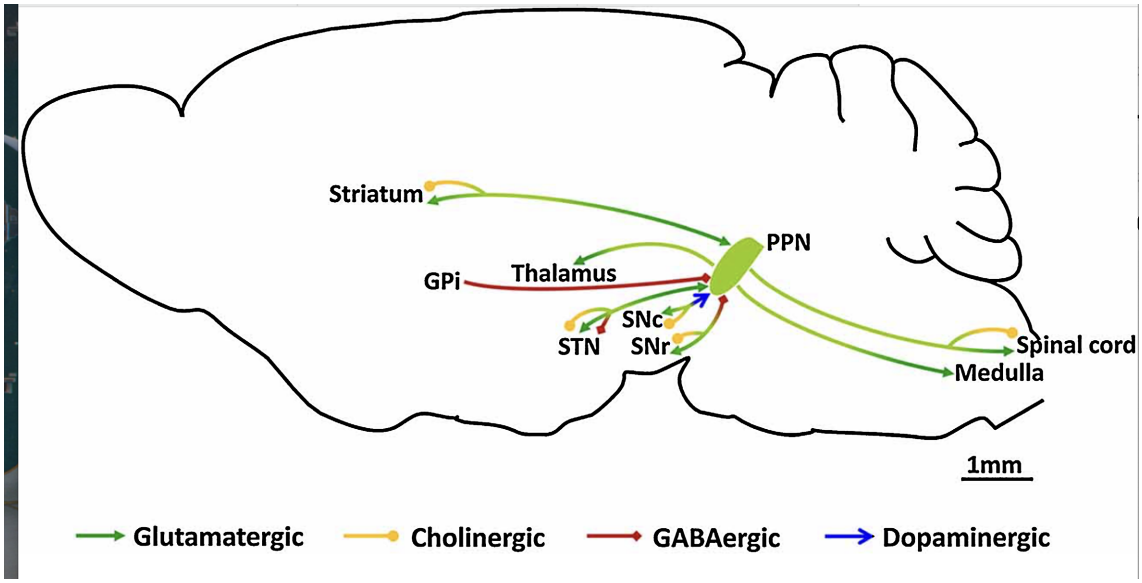

Figure 5. Diagram showing the cholinergic as well as glutamatergic input from the PPN to the SNc, and how the PPN integrates itself within the larger basal ganglia circuitry [16].

this balance, leading to cholinergic overactivity. Consequently, there is an excess of acetylcholine release, leading to the overactivation of the indirect pathway and contributing to the symptoms of PD. This mechanism explains why anticholinergic medications, such as trihexyphenidyl, can alleviate motor symptoms in some patients.

Beyond the striatum, the PPN—located in the upper brainstem—provides cholinergic projections to the SNc. This cholinergic input excites dopaminergic neurons during movement initiation, reinforcement learning, and arousal/attention. This leads to a subsequent burst of firing and dopamine release in the striatum. In PD, however, the PPN undergoes degeneration, and its loss is associated with gait freezing, postural instability, and REM sleep behavior disorder [15].

Serotonergic system (serotonin):

The serotonergic system, originating primarily from the raphe nuclei in the brainstem, is another neurotransmitter network affected in PD. Serotonin is conventionally known to regulate mood, sleep, appetite, and sensory processing, and the reasons for its degeneration largely overlap with those of dopaminergic neurons in the SNc. For example, serotonergic neurons have been shown to accumulate in Lewy bodies, impairing their function. Not only this, but serotonin neurons are prone to experiencing mitochondrial dysfunction and elevated oxidative stress via the enzyme monoamine oxidase (which breaks down serotonin but produces hydrogen peroxide as a byproduct, an ROS). Furthermore, based on the body-first hypothesis of PD progression, the raphe nuclei are involved earlier than the substantia nigra; that is, PD pathology begins in lower brain stem structures, including serotonergic neurons in the raphe nuclei, and only later does it spread (via α-synuclein prion-like mechanisms) to other regions like the substantia nigra.

The loss of serotonergic neurons is linked to many non-motor symptoms, such as depression, anxiety, sleep disturbances, and fatigue, which may predate motor symptoms by years.

Importantly, serotonergic neurons can take up exogenous levodopa during levodopa therapy and convert it into dopamine using the enzyme aromatic L-amino acid decarboxylase. However, unlike dopaminergic neurons, serotonergic neurons lack the machinery to regulate dopamine release—that is, they do not possess dopamine transporters or D2 autoreceptors. As a result, dopamine is released in an erratic manner, which has been strongly implicated in the development of levodopa-induced dyskinesias. Therefore, not only is the serotonergic system in PD a victim of degeneration, but it can also worsen the side effects of dopamine replacement therapy [17].

Noradrenergic system (norepinephrine):

The noradrenergic system is centered in the locus coeruleus, which is located in the pons of the brainstem. The LC is the brain's principal source of norepinephrine, a neurotransmitter essential to the sympathetic nervous system, with functions related to arousal, attention, stress response, and autonomic regulation. In PD, degeneration of LC neurons occurs early, often even before the loss of dopa-

minergic neurons in the SNc, supporting the body first hypothesis; emerging evidence suggests that α-synuclein pathology appears early in LC neurons, and these cells are highly prone to misfolded α-synuclein aggregation due to their long, thin axons, high metabolic demand, and complex arborization. This early loss of noradrenergic neurons has been associated with a wide array of non-motor symptoms, including orthostatic hypertension (increased blood pressure when one stands up from a resting position), cognitive decline, and anxiety and depression. Moreover, norepinephrine is known to modulate neuroinflammatory responses by acting on microglia to suppress the production of pro-inflammatory cytokines. Therefore, LC degeneration may also exacerbate neuroinflammation, potentially accelerating the degeneration of vulnerable SNc neurons [18].

Glutamatergic system:

The prevalent excitatory neurotransmitter glutamate plays a crucial and multifaceted role in the pathophysiology of PD. Decreased dopamine in PD leads to hyperactivity of the STN, which provides excitatory glutamatergic input to the GPi and SNr. This heightened glutamatergic drive leads to overinhibition of thalamocortical output, which causes motor symptoms.

The glutamatergic system has two well-studied receptors: NMDA and AMPA receptors. These two receptors work in tandem, both of which are ionotropic. While AMPA works as a conventional ligand-gated ion channel for Na^{2+} ions, NMDA receptors are physically blocked by Mg^{2+} ions. This means that NMDA receptors require the postsynaptic neuron to be depolarized to repel the Mg^{2+} block, in addition to binding to glutamate. What's unique about NMDA receptors, however, is that they allow for the passage of Ca^{2+} ions in conjunction with Na^{2+}. An increase in Ca^{2+} concentration activates downstream targets, CaMKII and CaMKIV, promoting the insertion of additional AMPA receptors into the postsynaptic membrane and activating CREB (a transcription factor that supports synaptic plasticity and memory formation), respectively. Therefore, NMDA receptors are critical for long-term potentiation and learning.

Hyperactivity of the STN in PD increases the risk of excitotoxicity, in which excessive glutamate release leads to the hyperactivation of NMDA receptors. This leads to an increase in Ca^{2+} entry, which promotes mitochondrial dysfunction and ultimately results in neuronal cell death.

Also, glutamatergic hyperactivity contributes to levodopa-induced dyskinesias. During L-DOPA therapy, fluctuating stimulation of dopamine can induce the phosphorylation of NMDA receptor subunits through increased cAMP and PKA activity. This sensitization contributes to abnormal synaptic plasticity that underlies the erratic movements seen in dyskinesia. Moreover, enhanced NMDA activity leads to an excessive influx of calcium, promoting excitotoxicity. It is because of this that NMDA receptor antagonists, such as amantadine, have found clinical utility in preventing levodopa-induced dyskinesias and providing protection against excitotoxicity [19].

GABAergic systems:

The GABAergic system provides the primary inhibitory tone to the basal ganglia circuitry, and its balance with dopamine is central to the control of movement. In PD, striatal GABAergic MSNs are hyperactive and hypofunctional in the indirect and direct pathways, respectively. This leads to excessive inhibition of the thalamus via the GPi and SNr.

In addition to projection neurons, GABAergic interneurons in the striatum play a crucial role in providing rapid, local inhibition of MSNs to regulate the timing of MSN firing. The primary GABAergic interneuron in the striatum is the Fast-Spiking Interneuron (FSI), which strongly inhibits MSNs by firing very brief GABAergic action potentials at high rates, contributing to the synchronization of gamma-band (30 - 100 Hz) oscillations in the brain.

In PD, the loss of dopaminergic input causes FSIs to exhibit altered firing patterns, thereby disrupting the precision of striatal output. Such dysregulation contributes to abnormal beta oscillations (13 - 30 Hz). Beta oscillations represent the electrical activity within the brain, which plays a crucial role in sustaining proper motor function. These oscillations decrease when preparing to move and increase after movement. In PD, however, they become sustained in an elevated state, which is heavily associated with bradykinesia.

Additionally, alterations in the expression of GABA receptors and synaptic plasticity have been discovered in animal models and human PD patients. These include modifications in the structure of ionotropic GABAA and metabotropic GABAB receptors. GABAA receptors, which mediate fast inhibitory transmission via chloride ion influx, exhibit increased expression of subunits in the GPi and thalamus, which contributes to excessive thalamic inhibition. GABAB receptors, which mediate slow and long-lasting inhibitory transmission, exhibit reduced expression of subunits in the STN and striatum, leading to weakened inhibitory buffering.

Importantly, these receptor-specific changes offer therapeutic targets. For example, GABAB receptor agonists, such as baclofen, have been shown to reduce levodopa-induced dyskinesia by dampening overactive pathways [20].

Neurotransmitter	Anatomical Source	Related Symptoms
Acetylcholine	Striatal cholinergic interneurons; Pedunculopontine nucleus (PPN); (also basal forebrain)	Slowness and stiffness; resting tremor. With PPN loss—gait freezing, poor balance, REM sleep behavior disorder, and attention slips.
Serotonin (5-HT)	Raphe nuclei (dorsal/median)	Slowness and stiffness; resting tremor. With PPN loss—gait freezing, poor balance, REM sleep behavior disorder, and attention slips.
Norepinephrine	Locus coeruleus (pons)	Lightheadedness on standing (orthostatic hypotension), constipation/urinary issues, trouble focusing, and anxiety often appear early.

Continued

Glutamate	Subthalamic nucleus (STN) → GPi/SNr; cortex → striatum	STN "overdrive" adds extra brake on movement → Bradykinesia/rigidity; risk of excitotoxicity; with L-DOPA, sensitized NMDA signaling is linked to dyskinesias
GABA	Striatal medium spiny neurons (MSNs); GPi/GPe; SNr; striatal fast-spiking interneurons (FSIs)	Too much inhibitory output → slow, small, hard-to-start movements; disrupted FSI timing → abnormal beta oscillations linked to slowness and bradykinesia

6. Clinical Symptoms of Parkinson's Disease

Motor symptoms:

The clinical symptoms of PD typically manifest as "the four cardinal symptoms," including tremor at rest, bradykinesia (slow movement), muscle rigidity, and postural instability.

Tremor at rest:

Resting tremor is often the initial and most recognizable motor symptom of PD; it is the rhythmic shaking that occurs when a body part is at rest. It typically manifests asymmetrically, affecting only one side of the body initially before progressing to the other side. A tremor in PD is generally observed at rest, with a frequency of 4 - 6 Hz (4 - 6 oscillations per second), and can affect the hands, feet, chin, jaw, or tongue. Tremor is most apparent when a person is at rest; however, it is suppressed when that person sleeps or performs a voluntary movement [21]. Furthermore, there are other types of tremors, including pure postural and re-emergent tremors, the latter being a variant of the former. Pure postural tremors appear immediately when maintaining a posture (such as holding the arms out). In contrast, a re-emergent tremor occurs during the maintenance of a posture after a delay of a few seconds [22].

Bradykinesia:

Bradykinesia refers to the slowness of movement, which includes difficulties in planning, initiating, and executing movements. Bradykinesia presents not only as slowness, but also as reduced movement amplitude, intermittent arrests during the performance of actions, and the "sequence effect," where repeated movements become progressively slower and smaller (such as tapping your finger on a surface). Bradykinesia can manifest in a wide array of ways, including reduced facial expression (hypomimia), decreased arm swing while walking, reduced vocal volume (hypophonia), and impairments in fine motor control, such as difficulty writing or using utensils. Clinically, bradykinesia is highly responsive to dopaminergic therapies, including L-DOPA therapy. Bradykinesia is closely associated with abnormal brain rhythms, specifically the emergence of pathological beta-band oscillations (13 - 30 Hz). Beta oscillations represent the electrical activity within the brain, which plays a crucial role in sustaining proper motor function. These oscil-

lations decrease when preparing to move and increase after movement. In PD, however, they become sustained in an elevated state, which is heavily associated with bradykinesia [23].

Muscle Rigidity:

Muscle rigidity is characterized by an increase in muscle tone (muscle tension), resulting in increased resistance to passive movement across joints, which is independent of the direction and velocity of movement. Therefore, muscle rigidity differs from spasticity, which is typically seen in upper motor neuron lesions and is velocity-dependent. Clinically, rigidity may present as "lead-pipe" rigidity (uniform resistance throughout the entire range of motion) or "cogwheel" rigidity (rigidity combined with underlying tremor that causes a jerky, ratchet-like manner of movement). This reflects the co-contraction of agonist and antagonist muscles. Like resting tremors, rigidity often begins asymmetrically and may affect the neck, shoulders, arms, or legs. Thus, rigidity contributes to difficulty with movement, increased pain, cramping, reduced arm swing during walking, and a stooped posture, which can increase the risk of falls. It also impairs fine motor tasks such as writing, eating, or buttoning clothes. At the pathophysiological level, rigidity is not solely due to basal ganglia dysfunction, but also involves downstream brainstem motor pathways involving the reticular formation and pedunculopontine nucleus. These centers form parts of descending tracts such as the reticulospinal tract, which exert tonic control over alpha motor neurons in the spinal cord (they directly innervate skeletal muscles). In PD, excessive inhibitory output from the basal ganglia disrupts the regular activity of these brainstem nuclei, leading to increased excitation of alpha motor neurons and sustained involuntary muscle contraction [24].

Postural instability:

Postural instability typically emerges in the later stages of PD and is a major contributor to falls and gait abnormalities. Postural instability is characterized by a loss of balance and impaired postural reflexes (the ability to respond to external disturbances toward one's body position). Unlike tremor and bradykinesia, however, postural instability emerges later in PD and is less responsive to dopaminergic therapies, suggesting that other non-dopaminergic circuitries are involved. Postural instability consists of the dysfunction of multiple systems, including the basal ganglia, vestibular system, cerebellum, frontal cortical areas, and brainstem locomotor centers (such as the Pedunculopontine nucleus), which are responsible for postural adjustments. Damage to these regions leads to balance deficits, impairing the body's ability to coordinate responses that prevent falls [25].

Non-motor symptoms:

Cognitive impairment:

Cognitive impairment is a core non-motor symptom of PD, often manifesting gradually in the early or mid-stages and worsening over time. The most commonly impaired domains are executive function, working memory, attention, and visuospatial function. All these impairments result from dysfunction of the frontostriatal network, which is caused by dopaminergic loss in the striatum and, in

more advanced stages of PD, the ventral tegmental area. As the disease advances, some individuals eventually develop PD dementia, which manifests with global cognitive impairment, including impairment of memory, language, and orientation. This dementia is associated with the progression of Lewy pathology into the cortex, particularly in the posterior parietal and temporal lobes, and with cholinergic degeneration, most notably in the nucleus basalis of Meynert. Importantly, noradrenergic and serotonergic systems also control cognitive impairment, and therefore, it is not entirely a dopamine issue. In brain-first PD, cognitive symptoms typically emerge earlier. In contrast, body-first PD usually exhibits cognitive decline in later stages, following the onset of autonomic, sleep-related, and motor symptoms [26].

Mood disorders:

Mood alterations, depression, anxiety, and lack of enthusiasm (apathy) are some of the most frequent and relevant non-motor symptoms of PD. While such symptoms occur in both subtypes of PD, body-first PD tends to display greater prevalence and severity of such symptoms in prodromal stages compared to brain-first PD. Depression in PD is typically characterized by loss of pleasure, low mood, fatigue, panic attacks, or social withdrawal. Biologically, these diseases are associated with early degeneration of the serotonergic raphe nucleus, the noradrenergic locus coeruleus, and the dopaminergic mesolimbic projections—all three of which project to sites that regulate emotion, including the prefrontal cortex and the amygdala. Impaired operation of these particular systems is the basis of emotional dysregulation in PD. These symptoms often remain underdiagnosed and greatly affect the quality of life [27].

Sleep disturbances:

Sleep dysfunction is highly prevalent in PD and includes REM sleep behavior disorder (RBD), insomnia, fragmented sleep, and excessive daytime sleepiness. RBD, in which individuals physically act out their dreams due to a loss of normal REM muscle paralysis, is a significant symptom because it can precede motor symptoms by years. Early RBD is particularly seen in body-first PD, whereas it manifests after motor symptoms appear in brain-first PD. It is associated with the degeneration of the subcoeruleus nucleus in the brainstem. Insomnia in PD is related to many factors: it may result from the inability to move, urinary frequency, restless legs, or medication side effects.

Additionally, degeneration of the hypothalamic sleep-wake regulatory structures, including the suprachiasmatic nucleus, contributes to the disruption of the circadian rhythm. Sleep disturbances can also result from dopaminergic therapies, such as levodopa or dopamine agonists, which alter alertness and disrupt the regulation of REM and wake transitions. Sleep disturbances not only impair quality of life but also worsen cognitive performance [28].

7. Pathological β-Band Oscillations

Dopamine loss changes not only how much basal-ganglia neurons fire but also

when they fire together. In Parkinson's disease, the motor loop (cortex, basal ganglia, thalamus) slips into brief bursts of synchronized activity in the β band (about 13–30 cycles per second). These β bursts act like a soft "hold" signal: when they last longer or happen more often, the network is more likely to keep the current motor state instead of updating it. On the surface, that appears as bradykinesia—movements that start late, are smaller than intended, and feel braked.

What drives the rhythm? With dopamine depleted, several pieces of the loop nudge the system toward β timing:

- The STN-GPe pair (excitatory STN, inhibitory GPe) forms a feedback loop with just enough delay to resonate at β; dopamine usually dampens this tendency.
- Increased inhibitory output from the GPi/SNr to the thalamus makes it harder for the cortex to push the system out of the "hold" state.
- In the striatum, fast-spiking interneurons that usually support faster (gamma) timing become less precise, so slower β rhythms have an easier time organizing the population.
- Cortical inputs themselves carry β bursts, which can entrain subcortical nodes when dopamine's stabilizing influence is missing.

Put simply, β bursts are windows when many neurons line up their timing; during those windows, changes in movement are less likely to break through.

Link to Bradykinesia:

In an extensive intraoperative study of >100 people with PD, Lofredi *et al.* (2023) showed that longer low-β bursts and more time spent in β in the subthalamic nucleus tracked worse bradykinesia off medication, and levodopa shortened those bursts alongside clinical improvement. This ties β bursting to slowness itself rather than treating it as background noise.

Clinical angle:

Treatments that trim β bursts—dopaminergic medication, standard high-frequency DBS, and newer adaptive DBS that triggers when β rises—tend to ease slowness and rigidity. Framing PD as a timing problem links the cellular changes reviewed earlier (dopamine depletion, cholinergic/GABAergic imbalance, glutamatergic drive) to what patients feel day to day, and it points to a practical target for closed-loop therapies: shorten β bursts, restore quicker rhythms, and movement follows [29].

8. Stem Cell Therapies and Dopaminergic Neuron Replacement

Stem cell-based therapies have recently emerged as a promising strategy for restoring dopaminergic function in PD. Various types of stem cells are being explored for this purpose, each with distinct advantages and limitations.

Embryonic Stem Cells (ESCs) are derived from the inner cell mass of blastocysts and are inherently pluripotent, meaning they can differentiate into any cell type, including midbrain dopaminergic neurons. ESCs are highly proliferative and well-

studied, but their use is limited by ethical concerns (due to the destruction of human embryos to obtain ESCs), potential immune rejection, and the risk of teratoma (tumors that contain a variety of tissues) formation if not fully differentiated before transplantation.

In contrast, induced Pluripotent Stem Cells (iPSCs) are generated by reprogramming somatic cells (most commonly skin fibroblasts). This is accomplished by introducing four transcription factors, including Oct4, Sox2, Klf4, and c-Myc (collectively known as the Yamanaka factors), into adult cells, thereby returning them to a pluripotent state. Once reprogrammed, iPSCs can differentiate into any cell type, particularly midbrain dopaminergic neurons, which can be used in cell replacement therapies for PD. Unlike ESCs, iPSCs are advantageous in that they can be derived from a patient's cells, bypassing concerns of immune rejection. Additionally, patient-derived iPSCs enable researchers to create in vitro models of genetic forms of PD by differentiating them into dopaminergic neurons, allowing for the study of disease mechanisms in PD and drug screening using human neuronal systems, rather than animal cells.

Adult stem cells, such as mesenchymal stem cells and neural stem cells, are multipotent and thus have a more restricted differentiation potential than the aforementioned cells. However, they possess immunomodulatory, trophic, and anti-inflammatory properties that may support neuronal survival and reduce neuroinflammation, while also carrying a lower risk of tumorigenesis. While adult stem cells are less likely to form tumors and are easier to obtain, they are not generally used to generate dopaminergic neurons as frequently as ESCs and iPSCs. For example, mesenchymal stem cells sourced from bone marrow and adipose tissue can play a therapeutic role by secreting neurotrophic factors (like BDNF, GDNF, and IGF-1), signaling molecules that play a vital role in neuronal survival, enhancing synaptic plasticity, and reducing neuroinflammation. They can modulate microglial activation (resident macrophages of the CNS). Essentially, adult stem cells are used to modify the disease environment rather than directly replacing dopaminergic neurons in the SNc [30].

Formation of dopaminergic neurons from stem cells:

For iPSCs and ESCs, robust procedures for dopaminergic differentiation are required. The first step is to differentiate pluripotent stem cells into neuroectoderm, the embryonic tissue that gives rise to the nervous system. This is achieved through dual SMAD inhibition, which blocks bone morphogenetic protein and transforming growth factor-beta pathways with molecules such as noggin, SB431542, or LDN193189. This yields progenitor neurons that are equivalent to those inside a developing neural tube.

Specific morphogens (developmental signaling molecules used in cell fate determination through concentration gradients) are then employed to replicate the embryonic context, which determines midbrain development, such as Sonic Hedgehog, Fibroblast Growth Factor 8, and WNT. Upon the development of these signaling molecules, cells begin to express transcription factors that define the char-

acteristics of dopaminergic progenitors [31].

After regional patterning, cells are treated with factors that promote terminal dopaminergic differentiation, including ascorbic acid, Brain-Derived Neurotrophic Factor (BDNF), Glial-Derived Neurotrophic Factor (GDNF), and transforming growth factor-β (TGF-β).

Lastly, the derived cells are checked for markers of mature dopaminergic neurons. For example, tyrosine hydroxylase is responsible for catalyzing the conversion of tyrosine to L-DOPA. NURR1, LMX1A, and PITX3 are transcription factors unique to midbrain dopaminergic neurons, and VMAT2 and DAT are proteins responsible for dopamine packaging and reuptake, respectively.

Ultimately, spontaneous electrical activity and release of dopamine begin after 3 - 6 weeks [32].

Transplantation strategies:

Firstly, it is worth noting that transplantation therapies primarily utilize dopaminergic progenitors rather than completely mature ones. This is because progenitor cells are more robust and are likely to resist the mechanical stress of injection and the inflammatory conditions of the host brain. Moreover, dopaminergic precursors have greater axonal growth and integration potential, enabling the formation of new synaptic connections to reconstruct the nigrostriatal circuitry. Research simulating PD with genetic mutations or drug screens relies on fully mature, differentiated dopaminergic neurons, on the other hand.

The most common approach is the intrastriatal transplantation of dopaminergic neurons (stem cells) to the putamen, the primary recipient of projections from the substantia nigra. This approach allows the transplanted cells to secrete dopamine where it is needed most, thereby bypassing the requirement for long-distance axonal extension.

However, other strategies also examine midbrain-directed transplantation to rebuild the entire nigrostriatal pathway. Successful integration requires transplanted neurons to survive, mature into dopaminergic neurons, and project their axons to the appropriate targets, including both afferent and efferent connections. To further promote survival and integration, transplanted cells are often co-administered with trophic factors like BDNF or GDNF, or seeded in biomaterial scaffolds (e.g., hydrogels, fibrin, or PLGA) that offer greater structural support and lower immune response.

In each case, immune suppression is typically required. That worry, however, is circumvented if the patient is treated with iPSCs from the same individual.

Further, clinical approaches using stem cell transplantation still require L-DOPA or related therapies in conjunction. That is, dopaminergic progenitors can take months or even years to mature, integrate, and begin producing dopamine effectively. L-DOPA medication is used to maintain symptom control during this time, providing a baseline for researchers to distinguish improvements by assessing "ON" periods (when medication is effectively alleviating symptoms) and "OFF" periods (when medication wears off and symptoms return to normal) before and

after transplantation.

Moreover, multiple clinical studies have demonstrated the effectiveness of this method. In a Phase 1 trial with 12 patients, BlueRock Therapeutics implanted allogeneic human embryonic stem cell-derived dopaminergic progenitors bilaterally into the putamen. At 18-24 months, no serious side effects were observed, and PET imaging provided evidence that the transplanted cells survived and began producing dopamine. Patients in the high-dose group experienced an average improvement of 23 points in OFF-period motor scores and an increase in "ON" periods of, on average, 2.7 hours. The therapy is now advancing into phase 3 in 2025. [33]

On the other hand, Kyoto University recently performed landmark Phase 1 and Phase 2 trials, in which seven patients received HLA-homozygous donor iPSC-derived dopaminergic progenitors bilaterally into the putamen. Over 24 months, no tumor formation or graft-induced dyskinesias were reported, and PET imaging confirmed dopamine uptake by the putamen. Among the 6 participants, motor scores improved by 20.4% during "OFF" periods and by 35.7% during "ON" periods, indicating successful symptom control [34].

But difficulties remain. For example, cell identity and purity must be dealt with in stem cell treatments. Differentiation of dopaminergic cells from stem cells is a sensitive and accurate process that requires precise developmental signals. Even slight contamination of differentiating cells with non-dopaminergic neurons or undifferentiated stem cells can lead to failed grafts or tumor formation. Moreover, most current clinical trials focus on transplanting dopaminergic cells into the putamen. Although this compensates for neuron loss in the SNc by locally producing dopamine, it does so only partially because it does not fully integrate into downstream pathways. The physiological release of dopamine is dependent on feedback, as the SNc is regulated by input from the cortex, striatum, and brainstem. This enables the highly sensitive release of dopamine in response to behavior and movement. Without integration, transplanted cells can only release dopamine tonically, which is not optimal for complex motor control or learning. Therefore, repair of basal ganglia function essentially means allowing dopaminergic neurons to form afferent and efferent connections. Other practical hurdles include scalability and manufacturing. To produce clinical-grade stem cell products, protocols must deliver both purity and safety, as well as scalability and affordability for generalized application. However, producing patient-specific therapy is less scalable than allogeneic (donor-derived) transplantation.

9. Conclusions and Future Directions

PD is no longer viewed as merely a loss of dopaminergic neurons in the SNc, but as a complex disease encompassing several brain structures and neurotransmitter systems. The change in activity of other brain structures contributes not only to classical motor symptoms, but also to a broad range of non-motor symptoms.

While current treatments, such as levodopa, improve motor symptoms via do-

pamine replenishment, they do not halt neuronal degeneration or the non-dopaminergic aspects of PD. This article also reviewed how chronic levodopa treatment can lead to complications such as dyskinesia via abnormal glutamate sensitization and dysregulated dopamine release by serotonergic neurons. Stem cell-based treatments are, therefore, a promising direction. iPSCs, in particular, offer the hope of patient-specific, immunocompatible transplantation of dopaminergic neurons. The integration of these stem cells into host neural circuitry, *i.e.*, the reconstruction of the entire nigrostriatal pathway rather than merely local dopamine release, remains problematic nonetheless.

Beyond stem-cell therapies, a variety of clinical research studies are being conducted, for example, testing monoclonal antibodies targeting extracellular α-synuclein to prevent its spread. Gene therapy is also being explored, and FGF-1 drugs are being created to promote angiogenesis and increase blood flow to the SNc. Furthermore, skin biopsy tests are being used to detect α-synuclein in nerve cells in the skin, facilitating early detection of PD.

The long-term goal is to replenish dopamine and rebalance the entire neural circuitry, targeting the whole brain to develop effective treatments for both motor and non-motor symptoms of PD.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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