Movement Disorders (MD)

Majed Habahbeh MBBS FRCP

MD are due to dysfunction of the Extrapyramidal System (Basal Ganglia and connections)

The Basal Ganglia are “large subcortical nuclei derived from the telencephalon forming connections between the cortex and thalamus providing for the ease and quickness of human movement”

- Striatum
  - caudate
  - putamen
- Globus Pallidus
  - Externa/Interna
- Substantia Nigra

  Pars compacta/reticulata
- Subthalamic Nucleus

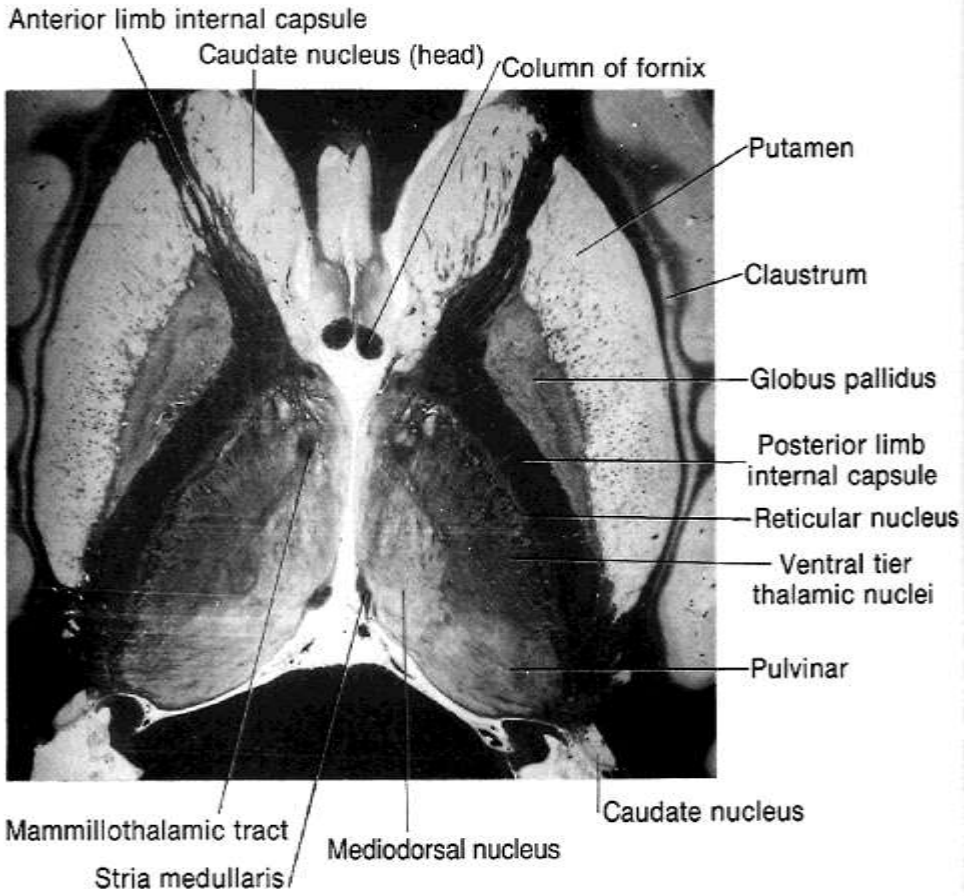
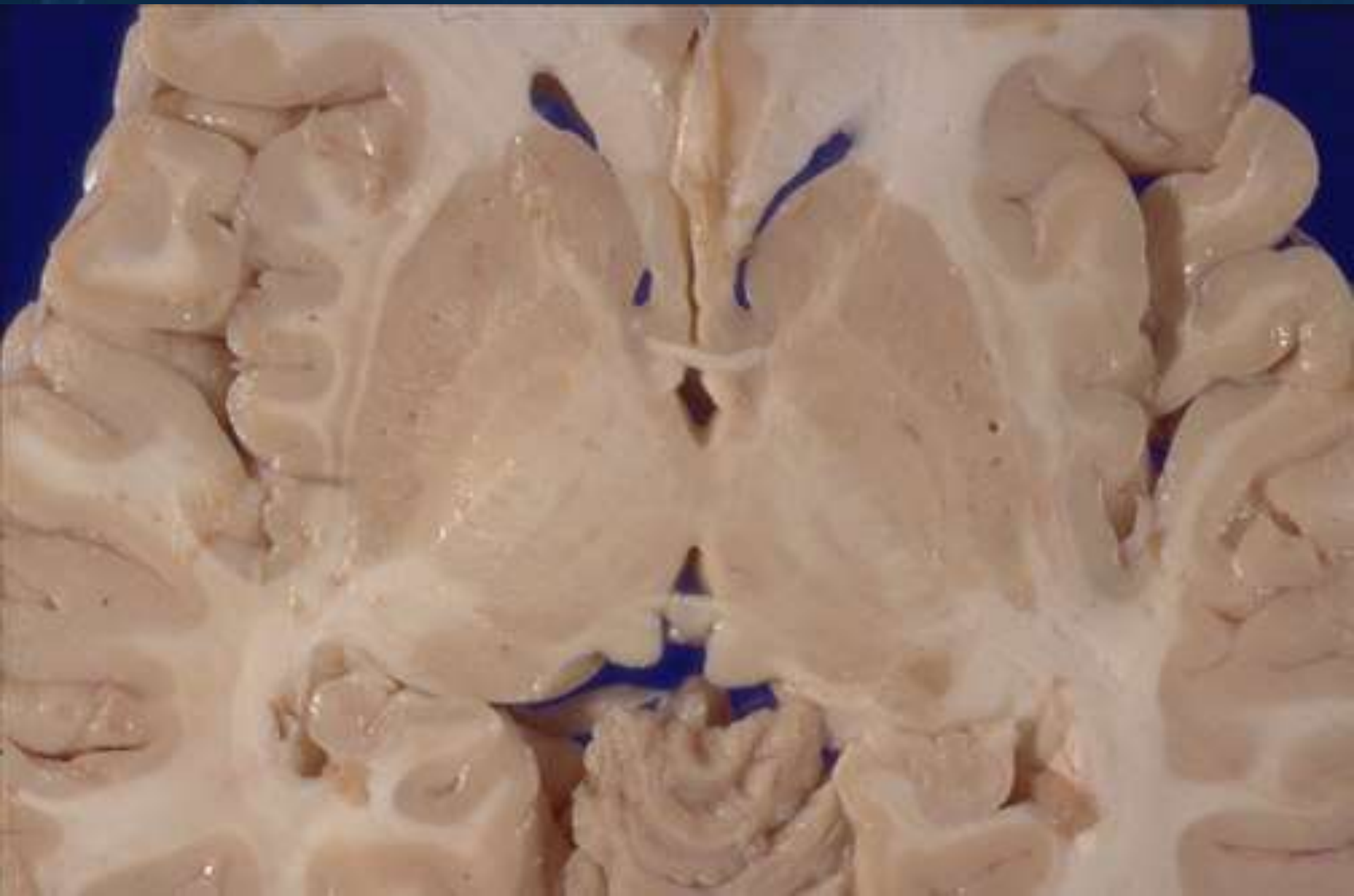


Figure 11.5. Horizontal section of the thalamus, internal capsule, and corpus striatum. Weigert's myelin stain. Photograph. (From Carpenter and Sutin, *Human Neuroanatomy*, 1983; courtesy of Williams & Wilkins.)

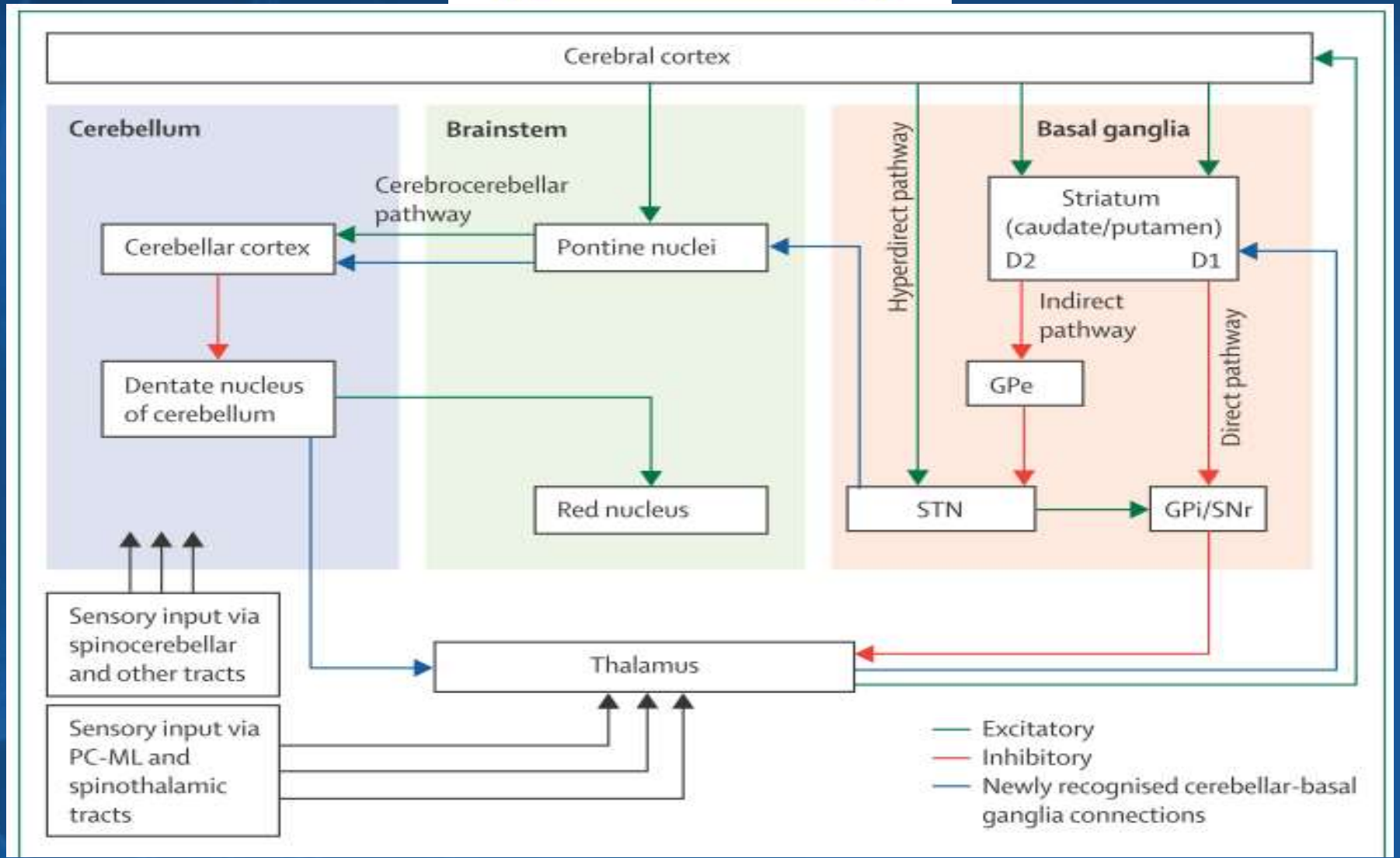
Cross section of the Brain at the level of the BG



Function of the basal ganglia

- Finesse the cortical network involved in motor performance
- Reinforce learning and memorization of behavioral routines
  - Sequences of action, nearly automatic
  - Performed without thinking
- Writing, knitting, playing a musical instrument, riding a bicycle


WARNING
THE BASAL GANGLIA ARE COMPLICATED!


Cerebral cortex
Cerebellum
Brainstem
Basal ganglia
Cerebrocerebellar pathway
Cerebellar cortex
Pontine nuclei
Hyperdirect pathway
Striatum (caudate/putamen)
D2
D1
Indirect pathway
Direct pathway
GPe
Dentate nucleus of cerebellum
Red nucleus
STN
GPi/SNr
Sensory input via spinocerebellar and other tracts
Thalamus
Sensory input via PC-ML and spinothalamic tracts
Excitatory
Inhibitory
Newly recognised cerebellar-basal ganglia connections

Phenomenological Classification of Movement Disorders

- Movement Disorders are classified broadly into two main groups:

  HYPOKINETIC DISORDERS: too little movement

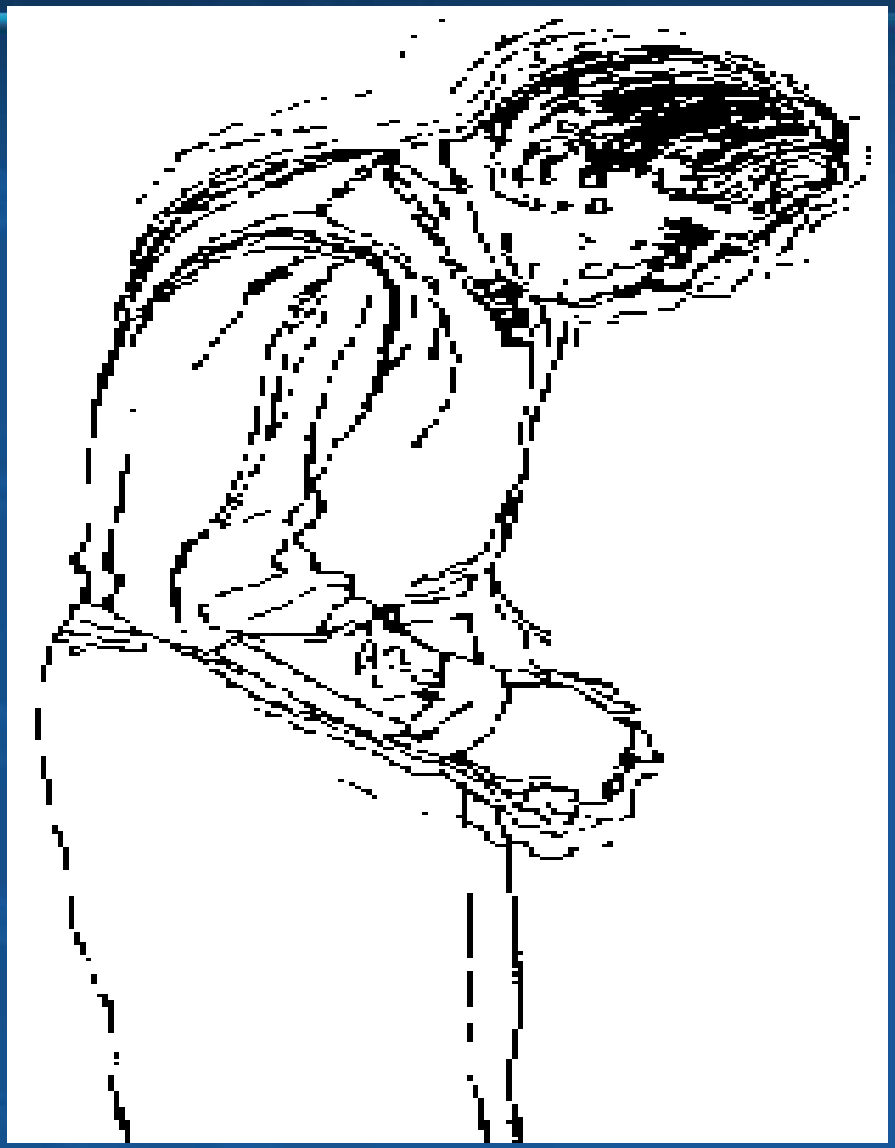
  bradykinesia (slowness of movements)

  (Parkinson's Disease and other akinetic rigid syndromes)

  HYPERKINETIC DISORDERS: too much movement

  dyskinesias- (different types of involuntary movements)

Parkinson's Disease



- **Published 1817**

AN

ESSAY

ON THE

SHAKING PALSY.

JAMES PARKINSON,

LONDON:

FOR SHERWOOD, NEELY, AND JONES,

AN

ESSAY

ON THE

SHAKING PALSY.

CHAPTER I.

DEFINITION–HISTORY–ILLUSTRATIVE CASES.

SHAKING PALSY. *(Paralysis Agitans.)*

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.

Parkinson's Disease

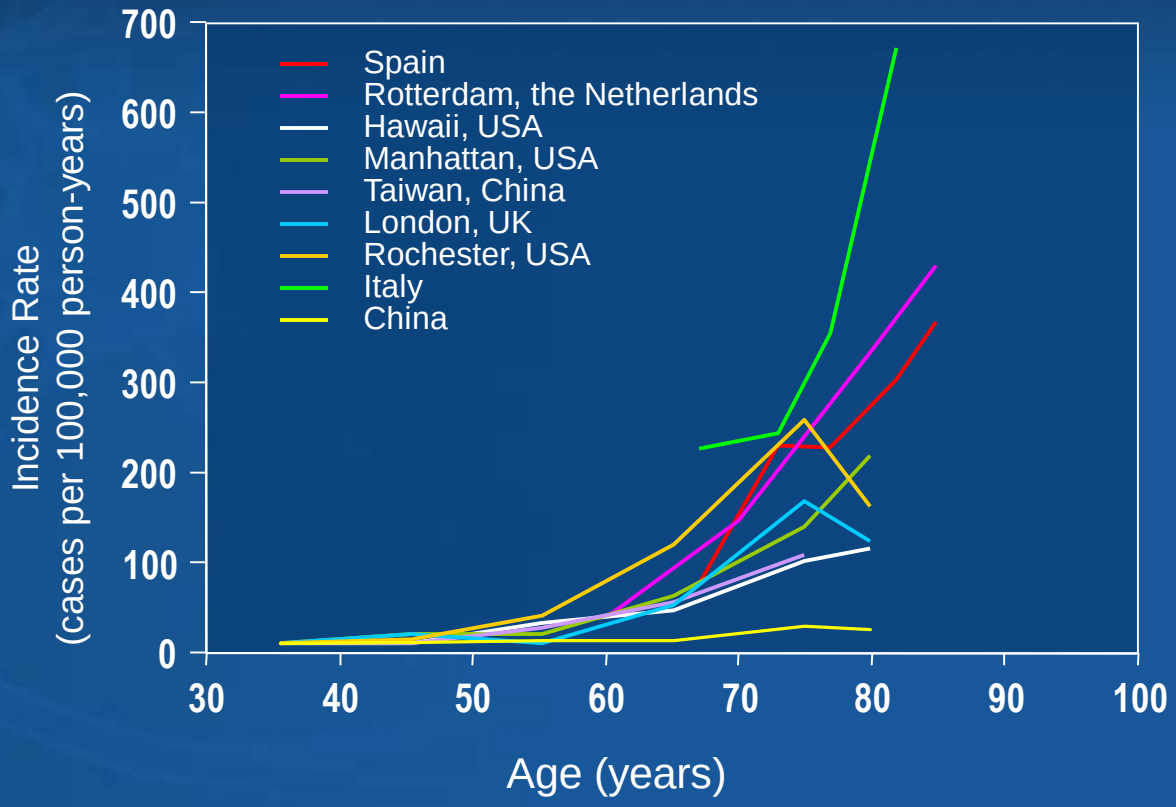
- **Parkinson's disease is the second most common neurodegenerative disease after AD.**

- A clinical and neuropathological entity characterised by:
  - Bradykinesia
  - Rigidity
  - Tremor

- **Parkinsonism:**
  - Any bradykinetic-rigid syndrome that is not Parkinson's disease

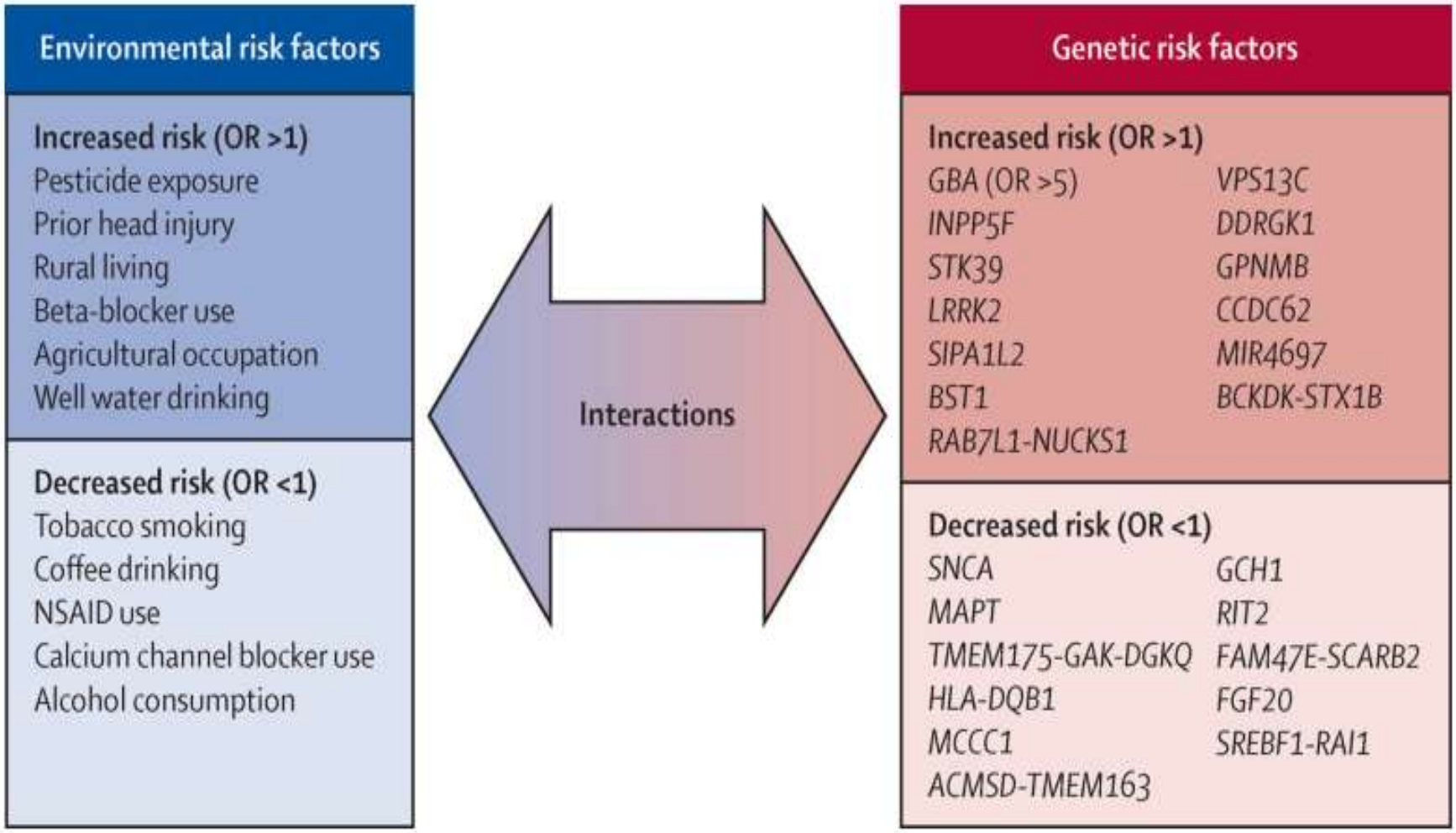
Epidemiology of Parkinson's Disease – Incidence

- **Idiopathic Parkinson's disease is uncommon before the age of 50**
- **There is a sharp increase in incidence after the age of 60**

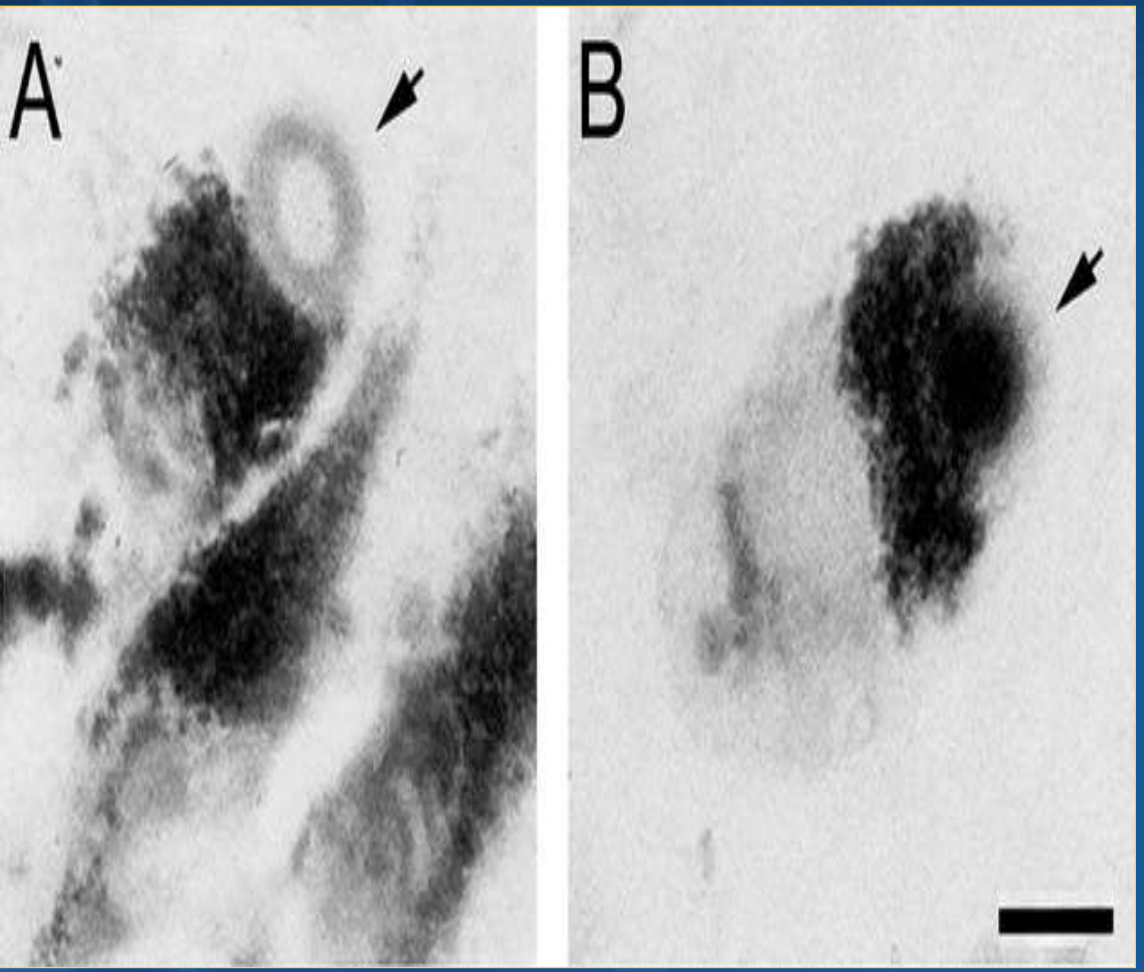


Prospective population-based incidence studies of Parkinson's disease

Risk Factors for PD



Parkinson's Disease Pathology
Lewy bodies

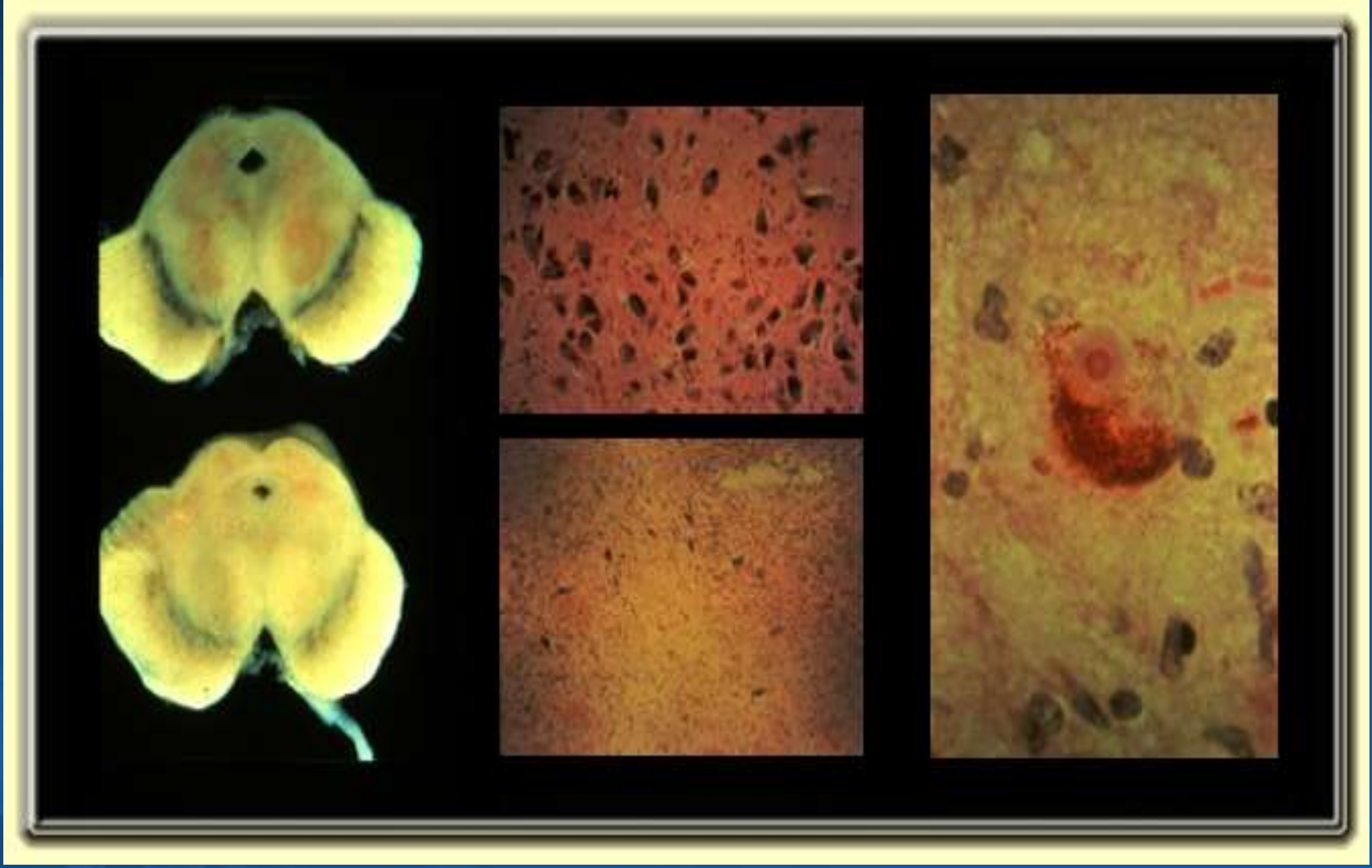


- Neuronal loss and gliosis in the substantia nigra and other brain regions.
- Lewy bodies, 5-25 μm eosinophilic intracytoplasmic inclusions with a dense core and more transparent halo, and Lewy neurites are typically present. Lewy bodies stain for both α-synuclein and ubiquitin

α-synuclein

Ubiquitin

Pathology of Parkinson's Disease

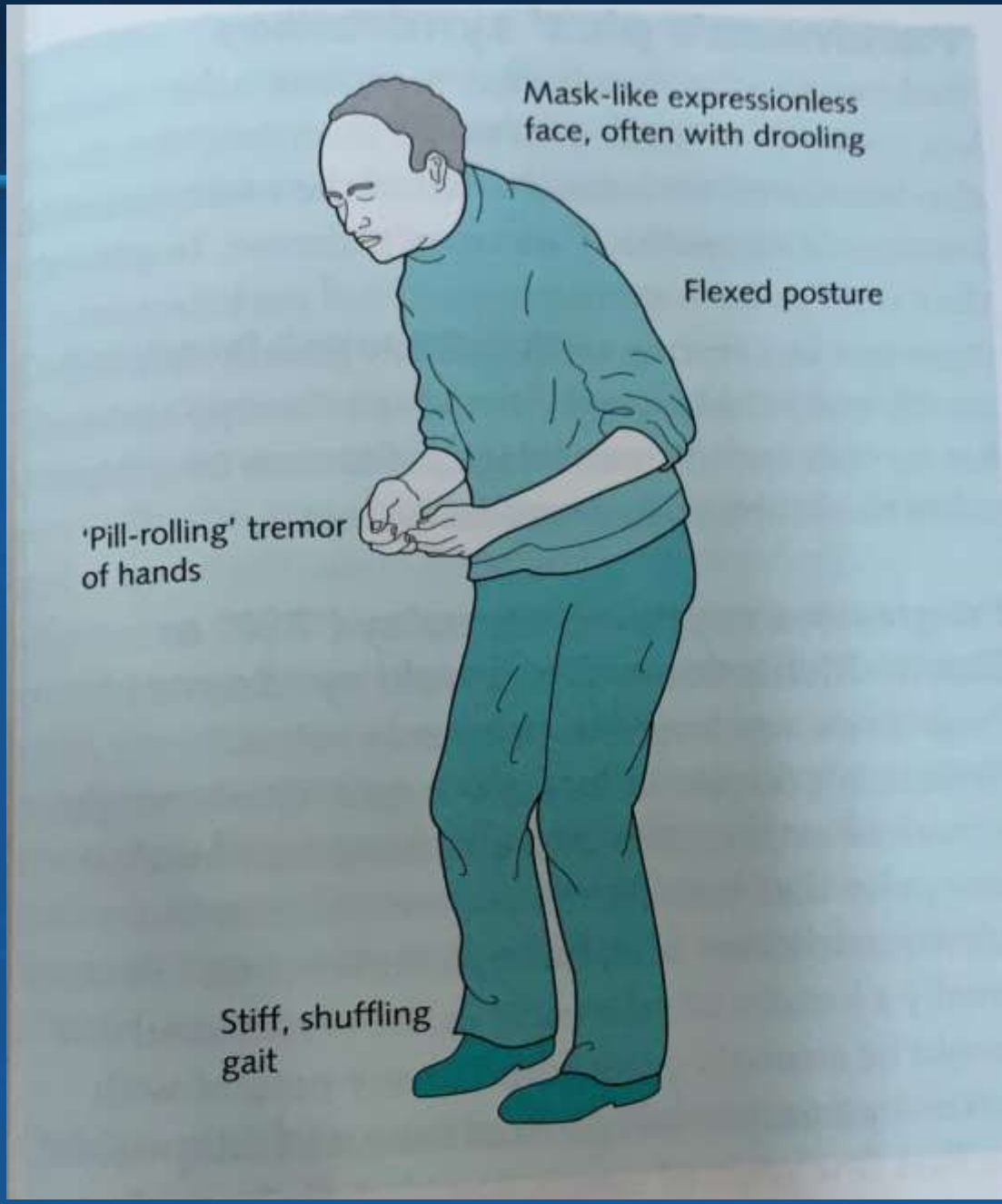


Main Biochemical Abnormality

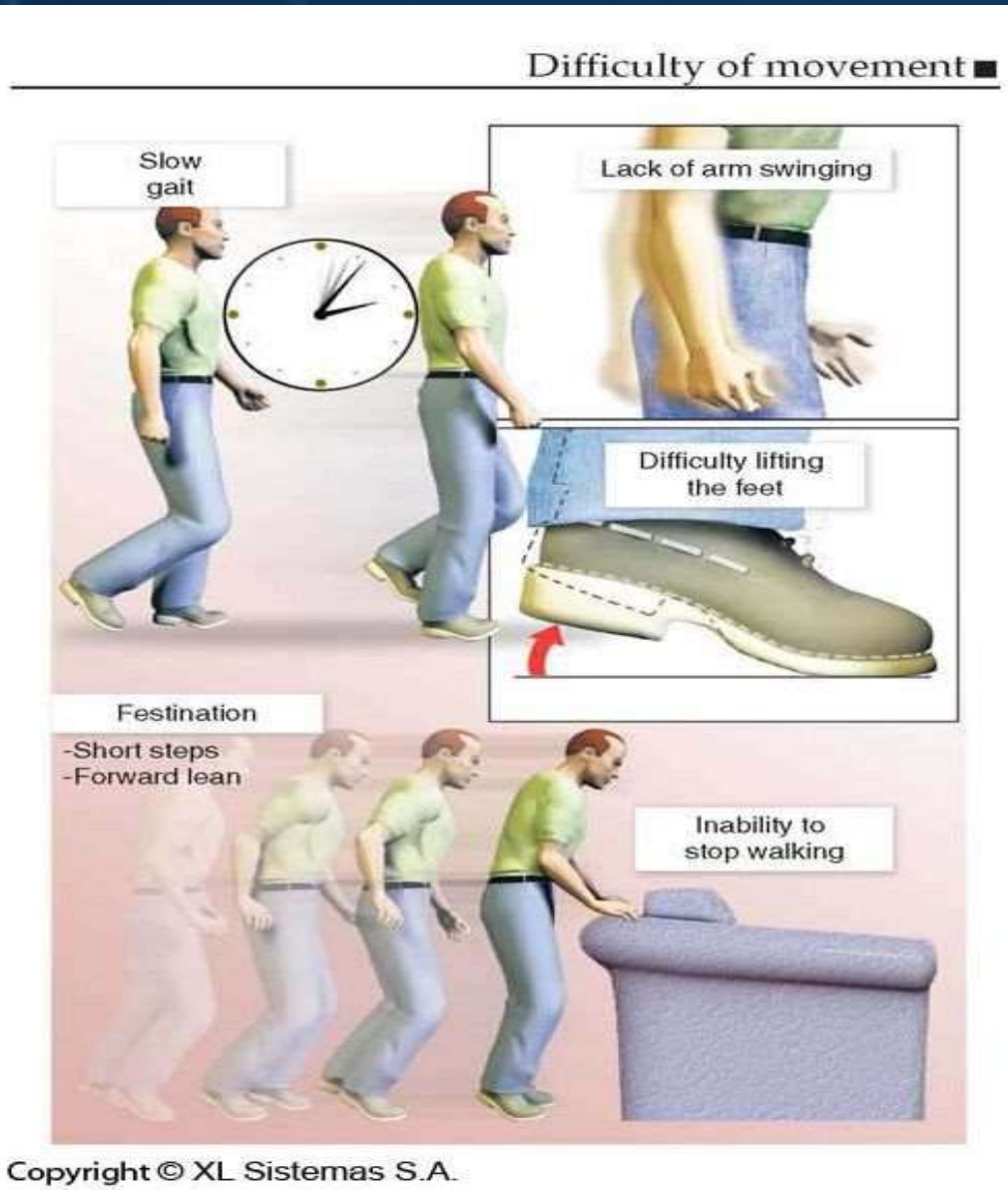
- Marked striatal Dopamine (DA) depletion
- <50% DA loss is asymptomatic
- ~70% DA loss for symptom manifestations
- At death, DA loss > 90%

Diagnosis / differential diagnosis

- Tremor
- Rigidity
- Akinesia
- Postural Instability



Bradykinesia



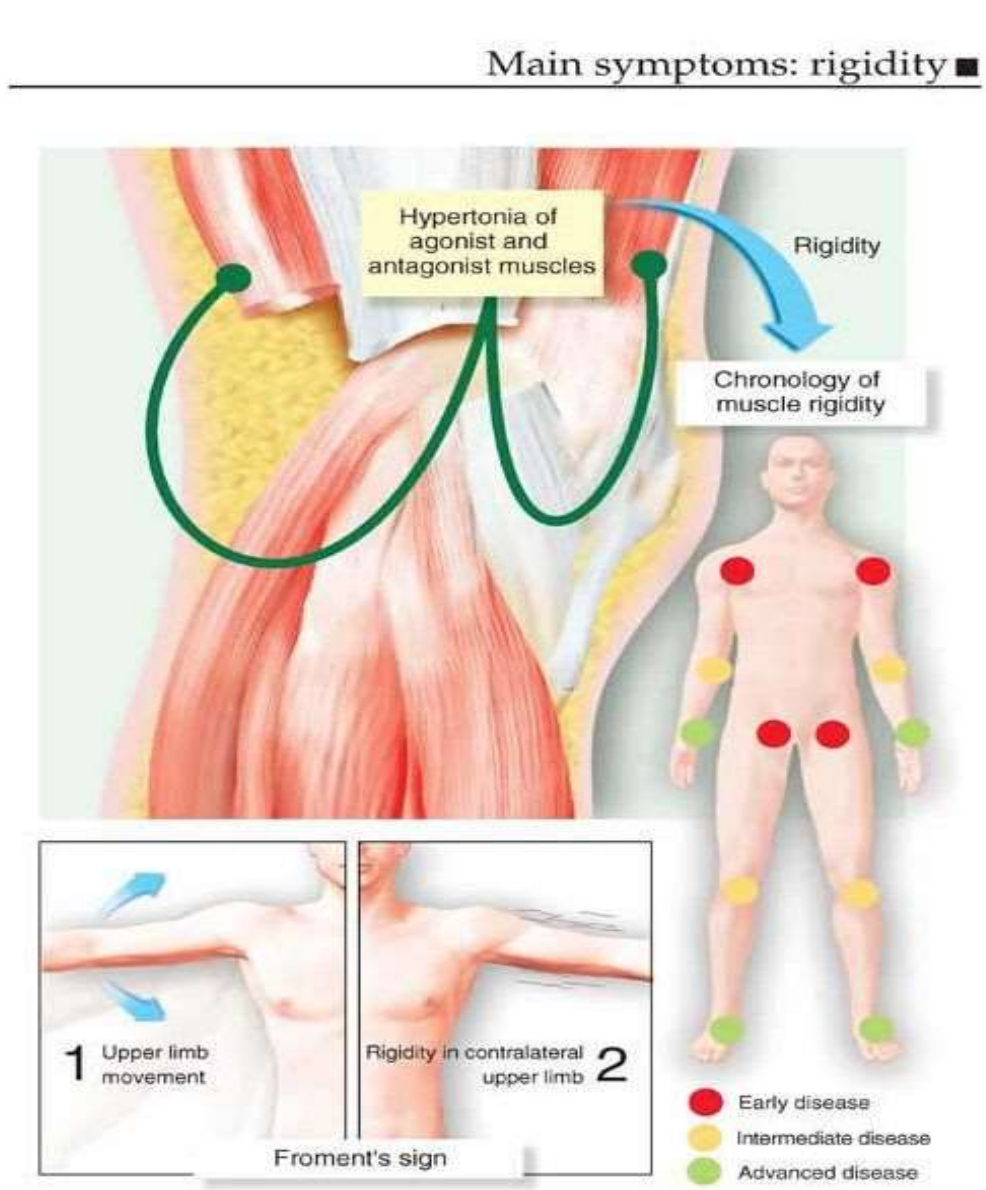
Bradykinesia includes such motor phenomena as delayed initiation, slow performance, low amplitude and intermittent arrests of voluntary movement.

Tremor

The tremor of parkinsonism is seen at rest- frequency is typically 4-6 Hz.

Postural tremor is commonly seen, but is much less specific for the syndrome.

Rigidity



Rigidity describes increased resistance to passive range of motion in the limbs. Rigidity is present in both flexor and extensor muscles.

Rigidity, unlike spasticity, is not velocity dependent.

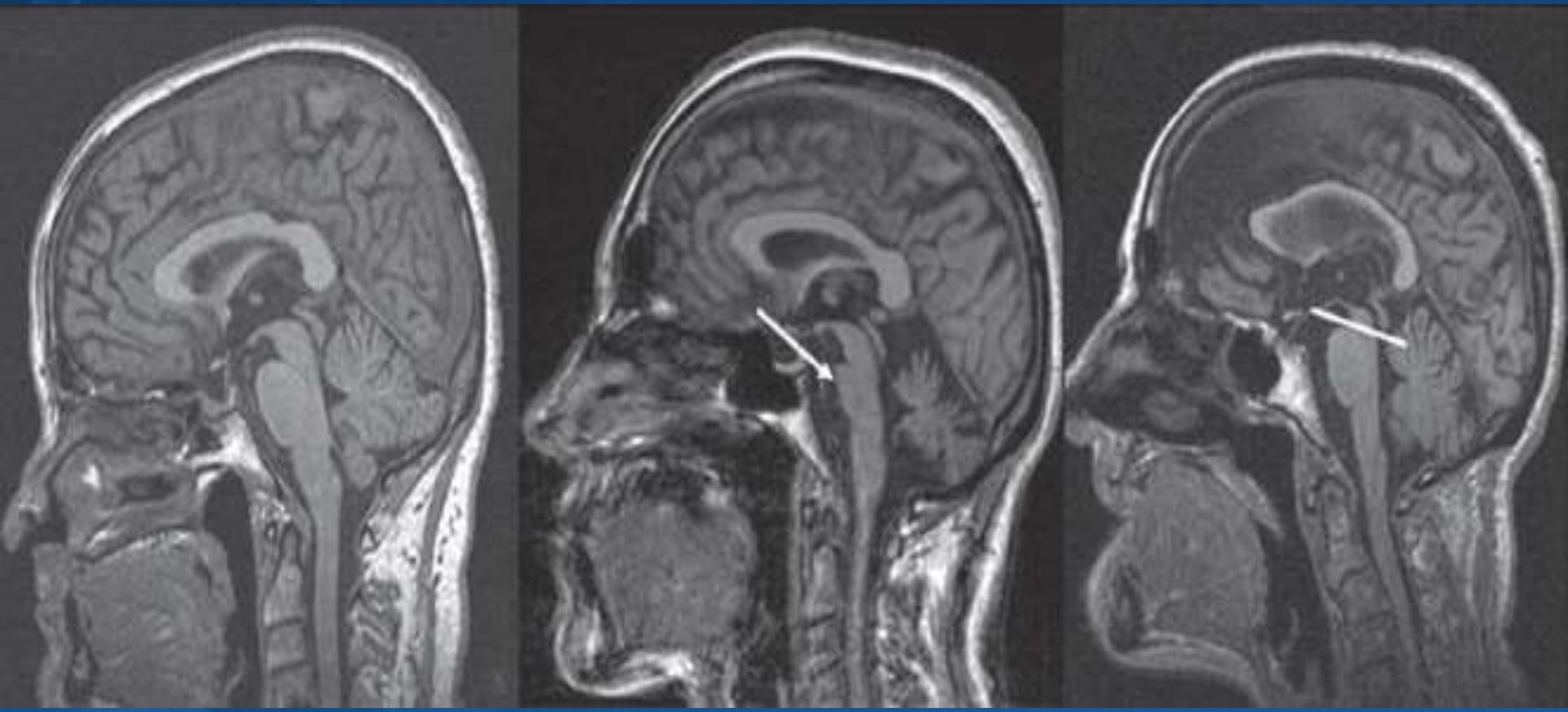
Classification of Parkinsonian Syndromes

- Primary (Degenerative)
- Secondary

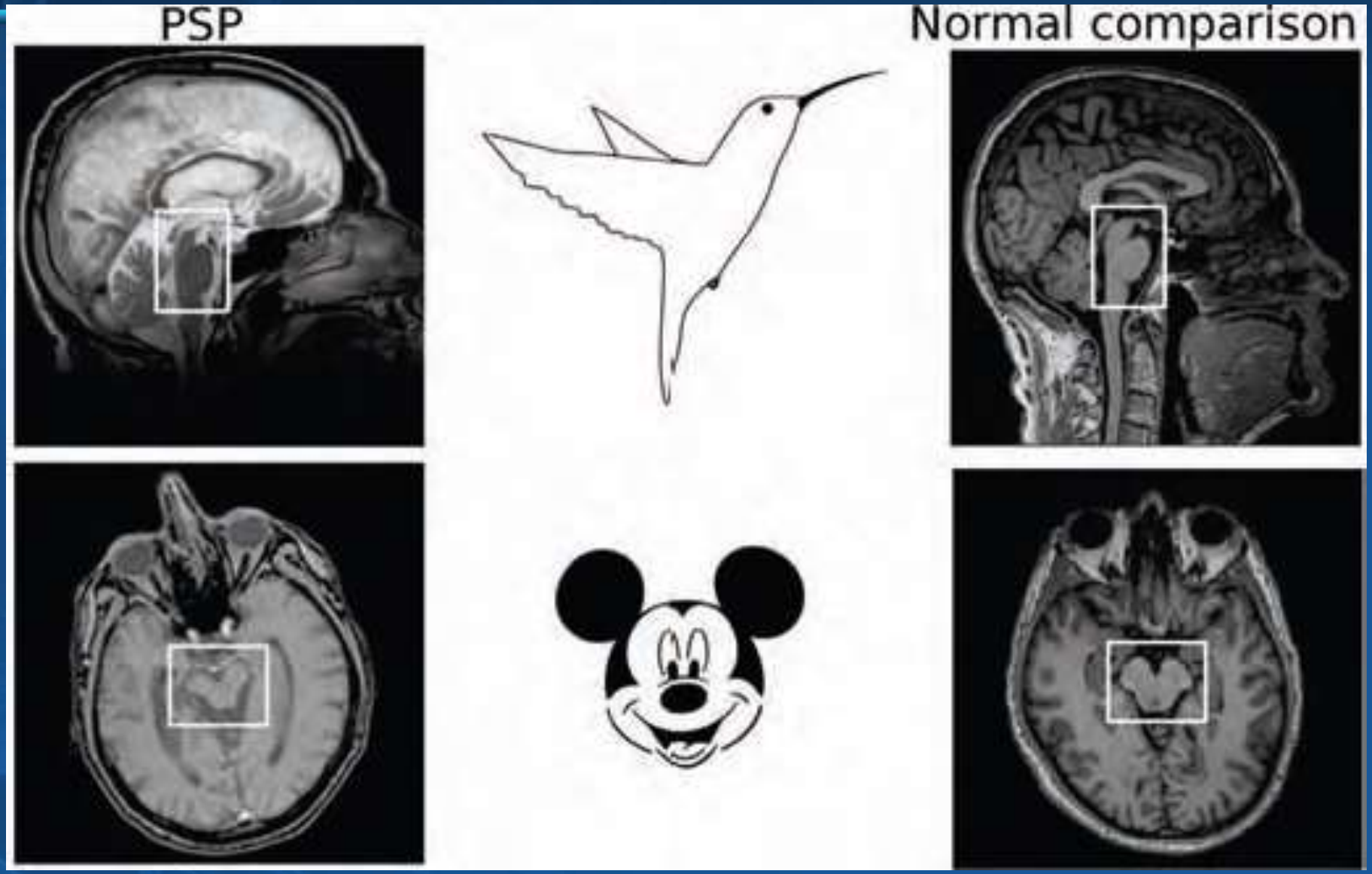
Degenerative PS

- Parkinson's disease
  - Sporadic
  - Hereditary forms
- Multiple system atrophy (MSA)
- Dementia with Lewy Bodies.
- Progressive supranuclear palsy (PSP)
- Corticobasal degeneration

PD MSA PSP



“Humming Bird” and “Mickey Mouse Ears” MRI signs in PSP



Degenerative PS

- Huntington's disease
  - Juvenile presentation (Westphal variant)
  - Later in disease course.
- **Wilson disease**
- Acquired hepatolenticular degeneration
- Parkinsonism Dementia Complex of Guam
- PKAN (Hallervorden-Spatz disease)- “Eye of the Tiger” sign on MRI
- Basal Ganglia calcification : Fahr’s Disease.
- Chorea-acanthocytosis

Secondary Parkinsonism

- Post-encephalitic
- Post-traumatic
- Vascular/SDH
- Metabolic: Wilson's disease, Hypo/hyper-parathyroidism
- Hydrocephalus and Space-occupying lesion
- Toxic
  - Manganese
  - MPTP
  - Carbon monoxide
  - Cyanide
- **Drug-induced**
  - DA-receptor blockers
    - Antipsychotics
    - Anti-emetics
    - Ca-channel blockers
  - Anticonvulsants
    - Phenytoin
    - Valproic acid
  - Antiarrhythmics
    - Amiodarone
  - Others
    - Lithium

Mendelian Parkinson's Loci: one process or more?

LOCUS1	Inheritance	Onset	Protein	Path
PARK-1/4	AD	~45	Alpha-synuclein	LB
PARK-2	AR	7-60	Parkin	None
PARK-6	AR	36-60	PINK-1	one case with LB
PARK-7	AR	27-40	DJ-1	Nigral degeneration, diffuse LBs spheroids
PARK-8	AD	45-57	LRRK2	Usually LB, variable tau deposition
PARK-9 (Kufor-Rakeb sy.)	AR	Teens	ATP13A2	Absent LBs; neuronal & glial lipofuscinosis
PARK-14	AR	Teens	PLA2G6	LB, also spheroids brain iron Xs
PARK-15	AR	Teens	FBXO7	?
PARK-17	AD	50-70	VPS35	?
PARK-18				

	AR	Teens	PLA2G6	LB, also spheroids brain iron Xs
	AR	Teens	FBXO7	?
	AD	50-70	VPS35	?
PARK-18	AR	Late onset	EIF4G1	LBs
PARK-19	AR	Juvenile onset	DNAJC6	?
PARK-20	AR	Early onset	SYNJ1	?
PARK-21	AD	Late onset PD/PSP	DNAJC13	Brain stem or transitional LB. tauopathy
PARK-22 ?	AD	Late onset (Japanese)	CHCHD2	?
PARK-23	AR	Early onset, rapid	VPS13C	LB present

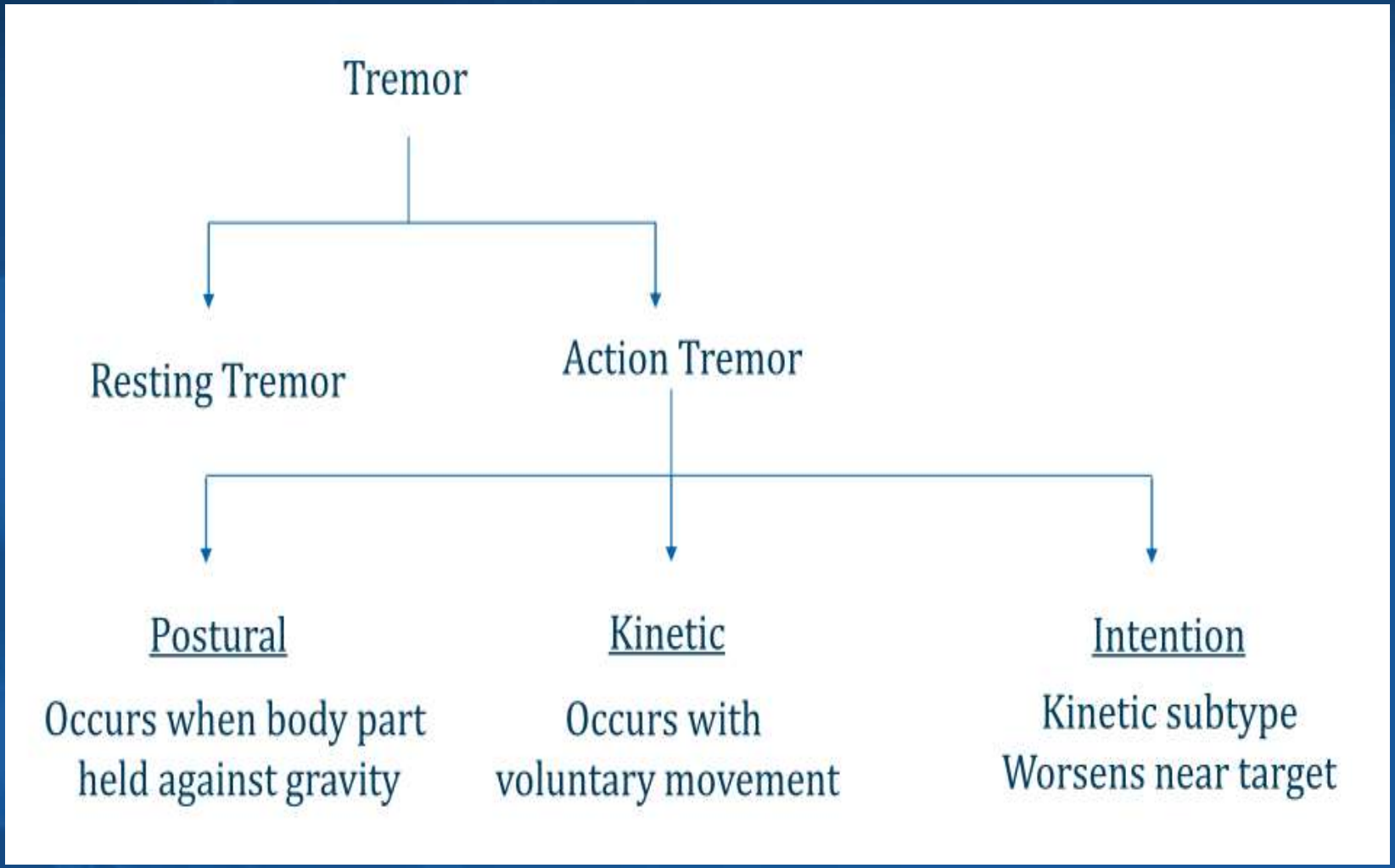
Classification of Parkinsonian Syndromes in a Community

- Idiopathic PD ~ 85% of all PS cases
- Drug-induced parkinsonism (DIP) 7% - 9%
- MSA ~ 2.5%
- PSP and CBD ~ 1.5%
- Vascular Parkinsonism ~ 3%
- PS due to MPTP, CO, Mn, recurrent head trauma is rare
- No definite new cases of encephalitic lethargica since l960s

Conditions Mimicking Parkinsonism

- Essential Tremor.
- Normal pressure Hydrocephalus.
- Cerebrovascular Disease.
- Elderly patients with slowness and tremor.

Tremor


Tremor
Resting Tremor
Action Tremor
Postural
Occurs when body part held against gravity
Kinetic
Occurs with voluntary movement
Intention
Kinetic subtype
Worsens near target

Tremor

- **Definition**: Rhythmic oscillation of a body part.
- Tremors can be classified as:
  - *Rest*: occurs when affected body part is at rest
  - *Postural*: occurs when arms are outstretched
  - *Kinetic*: occurs during movement of body part.

Tremor

Resting tremor:

- Parkinson's disease and other parkinsonian disorders, dystonic tremor, one component of rubral tremor, severe ET,

Postural:

- Essential tremor, Physiological
- PD, Dystonic tremor etc

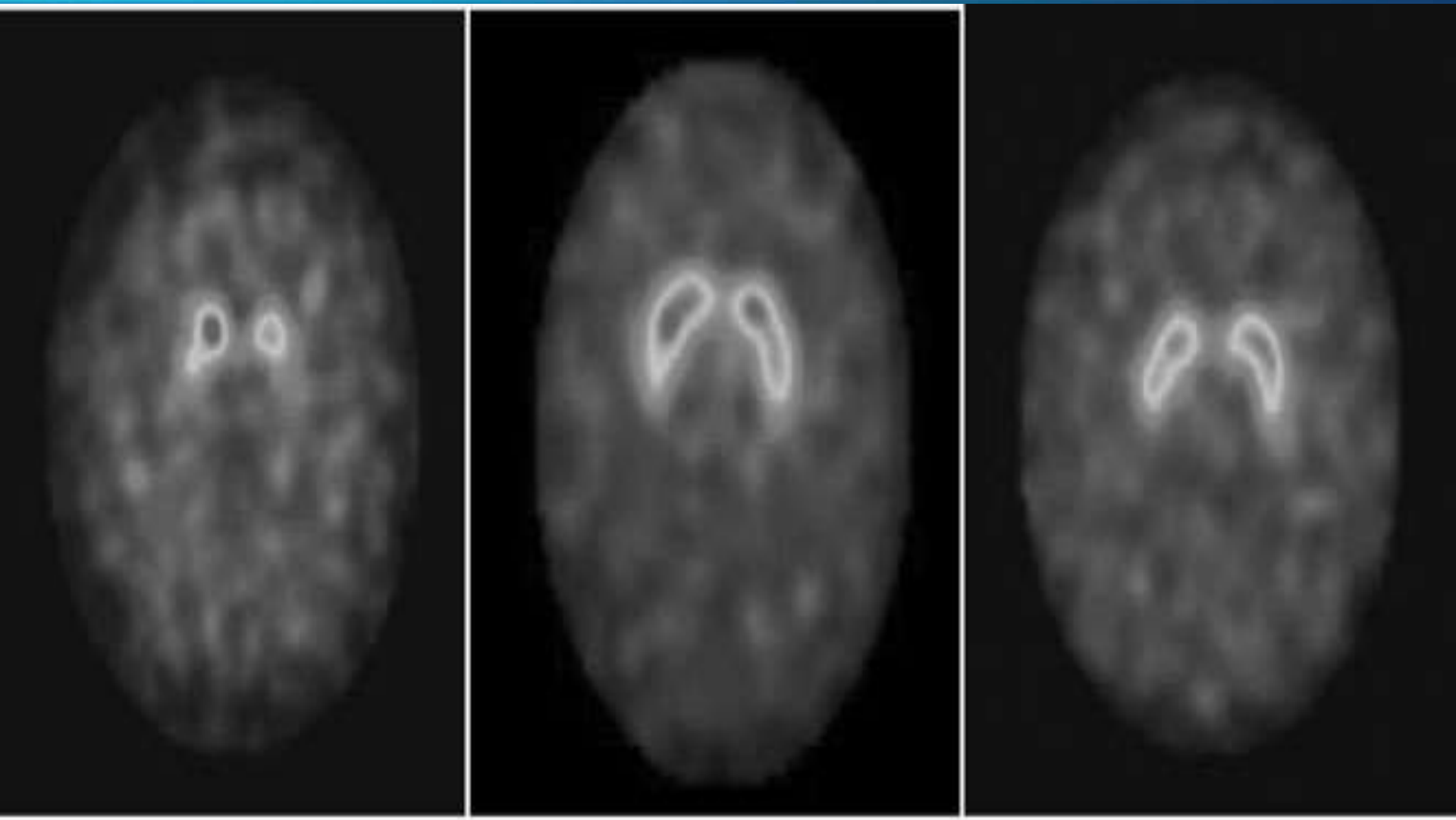
Kinetic:

- Cerebellar disorders

Essential Tremor

- Essential tremor is an action tremor characterised by rhythmic shaking of the arms in almost every case; it may also involve tremor of the head, tongue, lower limbs, voice and face.
- Essential tremor is commonly autosomal dominant, so a family history is important.
- Enhanced physiological tremor is commonly misdiagnosed as essential tremor.
- First-line agents for the treatment of essential tremor include propranolol and primidone. DBS (Vim nucleus of thalamus) for severe cases

B-CIT SPECT Imaging



PD | Essential tremor | Healthy subject

Non-Motor Symptoms of Parkinson's Disease

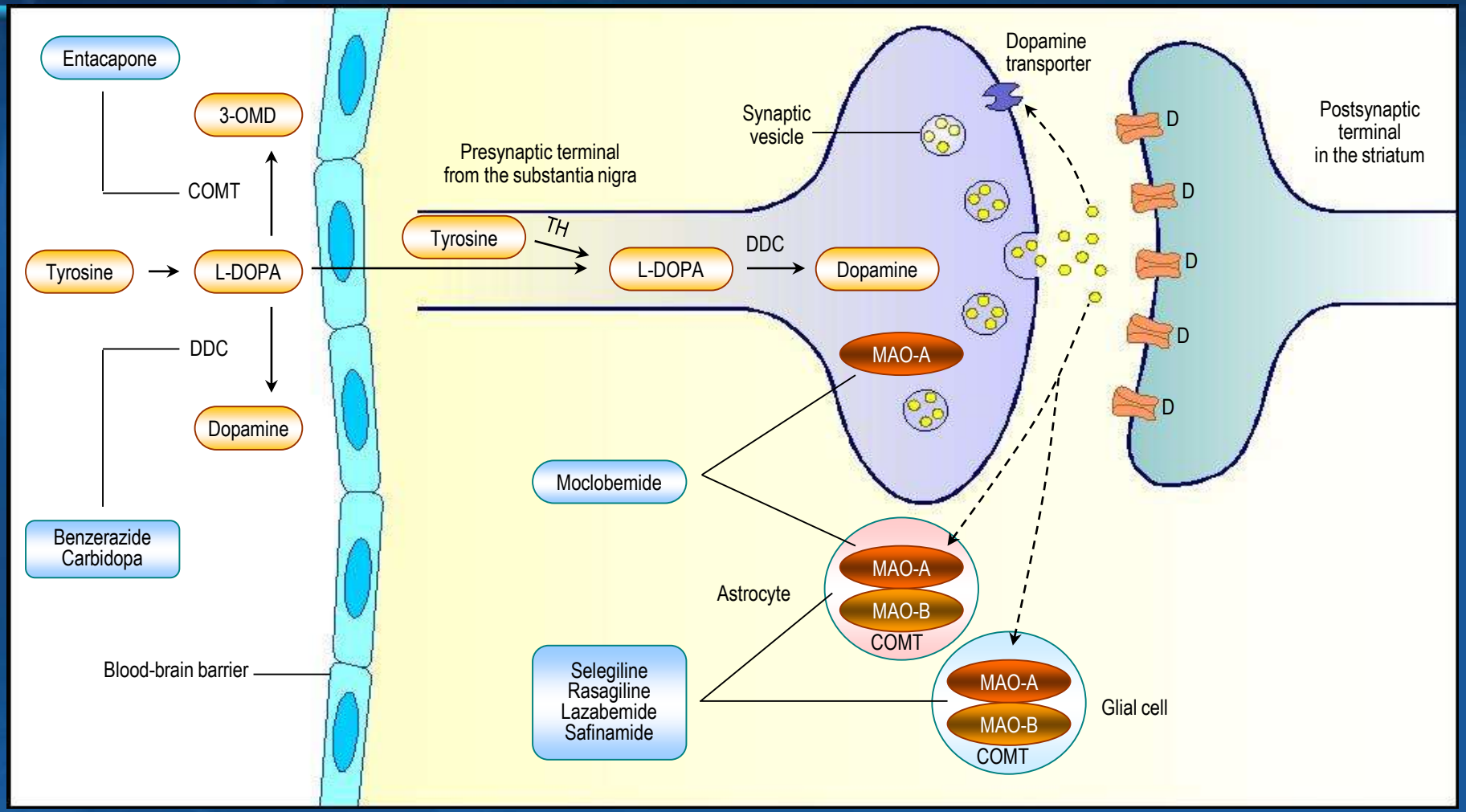
Neuropsychiatric symptoms
Depression, apathy, anxiety
Anhedonia
Hallucinations, illusions, delusions

Sleep disorders
Restless legs and periodic limb movements
Rapid eye movement (REM) sleep behaviour disorder
Insomnia

Autonomic symptoms
Constipation
Bladder disturbances
Orthostatic hypotension
Falls related to orthostatic hypotension
Impotence

Drug Therapy in PD

The Basis for Symptomatic Drug Therapy of Motor Symptoms in Parkinson's Disease



Abbreviations: DDC, dopa decarboxylase; TH, tyrosine hydroxylase; L-DOPA, levodopa; MAO-A, monoamine oxidase A; MAO-B, monoamine oxidase B; COMT, catechol-O-methyltransferase; D, dopamine receptors; 3-OMD, 3-O-methyldopa

Drug Therapy – Symptomatic Treatment of Motor Symptoms-Dopaminergic agents

- Levodopa
  - Levodopa + carbidopa
  - Levodopa + benserazide
  - COMT inhibitors (entacapone, tolcapone)
- Selective MAO-B inhibitors
  - Selegiline
  - Rasagiline
  - Safinamide
- Dopamine agonists
  - Non-ergot
    - Pramipexole
    - Ropinirole
    - Rotigotine
    - Piribedil
  - Ergot
    - Bromocriptine
    - Pergolide
    - Cabergoline
    - Dihydroergocryptine
    - Lisuride

Non-dopaminergic agents

- Anticholinergic agents:
  - Trihexyphenidyl
  - Benztropine
- NMDA antagonists
  - Amantadine

Main Mechanisms of Action of Therapeutic Interventions in Parkinson's Disease

	Action			
Drugs	**Promote dopamine synthesis**	**Activate specific receptors**	**Prolong dopamine availability**	**Prolong levodopa bioavailability**
Dopaminergic	Levodopa	DAs	MAO-B inhibitors	COMT inhibitors
Antiglutamatergic	Amantadine			
Anticholinergic		Trihexyphenidyl Benztropine		
Surgery	**Lesion** Thalamotomy Pallidotomy Subthalamic nucleotomy	**DBS** Thalamus Pallidum Subthalamic nucleus	**Transplantation** Foetal mesencephalic cells	
Rehabilitation procedures	Physical therapy Occupational therapy Speech therapy			

Levodopa in the Management of Parkinson's Disease

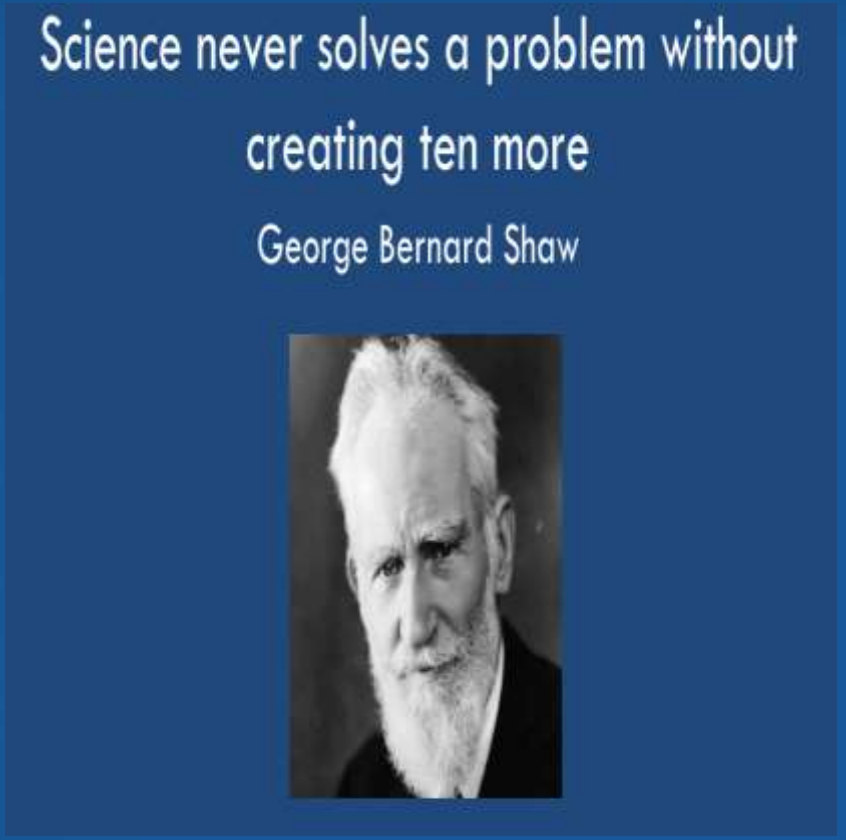
- First of the dopaminergic drugs
  - Used since late 1960s
- Highly effective drug
  - Relatively rapid relief of bradykinesia, rigidity and associated pain
  - Reduces tremor in many patients

Levodopa improves quality of life and life expectancy in patients with PD

Levodopa induces motor complications

- Up to 80% of PD patients suffer from motor fluctuations and dyskinesias after approximately 5 to 10 years of treatment with levodopa

- 70% of young-onset PD patients develop motor complications after 3 years



Definition of motor complications

- **Motor complications**: The dyskinesias and motor fluctuations which occur during the long term management of patients with Parkinson's disease
- **Motor fluctuations**:

  (1) Predictable wearing *OFF*

  (2) unpredictable ON–OFF fluctuations

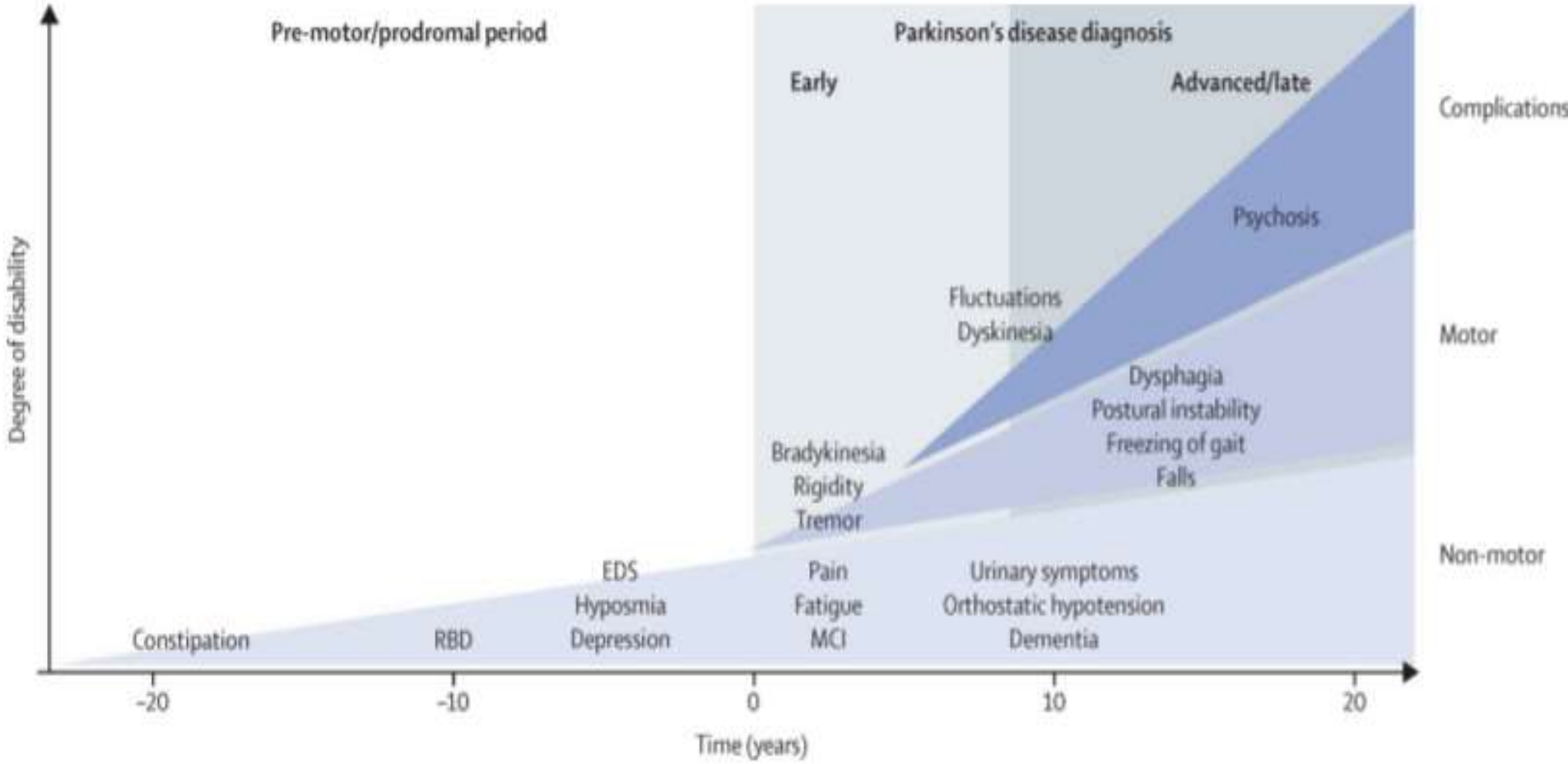
  (3) sudden OFF periods
- **Dyskinesias:**

  (1) Peak dose dyskinesias

  (2) diphasic dyskinesias

  (3) OFF period dystonia

Clinical symptoms & time course of PD progression



Phenomenological Classification of Movement Disorders

- Movement Disorders are classified broadly into two main groups:

  HYPOKINETIC DISORDERS: too little movement

  bradykinesia (slowness of movements)

  (Parkinson's Disease and other akinetic rigid syndromes)

  HYPERKINETIC DISORDERS: too much movement

  dyskinesias- (different types of involuntary movements)

Hyperkinetic Disorders

- Five main types:
  - Tremor
  - Tics
  - Chorea
  - Myoclonus
  - Dystonia

Decide which group does the patient best fit

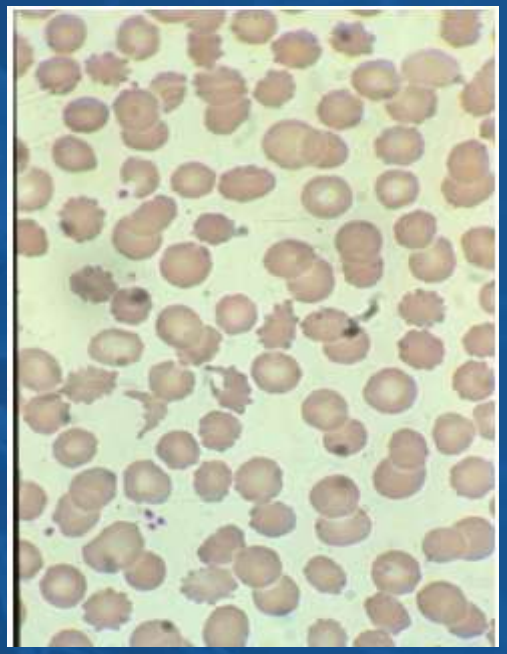
Chorea

- Chorea is characterized by brief, nonstereotyped, rapid movements that travel randomly among body parts often giving the patient a ‘‘fidgety’’ appearance.

- When it travels in a flowing manner between body parts, as opposed to jumping, it is referred to as choreoathetosis.
- In its extreme form, with large amplitude, proximal, flinging movement, it is called ballismus.

Chorea

Definition: Irregular, brief, purposeless movements that flit from one body part to another



Many causes: Acquired and inherited

-Drugs/ Oral contraceptives

- Basal ganglia lesions

- Sydenham's chorea

-Antiphospholipid antibody syndrome

-Huntington's disease/ HD like diseases

-Neuroacanthocytosis

Huntington's Disease

- An AD trinucleotide (CAG) repeat expansion disorder with the cardinal manifestations of chorea, psychiatric disease and cognitive decline.
- Chorea involves limbs ,head and face
- Motor impersistence (of grip, tongue protrusion or gaze fixation) is a classic feature
- Caudate atrophy on MRI

Tics

- Brief, repetitive and stereotyped movements or vocalisations.
- Tics are usually suppressible for a short period of time, but at the expense of mounting inner tension.
- Very common: 3-4% of the population are affected at some time in their lives, almost always starting in childhood.

Motor:
- eye blinking
- head jerks
- arm/leg jerks
-complex sequence

Vocal:
- sniffing
- grunting
- snorting

Gilles de la Tourette Syndrome

- Typically, onset of persistent multiple motor and vocal tics, often with associated psychiatric disturbance [Attention deficit hyperactivity syndrome (ADHD); Obsessive compulsive disorder (OCD); copropraxia; coprolalia]

Myoclonus

- Myoclonus refers to brief, shock-like muscle jerks.
- The major categories of myoclonus include physiologic, epileptic, essential, and symptomatic
- Myoclonus can also be classified anatomically as cortical, subcortical, brainstem, spinal , or peripheral.

Dystonia

- Involuntary muscle spasms leading to abnormal posturing of limbs and writhing movements (athetosis).
- P*rimary dystonia*: without any structural damage often inherited
- *Secondary dystonia*: Due to variety of environmental or heredodegenerative causes with structural damage to the CNS
- *Paroxysmal dystonia*: brief episodes of dystonia/dyskinesia

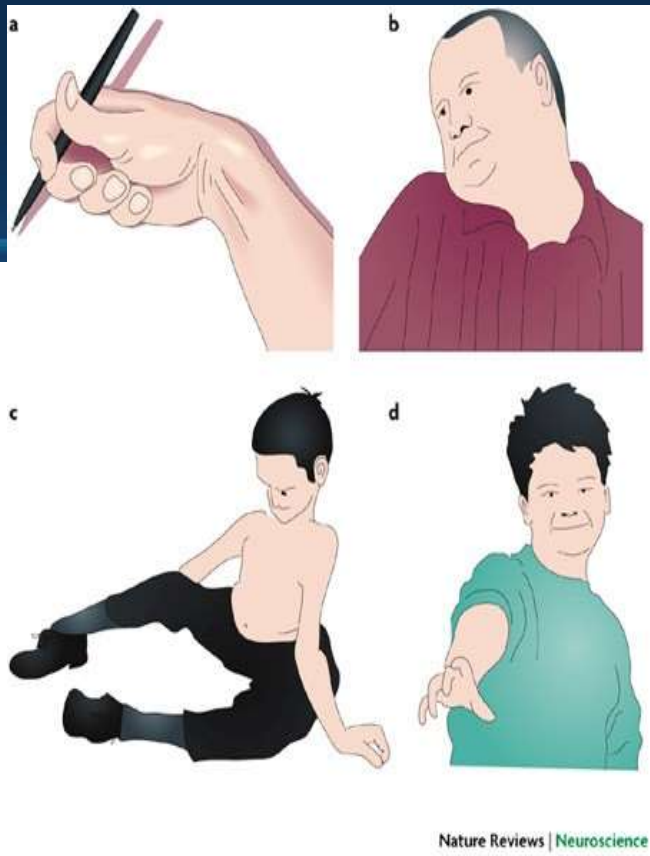
Primary dystonia:

Two main phenotypes depending on age of onset

Young onset: (below 28 yrs)
lower limb onset,
spreads,
tends to generalise;
cranial-cervical
less affected/spared
often familial: DYT1 gene +ve

Prevalence: 3/100,000

Adult onset:
affects upper body;
focal or segmental;
cranio-cervical most common
(F>M)
mostly sporadic
Non-DYT-1
Prevalence: 8, 33, 58*, and even 732**/ 100,000



Three features unique to dystonia

- **Task-specificity:** selective activation of involuntary movements by specific tasks (e.g. writing, using a computer mouse, playing a musical instrument).
- **Geste antagoniste:** a sensory trick that improves the dystonic phenotype while it is applied (touching the chin, touching the eyes, holding an object between the teeth).
- **State function:** variation in severity of dystonia with specific actions (walking backwards but not forwards, speaking but not eating).

Geste Antagoniste/sensory trick

Treatment of dystonia

- All children with dystonia should receive a trial of levodopa, in order not to miss the diagnosis of dopa-responsive dystonia.
- "ABCs" of dystonia Rx : Anti-cholinergics (trihexiphenidyl), baclofen, clonazepam
- Other useful drugs-diazepam,L-Dopa,Amantadine,AED,DA
- Add one drug at a time, titrate to efficacy or until side effects develop.
- Polypharmacy is the rule rather than the exception.
- Tardive dystonia responds particularly well to tetrabenazine.
- Botox and surgery

Treatment of the underlying disease !

What is this sign/disease

Kayser-Fleischer Rings of Wilson Disease

The two most important causes of dystonia to consider in every young person are

- Wilson’s disease
- Dopa-responsive dystonia (DRD)

Wilson's disease

- Wilson's disease is a monogenic, autosomal recessive condition. The causative gene, ATP7B, encodes a copper-transporting P-type ATPase

- Cu deposition in many organs

Progressive Lenticular Degeneration: A Familial Nervous Disease Associated with Cirrhosis of the Liver - 1912

Samuel Alexander Kinnier Wilson
1878 – 1937

- Born in Cedarville, NJ, moved to Edinburgh at one year of age after the death of his father
- Graduated with MB from University of Edinburgh in 1902
- Trained in Paris with Pierre Marie and Joseph Babinski
- Returned to King's College in London
- MD in 1912: "Progressive lenticular degeneration" and introduced the word "extrapyramidal"

Wilson's original description

There is a most unusual thing
Known as the Kayser Fleischer ring.
In fact, it is so very rare
Few doctors know when it is there.
So, whether brown or whether green
It's very, very seldom seen.
Had it been red, or even pink,
Why then I really dare to think
That most physicians would perchance
See it with a perfunctory glance.
So, let us deem it right and proper
To seek this little ring of copper.

The Lancet, 1969, II, 740

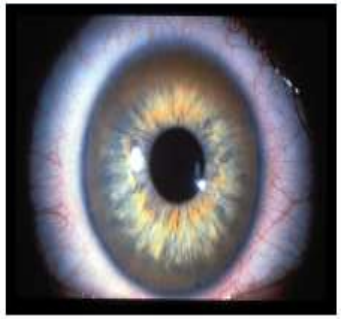


FIG. 1. Patient with hepatolenticular degeneration described by S. A. K. Wilson in 1912[10] (from *Brain*, vol. 34, page 327, with the courtesy of the Editor).

Wilson's disease

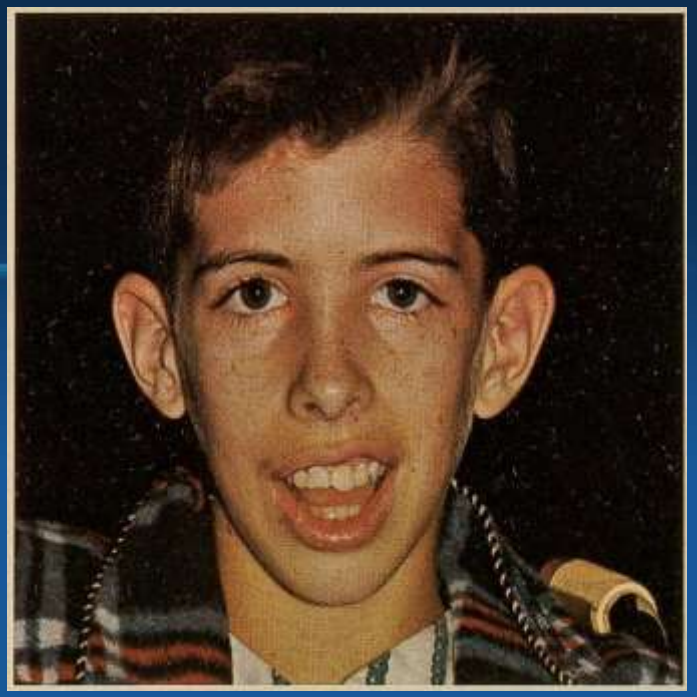
Clinical Presentation

- Younger patients often develop hepatic manifestations
- Older patients with WD -neurological issues
- 20-30% of the patients have prominent psychiatric and behavioral issues
- Movement Disorders –often in combination
  - -dystonia
  - -parkinsonism
  - -tremor
  - -ataxia
  - -dysarthria
  - -rarely chorea

Dysphagia and drooling may occur

Wilsonian face/smile

Fig. 1 : Showing typical orofacial dystonia and carpopedal spasm

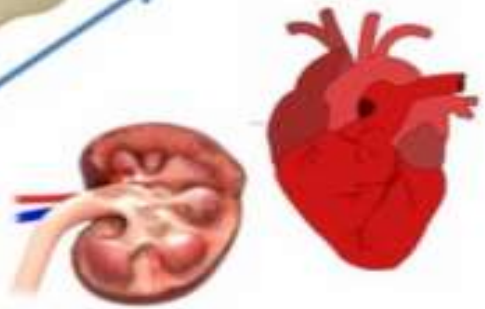


Wilson's disease

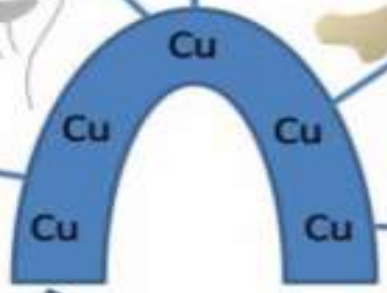
- Personality disorders
- Mood disorders
- Psychosis
- Cognitive impairment
- Involuntary movements
- Speech disturbances
- Drooling
- Gait and balance disturbances

- Thrombocytopenia
- Haemolytic anaemia
- Leukopenia

- Osteoporosis
- Chondrocalcinosis
- Osteoarthritis
- Joint pain



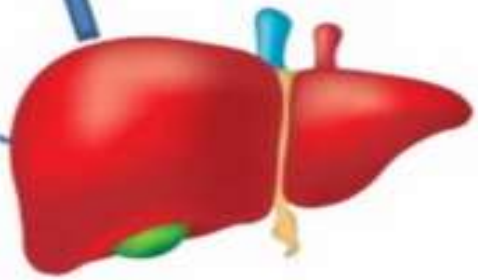
- Kayser-Fleischer ring (common)
- Sunflower cataract (rare)



Others

- Cardiac arrhythmia
- Cardiomyopathy
- Myopathy
- Tubular dysfunction
- Nephrolithiasis and nephrocalcinosis
- Aminoaciduria
- Hypercalciuria
- Hyperphosphaturia

- Asymptomatic elevation of liver enzymes
- Acute hepatitis
- Acute liver failure
- Compensated liver cirrhosis
- Decompensated liver cirrhosis



Diagnostic Tests

Useful

- Serum ceruloplasmin
- 24-hour urinary copper
- Liver copper (gold standard but invasive)
- Kayser-Fleischer rings by slit lamp
  - Copper deposition in Descemet's membrane
  - Requires neuro-ophtalmologist
  - Asymptomatic
  - More common in neuropsychiatric vs hepatic presentation

Not useful

- Serum copper
  - Non-ceruloplasmin bound copper* is not routinely checked

*In plasma, copper is mostly bound to ceruloplasmin; a small proportion of copper, the non-ceruloplasmin-bound copper (NCC), is loosely bound to albumin, transcuprotein, amino acids or peptides for transport, and as this copper can be mobilized more easily in the literature it is often called 'free copper'.

European Association for the Study of the Liver. Journal of Hepatology. 2012;56:671.

Dopa Responsive dystonia

- An inherited condition characterised by early onset dystonia and parkinsonism.
- Responds very well to small doses of levodopa, and response lasts for life.
- Many people with DRD are misdiagnosed as having other conditions e.g cerebral palsy.
- *Therefore, levodopa should be considered in all patients with dystonia, particularly those with young onset.*

Drug-induced MD

Acute dystonic reactions/oculogyric crisis

- Acute dystonic reactions are best treated with anticholinergic agents and benzodiazepines

- This reaction is short-lived and does not produce long-term consequences

Parkinsonism

- This may occur as the result of long-term use of any neuroleptic agent

- The symptoms are similar to those seen in Parkinson disease, but tremor is less common and patients tend to be less responsive to levodopa

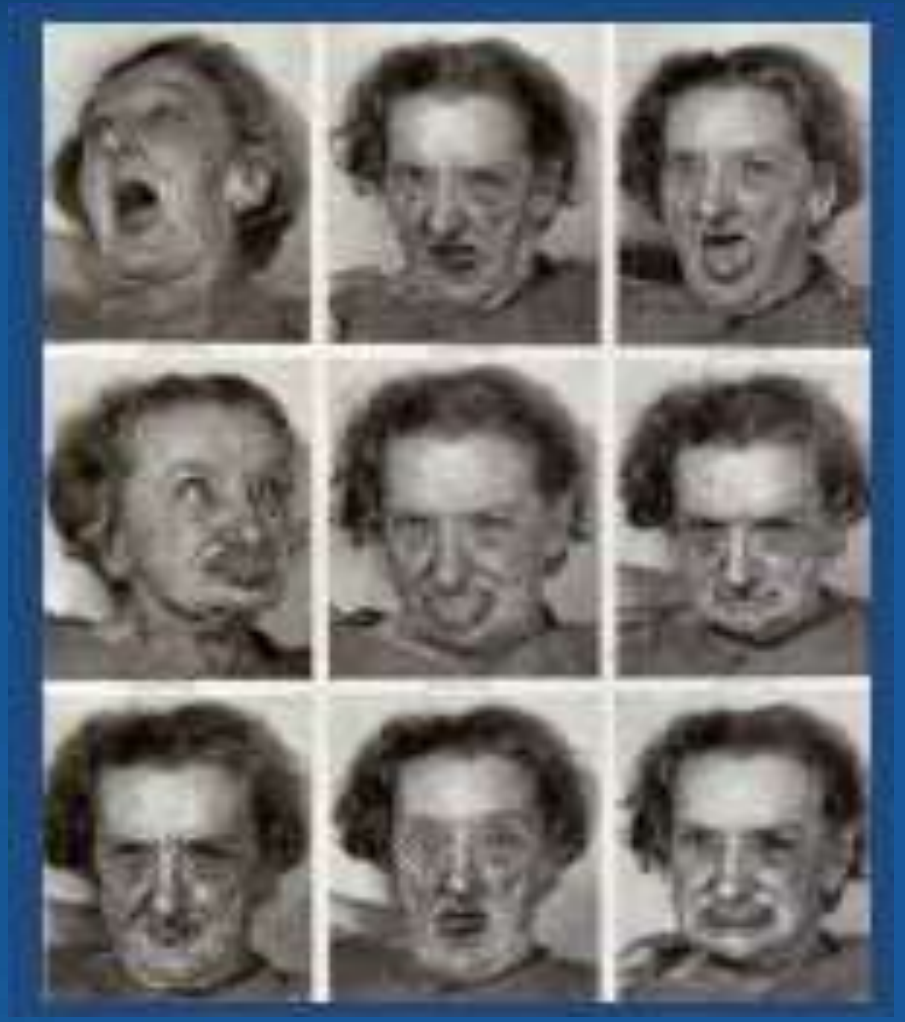
Neuroleptic malignant syndrome

- This occurs when patients are exposed to high doses of dopamine-blocking medications or when levodopa or dopamine agonists are withdrawn rapidly
- The syndrome includes fever, autonomic instability, encephalopathy, and muscular rigidity
- The offending agent must be stopped , but a combination of bromocriptine, dantrolene, and benzodiazepines is usually required to control the muscle rigidity

Drug class	Examples of drugs
Psychiatric	Risperidone, ziprasidone Haloperidol Clozapine, loxapine, quetiapine Chlorpromazine, fluphenazine, thioridazine Thiothixene Olanzapine
Antiemetics	Prochlorperazine, promethazine
Properistaltic	Metoclopramide, domperidone
Antiparkinsonian	Dopamine agonists, Levodopa

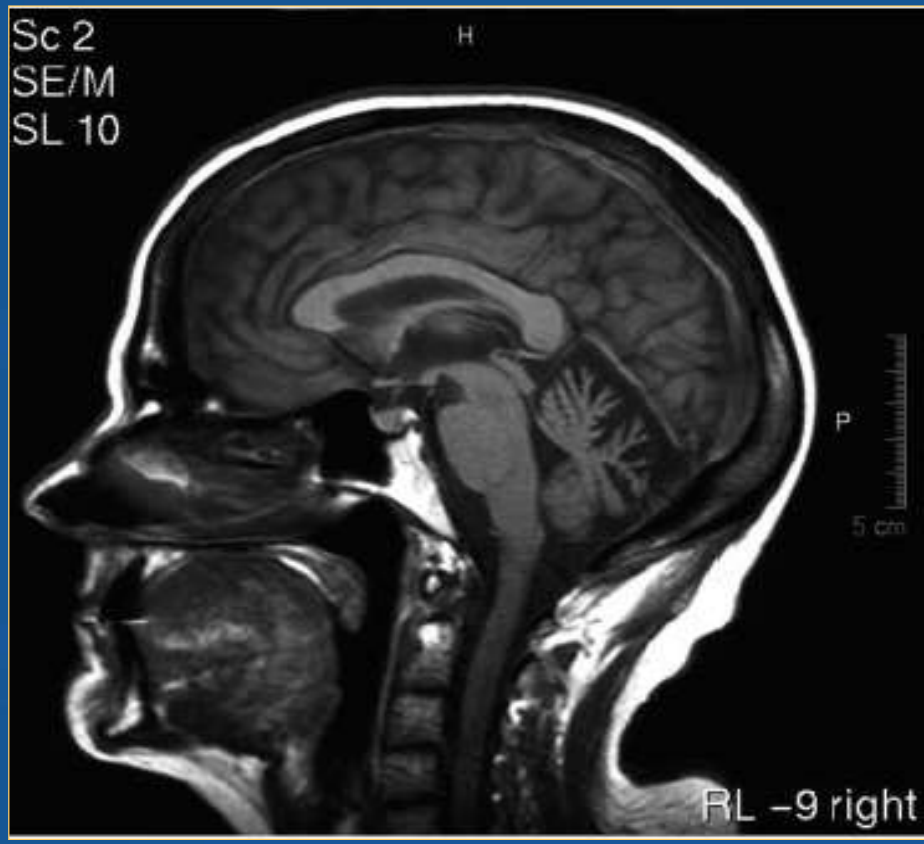
Tardive dyskinesia

- This is a disorder that occurs after chronic exposure to dopamine-blocking agents- leading to receptor hypersensitivity ??
- Commonly observed movements include chewing , grimacing, lip smacking, and tongue thrusting
- The trunk is commonly affected
- The limbs may be affected
- Treatment is challenging



Ataxias

- Ataxia (Gk. Taxis = Order; means lack of order)
- Ataxia denotes a syndrome of imbalance and incoordination involving gait, limbs, and speech and usually results from the disorder of the cerebellum or its connections
- It is characterized by dyssynergia, dysmetria, dysdiadochokinesia
- It is a disorder of rate, range, direction and force of movements



Examination

- Titubation
- Nystagmus and other ocular movement abnormalities
- Dysarthria
- Intention tremor
- Hypotonia
- Past pointing
- Rebound phenomenon
- Macrographia
- Stance
- Ataxic Gait
- Pendular knee jerk

Differentiation of sensory and cerebellar ataxia

- Sensory ataxia is due to severe sensory neuropathy, ganglinopathy or lesions of the posterior column of the spinal cord. e.g, B12 deficiency (SACD) , Tabes dorsalis.

Cerebellar ataxia	Sensory ataxia
Scanning speech	Normal speech
Nystagmus and other ocular signs	Absent
Sensory exam normal, Romberg test negative	Sensory loss, Romberg's test positive
Pendular reflexes	Hypo to areflexia
Reeling, ataxic gait	Stamping gait

Good luck

- Register your attendance with your university number
- Make sure that the settings of your phone allow tracking location

Go to settings > privacy> location> services> make sure that location services is ON