Biomedical Science

Molecular Genetics

HMG 44110A | Fall 2026-2027

Inherited Neurological Disorders

Parkinson's Disease — Pathophysiology & Mechanisms

جميع الأوراق والمحتويات التابعة للمنصة محمية بموجب حقوق الملكية الفكرية.
يُمنع منعاً باتاً نسخ، أو نشر، أو مشاركة أي محتوى أو مستندات تخص المنصة بأي شكل دون إذن مسبق. ويُعد أي تجاوز أو مخالفة لهذا القرار خرقاً قانونياً يعرض مرتكبه للمساءلة والملاحقة القانونية الفورية

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01 INTRODUCTION

FOUNDATIONS

Introduction

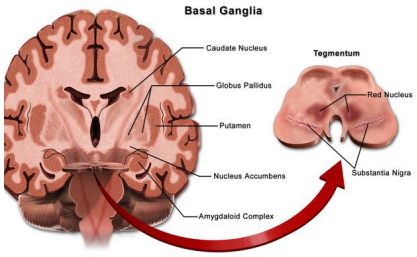
01

What is PD? | Normal movement control | Basal ganglia motor loop | Direct & indirect pathways

PARKINSON'S DISEASE (PD)

Definition

A **degenerative** and **progressive** neurological disorder caused mainly by the **loss of dopamine-producing neurons** in the **substantia nigra** of the midbrain, which disrupts the **basal ganglia** circuits that control movement.



Basal ganglia, tegmentum & substantia nigra · Image: WikiJournal of Medicine / CC BY-SA 4.0

HISTORY

First described by **Dr. James Parkinson** in a little book entitled An Essay on the Shaking Palsy, published in **1817**.

REMEMBER

No disease makes sense until normal makes sense first!

How Normal Movement Is Controlled

Substantia nigra → striatum

Neurons in the substantia nigra produce the neurotransmitter **dopamine** and send it to the **striatum** (the **nigrostriatal pathway**).

Dopamine fine-tunes

Dopamine does **not** carry the movement command itself – it **fine-tunes** how the basal ganglia handle movement signals.

A cortex–basal ganglia–thalamus loop

The striatum is part of a loop linking the **cortex, basal ganglia and thalamus** that helps **start wanted movements** and **stop unwanted ones**.

Basal ganglia + cerebellum

Both help movement run smoothly: the basal ganglia help **select and start** movements, while the cerebellum **coordinates** them.

01 INTRODUCTION

Normal Function of the Basal Ganglia – Simple Overview

The basal ganglia act like a **traffic controller** for movement signals from the **cerebral cortex**, deciding which movements are **allowed** and which are **blocked**.

THESE SIGNALS TRAVEL AROUND A MOTOR LOOP

Cortex

Plans and starts the movement.

Striatum

The main input of the basal ganglia. Receives signals from the cortex and dopamine from the substantia nigra.

GPi

Globus pallidus internus: the main output of the basal ganglia.

Thalamus

Sends the final signal back to the motor cortex.

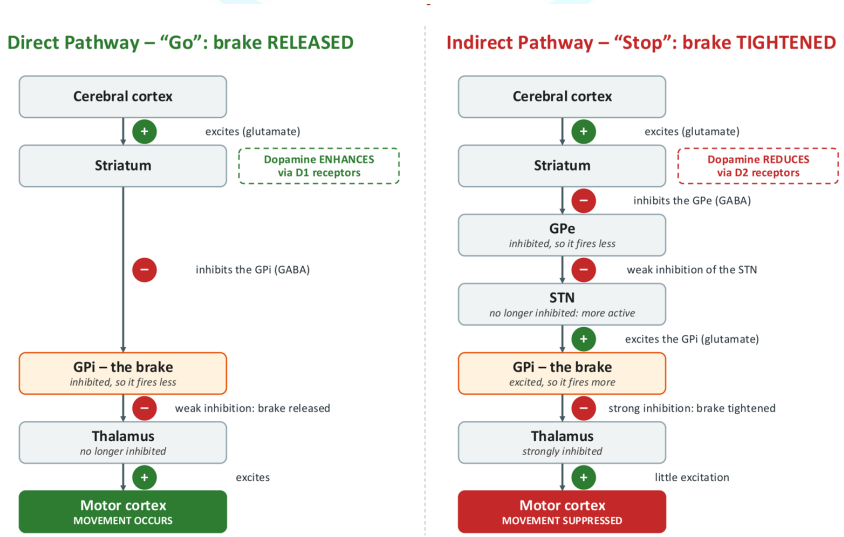
At rest – the brake

The **GPi continuously inhibits the thalamus** (GABA) and acts as the **'brake' on movement**.

Two pathways control the brake

Two pathways from the striatum control this brake: the **direct pathway releases it**, and the **indirect pathway tightens it**.

Direct vs Indirect Pathway – How the Brake Works



Dopamine enhances "Go" (D1) and reduces "Stop" (D2): the balance gives smooth, controlled movement.

Left: direct pathway – brake RELEASED · Right: indirect pathway – brake TIGHTENED

BALANCE

Dopamine **enhances "Go" (D1)** and **reduces "Stop" (D2)**: the balance gives smooth, controlled movement.

01 INTRODUCTION

DIRECT PATHWAY — "Go" Path – initiates and allows voluntary movement

1. The **cortex excites the striatum** (glutamate). Dopamine **enhances** this response through **D1 receptors**.
2. The **striatum inhibits the GPi** (GABA).
3. The GPi can no longer inhibit the thalamus, so the **brake is released**.
4. The **thalamus excites the motor cortex**, and movement occurs.

KEY IDEA

Inhibiting the brake allows movement.

INDIRECT PATHWAY — "Stop" Path – suppresses unwanted or excessive movement

TWO NEW STRUCTURES IN THIS PATHWAY

↑ STN · subthalamic nucleus	↓ GPe · globus pallidus externus
Excites the GPi, so it presses the brake harder.	Normally **inhibits the STN**, keeping its activity low.

HOW THE BRAKE IS TIGHTENED

1. The **cortex excites the striatum** (glutamate). Dopamine **reduces** this response through **D2 receptors**.
2. The **striatum inhibits the GPe** (GABA).
3. With the GPe inhibited, the **STN is no longer held in check** and becomes more active.
4. The **STN excites the GPi** (glutamate), so the brake is tightened and **movement is suppressed**.

KEY IDEA

Releasing the STN tightens the brake.

02 PATHOPHYSIOLOGY

MECHANISMS

Pathophysiology

02

Dopamine loss | Circuit dysfunction | Molecular mechanisms | α-Synuclein | Disease characteristics

What Happens When Dopamine Is Lost?

In Parkinson's disease, **dopamine-producing neurons in the substantia nigra degenerate and die**. This upsets the balance between the direct ("Go") and indirect ("Stop") pathways.

↓ Direct pathway	↑ Indirect pathway
Loses dopamine's **enhancement (D1)**, so the **"Go" signal is weaker**.	Loses dopamine's **dampening (D2)**, so the **"Stop" signal is stronger**.

Weaker "Go" + stronger "Stop" → Both changes make the **GPi overactive** → The **brake on the thalamus** tightens → Movements become **slow, small and hard to start**

Pathophysiology – Overview

PARKINSON'S DISEASE (PD)

Overview

A **progressive neurodegenerative disorder** primarily affecting **movement** due to the loss of dopamine-producing neurons in the substantia nigra.

Dopamine beyond movement

Dopamine also works in other brain pathways involved in **motivation, reward and cognition**, which helps explain some **non-motor symptoms**.

Beyond dopamine deficiency

PD involves several **complex molecular mechanisms**.

02 PATHOPHYSIOLOGY

Circuit Dysfunction

In PD, the dysfunction lies in the **basal ganglia motor loop**: loss of dopamine from the substantia nigra to the striatum makes the **GPi overactive**, so the brake on the thalamus is pressed too hard.

RESULT – THE CLASSIC MOTOR SIGNS

Bradykinesia
Slow, small movements – **best explained by the Go/Stop imbalance**.

Rigidity
Muscles stay stiff.

Tremor at rest
Also involves **other circuits** (e.g., cerebellum–thalamus), so it is **not fully explained by dopamine loss alone**.

Postural instability
Poor balance – **usually a later feature**.

Dopamine Loss Effects

- In Parkinson's disease (PD), **dopaminergic neurons** in the substantia nigra **progressively degenerate**.
- Dopamine is a neurotransmitter that facilitates **smooth and coordinated muscle movements** by fine-tuning basal ganglia circuits.
- The motor symptoms associated with PD, such as **tremors and rigidity**, arise due to disrupted signalling in these circuits.

Other neurotransmitters are also affected

- **Glutamate** signalling from the **subthalamic nucleus** becomes **overactive**.
- **Acetylcholine, noradrenaline** and **serotonin** systems contribute to **non-motor symptoms**.

Molecular Mechanisms

α-Synuclein aggregation

This **presynaptic protein** misfolds and clumps into **Lewy bodies**. Small intermediate clumps (**oligomers and protofibrils**) are thought to be the most toxic to neurons.

Oxidative stress & mitochondrial dysfunction

These processes **impair cellular energy production** and promote neurodegeneration.

Faulty cellular 'clean-up'

Poor removal of damaged proteins (**autophagy–lysosome system**) and damaged mitochondria (**mitophagy**) – **several PD genes act here**.

Ferroptosis

An **iron-dependent** form of regulated cell death, **distinct from apoptosis**, increasingly recognised in PD.

Neuroinflammation & gut dysbiosis

Chronic inflammation and altered **gut–brain signalling** may contribute to PD progression.

α-Synuclein

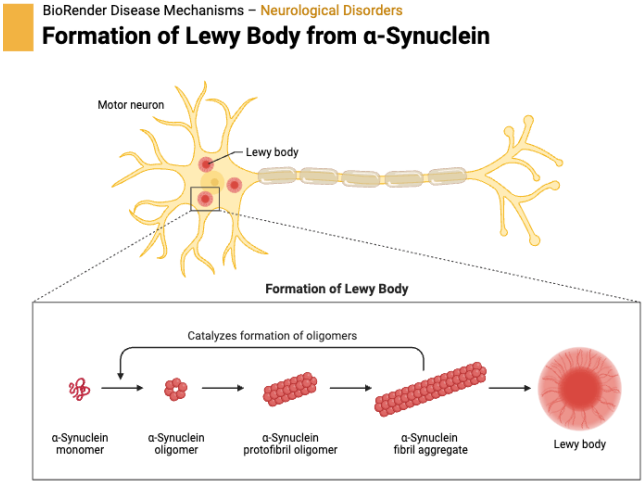
What is it?

- α-Synuclein is a **pre-synaptic neuronal protein** encoded by the **SNCA gene** (chromosome **4q22**).
- Its exact function is **not fully understood**; it is thought to help **release neurotransmitter from synaptic vesicles**.
- It is linked to PD both **genetically** (SNCA variants cause familial PD) and **pathologically** (it is the main protein in Lewy bodies).

How it harms

- Several mechanisms are involved, but the **small soluble clumps** of α-synuclein (**oligomers and protofibrils**) are thought to be the most toxic, disrupting cell function and leading to **neuronal death**.
- The brains of people with PD contain abnormal aggregates of α-synuclein as **Lewy bodies** (in nerve cell bodies) and **Lewy neurites** (in nerve fibres).

Formation of Lewy Body from α-Synuclein





Lewy body (arrow) in a neuron

BioRender Disease Mechanisms – Neurological Disorders: α-synuclein monomer → oligomer → protofibril oligomer → fibril aggregate → Lewy body

NOTE

In PD the neurons mainly affected are the **dopamine neurons of the substantia nigra**; the 'motor neuron' label in this figure is generic.

Disease Characteristics

Idiopathic

Most cases of PD are **idiopathic (sporadic)**.

Monogenic

Only about **5–10% of cases** are monogenic (caused by a single gene). These are more common in **early-onset PD**, but some (e.g., **LRRK2**) usually start later in life.

Course

The disorder has a **slow onset** but is **progressive**.

First symptoms

Tremor is often the first motor symptom; bradykinesia and rigidity follow. Non-motor symptoms (**loss of smell, constipation, sleep problems**) may appear **years earlier**.

Late feature

Postural instability is usually seen late in the disease and seriously affects quality of life.

Threshold

Motor symptoms appear only after **substantial loss** of the nigrostriatal pathway – classically estimated at **~60% of nigral neurons and ~80% of striatal dopamine**.

GENETICS & RISK

Genetic Causes & Risk Factors of PD

03

Monogenic PD | Gene profiles | PARK loci | Age of onset | Genetic & environmental risk

PD genetics has **two parts**:

Monogenic (Mendelian) PD

About 5–10% of all cases

- **Autosomal dominant:** **SNCA, LRRK2, VPS35**
- **Autosomal recessive:** **PRKN (parkin), PINK1, PARK7 (DJ-1)** – usually early onset

⚠ Genetic risk factors

- Variants that **raise the risk**, but **most carriers never develop PD** (e.g., **GBA1**).

NAMING

Older 'PARK' numbers (PARK1, PARK2…) name **gene loci**; today we use the **gene names**.

GENE NAMES IN FULL

Gene	Full name	Gene	Full name
PRKN	Parkin RBR E3 ubiquitin protein ligase. Its protein is **parkin**.	**SNCA**	Synuclein alpha (the gene encoding α-synuclein)
PINK1	PTEN-induced kinase 1	**LRRK2**	Leucine-rich repeat kinase 2
PARK7	Parkinsonism-associated deglycase. Its protein is **DJ-1**.	**VPS35**	Vacuolar protein sorting 35

Genetic Causes of PD – Gene by Gene

SNCA — AUTOSOMAL DOMINANT

Makes **α-synuclein**, the main protein in **Lewy bodies**.

PRKN (PARK2) — AUTOSOMAL RECESSIVE

Makes **parkin**, which tags damaged proteins and damaged mitochondria for removal.
The **most common cause of early-onset recessive PD**.

PARK7 — AUTOSOMAL RECESSIVE

Makes **DJ-1**, which protects cells against **oxidative stress**.
A **rare** cause of early-onset PD.

VPS35 — AUTOSOMAL DOMINANT

Part of the cell's **protein-recycling system** that sorts proteins for reuse or lysosomal breakdown.
A **rare** cause of **late-onset PD** resembling sporadic PD.

PINK1 — AUTOSOMAL RECESSIVE

A **kinase** that **senses damaged mitochondria** and works with parkin to remove them (**mitophagy**).
Causes **early-onset PD**.

LRRK2 — AUTOSOMAL DOMINANT

A large enzyme (**kinase**); disease-causing variants make it **overactive**.
The **most common cause of dominant PD**, usually **late onset** and similar to sporadic PD.

LRRK2 · G2019S — The most common variant (glycine → serine at position 2019)

~1%
of sporadic PD worldwide

~4%
of familial PD worldwide

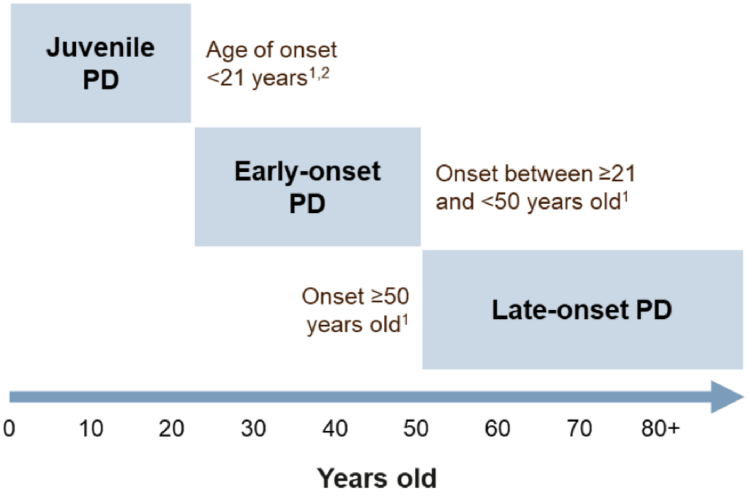
- **Much more frequent** in **Ashkenazi Jewish** and **North African Arab-Berber** populations.
- **Incomplete penetrance:** many G2019S carriers **never develop PD** (estimates vary between populations) – **important for genetic counselling**.

Table 3.1 · Mendelian Genes Associated with Parkinson's Disease

Gene	Locus	Inheritance	Protein	Pathology	Mechanism
Mendelian causes					
PARK1 & 4 (SNCA)	4q21-23	AD	Synuclein	Lewy pathology	Protein aggregation, oxidative stress, inflammation, macroautophagy, chaperone-mediated autophagy
PARK2	6q25-27	AR	Parkin	Lewy pathology rare	Mitophagy, UPS
PARK6 (PINK1)	1p35-36	AR	PINK1	Lewy pathology	Mitochondrial dysfunction / mitophagy
PARK7 (DJ1)	1p36	AR	DJ-1	NK	Oxidation regulation, mitophagy
PARK8 (LRRK2)	12q12	AD	Dardarin	LP, tauopathy	Altered kinase and GTPase activity, inflammation, autophagy
PARK17 (VPS35)	16q11.2	AD	VPS35	NK	Lysosomal degradation

NK = not known · AD = autosomal dominant · AR = autosomal recessive · LP = Lewy pathology

Juvenile, Early-Onset and Late-Onset PD



Definitions and cut-offs for juvenile, early- and late-onset Parkinson's disease · Mehanna et al. Mov Disord Clin Pract 2022; Schrag & Schott. Lancet Neurol 2006

Juvenile PD →	Age of onset **<21 years**
Early-onset PD →	Onset between **≥21 and <50** years old
Late-onset PD →	Onset **≥50** years old

What Do the PD Genes Tell Us?

Handling α-synuclein & cellular clean-up

- **SNCA – too much or faulty α-synuclein**
- **LRRK2, VPS35 – disrupted protein transport and lysosome function**
- **GBA1 – less lysosomal enzyme (glucocerebrosidase), so α-synuclein is cleared poorly**

Outcome: α-synuclein builds up and forms Lewy bodies

Mitochondrial quality control

- **PINK1 – damaged mitochondria are not detected**
- **Parkin (PRKN) – damaged mitochondria are not tagged for removal (failed mitophagy)**
- **DJ-1 (PARK7) – less protection against oxidative stress**

Outcome: damaged mitochondria accumulate, causing energy failure and oxidative stress

BOTH ROUTES LEAD TO THE SAME END-POINT

Common end-point

Loss of dopamine neurons in the substantia nigra. Studying these rare genetic forms has revealed mechanisms that also operate in sporadic PD.

Risk Factors

The risk factors of PD can be categorized into **two main factors**: **genetic factors** and **environmental factors**.

GENETIC GBA1 (glucocerebrosidase gene)

- **Heterozygous variants** are the **most common genetic risk factor for PD** (roughly **5–10% of patients**; higher in Ashkenazi Jewish patients).
- **Two copies** of a GBA1 variant cause **Gaucher disease** (a lysosomal storage disorder); **one copy** raises PD risk – a good example of a **risk factor, not a Mendelian cause**.
- GBA1-associated PD tends to have **slightly earlier onset, faster progression** and **more cognitive problems**, though most carriers never develop PD.

ENVIRONMENTAL Environmental exposures may increase PD risk

Common associations include:

Pesticide exposure
e.g., farming, rural residence, well water consumption

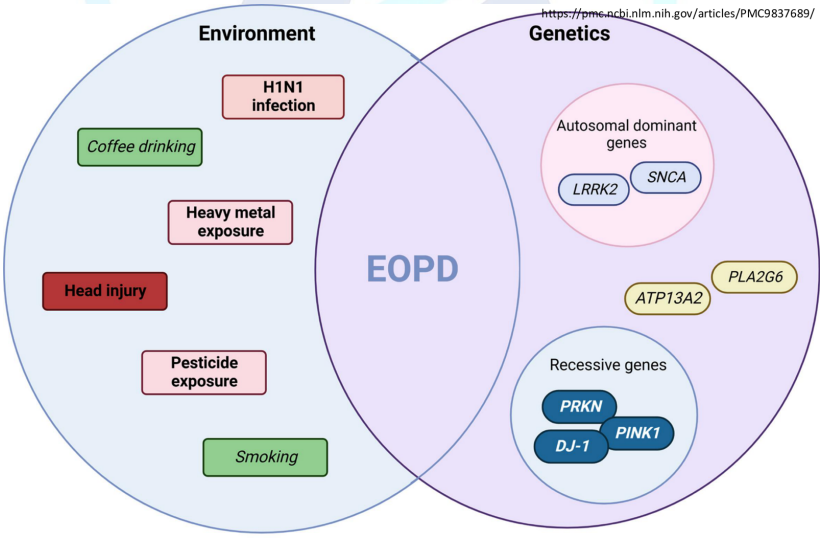
Heavy metals
like **manganese** (e.g., welding)

Head trauma

Chronic infections
e.g., Helicobacter pylori

Encephalitis
and other viral insults

Environment and Genetic Interplay in Early-Onset PD (EOPD)



Environment and genetic interplay in EOPD · PMC9837689

- An interpretation of the **multi-hit hypothesis** on early-onset Parkinson's disease suggests it is the **combination of environmental agents acting on the background of genetic determinants** that predisposes the individual to disease.
- Highlighted are both **risk** (pink-red or bold) and **protective** (green or italics) factors.
- This concept in early-onset forms of disease may be due to **stronger effect sizes** from exposure or **higher penetrant genetic mutations** observed in specific genes (e.g., SNCA or PRKN) and molecular pathways (e.g., mitophagy).

04 CLINICAL FEATURES

CLINICAL PICTURE

Signs & Symptoms; Clinical Features

04

Motor features | Cardinal features (TRAP) | Non-motor features | Progression | Disease stages

- PD was observed **mainly as a disorder of movement**, but increasing recognition of the **wide heterogeneity of PD** and the importance of **non-motor features** has been building for several years.
- Many non-motor features such as **cognitive impairment** and **autonomic dysfunction** significantly increase care needs.



Motor Features: Physical Capability

Bradykinesia

Slowness of movement with a **progressive decrease in speed or size** as a movement is repeated (e.g., finger taps get smaller and slower).

Slow and small movements

Reduced blinking, facial expression and gesturing. Soft voice. Difficulty getting out of a chair, shuffling steps, reduced arm swing.

Tremor

Usually **at rest** (**'pill-rolling'**), often starting in one hand/thumb; it **lessens with voluntary movement** and becomes more obvious with a mental task (e.g., counting backwards) or stress.

Rigidity

The limbs are stiff. When the examiner bends the patient's arm or leg, they feel a steady resistance all the way through the movement, **like bending a lead pipe**.

POSTURAL CHANGES

Imbalance, stooped posture / leaning forward when moving.

04 CLINICAL FEATURES

Cardinal Features – "TRAP"

T — Tremor

MOST COMMON SYMPTOM

- Most common presenting symptom of PD
- **Resting tremor:** presents at rest and disappears with activity
- **Postural tremor:** tremor of the head and trunk in upright position

R — Rigidity

ONE OF THE CLINICAL HALLMARKS OF PD

- Increased resistance to passive motion regardless of task, amplitude and speed
- **Cogwheel:** jerky ratchet-like resistance to passive ROM
- **Leadpipe:** sustained resistance to passive movement with no fluctuations

A — Akinesia / Bradykinesia

MOST DISABLING MOTOR FEATURE

- **Akinesia:** absence or lack of movement; deficits in preparatory phase of movement control
- **Bradykinesia:** slowness and difficulty in maintaining movement

P — Postural Instability

LEAST SPECIFIC & MOST DISABLING SIGN

- Leads to increased episodes of falling and sequelae of falls
- **"Phantom Pillow" syndrome:** in supine, head is flexed as if on a pillow
- Does not respond to drug treatment
- Due to ineffective sensory processing

Motor vs Non-Motor Impairments

Motor impairments	Non-motor impairments
Bradykinesia	Cognitive impairment
Hypersalivation	Sleeping disorders
Postural imbalance	Mood disturbances
Tremor	Gastrointestinal issues
Muscular rigidity	Sweat and olfactory disorders
Walking difficulties	Anxiety and depression
Freezing of movements	Pain

04 CLINICAL FEATURES

Non-Motor Features

NOTE

Symptoms can **fluctuate** from day to day and through the day and night.

up to ~90%
Loss of smell (hyposmia) – very common and often early

≥ ⅓
Depression and anxiety – common (roughly a third or more)

↑ with time
Dementia – risk rises with disease duration

Sleep disorders
REM sleep behaviour disorder, insomnia, daytime sleepiness

Bladder and bowel control
Urinary problems

Communication
Non-verbal communication, lack of vocal tone and facial expression

Swallowing
Swallowing / saliva control

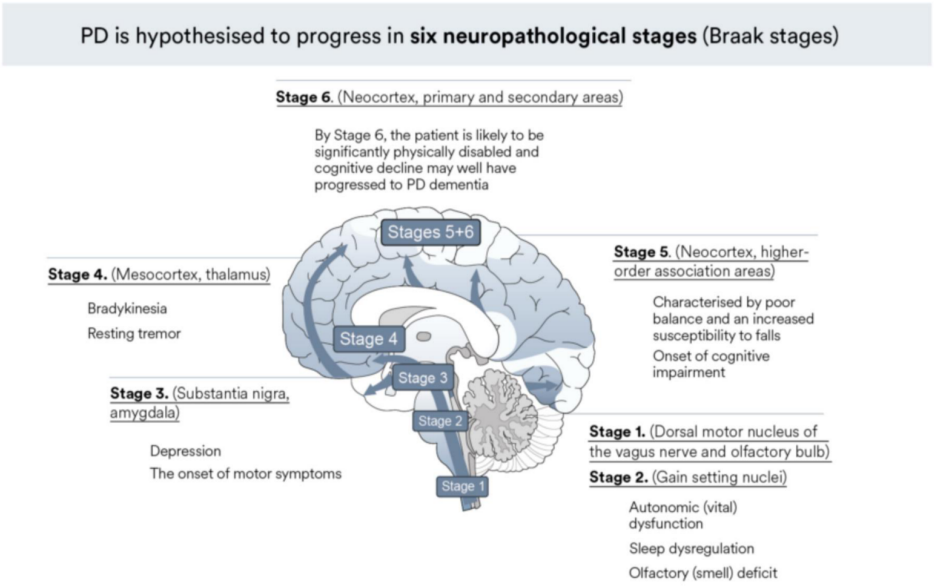
GI disturbance · Restless legs · Pain · Postural (orthostatic) hypotension

COGNITIVE Cognitive Affects

- **Dementia is common in PD**, and the **risk rises the longer a person has the disease**.
- **Not everyone develops it.** Newer studies suggest it may be less common, or appear later, than once thought.
- **Typical features:** confusion, fluctuating alertness and visual hallucinations.

Disease Progression Timeline

PD is hypothesised to progress in **six neuropathological stages** (**Braak stages**).



The six Braak stages, from Stage 1 (dorsal motor nucleus of the vagus nerve and olfactory bulb) to Stage 6 (neocortex, primary and secondary areas)

TIMELINE OF PARKINSON'S DISEASE

Braak staging	1 ~ 2 · Prodromal–early stage	3 ~ 4 · Mid stage	5 ~ 6 · Late stage
Lewy pathology	Peripheral autonomic neurons · medulla oblongata · olfactory bulb	Midbrain substantia nigra · amygdala · nucleus basalis of Meynert	Cerebral cortex
Symptom	Hyposmia/anosmia · REM sleep behavior disorder · constipation · anxiety · depression · cognitive change · subtle motor impairment	Bradykinesia, rigidity, tremor · dysphagia · sleep disturbance	Dementia · cognitive dysfunction · hallucinations · incontinence · sexual dysfunction · orthostatic hypotension
Symptom type	**Nonmotor symptoms**	**Motor symptoms**	

DIAGNOSIS

On the progression arrow, **diagnosis** falls between Braak stages **1~2** and **3~4.** Source: Recent advances in the pathology of prodromal non-motor symptoms olfactory deficit and depression in Parkinson's disease: clues to early diagnosis and effective treatment.

Disease Stages & Care Goals

DISEASE STAGES – EARLY

Diagnosis / Early

- Raise awareness and self management
- Education and consider therapy input
- Reduce symptoms and distress
- Acceptance of diagnosis

Maintenance

- Promotion of normal activities
- Maintenance of function and self care
- Consider therapy referral
- Assess carer needs
- Symptom reduction, treatment compliance

DISEASE STAGES – LATER

Complex

- Adaptations to promote self-care
- Optimise symptom control / compliance with meds
- Assess for complications of medication and fluctuations
- MDT input / annual review / carer support
- Minimisation of disability

Palliative

- Relief of symptoms
- Absence of distress / carer support
- Maintenance of dignity
- Good nursing care
- Analgesia, appropriate sedation, pressure care, continence, mouth care, communication

BIOMARKERS

Biomarkers of PD

Definition | Purposes | Why they help | α-Synuclein & SAAs | NfL & genetics | The future

BIOMARKER

Definition

The term "biomarker" is a portmanteau of "**biological marker**". A biomarker is a **defined characteristic that is measured objectively** as an indicator of **normal biological processes, disease processes**, or **responses to a treatment or exposure**.

TABLE 1 · PURPOSES OF BIOMARKER

Biomarker class	Application type
Diagnostic biomarker	For differential or presymptomatic diagnosis, screening for susceptibility and risks
Prognostic biomarker	For the prognosis / chance of healing, therapeutic decision support
Monitoring biomarker	For objective confirmation of therapeutic efficacy, detection of non-responsiveness, progression detection and classification, safety and quality control
Individualization biomarker	To stratify the individual patient profile to assign the patient characteristics to a better – more personalized – reference group

Tönges et al. (2022). Journal of Neural Transmission, 129(9), 1201–1217.

Biomarkers of PD

Why look for them?

Although PD is **diagnosed clinically**, biomarkers are a promising way to **identify disease in early stages**, **track progression** and **distinguish PD from other conditions** such as **progressive supranuclear palsy (PSP)** or **drug-induced parkinsonism**.

PD biomarkers from

- Cerebrospinal fluid (CSF)
- Serum
- Genetics
- Imaging

Discussed in detail in a later lecture.

05 BIOMARKERS

Biomarkers of PD – Why Are They Clinically Beneficial?

1

A **PD diagnosis is made clinically**; traditionally it could only be confirmed at **post-mortem**. The use of biomarkers would **decrease the subjectivity in diagnosis**.

- When checked against post-mortem findings, clinical diagnosis is only about **80% accurate** (Rizzo et al., 2016).
- Newer tests such as **α-synuclein seed amplification assays** can now detect the disease protein **during life**.

2

PD can be **difficult to distinguish from other Parkinsonian disorders**, especially in their early stages. Potentially, a specific biomarker may be able to **narrow a differential diagnosis**.

3

Finally, although there are currently **no disease-modifying therapies** for PD, treatment development could be aided with the use of biomarkers, since biomarkers could help **identify patients before they become symptomatic**.

Biomarkers of PD – Alpha-Synuclein

- In **1912**, **Friedrich Lewy** discovered and described **proteinaceous inclusions in neurons**, later to be called **Lewy bodies**.
- Lewy bodies were found to be primarily composed of **abnormal deposition of alpha-synuclein**, a small protein expressed in the brain that influences stability of neuronal membranes, presynaptic signaling, and membrane transport.
- Post-translational modification of alpha-synuclein – specifically **phosphorylation at Ser-129** – has been identified in Lewy bodies and is **thought to produce neurotoxic effects**.

CSF Alpha-synuclein in the cerebrospinal fluid

- Several studies found **lower total α-synuclein** in the CSF of PD patients than in controls – possibly because α-synuclein is **trapped in aggregates inside cells**.
- However, values **overlap with controls**, so total CSF α-synuclein is **not useful for diagnosis on its own**.
- More recently, **α-synuclein seed amplification assays (SAAs)** on CSF have proved **far more accurate**.
- SAAs use the ability of tiny amounts of misfolded α-synuclein to **'seed' further misfolding**, amplifying it until it can be detected.

05 BIOMARKERS

KEY STUDY

Siderowf et al. (2023) – α-synuclein SAA on CSF can accurately identify PD

1,123	88%	96%
participants	of people with PD correctly identified (sensitivity)	of healthy people correctly ruled out (specificity)

Sensitivity was **lower in LRRK2 carriers (~68%)** – a reminder that **genetic forms of PD can behave differently** on biomarker tests.

Other biomarkers under research include

- **GFAP (an astrocyte protein)**
- **Amyloid and tau (Alzheimer-type changes)**
- **Neurofilament light chain (NfL)**

→ NfL is a **structural protein of nerve axons**, released into **CSF and blood** when neurons are damaged.

→ It is **not specific for PD**, but is **much higher in atypical parkinsonism (MSA, PSP)**, which helps tell them apart.

Biomarkers of PD – Genetic Biomarkers

GENETIC TESTING LOOKS FOR VARIANTS IN GENES FIRMLY LINKED TO PD

→ **SNCA, LRRK2** and **VPS35** – **autosomal dominant** PD

→ **PRKN** (parkin), **PINK1** and **PARK7** (DJ-1) – **autosomal recessive** PD, usually early onset

→ **GBA1** – the **most common genetic risk factor** (not a Mendelian cause)

The Future of PD Biomarkers

→ Although PD is common and debilitating, the search for biomarkers is beginning to yield **feasible techniques for objective and early diagnosis** of PD and other Parkinsonian syndromes.

→ In the future, clinical PD diagnosis will likely be aided by **CSF alpha-synuclein assays** combined with **serum biomarkers** such as **age-adjusted NfL**.

→ Genetic studies will help identify patients who **do not have the sporadic variant** and may therefore show **atypical testing profiles**.

06 TESTING & MANAGEMENT

DIAGNOSIS & CARE

Testing, Evaluation & Management

Clinical diagnosis | MDS-UPDRS | Investigations | Genetic counselling | Drug therapy | Levodopa–carbidopa

DIAGNOSIS IS PRIMARILY CLINICAL

Testing & evaluation

Based on detailed **history and physical examination** to identify hallmark signs – **bradykinesia, rigidity, tremor, and postural instability**.

MDS-UPDRS – Movement Disorder Society–Unified Parkinson's Disease Rating Scale

The **most widely used clinical tool** to evaluate the **severity and progression** of Parkinson's disease. It assesses **four domains**:

I	II	III	IV
Non-motor experiences of daily living	Motor experiences of daily living	Motor examination	Motor complications

MDS Clinical Diagnostic Criteria (2015)

The **most widely used for in-life diagnosis**, offering better accuracy than older methods.

Queen Square Brain Bank (QSBB), London

An internationally recognized **archive of brain tissue** used for **neuropathological confirmation**. It:

- Specializes in Parkinson's disease, multiple system atrophy, progressive supranuclear palsy, and dystonia.
- Provides pathological standards for PD research and brain donation programs.

Testing & Evaluation – Investigations

What the investigations can and cannot do

- There is **no single laboratory or imaging test** that can definitively diagnose PD.
- **DaTscan** (dopamine transporter SPECT) shows **loss of dopamine nerve terminals** – useful to separate PD from **essential tremor** or **drug-induced parkinsonism**, but it **cannot distinguish PD from MSA or PSP**.
- Investigations aim to **exclude other causes of parkinsonism**, especially **drugs** (e.g., antipsychotics, metoclopramide):

MRI	In young patients
To rule out stroke, tumours, normal pressure hydrocephalus (NPH) and features of atypical parkinsonism.	Blood/urine **copper studies for Wilson's disease** and consider **genetic testing**.

Genetic Testing & Counselling in PD

Who may be offered testing?

- Onset before ~50 years
- Several affected relatives
- Ancestry with high carrier rates (e.g., Ashkenazi Jewish, North African Arab-Berber)

Risk to relatives

Dominant (SNCA, LRRK2, VPS35): each child has a **50% chance** of inheriting the variant – but not every carrier develops PD (**reduced penetrance**).
Recessive (PRKN, PINK1, DJ-1): parents are usually healthy carriers; each sibling has a **25% risk**.

Why test?

- Explains the cause of PD in the family
- Guides counselling of relatives
- Opens access to gene-targeted clinical trials (e.g., LRRK2 inhibitors, GBA1-targeted drugs)

Limitations

- A negative result does not rule out PD
- No gene-specific cure yet
- Testing healthy relatives (predictive testing) needs pre-test counselling

Management

Currently, there is **no cure for PD**, but **medications or surgery** can often provide improvement in the **motor symptoms**.

DRUG THERAPY – MEDICATIONS FOR PD FALL INTO THREE MAIN CATEGORIES

1 · Drugs that increase dopamine or mimic its action (dopaminergic drugs)

- The most common is the dopamine precursor **levodopa**, which crosses the blood-brain barrier and is converted into dopamine.
- Others: **dopamine agonists** (stimulate dopamine receptors), **MAO-B inhibitors** and **COMT inhibitors** (slow the breakdown of dopamine/levodopa).

2 · Drugs affecting other neurotransmitters

- **Anticholinergics** reduce acetylcholine activity and can help tremor (**avoided in older patients** because of confusion).
- **Amantadine** (blocks glutamate NMDA receptors) reduces levodopa-induced involuntary movements (**dyskinesia**).

3 · Drugs targeting non-motor symptoms

For example, **antidepressants** for depression and **rivastigmine** for PD dementia.

Management – Levodopa–Carbidopa

- Levodopa (L-dopa) is the **cornerstone of PD therapy**. It helps **replenish the brain's dopamine supply**.
- Because **dopamine itself can't cross the blood-brain barrier**, patients are given levodopa, which can.
- **Carbidopa** is combined with levodopa to **prevent premature conversion into dopamine outside the brain**, reducing side effects.

LEVODOPA IS USED AT EVERY STAGE OF PD

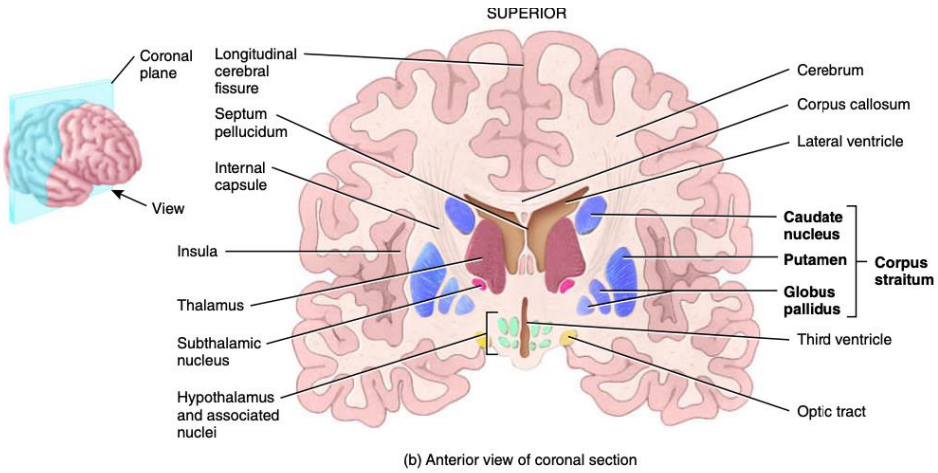
- **Early on** it gives smooth, stable control.
- **As more neurons are lost**, its effect wears off between doses and **dyskinesias** appear, so doses are given more often or combined with COMT or MAO-B inhibitors.
- **In late disease** it is given **continuously**, by intestinal gel or a subcutaneous pump.

Limitation: levodopa does **not halt disease progression** or **replace lost neurons**.

FOR YOUR UNDERSTANDING

Anatomy & Pathology – For Your Understanding

NOT FOR EXAM · FOR YOUR UNDERSTANDING

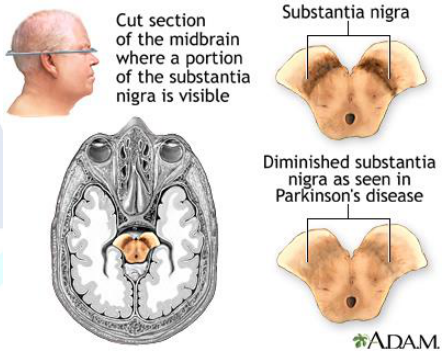


(b) Anterior view of coronal section

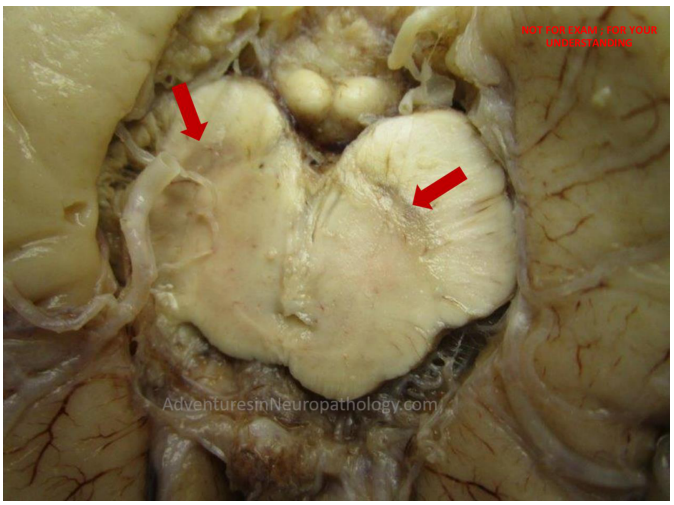
Anterior view of coronal section: caudate nucleus, putamen and globus pallidus (corpus striatum), thalamus, subthalamic nucleus, internal capsule, ventricles

BRAINSTEM – MIDBRAIN

- The midbrain contains several other nuclei, including the left and right **substantia nigra** (literal translation: "black substance") which are **large and darkly pigmented**.
- Neurons that release dopamine, extending from the substantia nigra to the **corpus striatum**, help control **subconscious muscle activities**.
- **Loss of these neurons is associated with Parkinson's disease.**



Cut section of the midbrain; diminished substantia nigra as seen in Parkinson's disease · A.D.A.M.



Midbrain (arrows: substantia nigra) · AdventuresInNeuropathology.com

RECAP

To Summarise...

Normal control & the brake

Loop	cortex → striatum (input) → GPi (output) → thalamus → motor cortex
Brake	GPi inhibits the thalamus (GABA)
Direct "Go"	D1; striatum inhibits GPi → brake released
Indirect "Stop"	D2; GPe inhibited → STN excites GPi → brake tightened

Clinical features

TRAP	tremor, rigidity, akinesia/ bradykinesia, postural instability
Non-motor	hyposmia up to ~90%; depression/anxiety; sleep; dementia risk rises with duration
Progression	six Braak stages; non-motor before motor
Care	early → maintenance → complex → palliative

Pathophysiology

Dopamine loss	weaker Go + stronger Stop → GPi overactive
Motor signs	bradykinesia, rigidity, rest tremor, later postural instability
Molecular	α-synuclein, oxidative stress, faulty clean-up, ferroptosis, inflammation
Threshold	~60% nigral neurons / ~80% striatal dopamine

Biomarkers

Why	clinical diagnosis only ~80% accurate
CSF α-syn	total overlaps with controls; SAAs far more accurate
Siderowf 2023	88% sensitivity / 96% specificity; ~68% in LRRK2
Future	CSF α-syn assays + age-adjusted NfL

Genetics & risk

Monogenic	5–10%; AD SNCA, LRRK2, VPS35; AR PRKN, PINK1, PARK7
LRRK2 G2019S	~1% sporadic, ~4% familial; incomplete penetrance
GBA1	most common genetic risk factor
Environment	pesticides, manganese, head trauma, infections

Testing & management

Diagnosis	clinical; MDS-UPDRS Parts I–IV; MDS criteria 2015
DaTscan	separates PD from ET/drug-induced, not from MSA/PSP
Drugs	dopaminergic; anticholinergics, amantadine; non-motor drugs
Levodopa	cornerstone, with carbidopa; no cure