

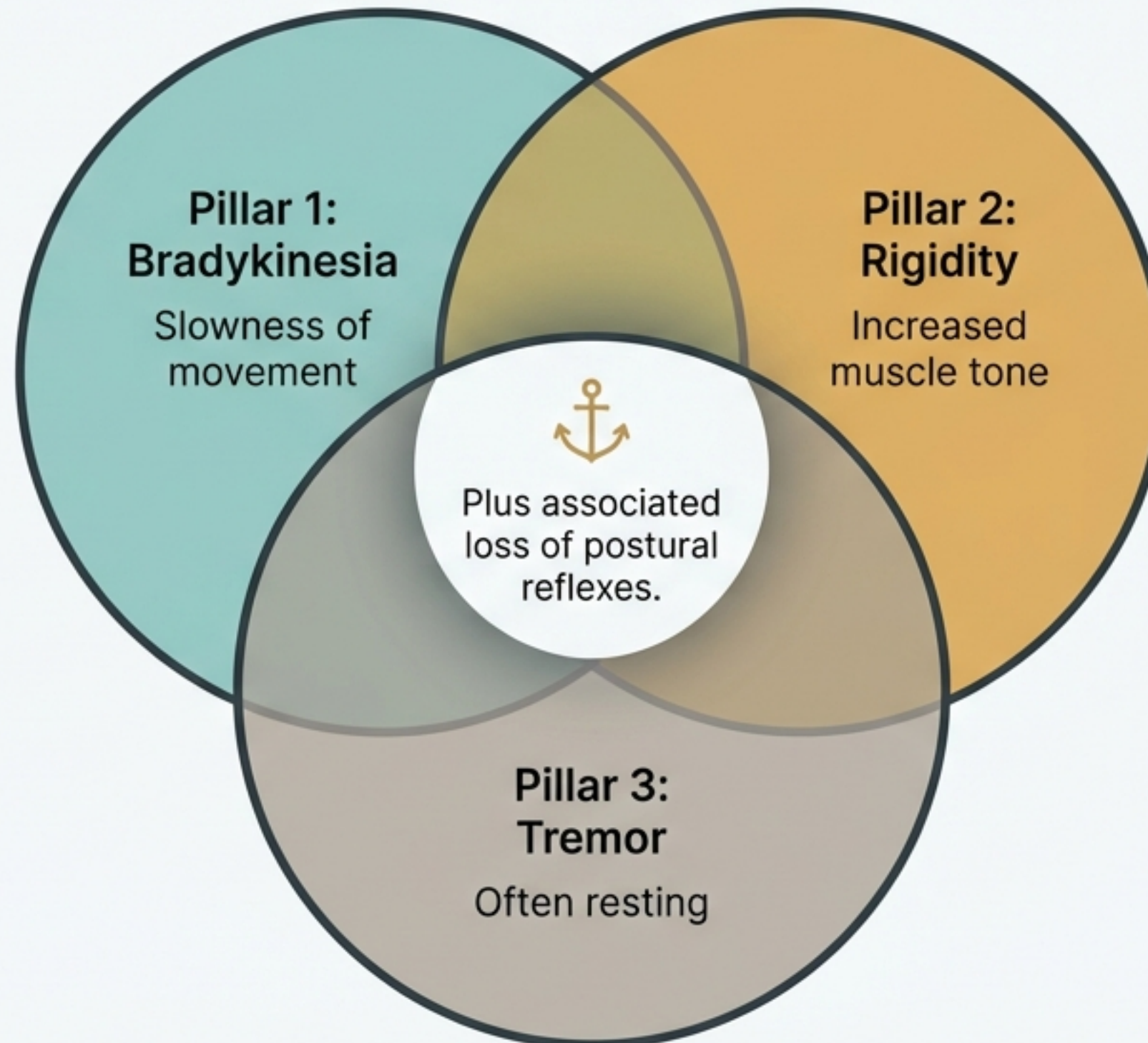
Parkinsonism

From Cellular Origins to
Clinical Management

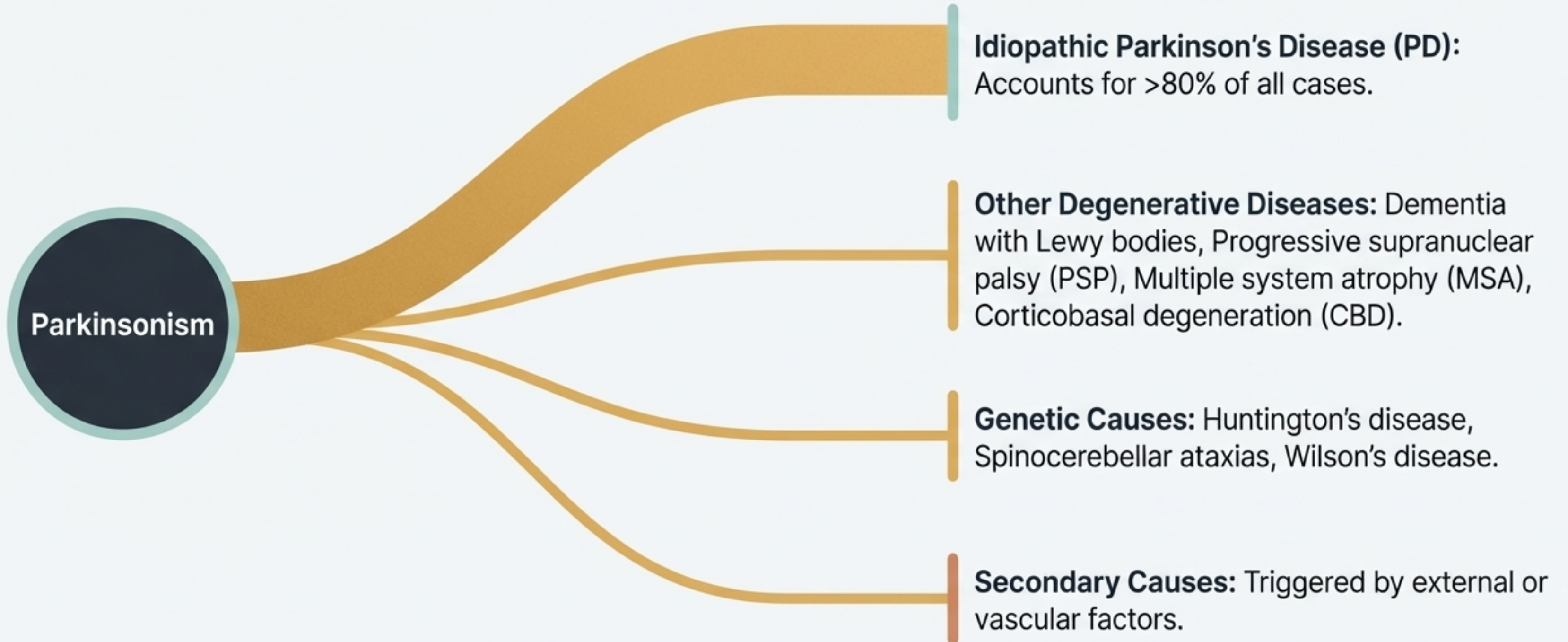


Defining the Syndrome

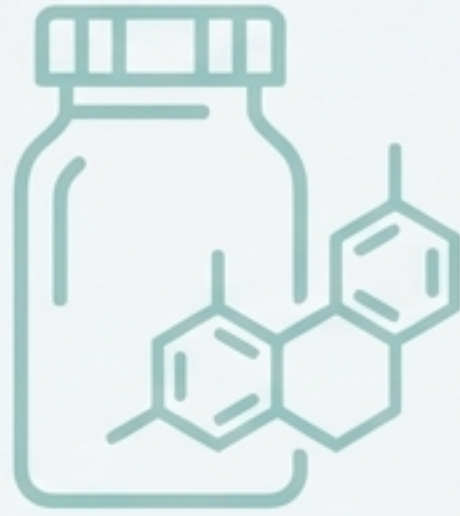
Parkinsonism is not a single disease, but a distinct clinical syndrome characterized by a triad of motor deficits:



The Spectrum of Etiology



Secondary Culprits



Drugs

Antipsychotics (older and 'atypical'), anti-emetics (metoclopramide, prochlorperazine), lithium, sodium valproate.



Toxins

MPTP (methyl-phenyl-tetrahydropyridine), manganese.



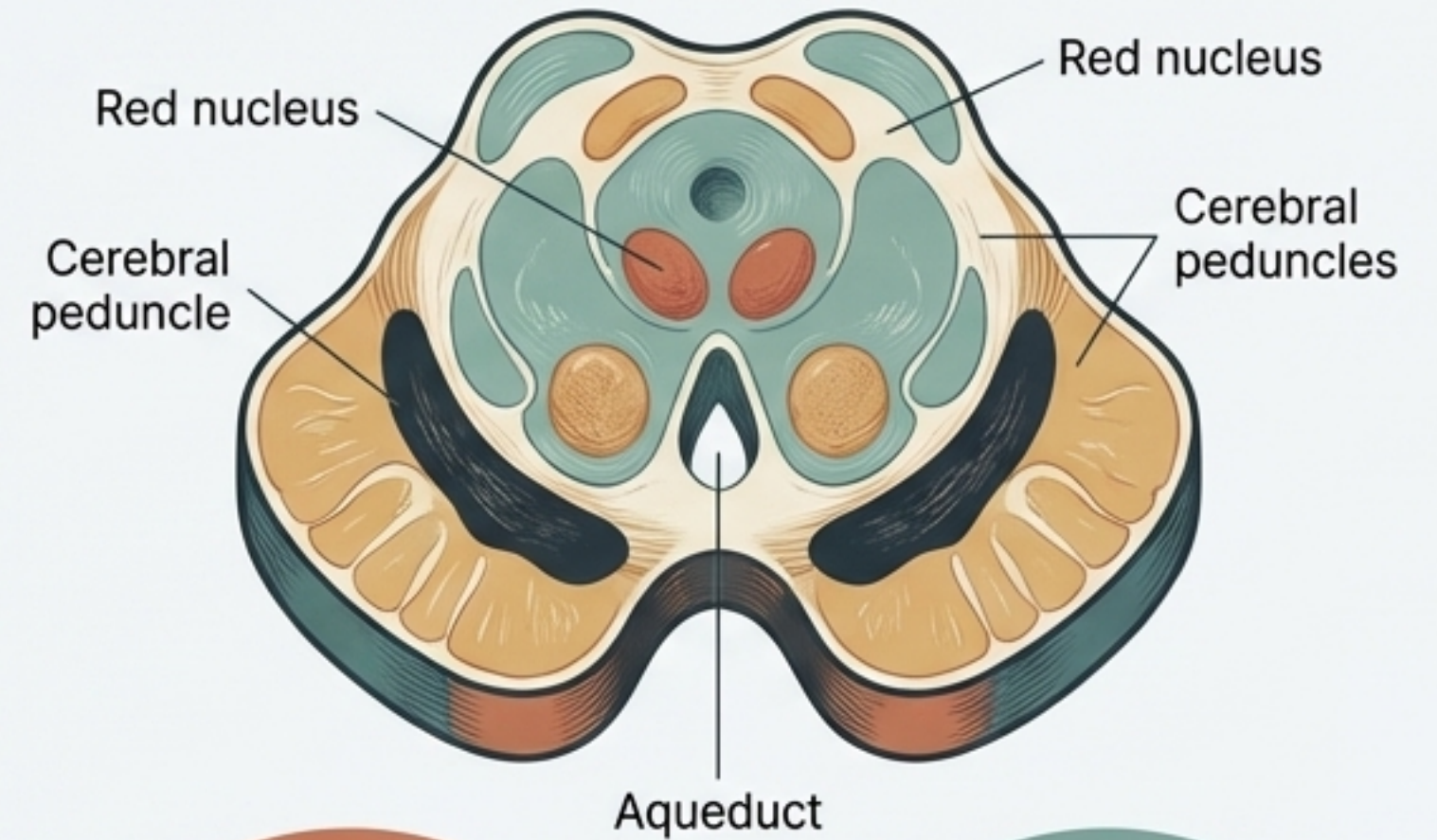
Vascular & Anoxic

Vascular: Cerebrovascular disease leading to multi-infarct or vascular parkinsonism.

Anoxic Brain Injury: Permanent damage following oxygen deprivation.

The Anatomic Failure

- The core mechanical failure lies in the substantia nigra.
- Pigmented dopaminergic neurons in this region are heavily depleted.
- This specific cellular death directly causes a massive loss of dopaminergic neurotransmission in the basal ganglia.
- This dopaminergic deficit is directly responsible for the classic motor features of the syndrome.



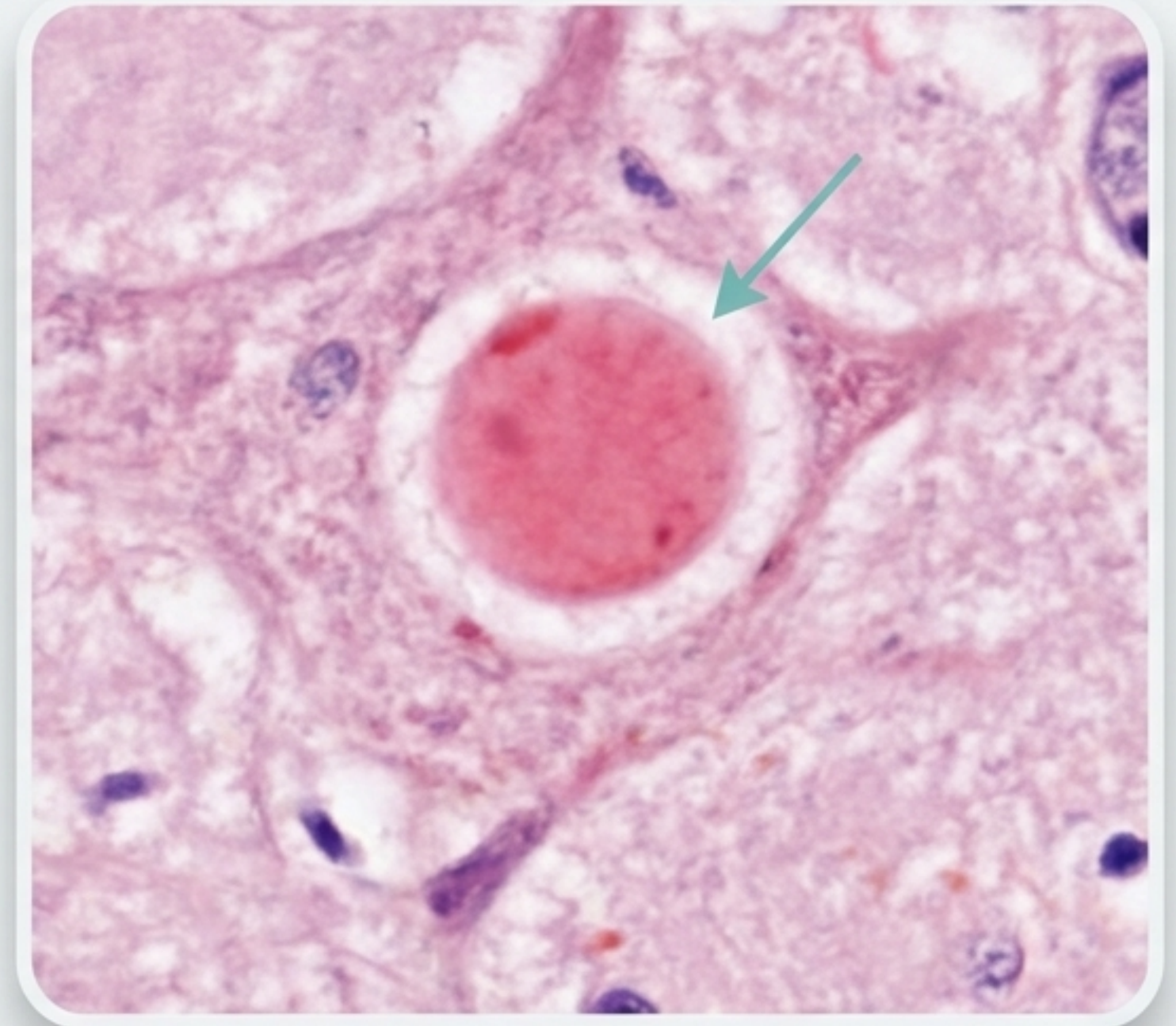
Normal



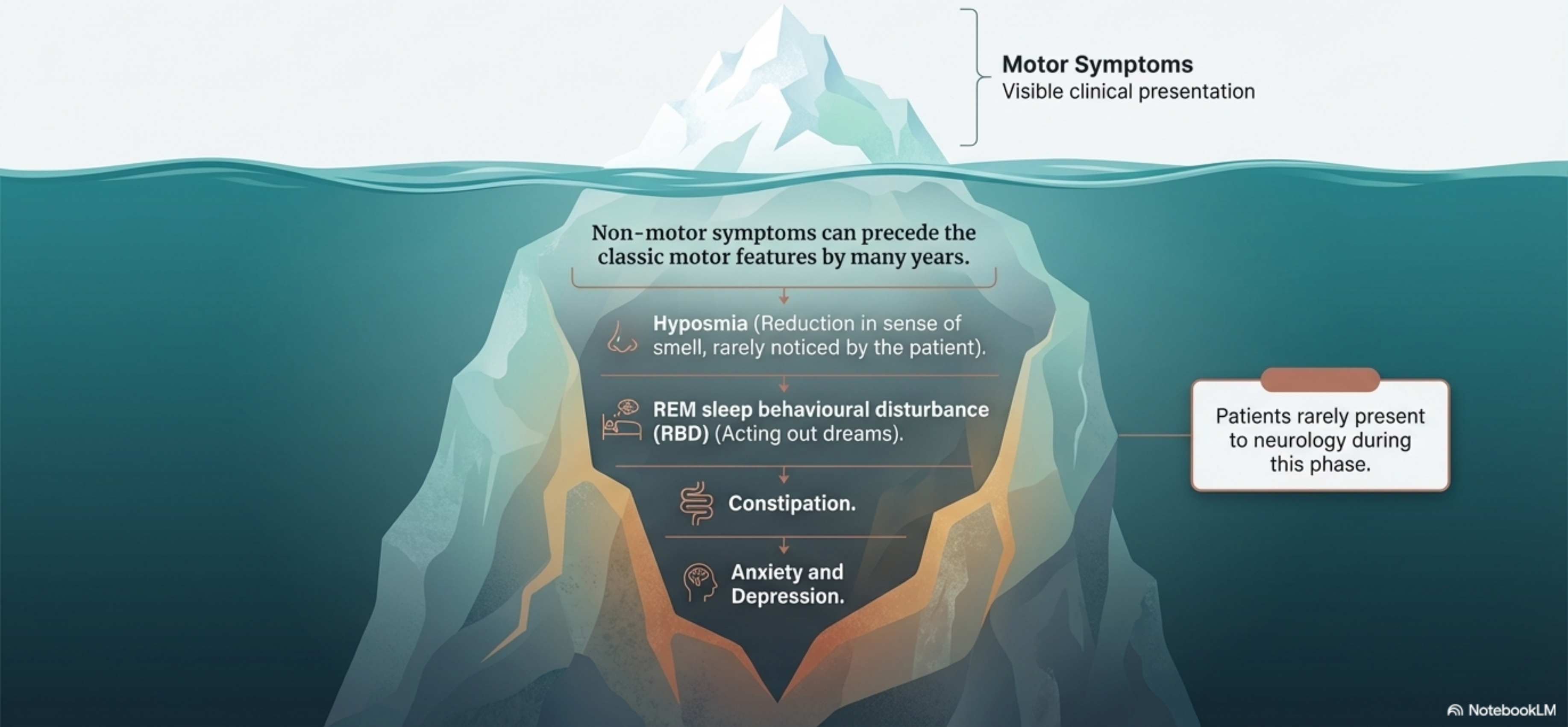
Parkinson's Disease

The Cellular Hallmark: Lewy Bodies

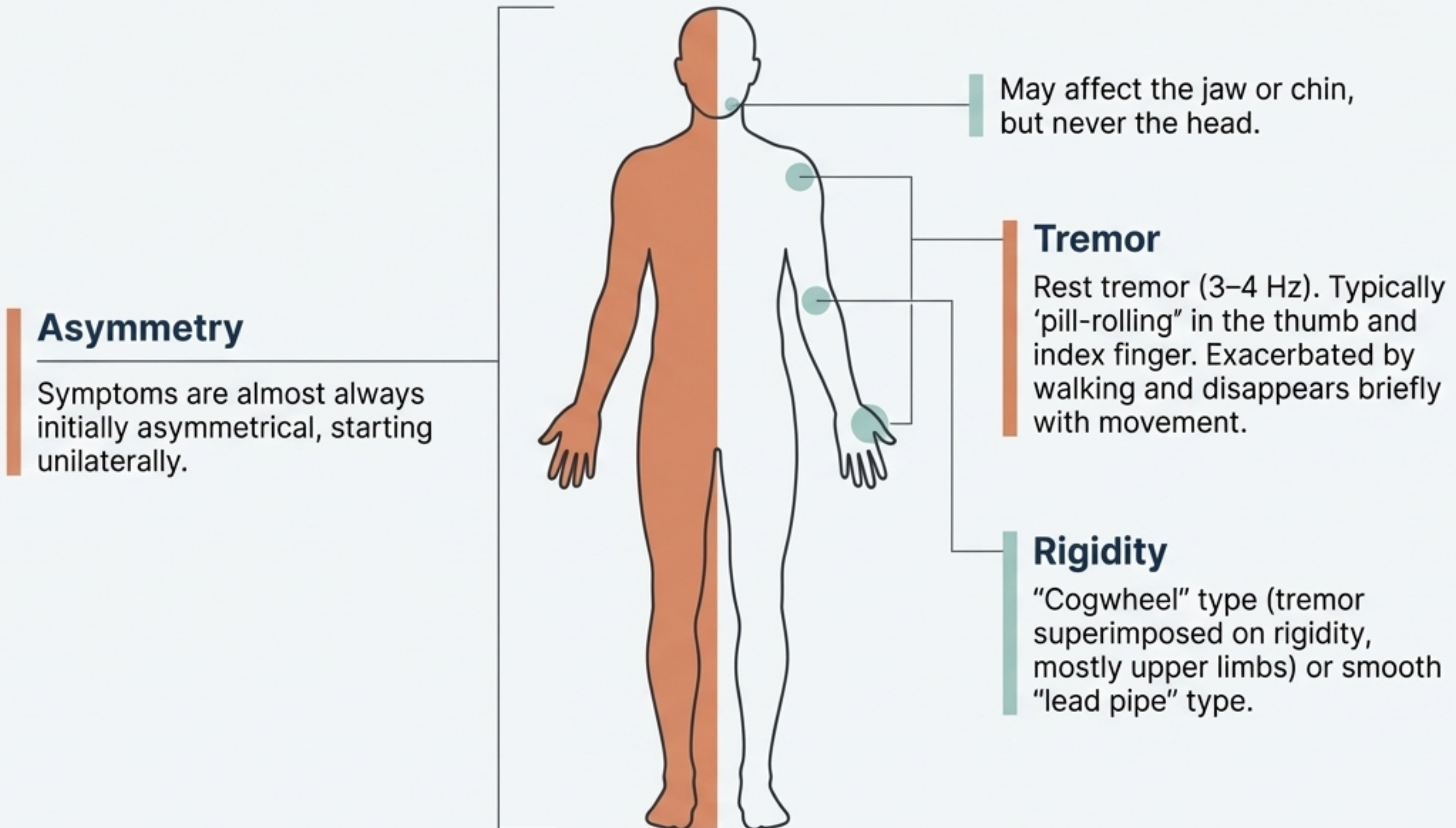
- Parkinson's disease is classified as a "synucleinopathy."
- Environmental or genetic factors alter the alpha-synuclein protein, rendering it toxic.
- These toxic proteins accumulate inside nigral cells to form Lewy bodies.
- Lewy bodies are not restricted to the midbrain; they are also found in the basal ganglia, brainstem, and cortex, increasing as the disease progresses.



The Hidden Prodromal Phase



The Motor Presentation



The Impact of Bradykinesia

Akinesia/bradykinesia is the fundamental feature, defined by slowness and decreasing size of repetitive movements.

Daily Impact:



Increasingly small handwriting (micrographia), difficulty tying shoelaces, buttoning clothes, and rolling over in bed.

Gait Profile:

Failure of gait ignition (slow to start).

Festination (rapid, short, shuffling stride length that tends to accelerate).

Reduced arm swing and impaired balance on turning.

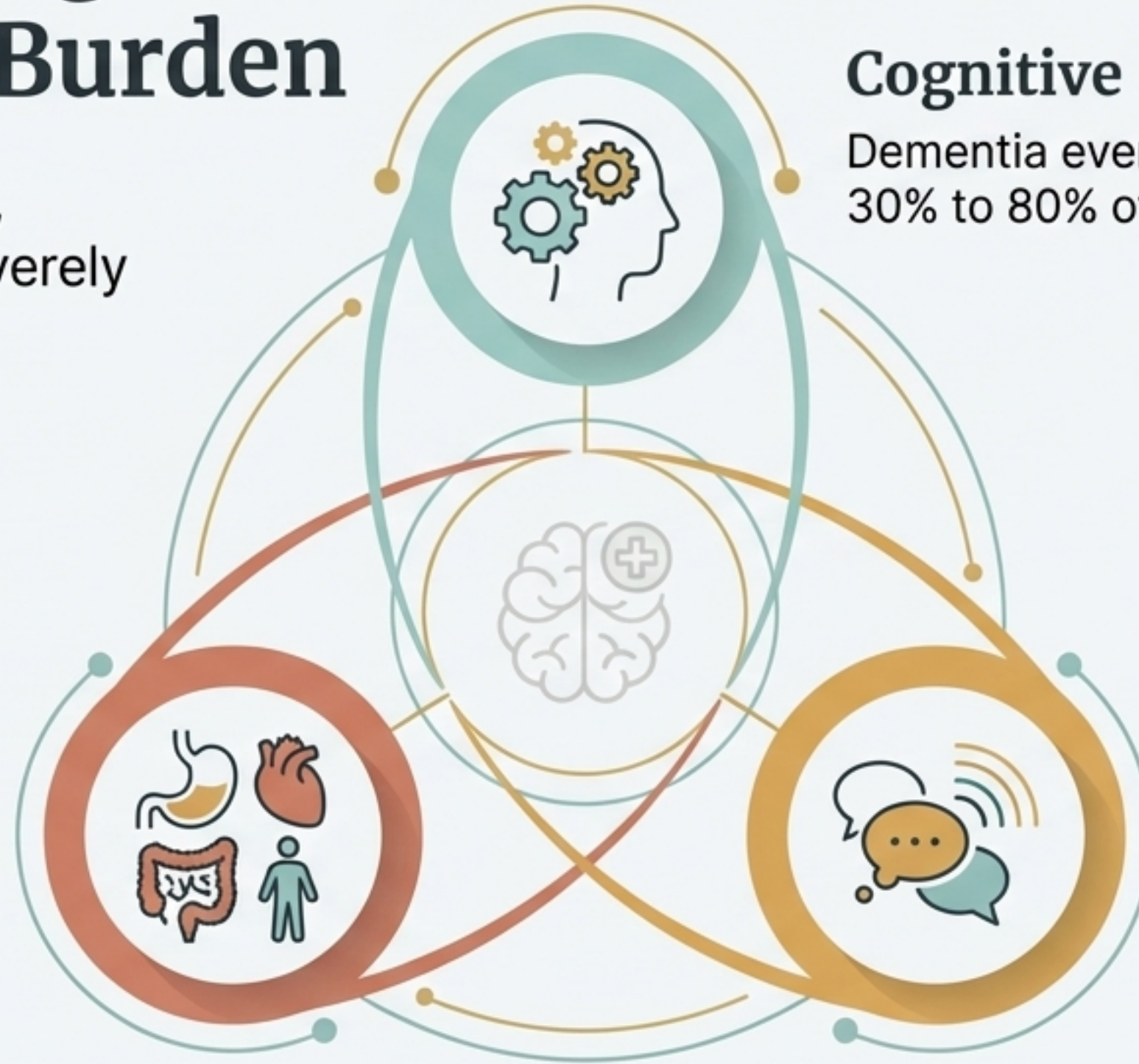


The Escalating Non-Motor Burden

As the disease advances, non-motor symptoms severely impact quality of life.

Autonomic & Other

Sphincter disturbance, drooling, severe fatigue, weight loss, and sexual dysfunction (including hypersexuality)



Cognitive

Dementia eventually affects 30% to 80% of patients.

Neuropsychiatric

Hallucinations, psychosis, apathy

Neurological Examination Findings

Key Abnormalities

- ⊗ • Expressionless face (hypomimia).
- ⊗ • Soft, rapid, indistinct speech (dysphonia).
- ⊗ • Flexed, stooped posture with impaired postural reflexes.

What remains normal? (Crucial for ruling out mimics)

- ✓ • Muscle power.
- ✓ • Deep tendon reflexes and plantar responses.
- ✓ • Eye movements.
- ✓ • Sensory and cerebellar examinations.

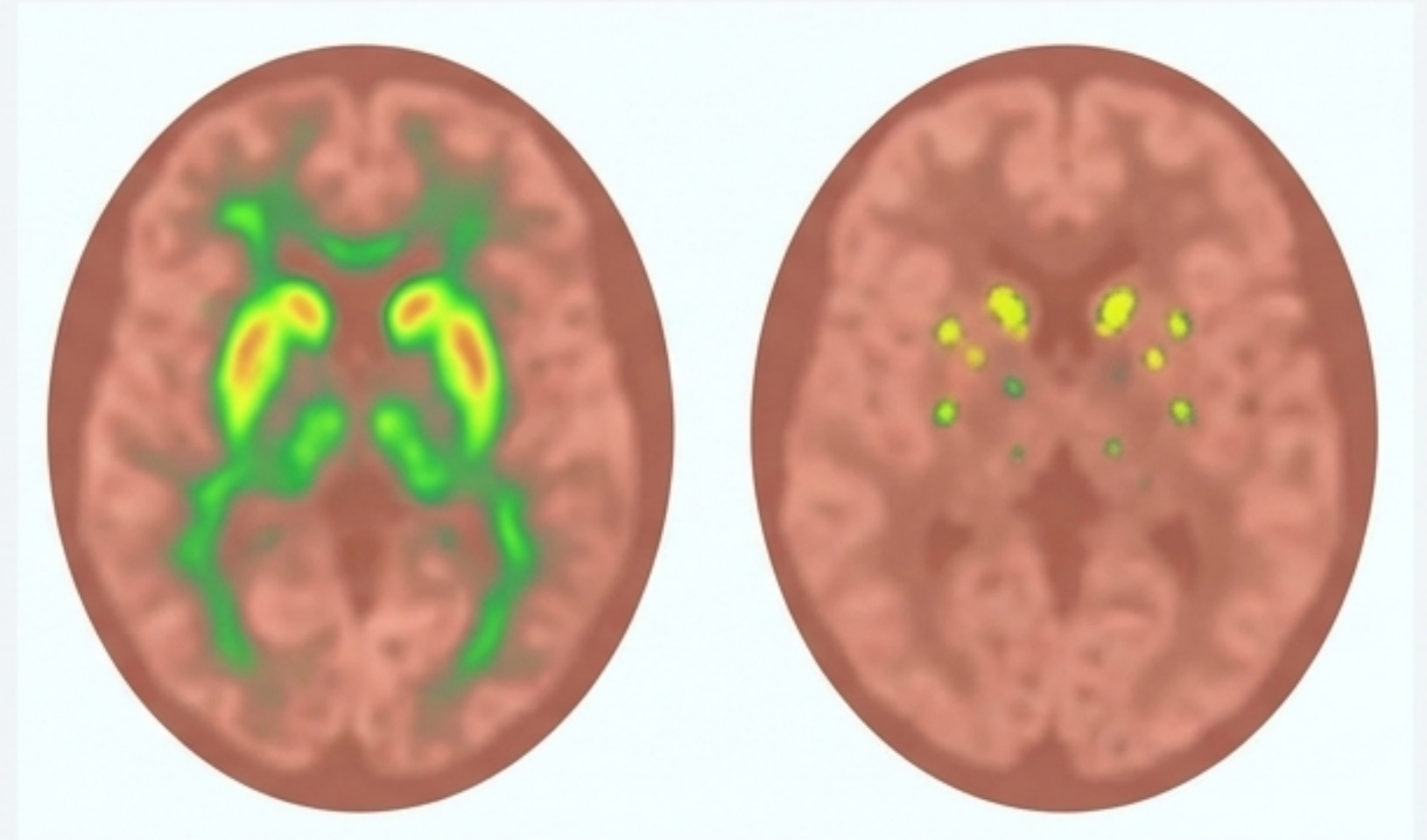
The Detective Work: Investigations



- The diagnosis of Parkinson's Disease is fundamentally clinical.
- Routine structural imaging (CT or MRI) is usually normal for age.
- **Role of Structural Imaging:** Used primarily to rule out alternative causes of parkinsonism, such as multi-infarct cerebrovascular disease or structural lesions.
- **Genetic testing:** May be considered for younger patients with a strong family history, though counseling is required.

Visualizing the Deficit: Functional Imaging

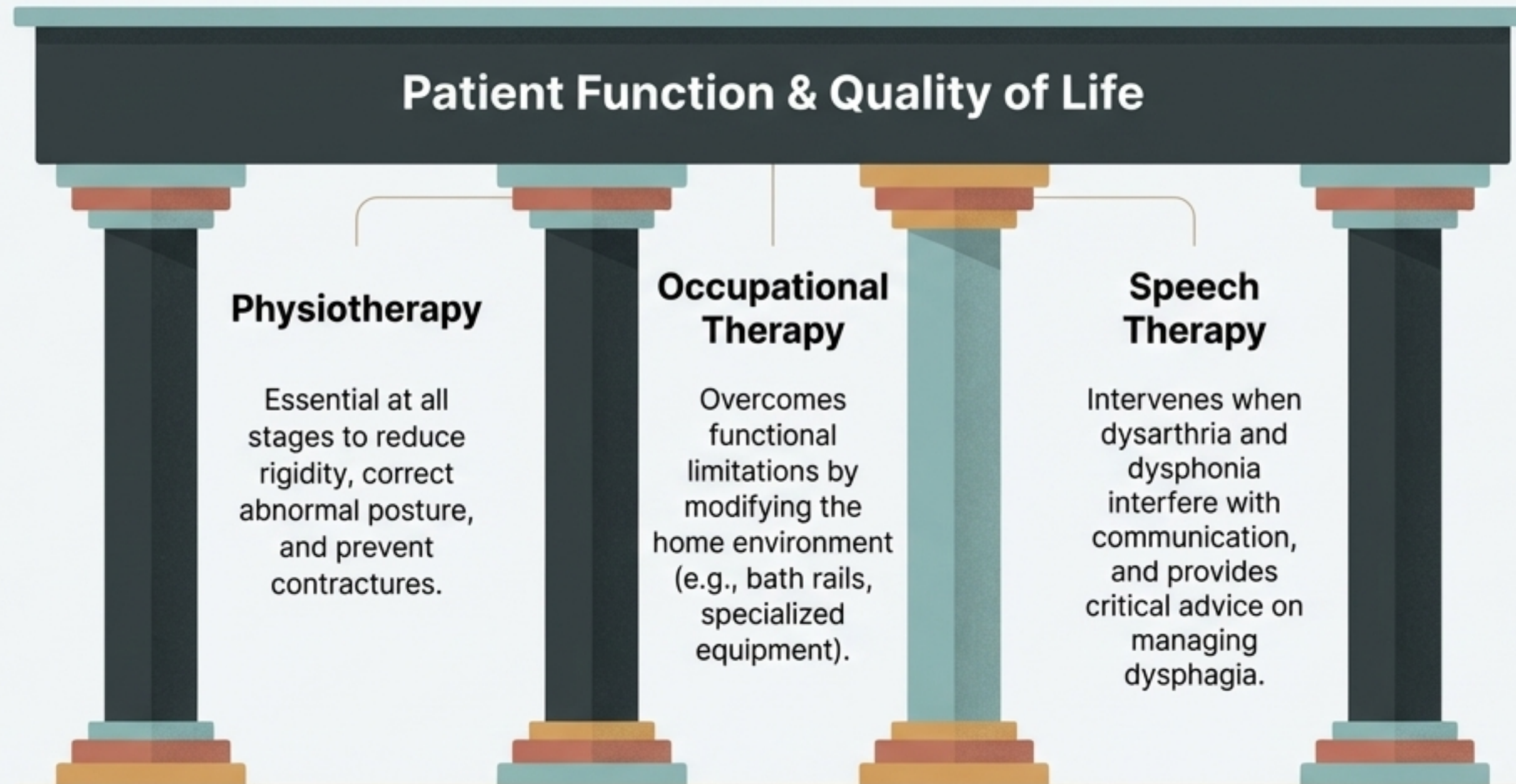
- Functional dopaminergic imaging (SPECT or PET scans) can visualize the specific neurochemical deficit.
- These scans show reduced dopamine activity in the basal ganglia even in early stages.
- Limitation: While highly sensitive for detecting dopaminergic loss, SPECT/PET cannot differentiate between Idiopathic PD and other degenerative mimics (like MSA or PSP).



Normal

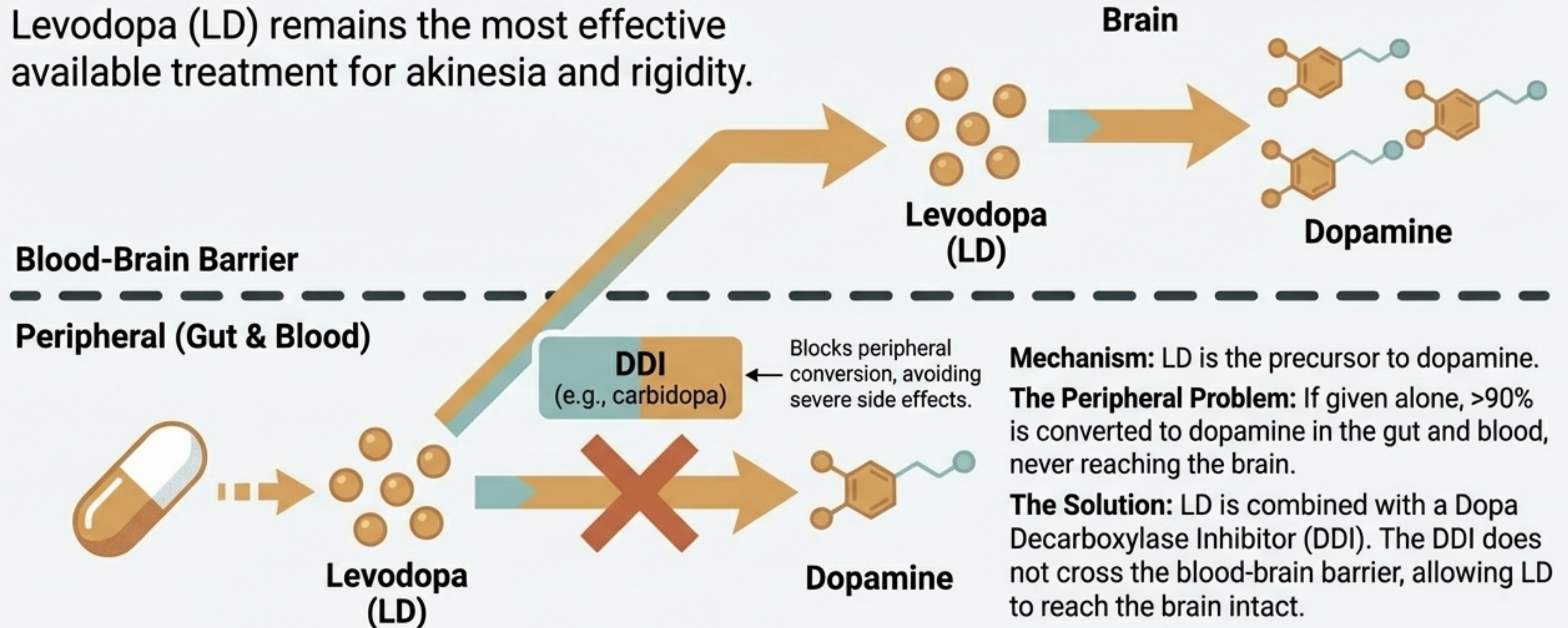
Reduced activity in
the basal ganglia

Management Phase 1: The Multidisciplinary Foundation



Management Phase 2: The Gold Standard

Levodopa (LD) remains the most effective available treatment for akinesia and rigidity.

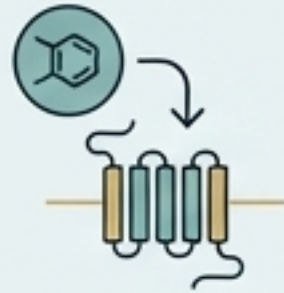


Expanding the Pharmacological Arsenal

Dopamine Agonists

(Ropinirole, Pramipexole, Rotigotine, Apomorphine)

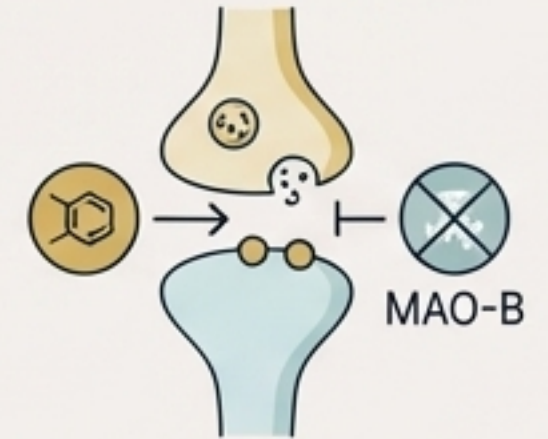
Direct receptor stimulation. Less effective than LD, with higher risk of hallucinations and impulse control disorders.



MAO-B Inhibitors

(Selegiline, Rasagiline)

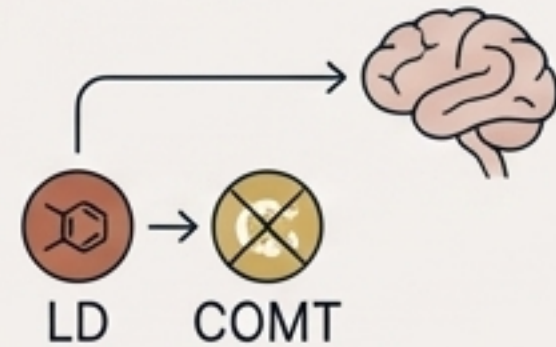
Block dopamine breakdown in the synapse. Modest effect, well-tolerated.



COMT Inhibitors

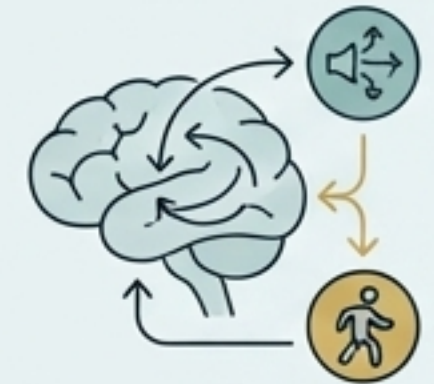
(Entacapone)

Prevent peripheral breakdown of LD, used strictly to extend LD half-life.



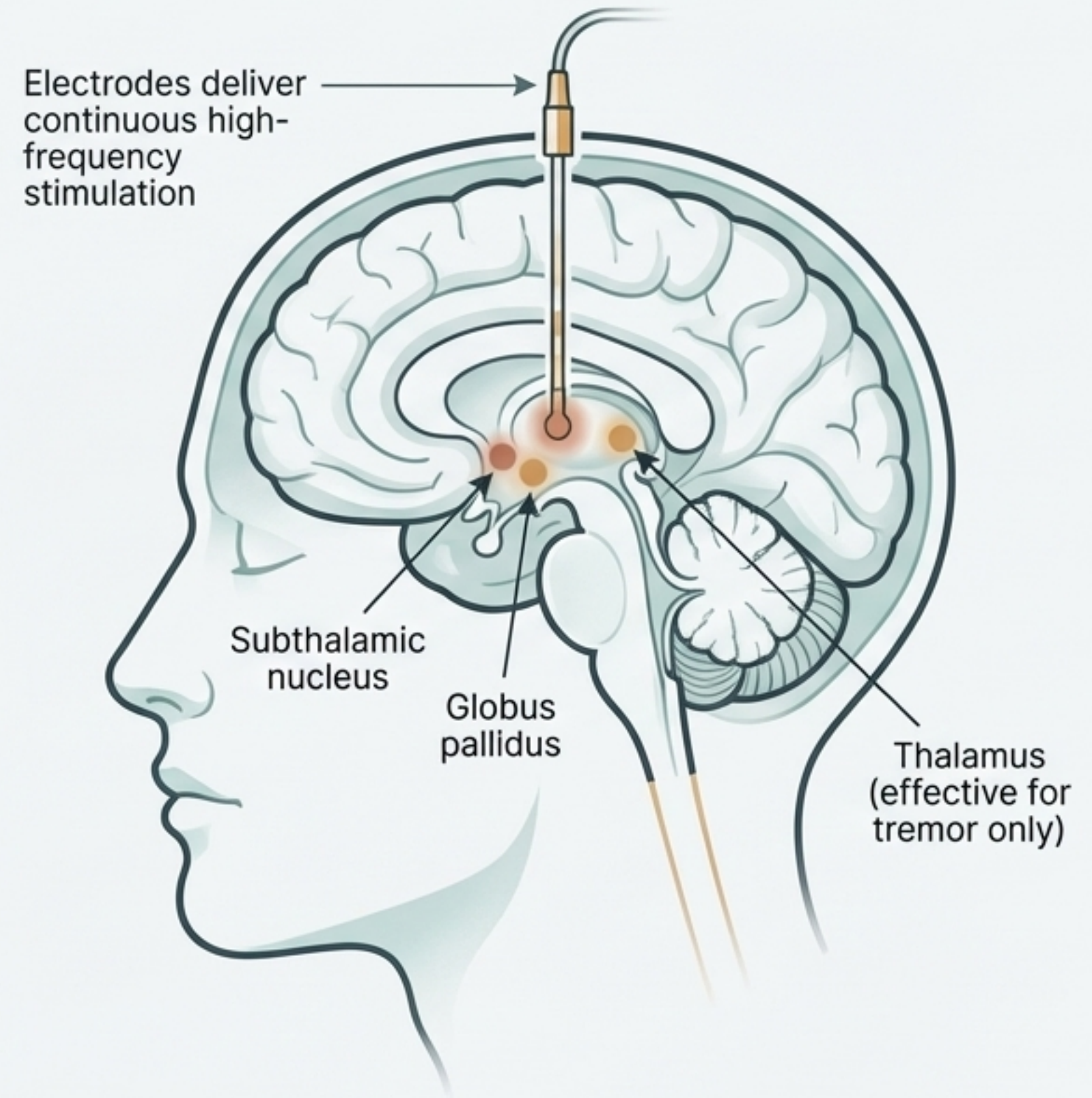
Amantadine

Mild effect on bradykinesia, primarily used to treat LD-induced dyskinesias.



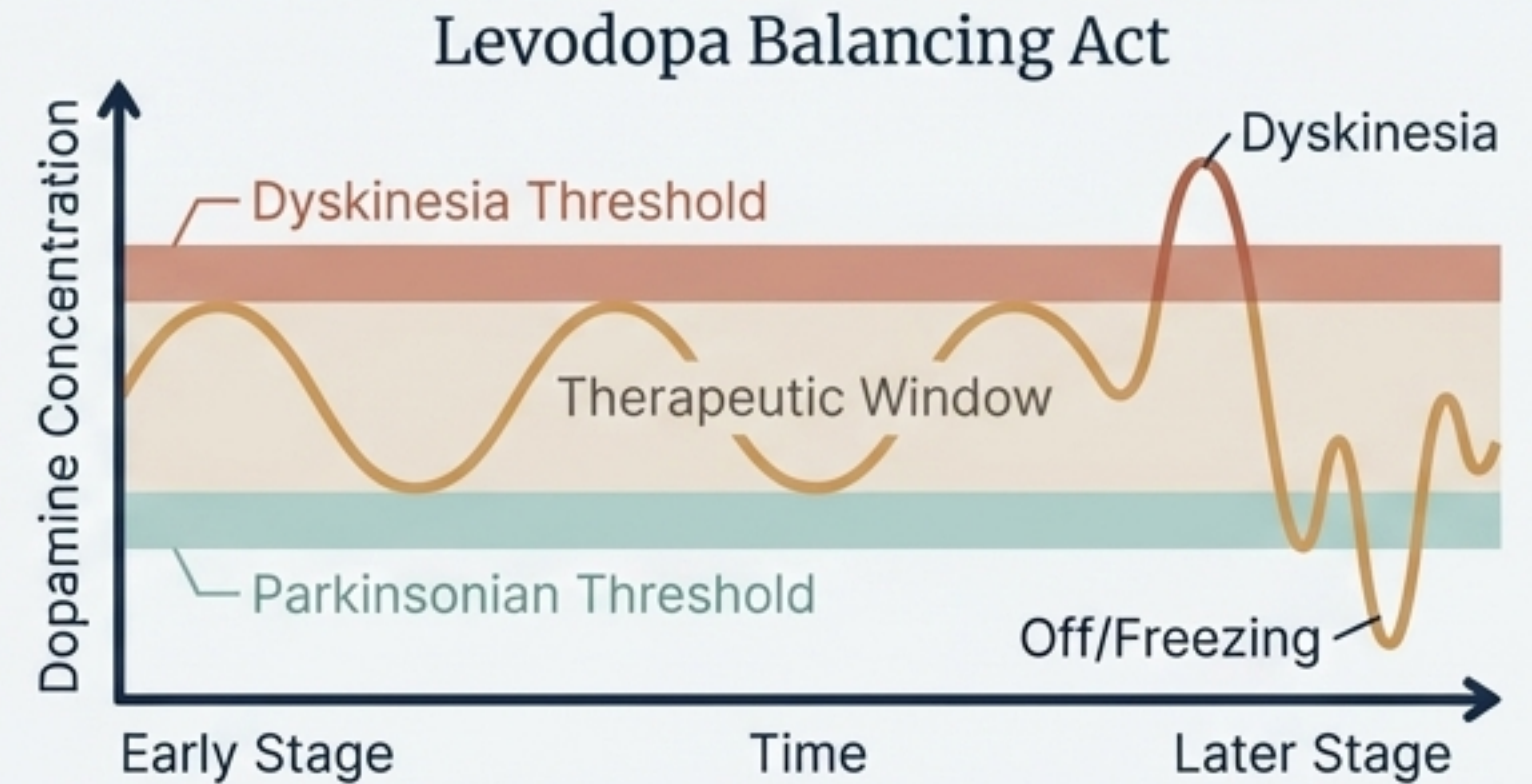
Management Phase 3: Surgical Intervention

- For patients with medically refractory tremor or severe motor fluctuations, stereotactic surgery is considered.
- Deep Brain Stimulation (DBS): The modern standard. Electrodes deliver continuous high-frequency stimulation.
- Key Targets: Subthalamic nucleus, Globus pallidus, and Thalamus (Thalamus is effective for tremor only).
- Careful patient selection is vital. Experimental treatments like fetal grafts remain unproven.



Complications: The Levodopa Balancing Act

Over time, progressive loss of dopamine storage capacity causes the response to LD to become unpredictable.



- End-of-Dose Deterioration: **'Wearing-off'** effects as the drug clears between doses.
- **Dyskinesias**: LD-induced involuntary movements. Can peak when the drug concentration is highest, or occur biphasically.
- Complex Fluctuations: Unpredictable, sudden shifts between severe parkinsonism (**'off' phases**) and mobility with dyskinesias (**'on' phases**).

Complications: The Burden of Progression

Cognitive Decline

PD-associated dementia is common. Rivastigmine (an anticholinesterase) is licensed for use, offering modest benefit.

Treatment Resistance

Many symptoms like freezing, head-drop, abnormal flexion, and postural instability eventually fail to respond to Levodopa.

Safety Risks

Abruptly stopping Parkinson's medications must be avoided as it can precipitate a life-threatening malignant hyperthermia-like state.

Recognizing the Mimics

Several degenerative conditions mimic Idiopathic PD but require different management and carry distinct prognoses.



- Rapid disease progression.



- Early onset of falls and severe postural instability.



- Lack of response to Levodopa therapy.



Crucial Rule: Wilson's disease must always be excluded in patients under age 50 presenting with any movement disorder.

Differentiating the Atypical Syndromes

Multiple System Atrophy (MSA)	Progressive Supranuclear Palsy (PSP)	Corticobasal Degeneration (CBD)
• A synucleinopathy. • Features severe autonomic failure alongside parkinsonism. • Prominent cerebellar symptoms.	• A tauopathy. • Hallmark is a vertical gaze palsy (impaired up- and down-gaze). • Severe cognitive impairment and early falls.	• A tauopathy. • Highly asymmetrical presentation. • Characterized by severe apraxia, myoclonus, and the “alien limb” phenomenon (unconscious limb movement).