Parkinson's Disease and other movement disorders

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A frequent disease …

- Prevalence increases with age:
  - From 0.6% *(65 to 69 yrs)* to 3.5% *(85 to 89 yrs)*
- Moderate male predominance
- Prevalence is more important in rural/urban zone
- Onset:
  - Mean age = 62.4 yrs, rare before age 30;
    4-10% of cases before 40

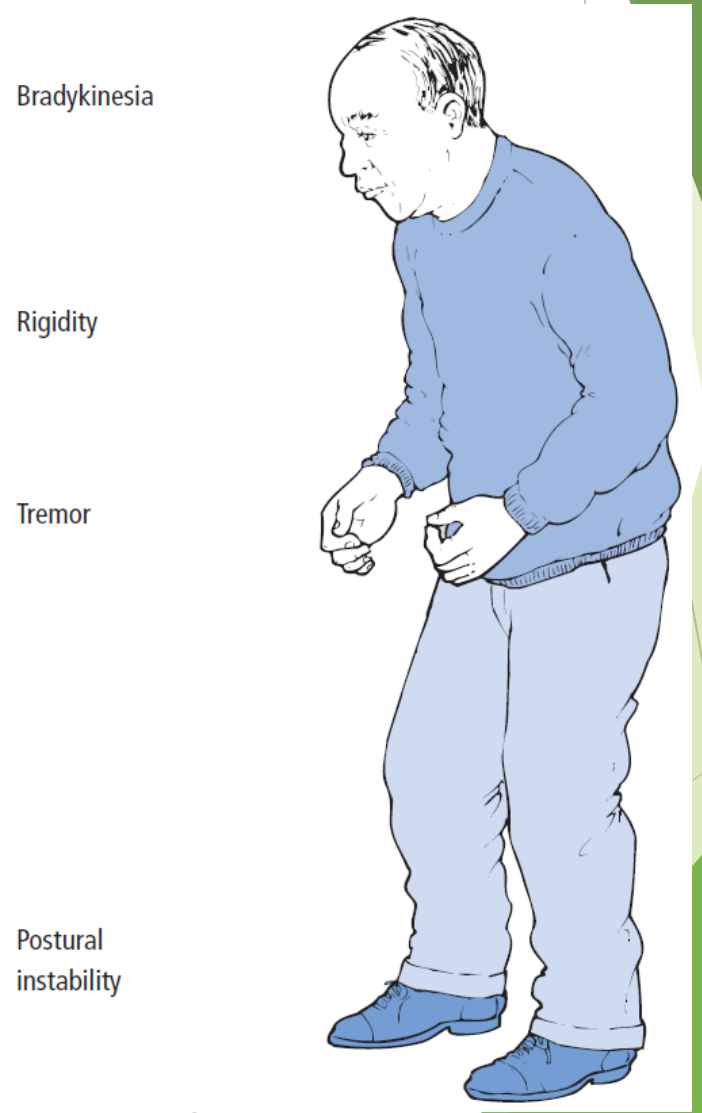
… Still underdiagnosed

35 to 42% of cases underdiagnosed at any time

De Rijk MC et al. *Neurology*. 1995;45:2143-2146.
Kusumi M et al. *Neuroepidemiology*. 1996;15:201-207.
Fisher PP et al. J *Comm Health Nursing*. 1999;16:191-204.

Parkinson’s disease and related disorders

- Epidemiology
- Clinical features
- Pathogenesis
- Treatment
- Other diseases

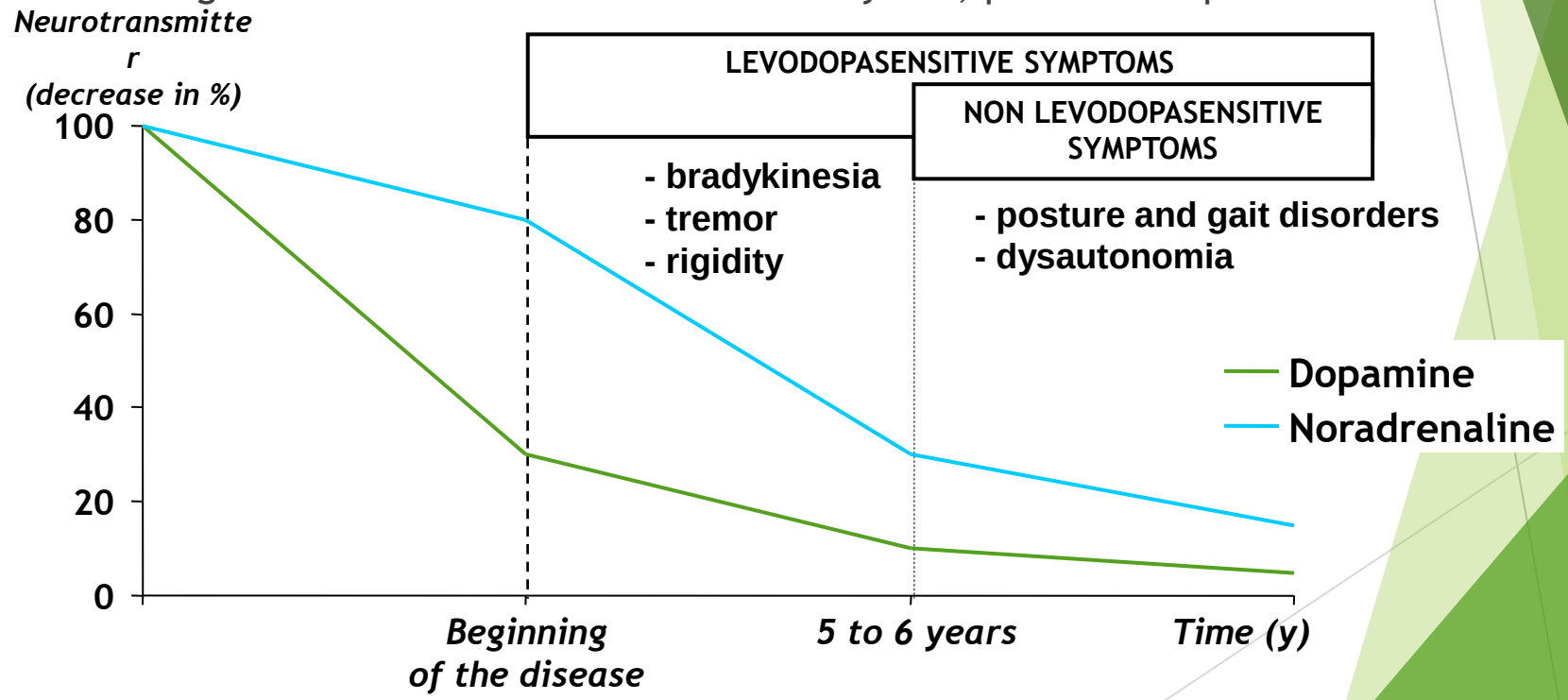


A chronic and disabling disease

- Reduced life expectancy
  - Mean survival after onset ~ 15 years
  - Longer in nondemented PD cases
  - Longer with dopaminergic treatment
- The most common causes of death:
  - Pulmonary infection/aspiration, urinary tract infection, pulmonary embolism and complications of falls
    and fractures

A striatal dopamine deficiency with additional disturbances…

- Noradrenergic: locus coeruleus
- Serotoninergic: raphe nucleus
- Cholinergic: nucleus basalis from Meynert, pedunculus-pontine nucleus

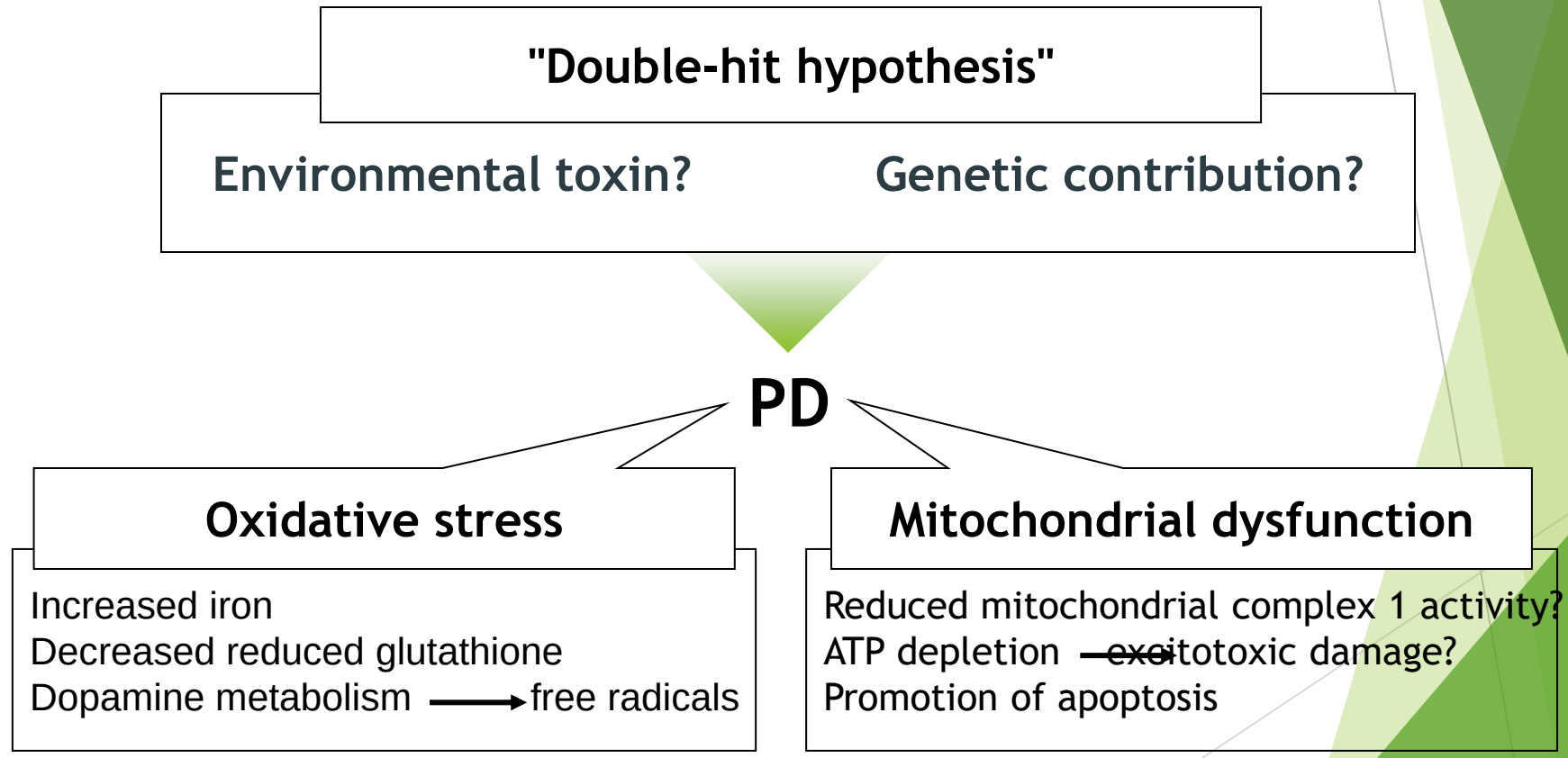


Adapted from Brefel-Courbon C *et al*. *CNS Drugs*. 1998;10:189-207.
Mann D. *Mech Ageing Development*. 1983;23:73-94.

Causes

- Locus niger stroke: 80%
  - Parkinson's disease
- Striatal or poststriatal lesions nonsensitive to levodopa: 20%
  - Postencephalitis parkinsonian syndrome
  - Iatrogenic parkinsonian syndrome *(euroleptics, metolopramide, sulpiride, fluramigine, etc.)*
  - Symptomatic parkinsonian syndrome *(traumatic, vasculitic, tumors, intoxication [CO], toxic [manganese, lead])* normal pressure hydrocephalus
  - Multiple system atrophy
  - Others *(Wilson's disease, etc.)*

Major hypothesis of Parkinson's disease pathogenesis



When do you have to think about a clinical diagnosis?

- Suggestive motor symptoms:
  - Slowness of certain gestures: buttoning clothes, shaving
  - Difficulties in turning over whilst in bed
  - General "slow down"
  - Micrographia
- Mistaking symptoms:
  - Periarticular pain *(shoulder)*
  - Depression *(initial in 15% of cases)*

Cardinal motor signs

- Diagnosis requires 2 out of 3:
  - Bradykinesia; rigidity; tremor *(primarily at rest)*
- Other signs:
  - Masked face, hypovolemic speech, dysphagia,
    flexed posture, shuffling gait, start hesitancy, and freezing
- Onset:
  - Insidious, unilateral progressing to bilateral

Parkinson's Disease and Other Movement Disorders

TABLE 372-1 Clinical Features of Parkinson's Disease

Cardinal Features	Other Motor Features	Nonmotor Features
Bradykinesia	Micrographia	Anosmia
Rest tremor	Masked facies (hypomimia) equalize	Sensory disturbances (e.g., pain)
Rigidity	Reduced eye blink	Mood disorders (e.g., depression)
Gait disturbance/ postural instability	Soft voice (hypophonia)	Sleep disturbances
	Dysphagia	Autonomic disturbances
	Freezing	Orthostatic hypotension
		Gastrointestinal disturbances
		Genitourinal disturbances
		Sexual dysfunction
		Cognitive impairment/Dementia

Parkinson's Disease and Other Movement Disorders

TABLE 372-2 Differential Diagnosis of Parkinsonism

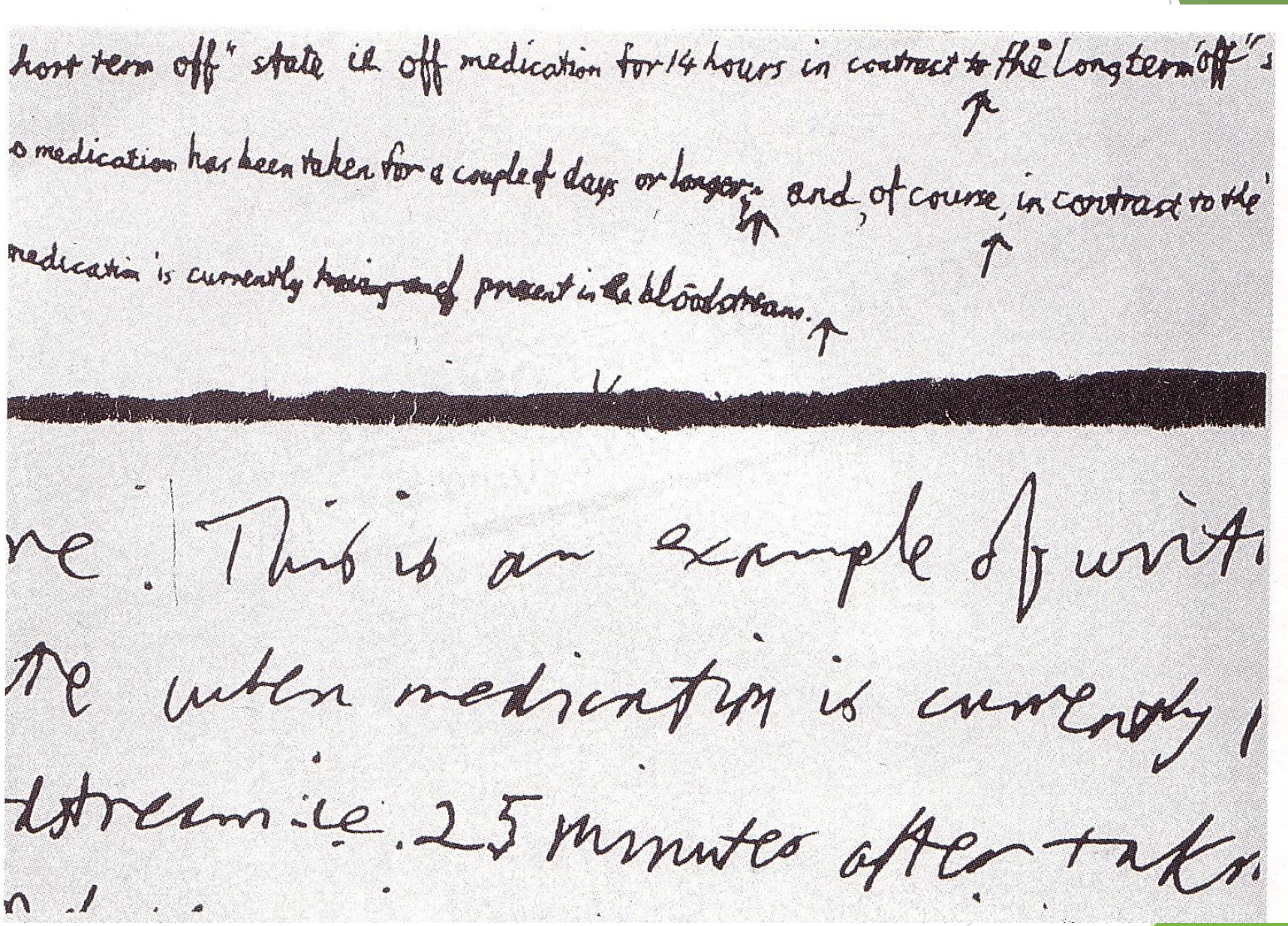
Parkinson's Disease	Atypical Parkinsonisms	Secondary Parkinsonism	Other Neurodegenerative Disorders
Genetic	Multiple-system atrophy	Drug-induced	Wilson's disease
Sporadic	Cerebellar type (MSA-c)	Tumor	Huntington's disease
Dementia with Lewy bodies	Parkinson type (MSA-p)	Infection	Neurodegeneration with brain iron accumulation
	Progressive supranuclear palsy	Vascular	SCA 3 (spinocerebellar ataxia)
	Corticobasal ganglionic degeneration	Normal-pressure hydrocephalus	Fragile X–associated ataxia-tremor-parkinsonism
	Frontotemporal dementia	Trauma	Prion disease
		Liver failure	Dystonia-parkinsonism (DYT3)
		Toxins (e.g., carbon monoxide, manganese, MPTP, cyanide, hexane, methanol, carbon disulfide)	Alzheimer's disease with parkinsonism

Parkinson's Disease and Other Movement Disorders

TABLE 372-3 Features Suggesting Alternate Diagnosis Than PD

Symptoms/Signs	Alternate Diagnosis to Consider
History	
Early speech and gait impairment	Atypical parkinsonism
Exposure to neuroleptics	Drug-induced parkinsonism
Onset prior to age 40	Genetic form of PD
Liver disease	Wilson's disease, non-Wilsonian hepatolenticular degeneration
Early hallucinations	Dementia with Lewy bodies
Diplopia	PSP
Poor or no response to an adequate trial of levodopa	Atypical or secondary parkinsonism
Physical Exam	
Dementia as first symptom	Dementia with Lewy bodies
Prominent orthostatic hypotension	MSA-p
Prominent cerebellar signs	MSA-c
Impairment of down gaze	PSP
High-frequency (8–10 Hz) symmetric postural tremor with a prominent kinetic component	Essential tremor

Abbreviations: MSA-c, multiple-system atrophy–cerebellar type; MSA-p, multiple-system atrophy–Parkinson type; PSP, progressive supranuclear palsy.


short term off" state ie off medication for 14 hours in contrast to the Long term "off"
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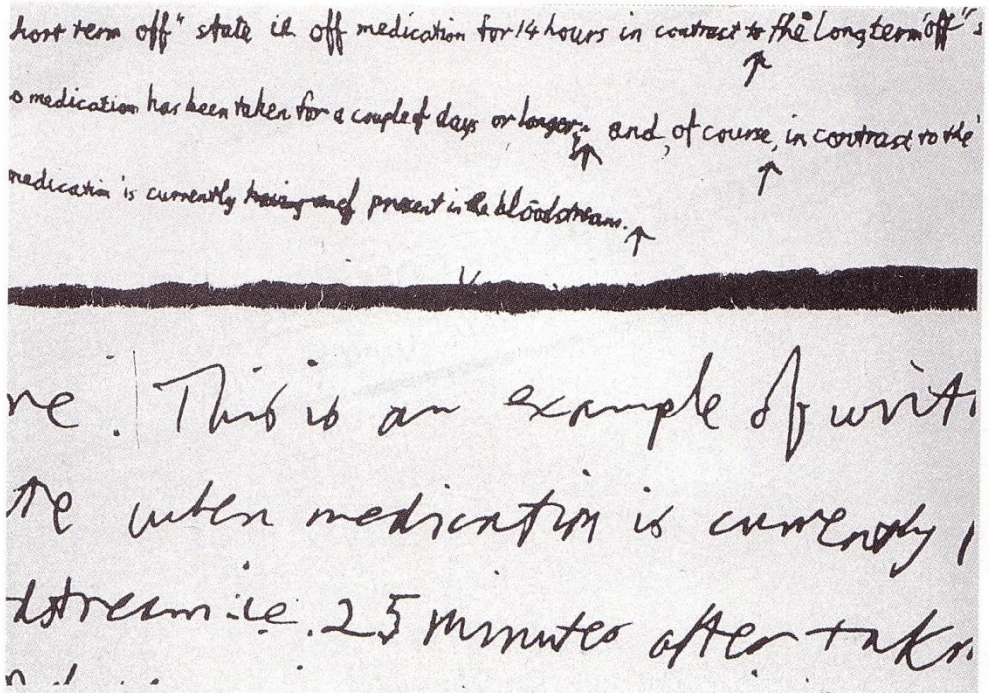
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Medical examination signs

- Restless legs syndrome
- Decrease in arm swinging
- Decrease in finger *(thumb-index grip)*, hand *(opening-closing)*, and foot *(beating)* agility
- Lead-pipe rigidity with "cogwheeling"
- Micrographia
- Brisk unrelenting nasopalpebral reflex

Nonmotor symptoms

- Psychological disorders:
  - Almost continuous anxiety
  - Depression, initial presentation *(15%)*, in 1 case out of 2 *(visual hallucinations linked to treatment)*
- Cognitive disorders:
  - Intellectual "slow-down"
  - Attention disturbances, distractibility
- Vegetative signs:
  - Hypersialorrhea
  - Sebaceous hypersecretion *(greasy skin)*

Two groups of symptoms

- Motor symptoms *(bradykinesia, rigidity, tremor)*:
  - Directly linked to dopaminergic nigostriatal neuronal lesion
  - Levodopasensitive during disease progression
- Other symptoms *(posture and gait disorders, cognitive disorders)*:
  - Appear secondarily
  - Linked to the lesion of non-DA systems *(eg noradrenaline)*
  - Non-levodopa sensitive
  - Worse prognosis

Clues suggesting atypical parkinsonian

- Early onset of, or rapidly progressing, dementia
- Rapidly progressive course
- Supranuclear gaze palsy
- Upper motor neurone signs
- Cerebellar signs, ataxia
- Urinary incontinence
- Early symptomatic postural hypotension

Basal Ganglia
Parallel Loops

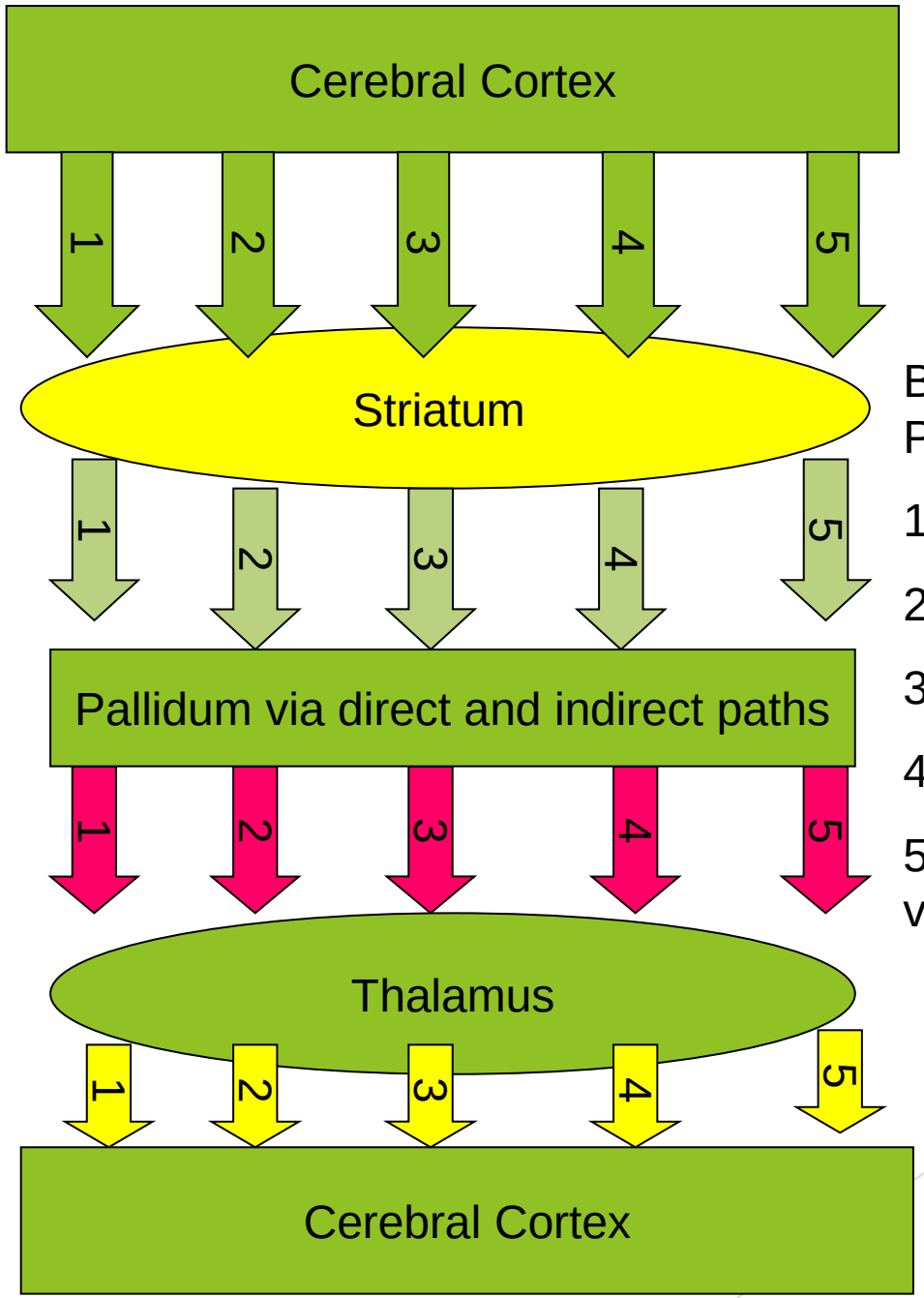
1: Motor

2: Oculomotor

3: Dorsolateral PF

4: Orbitofrontal

5: Limbic



Basal Ganglia
Parallel Loops

1: Motor function

2: Gaze function

3: Cognitive

4: Cognitive

5: Emotional/
visceral

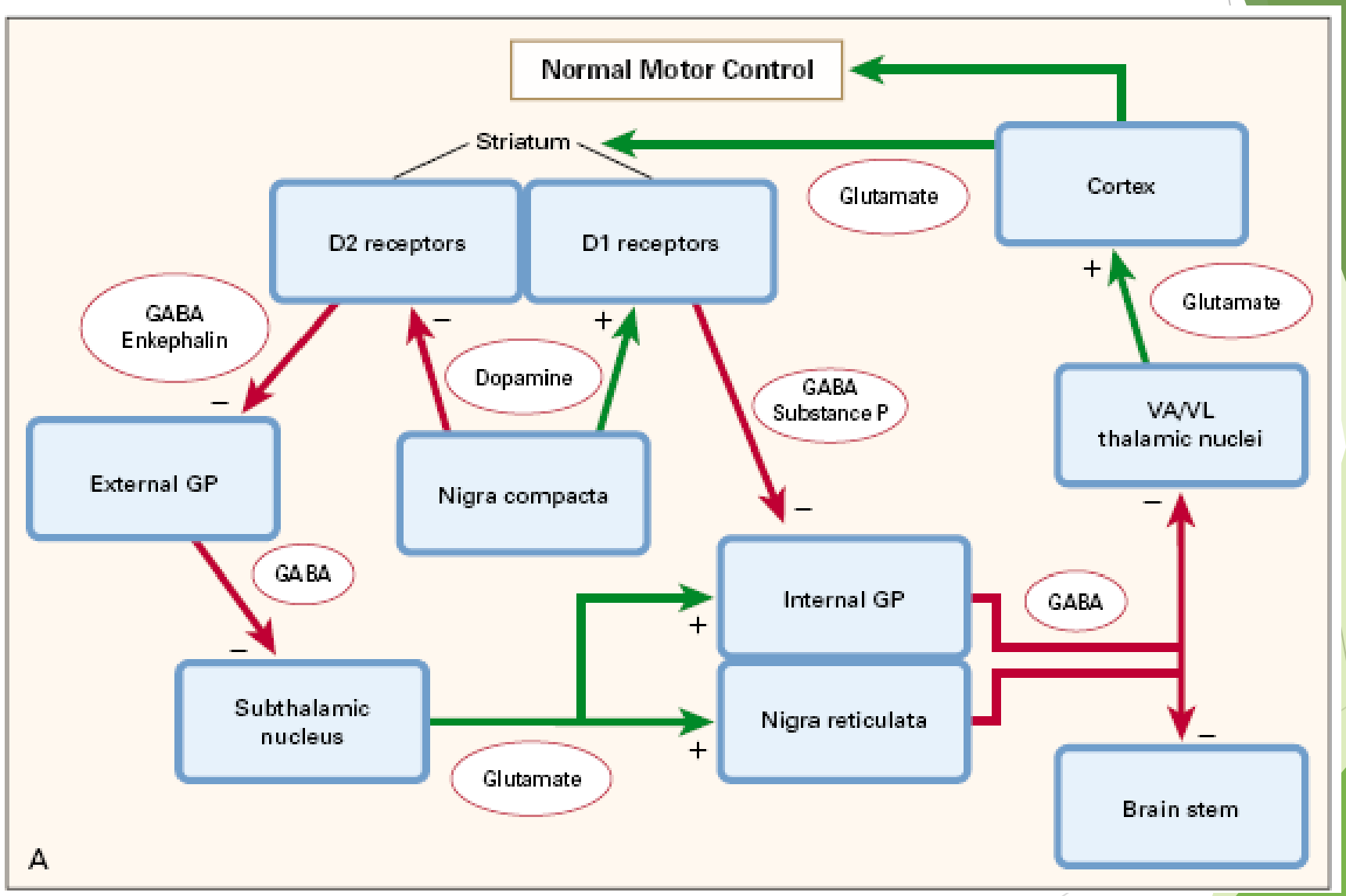
Pathogenesis of Neuronal Degeneration in PD

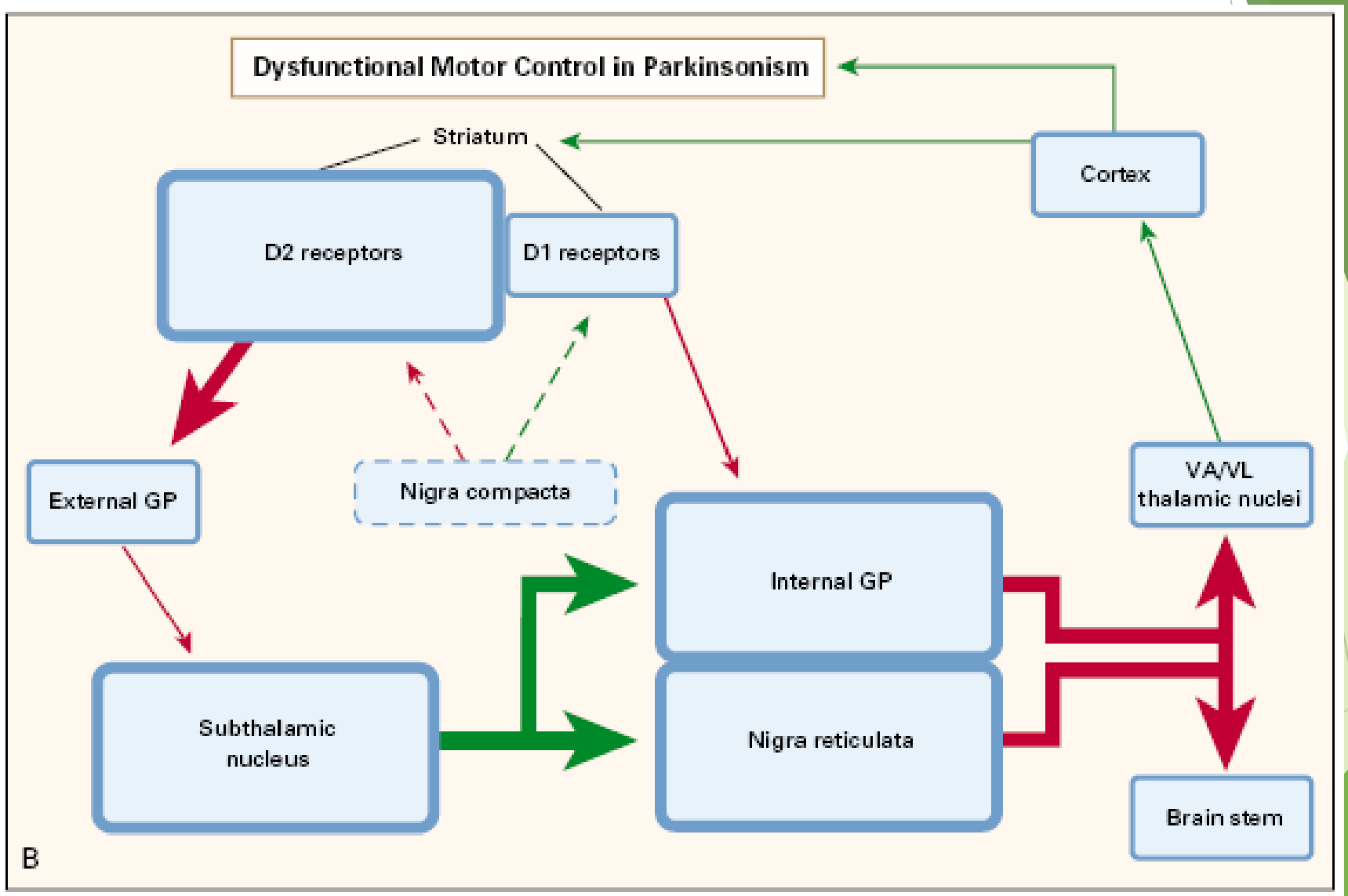
- Mitochondrial dysfunction and oxidative stress metabolism.
- Excitotoxins.
- Neurotrophic factor loss or dysfunction.
- Immune mediated.

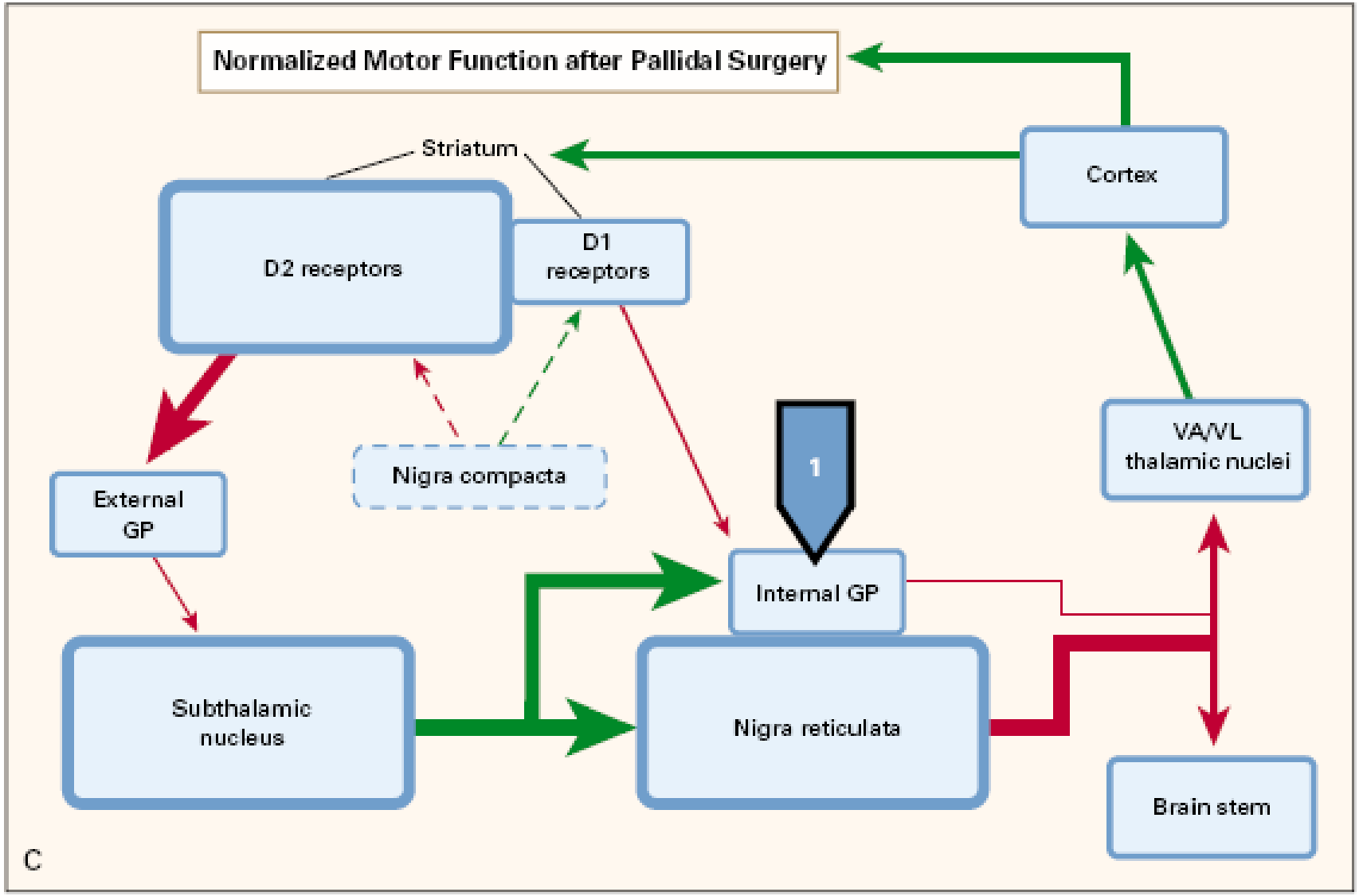
Figure 3 (following pages). Proposed Functional Model of the Basal Ganglia in Persons with Normal Motor Control (Panel A), Patients with Parkinsonism (Panel B), and Patients in Whom Motor Function Has Been Improved by Surgical Interventions in the Medial Globus Pallidus (Panel C) or the Subthalamic Nucleus (Panel D).

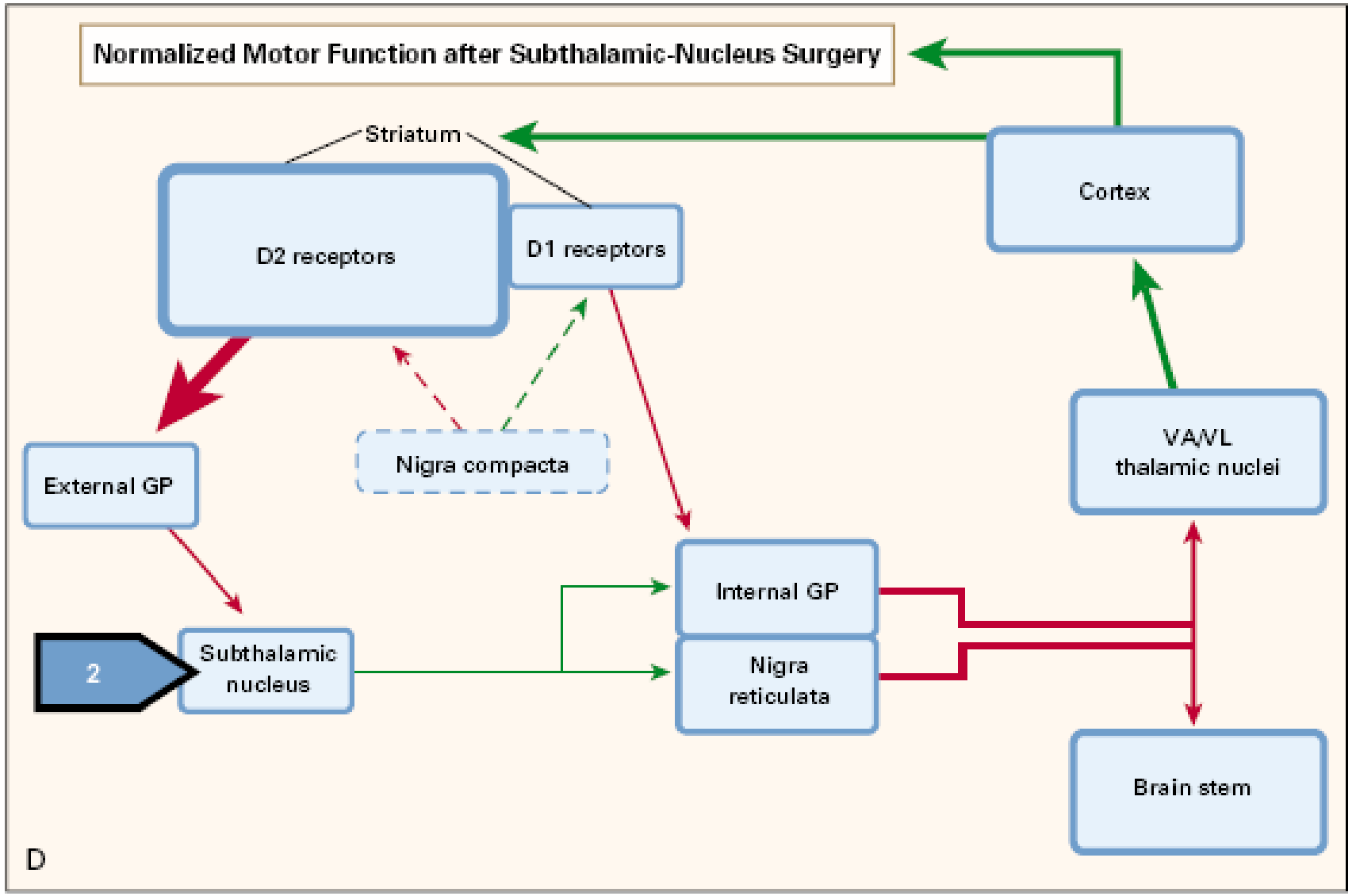
For the purposes of clarity, the neuroanatomy and interconnections shown are incomplete. Green arrows indicate excitatory pathways, and red arrows inhibitory pathways. In Panels B, C, and D, the width of the arrows indicates the degree of overall functional change in the activity of each pathway (changes in neuronal firing rates) as compared with the normal state (Panel A), and the size and outlining of each box indicate the activity of the brain region as compared with the normal level of activity (Panel A). Dashed lines and arrows indicate the dysfunctional nigrostriatal dopamine system in Parkinson's disease. The circled substances are neurotransmitters used by the neighboring pathway. The brain stem as depicted includes the pedunculopontine nucleus, and the cortex includes supplementary motor areas and premotor cortex. D1 receptors denotes neurons containing predominantly D1 dopamine receptors, D2 receptors neurons containing predominantly D2 dopamine receptors, nigra compacta the pars compacta of the substantia nigra, external GP the external portion of the globus pallidus, internal GP the internal portion of the globus pallidus, nigra reticulata the pars reticulata of the substantia nigra, VA/VL ventral anterior and ventrolateral, and GABA γ-aminobutyric acid. The 1 indicates a lesion or high-frequency stimulation in the internal segment of the globus pallidus, and the 2 high-frequency stimulation or lesion in the subthalamic nucleus. Plus signs indicate excitation, and minus signs inhibition.

Alterations in firing patterns in Panels B, C, and D (e.g., more bursting or irregular patterns of discharge, as compared with continuous or tonic firing in the normal state) may have an important functional role that is poorly understood at present. Parkinsonism (Panel B) is associated with increased inhibition of the motor thalamus (and, as a result, premotor cortexes) and brain-stem locomotor areas resulting from overactivity of the internal segment of the globus pallidus and pars reticulata of the substantia nigra. The excessive activity of these two areas is due to reduced direct inhibition from the striatum and especially to excessive stimulation from the overactive subthalamic nucleus. An increase in dopaminergic action at the level of the striatum due to drug therapy (e.g., levodopa or dopamine agonists) would partially reverse this state (not shown). Surgically reducing the activity of the internal segment of the globus pallidus (Panel C) would also partially reverse this state by eliminating the excessive inhibition due to this component of the output of the basal ganglia. On the other hand, reducing the excessive excitatory activity of the subthalamic nucleus (Panel D) would have the advantage of reducing the overactivity of both components of the output of the basal ganglia, the internal segment of the globus pallidus, and the pars reticulata of the substantia nigra.

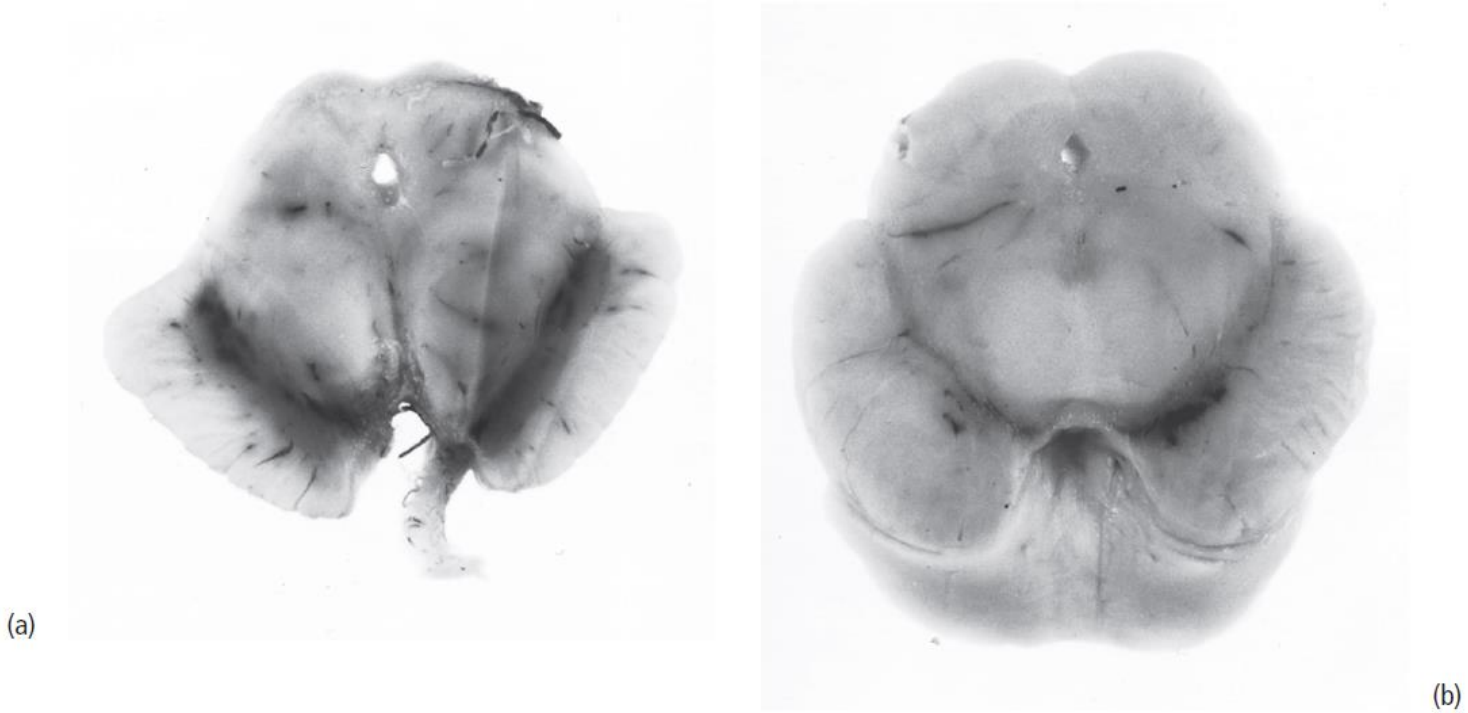

Normal Motor Control
Striatum
Cortex
Glutamate
D2 receptors
D1 receptors
GABA
Enkephalin
Dopamine
Glutamate
GABA
Substance P
VA/VL
thalamic nuclei
External GP
Nigra compacta
GABA
Internal GP
GABA
Subthalamic
nucleus
Nigra reticulata
Glutamate
Brain stem
A


Dysfunctional Motor Control in Parkinsonism
Striatum
Cortex
D2 receptors
D1 receptors
External GP
Nigra compacta
VA/VL
thalamic nuclei
Internal GP
Subthalamic
nucleus
Nigra reticulata
Brain stem
B

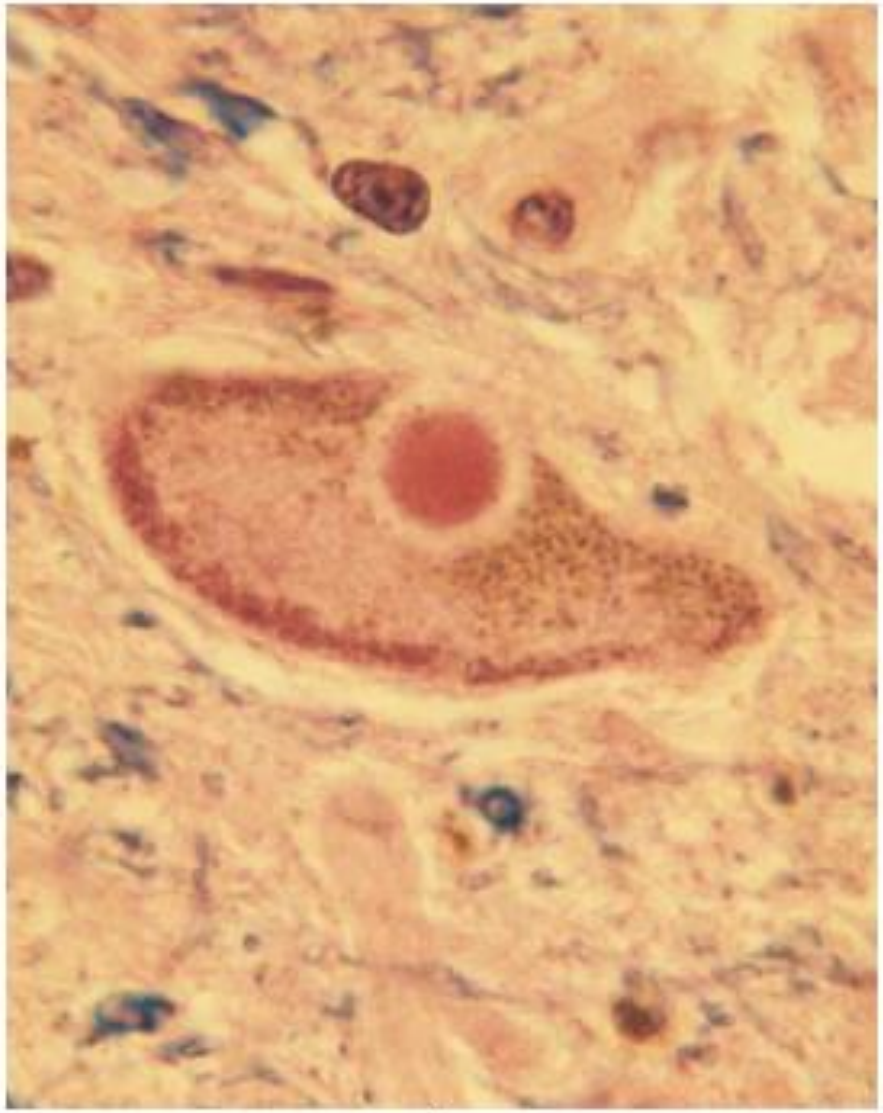

Normalized Motor Function after Pallidal Surgery
Striatum
Cortex
D2 receptors
D1
receptors
Nigra compacta
1
VA/VL
thalamic nuclei
External
GP
Internal GP
Subthalamic
nucleus
Nigra reticulata
Brain stem
C


Normalized Motor Function after Subthalamic-Nucleus Surgery
Striatum
D2 receptors
D1 receptors
Cortex
External GP
Nigra compacta
VA/VL
thalamic nuclei
Internal GP
2
Subthalamic
nucleus
Nigra
reticulata
Brain stem
D

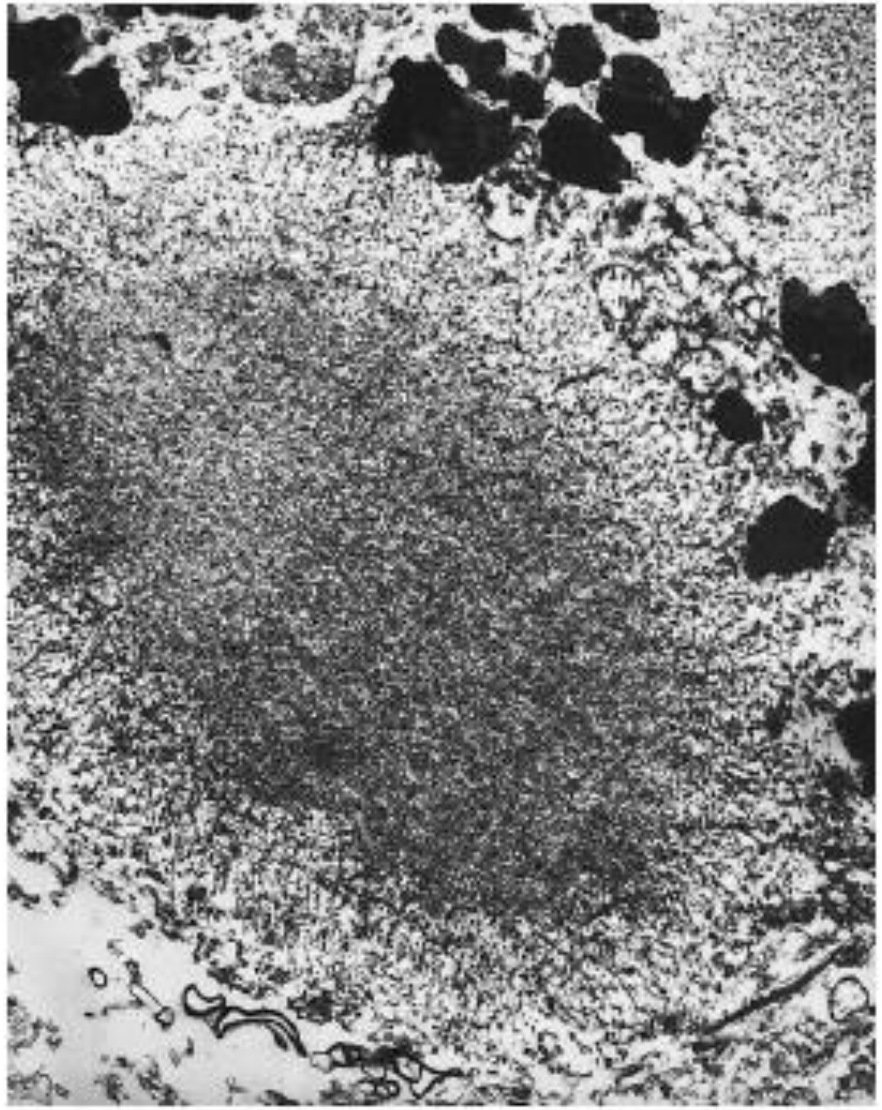
Pathology of PD



Loss of pigment in substantia nigra. (a) normal (b) PD



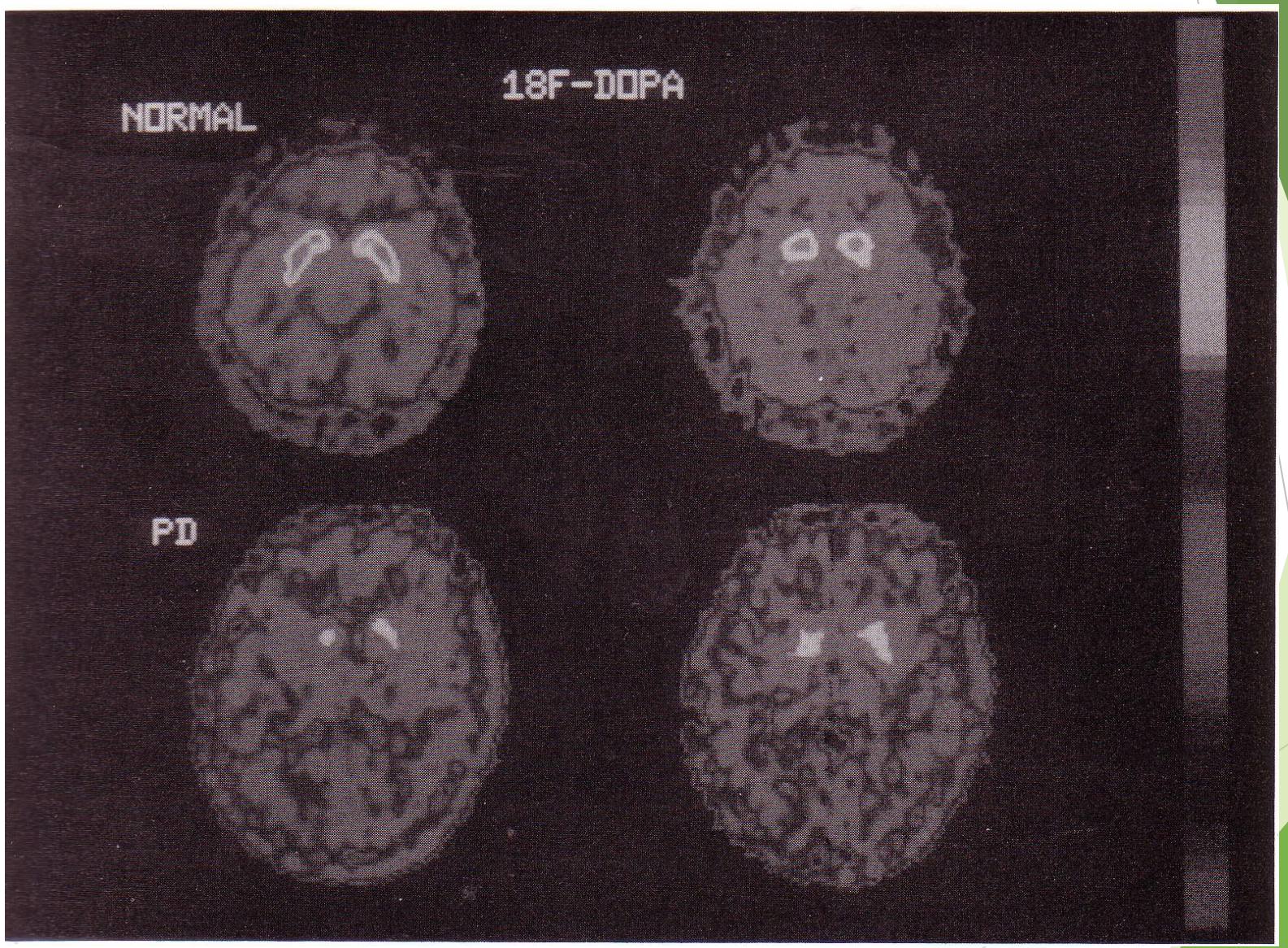
A

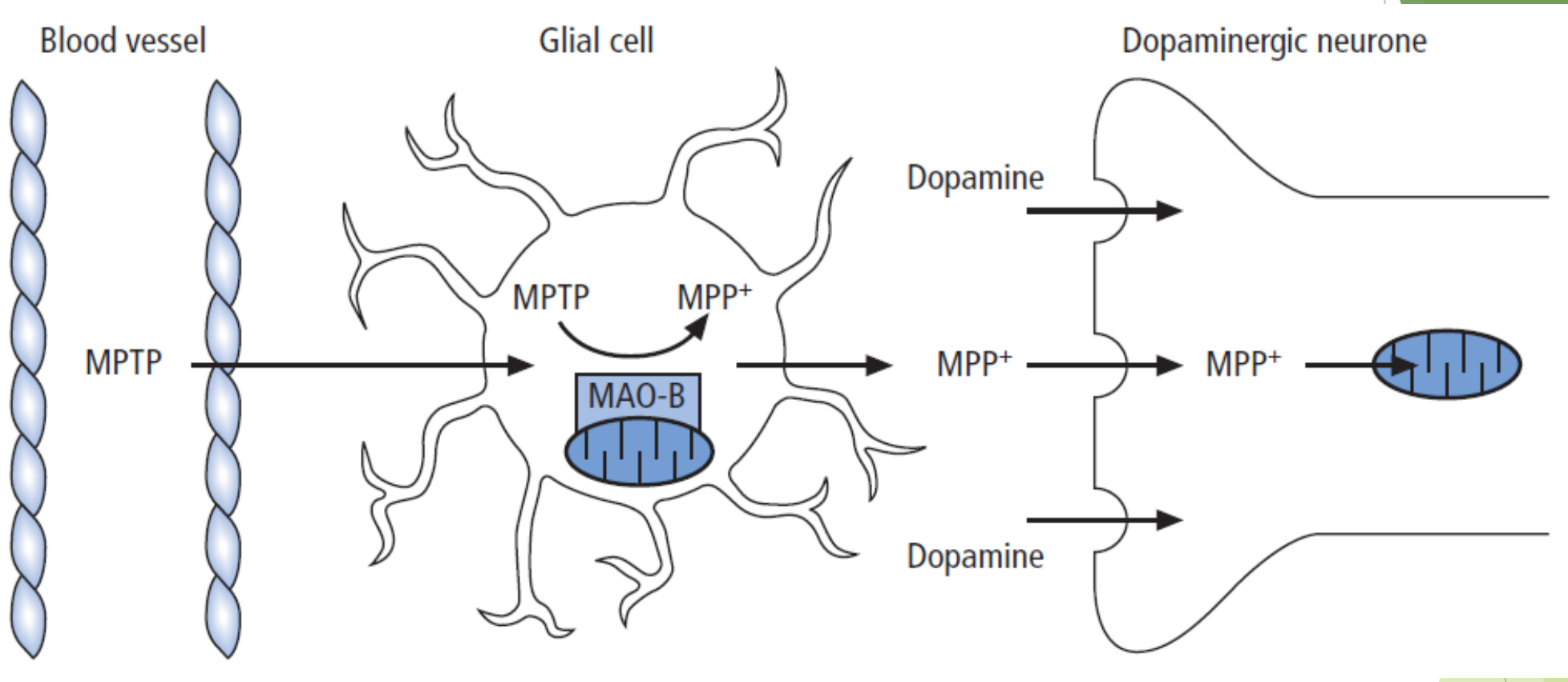


B

Figure 2. A Typical Lewy Body.

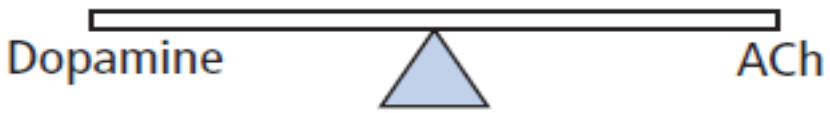
Panel A shows the Lewy body in the cytoplasm of a pigmented dopaminergic neuron in the substantia nigra (hematoxylin–eosin and Luxol fast blue, ×100). Ultrastructural examination (Panel B) shows an accumulation of filaments and granular material with a dense core and loose radiating peripheral filaments (×21,560). Courtesy of Dr. Catherine Bergeron.


18F-DOPA
NORMAL
PD



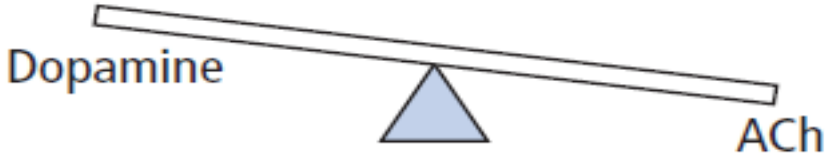
MPTP and the aetiology of Parkinson's disease. The toxin MPTP crosses the blood–brain barrier and is converted to its active metabolite MPP+ by the enzyme monoamine oxidase type B (MAO-B) in glial cells. MPP+, a free radical, is concentrated in dopaminergic neurones, entering via the dopamine reuptake mechanism, thereby selectively damaging these cells. MPP+ is a mitochondrial poison, inhibiting Complex I of the respiratory chain, and hence impairing cellular energy production.

(a)



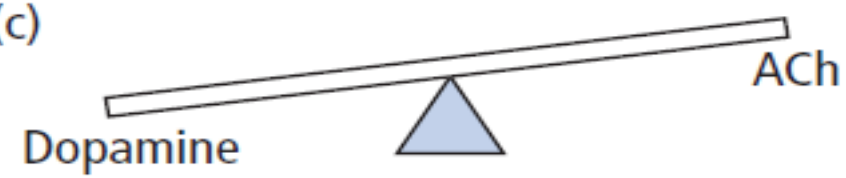
Normal-dopaminergic pathways balanced by those utilizing other neurotransmitters, predominantly acetylcholine (ACh).

(b)



Dopaminergic deficiency or cholinergic excess, resulting in an akinetic–rigid syndrome, e.g. idiopathic Parkinson's disease or drug-induced Parkinsonism (NB phenothiazines and related drugs are dopamine antagonists).

(c)



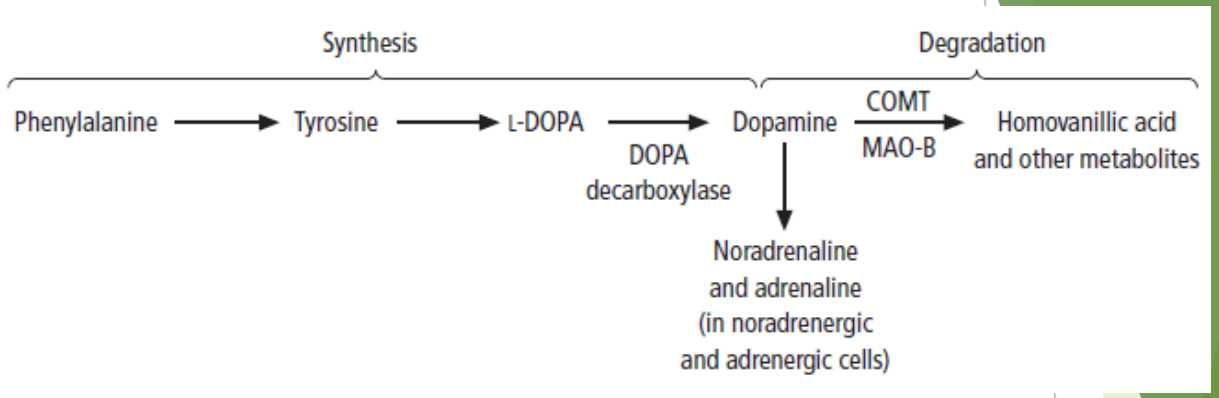
Dopaminergic excess or cholinergic deficiency, resulting in excessive involuntary movements – dyskinesia, e.g. due to overtreatment of Parkinson's disease with dopaminergic drugs, or to degenerative disease of non-dopaminergic pathways, as in Huntington's disease.

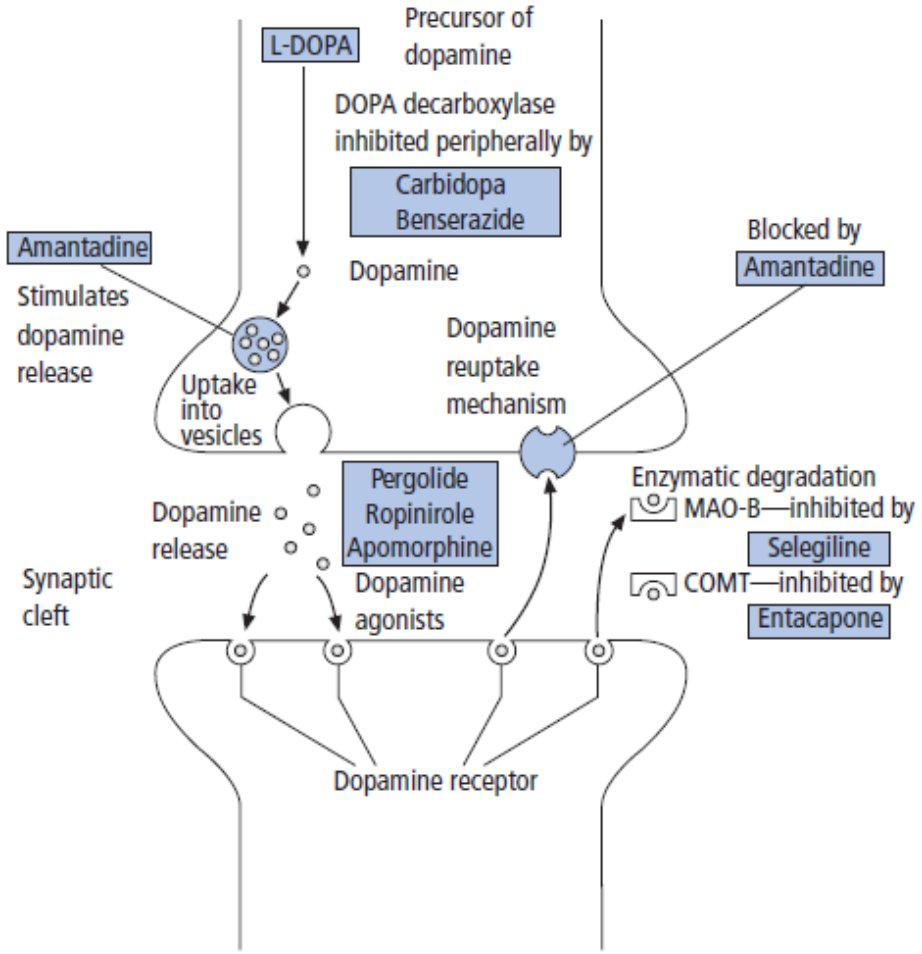
The concept of neurochemical balance in extrapyramidal system

Treatment options

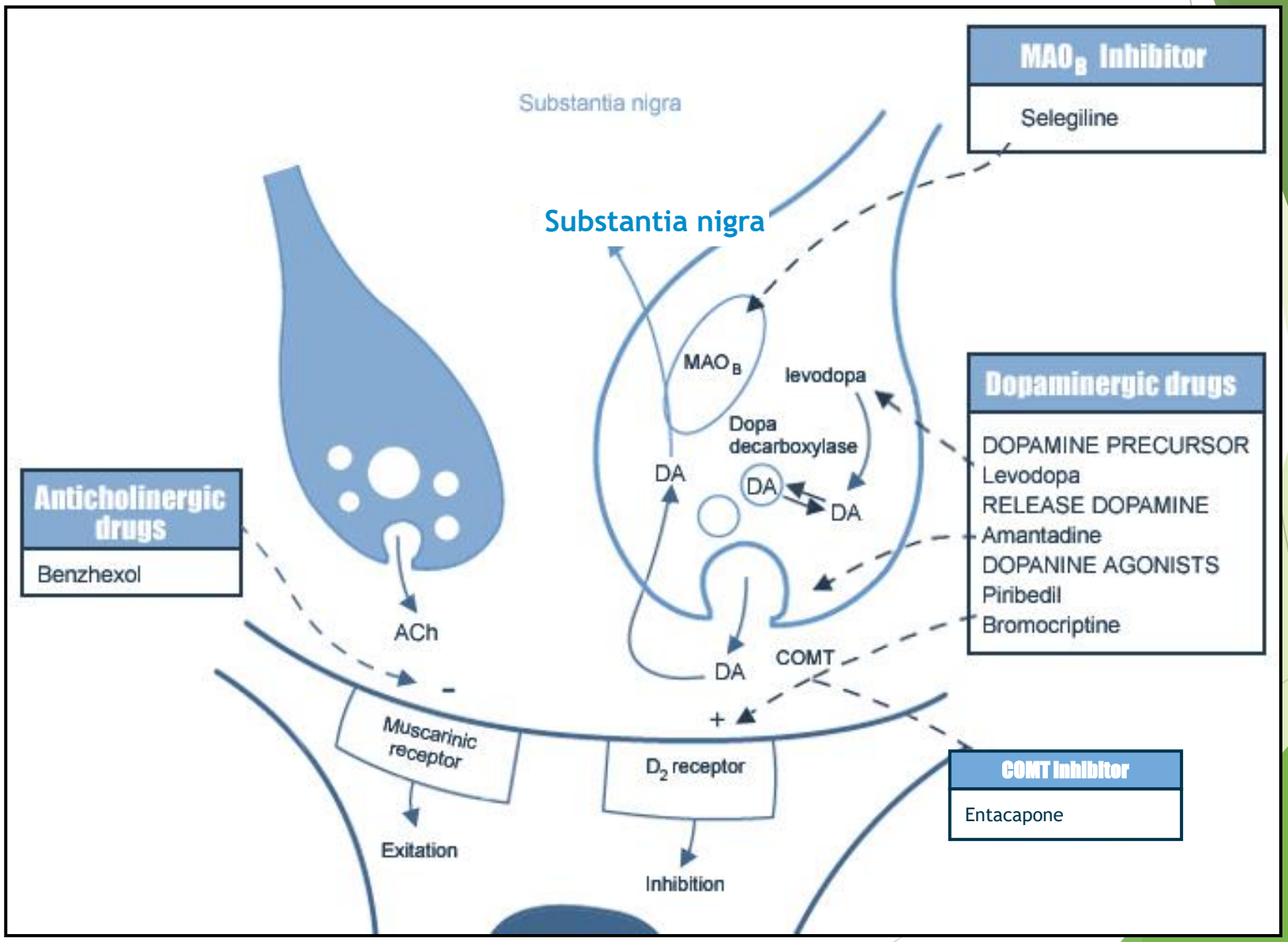
- Preventative treatment
  - No definitive treatment available
- Symptomatic treatment
  - Pharmacological
  - Surgical
- Nonmotor management
- Restorative-experimental only
  - Transplantation
  - Neurotrophic factors

Drugs mechanism of action in PD





Drug classes and their sites of action



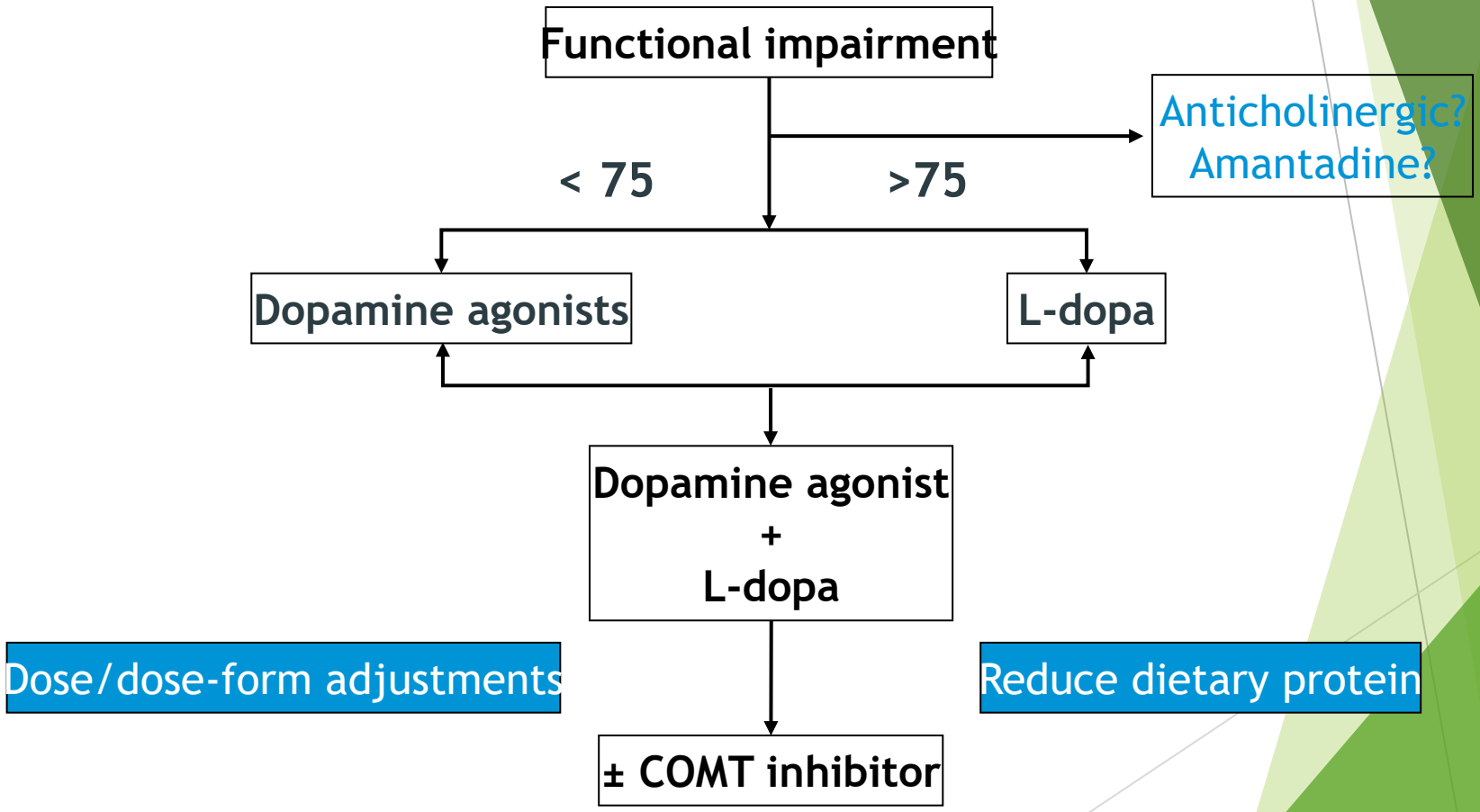
Levodopa

- First developed in the late 1960s
- Most effective drug for parkinsonian symptoms
- Rapid peripheral decarboxylation to dopamine without a decarboxylase inhibitor
  (DCIs: carbidopa, benserazide)
- Side effects:
  - Nausea, vomiting, postural hypotension, motor complications

Levodopa-induced motor complications

- Dyskinesia
  - Peak-dose, onset and end of dose biphasic dyskinesia
  - Typically late effect, at the time of maximal levodopa benefit
  - Rare in Levodopa-naive patients on DA monotherapy
- Motor fluctuations
  - Wearing off: regular and predictable decline in response 2-4 hour after Levodopa dose
  - "On-off" response: sudden and unpredictable "off" periods unrelated to dosing schedule
  - Freezing: motor block at initiation of gait, turning, in narrow spaces

Recommendations of the american academy of neurology



Adapted from Olanow CW et al.*Neurology*. 2001;56(suppl 5):S1-S88.

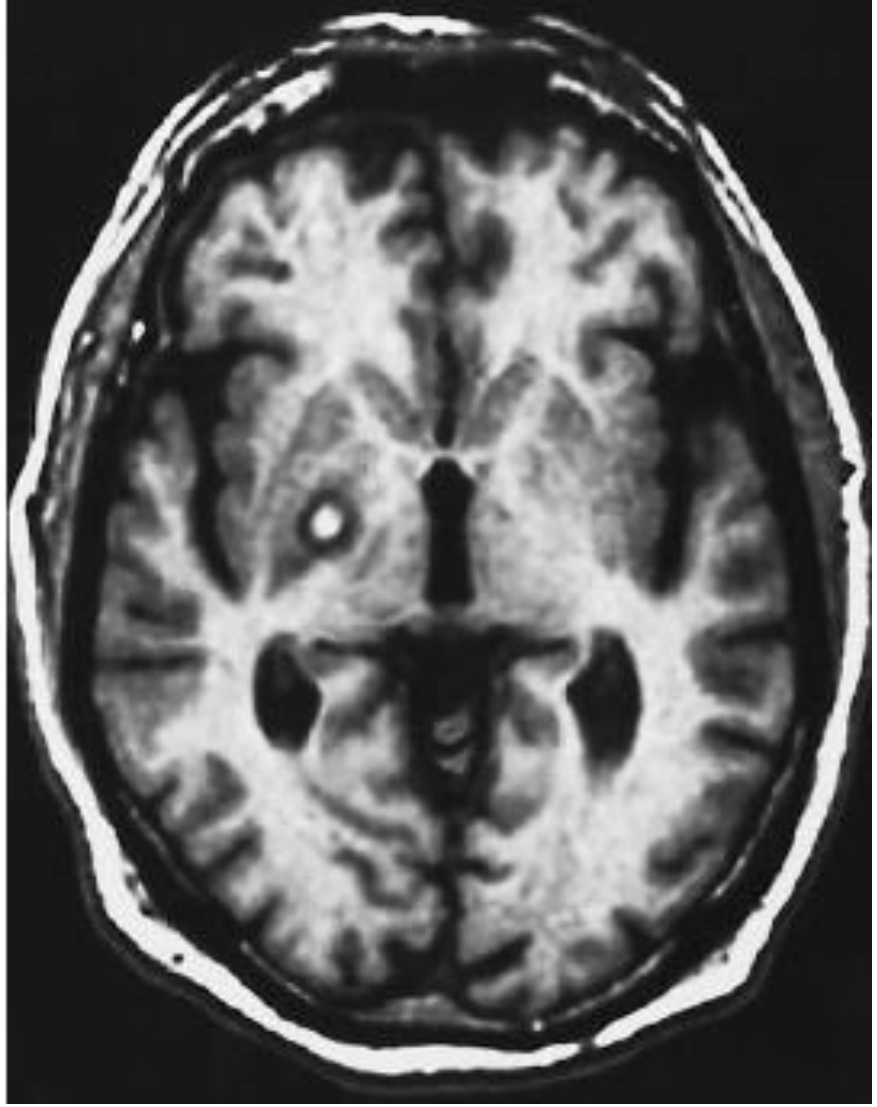
Dopamine agonists: a heterogeneous therapeutic class

Molecules	D1	D2	D3	Ergot	5-HT	NA	T1/2(h)
Bromocriptine	-	+	+	+	+	+	6
Pergolide	+	+	+	+	0	0	15-27
Piribedil	+[a]	+	+	0	0	-	21
Lisuride	-	+	+	+	++	+	1-7
Apomorphine	+	+	+	0	+	0	1
Pramipexole	0	+	+	0	0	++	7-9
Ropinirole	0	+	0	0	0	0	6
Cabergoline	0	+	+	+	+	+	65

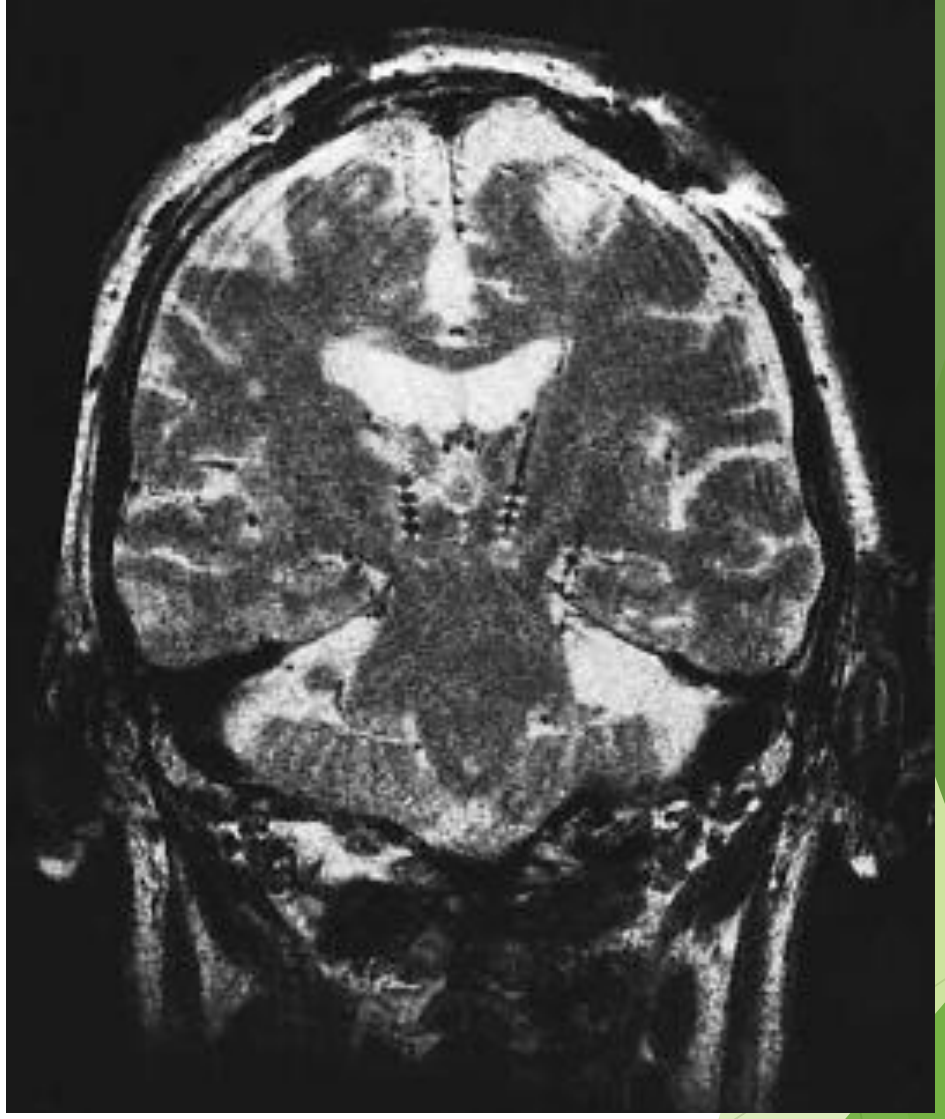
+ Agonist, - Antagonist, 0 No Action,

D1 to D5: dopaminergic receptor subtypes; 5-HT: serotoninergic receptors;
NA: presynaptic α2-noradrenergic receptors
a: active metabolite

Allain H. *Dis Man Health Outcomes*. 2001;9 (Special issue 1):41-48.



GPi Pallidotmy



Bilateral STN Stimulation

Idiopathic akinetic-rigid syndromes other than PD

- *Multiple system atrophy (MSA)*

Extrapyramidal features in combination with one or more of the following:

Autonomic failure (Shy–Drager syndrome)

Cerebellar dysfunction

Pyramidal features

Parkinsonism predominate (MSA-P)

Cerebellar predominate MSA-C

Autonomic failure(MSA-A)

- *Progressive supranuclear palsy (PSP, Steele-Richardson-Olszewski syndrome)*

Failure of voluntary gaze – first downgaze, then upgaze, then horizontal gaze – associated with extrapyramidal dysfunction (with early postural instability) and dementia

- *Syndromes combining parkinsonian features with cerebral cortical dysfunction*

Corticobasal degeneration (CBD) – extremely rare

Dementia with Lewy bodies (DLB)

Causes of akinetic rigid syndromes

- *Inherited*
- Wilson's disease –
- *Traumatic*
- 'Punch-drunk syndrome

  chronic head injury in boxers – patients have parkinsonian features often in combination with cerebellar damage and cognitive deficits (dementia pugilistica)
- *Inflammatory*

Postencephalitic Parkinsonism – following the epidemic of encephalitis lethargica after World War I, patients developed a chronic akinetic–rigid state, with certain characteristic features, particularly oculogyric crises (see text)

- *Neoplastic*

  Tumours of the basal ganglia presenting with contralateral hemiparkinsonism are extremely rare
- *Vascular*

  Multiple lacunar infarcts may occasionally result in pseudo-parkinsonian features, but usually inassociation with pyramidal and cognitive dysfunction
- *Drugs*

  Neuroleptics

  Antiemetics

  Amiodarone

  Toxins

  MPTP

  Manganese
- Chronic carbon monoxide poisoning
- *Idiopathic* Parkinson's disease
- (Other idiopathic syndromes

Parkinson's Disease and Other Movement Disorders

TABLE 372-6 Hyperkinetic Movement Disorders

Tremor	Rhythmic oscillation of a body part due to intermittent muscle contractions
Dystonia	Involuntary patterned sustained or repeated muscle contractions often associated with twisting movements and abnormal posture.
Athetosis	Slow, distal, writhing, involuntary movements with a propensity to affect the arms and hands
Chorea	Rapid, semipurposeful, graceful, dance-like nonpatterned involuntary movements involving distal or proximal muscle groups
Myoclonus	Sudden, brief (<100 ms), jerk-like, arrhythmic muscle twitches
Tic	Brief, repeated, stereotyped muscle contractions that are often suppressible. Can be simple and involve a single muscle group or complex and affect a range of motor activities

Parkinson’s Disease and Other Movement Disorders

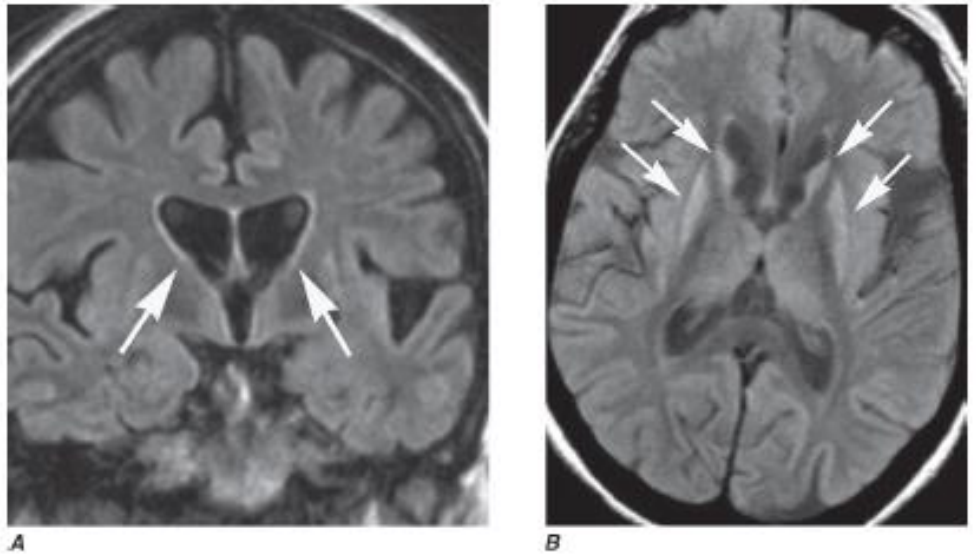
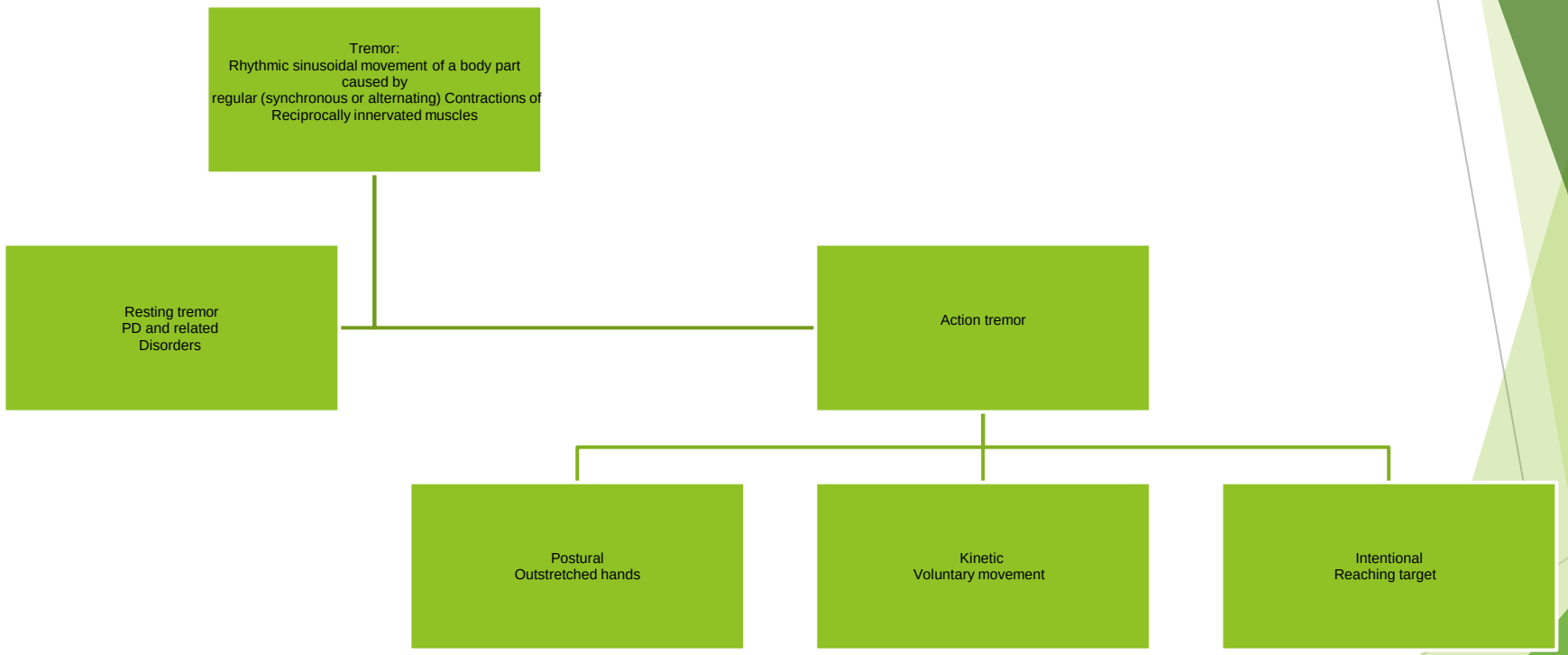


Figure 372-8 **Huntington's disease.** ***A.*** Coronal FLAIR MRI shows enlargement of the lateral ventricles reflecting typical atrophy (*arrows*). ***B.*** Axial FLAIR image demonstrates abnormal high signal in the caudate and putamen (*arrows*).

Tremor


Tremor:
Rhythmic sinusoidal movement of a body part
caused by
regular (synchronous or alternating) Contractions of
Reciprocally innervated muscles
Resting tremor
PD and related
Disorders
Action tremor
Postural
Outstretched hands
Kinetic
Voluntary movement
Intentional
Reaching target

Tremor classification

Type of tremor	Clinical features	Example
Action postural	A posture is maintained against gravity	Physiologic T, ET Drug induced T
Action Kinetic	With voluntary movement	PD, Writing T Cerebellar T, Holmes T
Action Isometric	With voluntary contraction against a rigid stationary object	Orthostatic T
Orthostatic	Tremor of lower limbs on standing and remits on walking and sitting	Orthostatic T Head trauma Neuropathic T
Dystonic T	Tremor in body parts affected by dystonia	Spasmodic torticollis
Resting T	Limb usually supported against gravity; improves with voluntary movement	PD
Psychogenic T	Acute onset, inconsistent, fatigues, decreases amplitude with distraction	Somatoform disorders Malingering , depression
Astrexis	Arrhythmic lapses of sustained posture	Toxic and metabolic encephalopathies

Other action type tremors

Type	Description
Isolated chin tremor	Familial syndrome with onset in infancy or childhood; often intermittent and stress induced
Dystonic tremor	A postural or kinetic tremor in an extremity or body part affected by dystonia; may at times be more obvious than dystonia itself
Isolated voice tremor	May be variant of ET or dystonic T accompanying dystonia of vocal cords (spasmodic dystonia)
Alcohol withdrawal tremor	Action/ postural tremor. Some may have persistent ET like tremor after recovery from withdrawal. May happen after withdrawal from other sedatives
Task specific tremor	Writing tremor is the most common, musicians , typists, sportsmen may have it
Neuropathic tremor	Irregular, asymmetric, distal with 3-12 Hz frequency. May occur at rest, with posture or movement and is associated with PN signs. May respond to beta blockers or to Rx of NP

THANK YOU