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

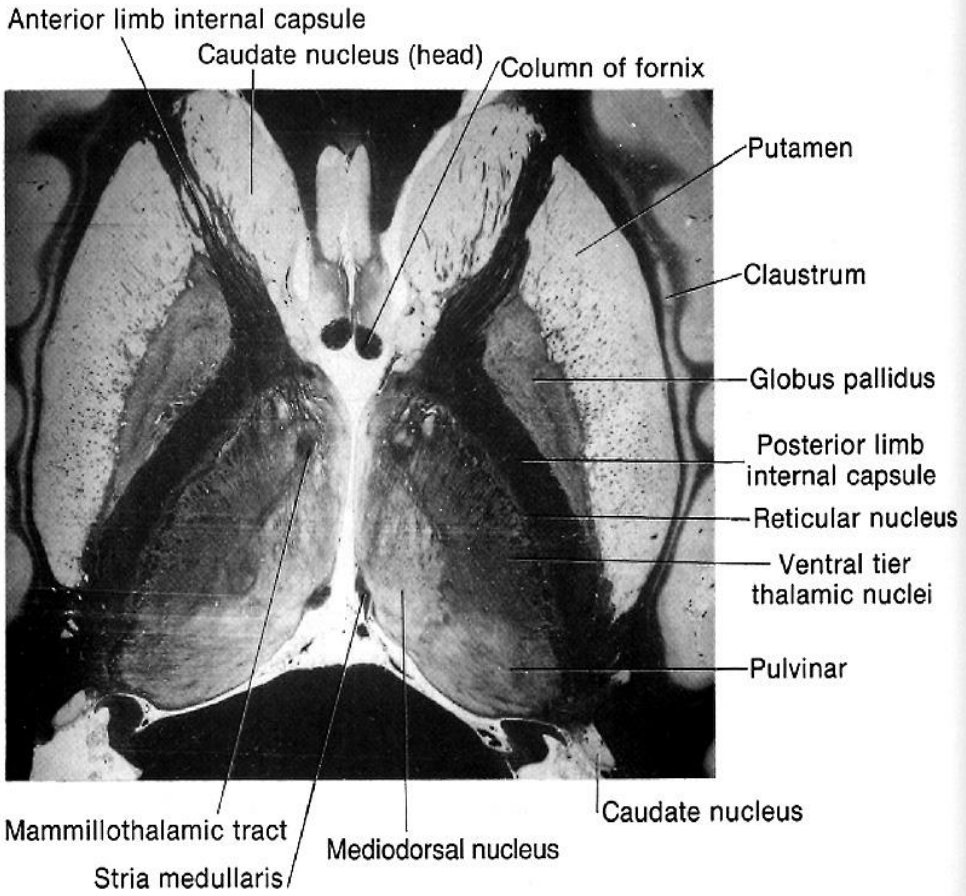


Figure 11.5. Horizontal section of the thalamus, internal capsule, and corpus striatum. Weigert's myelin stain. Photograph. (From Carpenter and Sutin, *Human Neuroanatomy*, 1983; courtesy of Williams & Wilkins.)

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

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

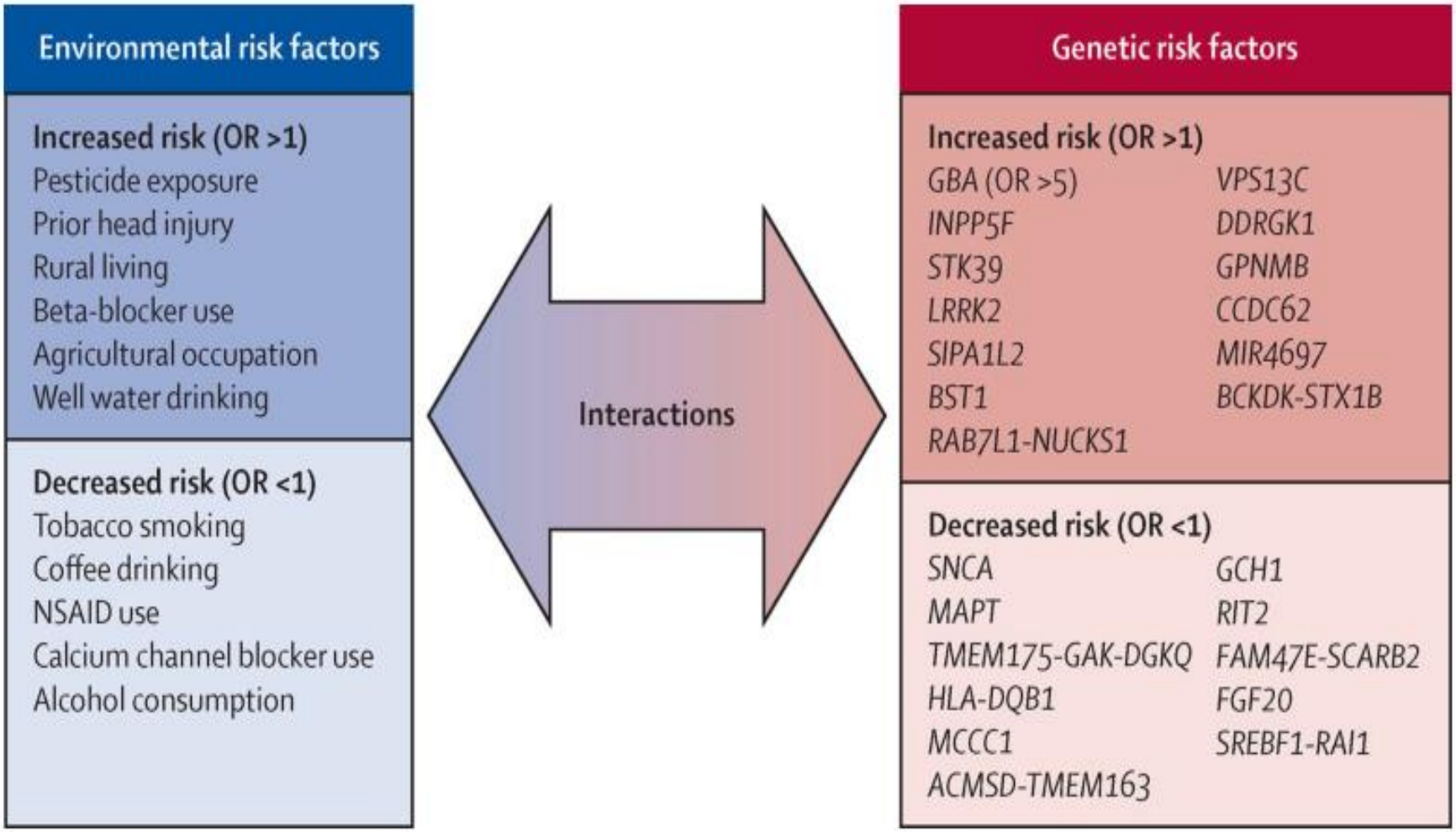
Parkinson's Disease

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

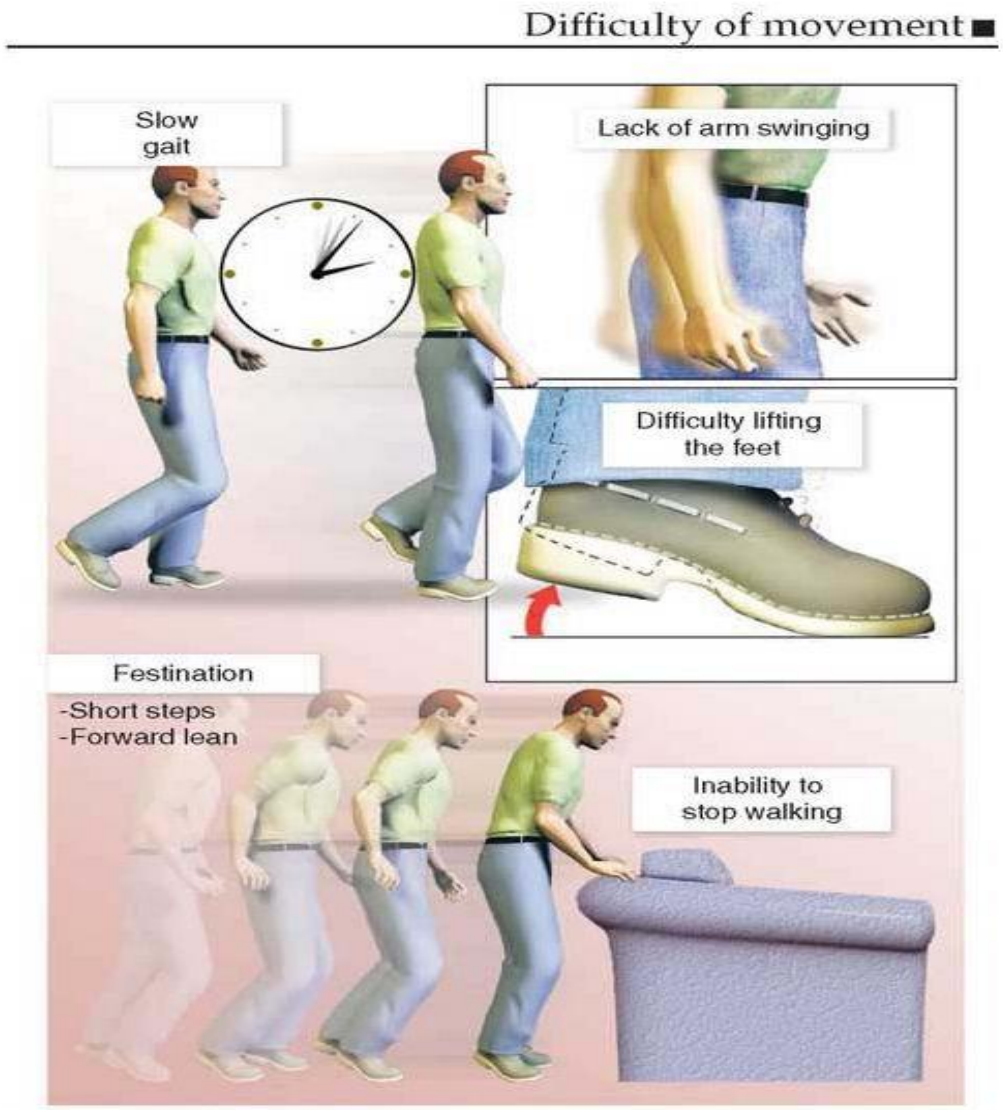
- A clinical and neuropathological entity characterised by:
  - Bradykinesia
  - Rigidity
  - Tremor

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

Risk Factors for PD

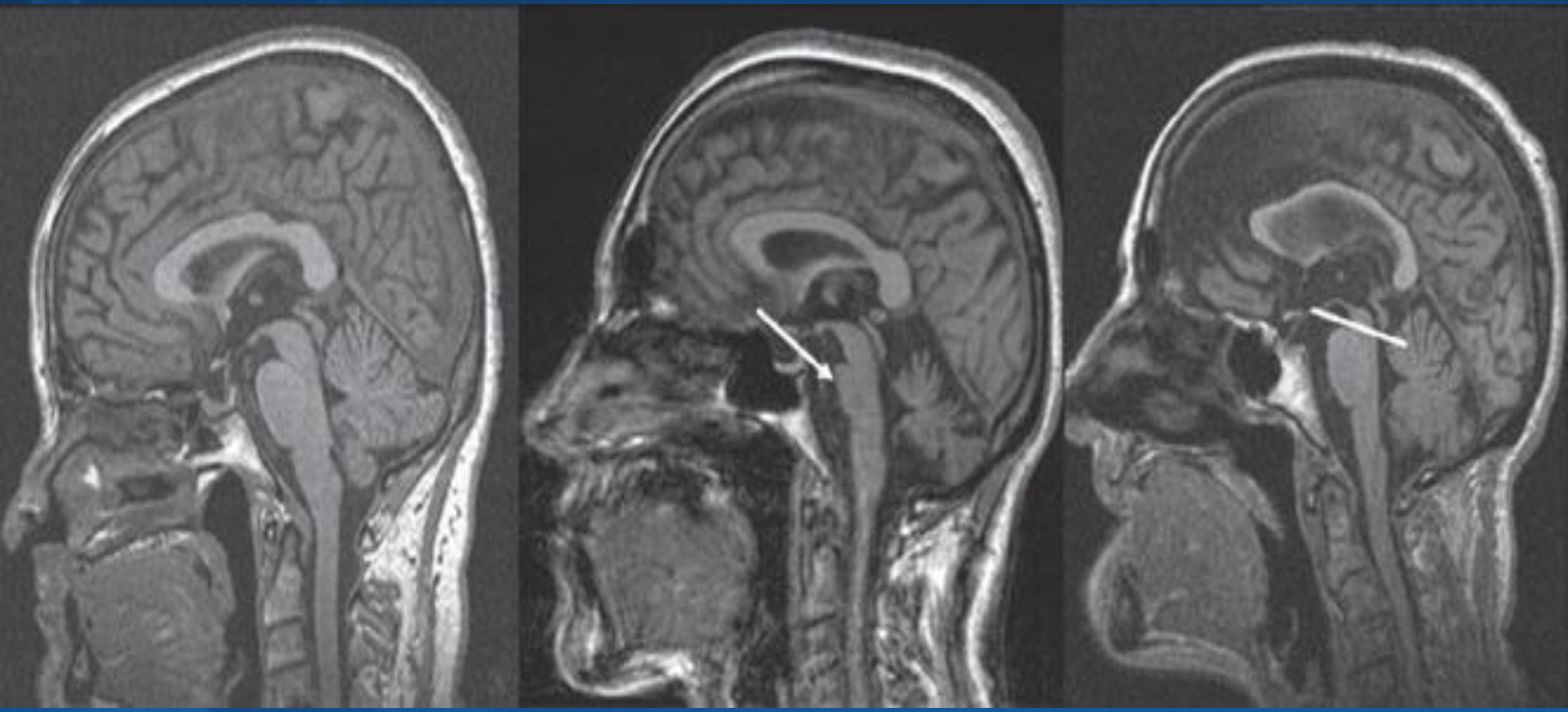


Bradykinesia

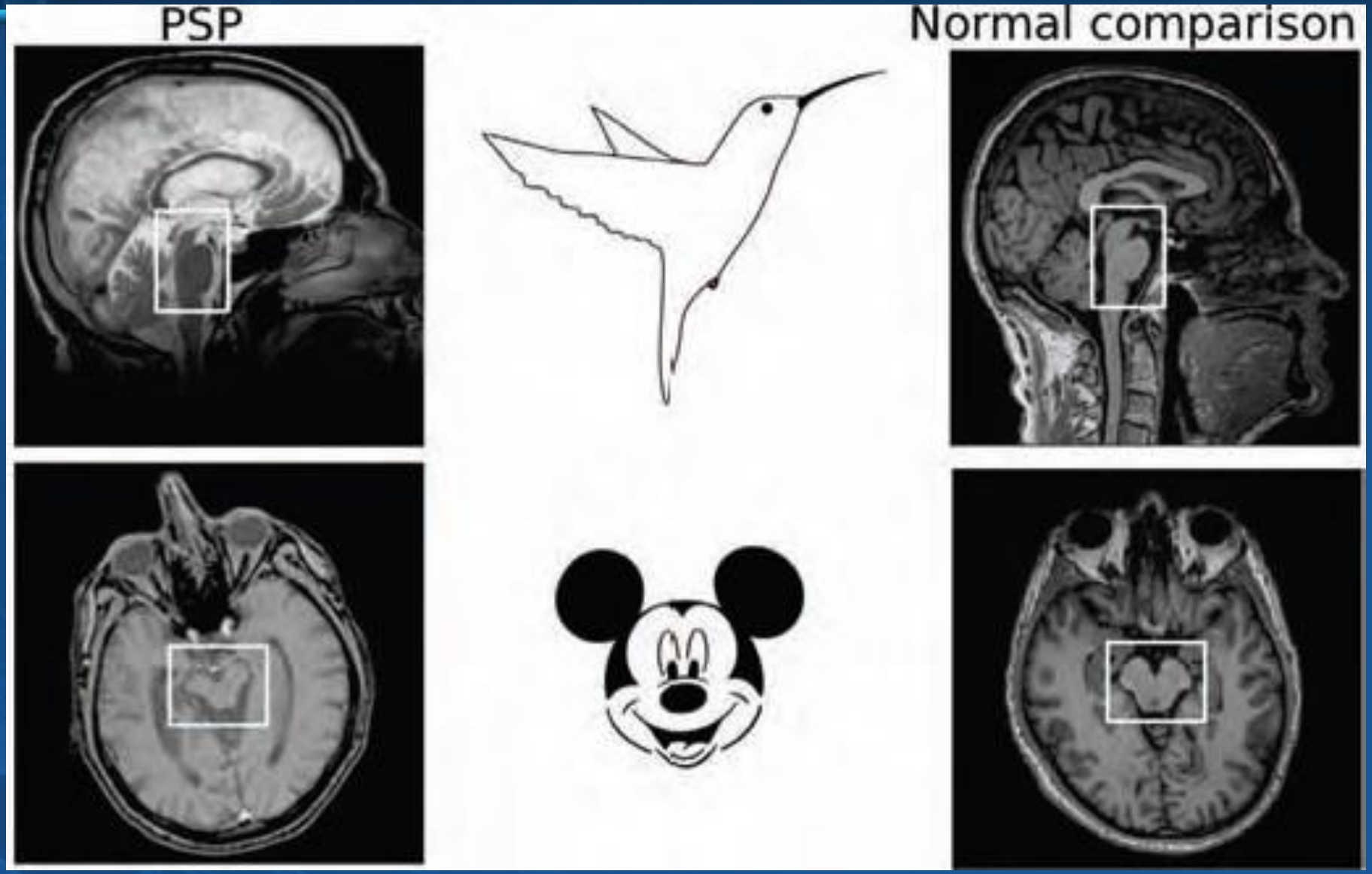


Bradykinesia includes such motor phenomena as delayed initiation, slow performance, low amplitude and intermittent arrests of voluntary movement.

PD MSA PSP



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

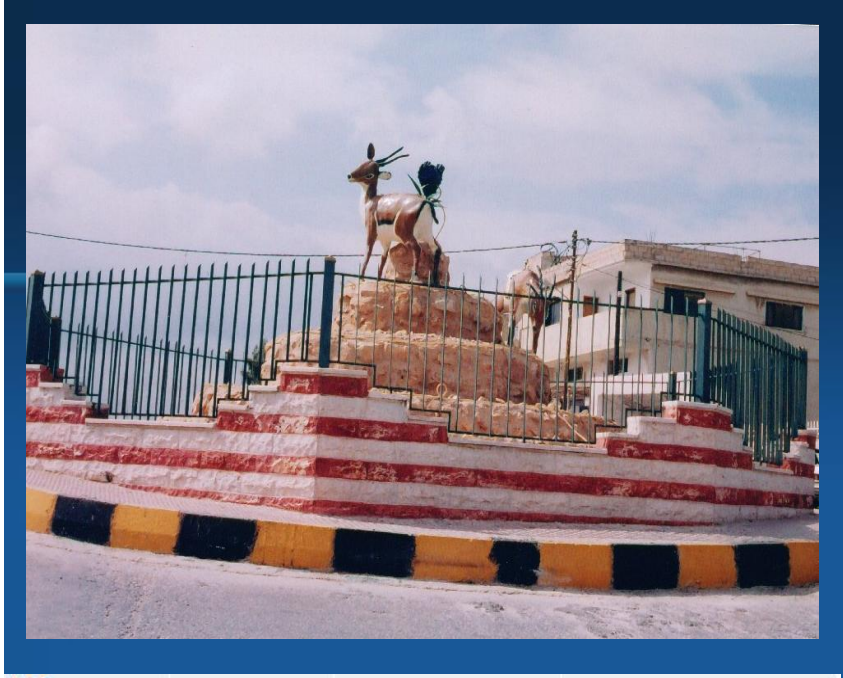


Degenerative PS

- 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

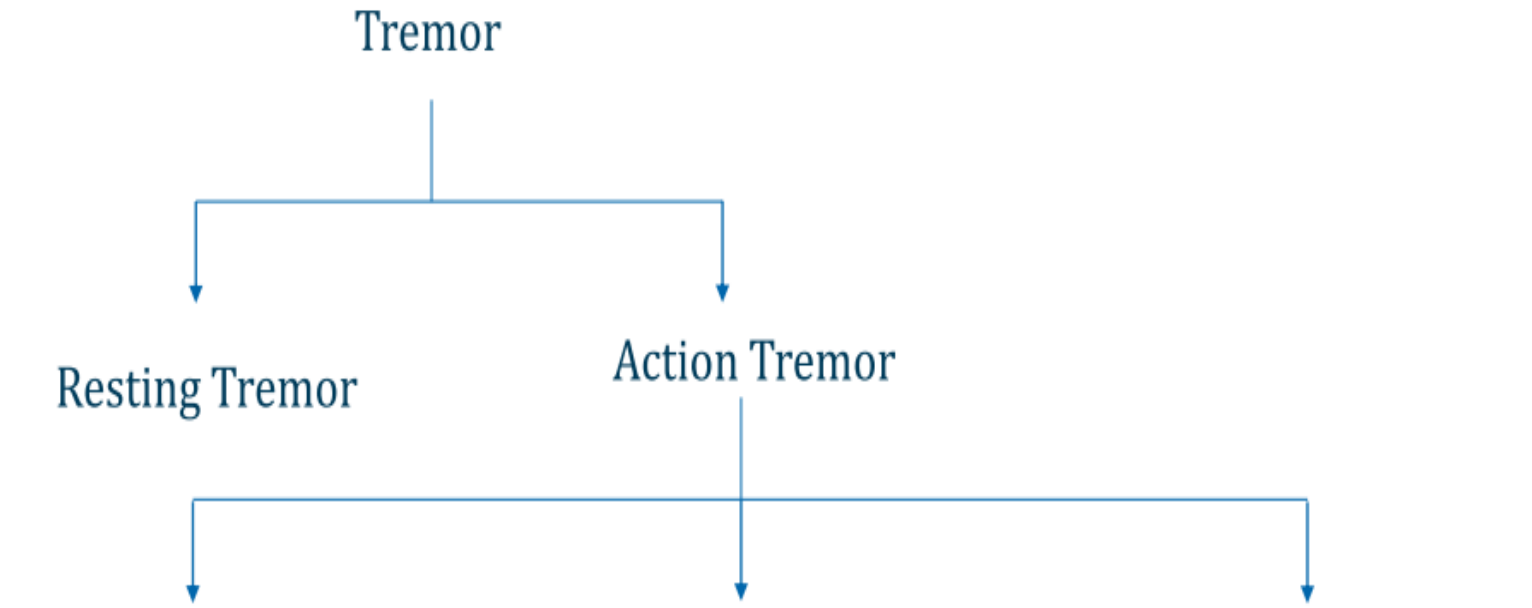
Mendelian Parkinson's Loci: one process or more?

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				

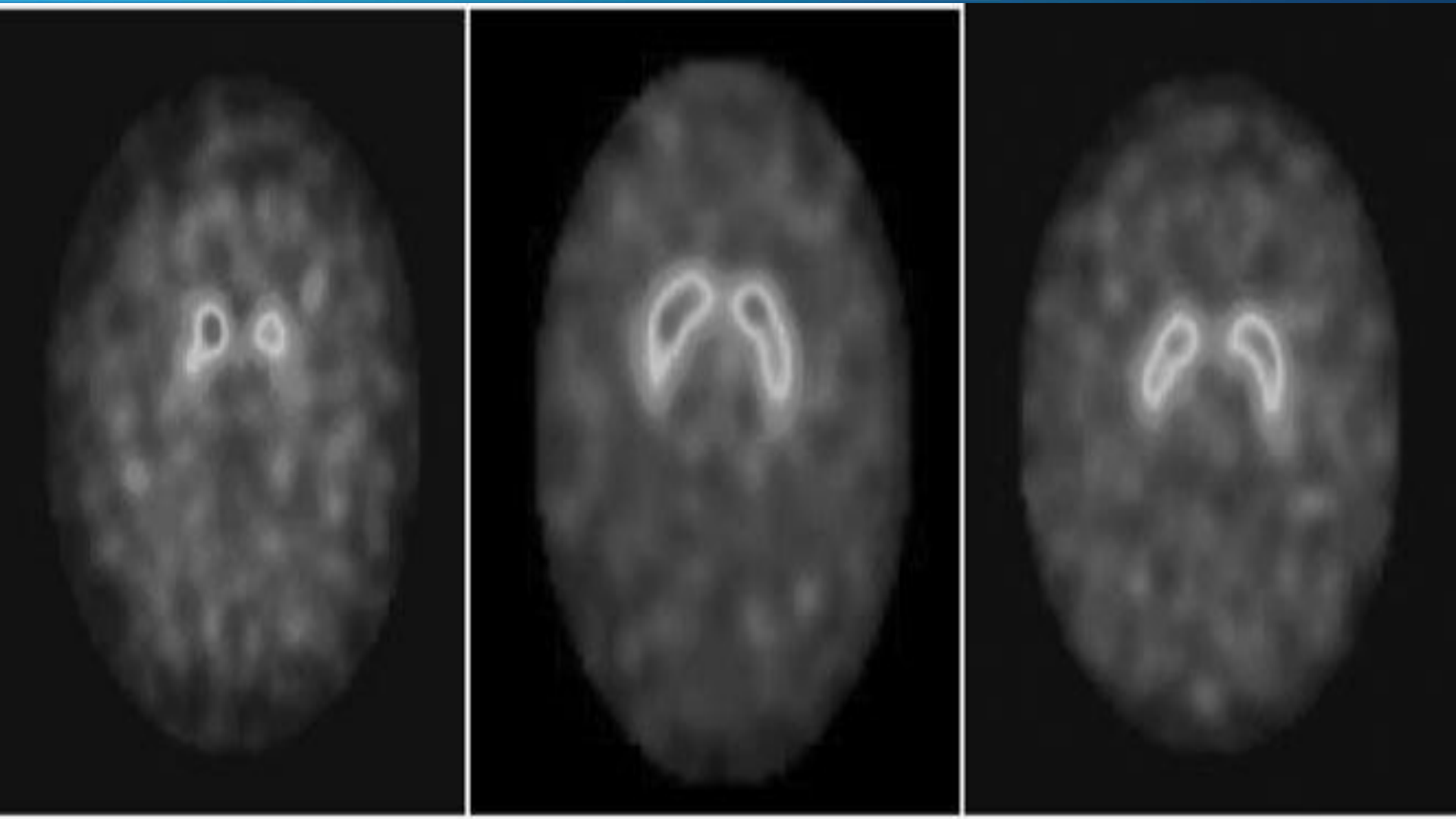


	AR	Teens	PLA2G6	LB, also spheroids brain iron Xs
	AR	Teens	FBXO7	?
	AD	50-70	VPS35	?
PARK-18	AR	Late onset	EIF4G1	LBs
PARK-19	AR	Juvenile onset	DNAJC6	?
PARK-20	AR	Early onset	SYNJ1	?
PARK-21	AD	Late onset PD/PSP	DNAJC13	Brain stem or transitional LB. tauopathy
PARK-22 ?	AD	Late onset (Japanese)	CHCHD2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

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

B-CIT SPECT Imaging



PD | Essential tremor | Healthy subject

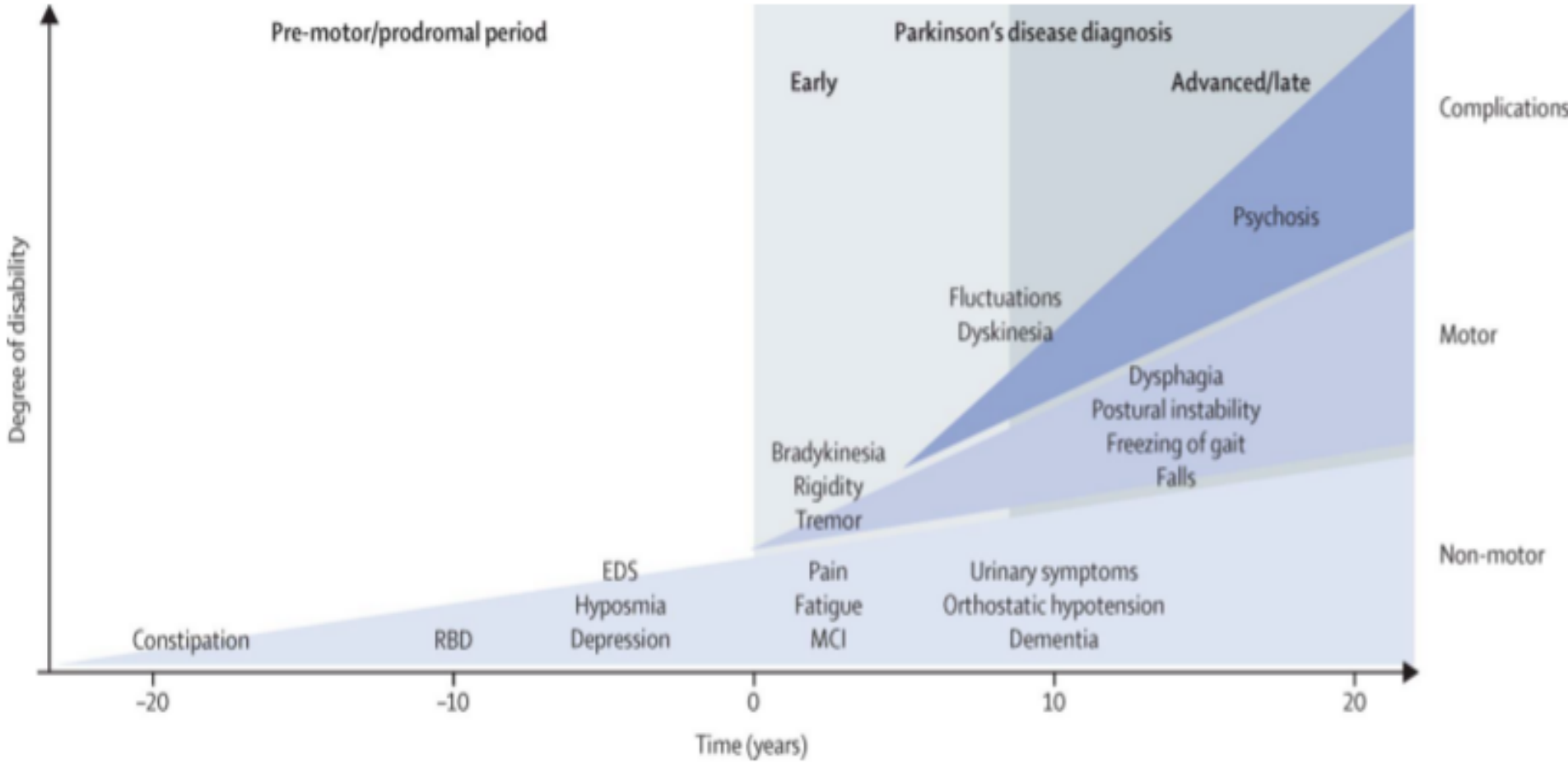
Non-Motor Symptoms of Parkinson's Disease

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

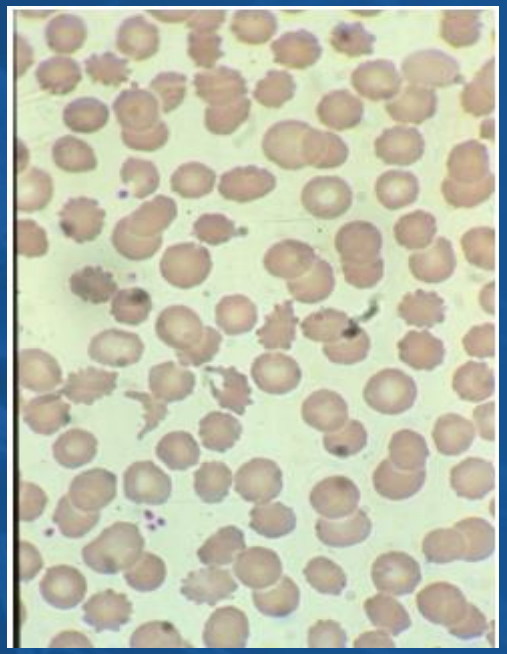
Autonomic symptoms
Constipation
Bladder disturbances
Orthostatic hypotension
Falls related to orthostatic hypotension
Impotence

Clinical symptoms & time course of PD progression



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

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.

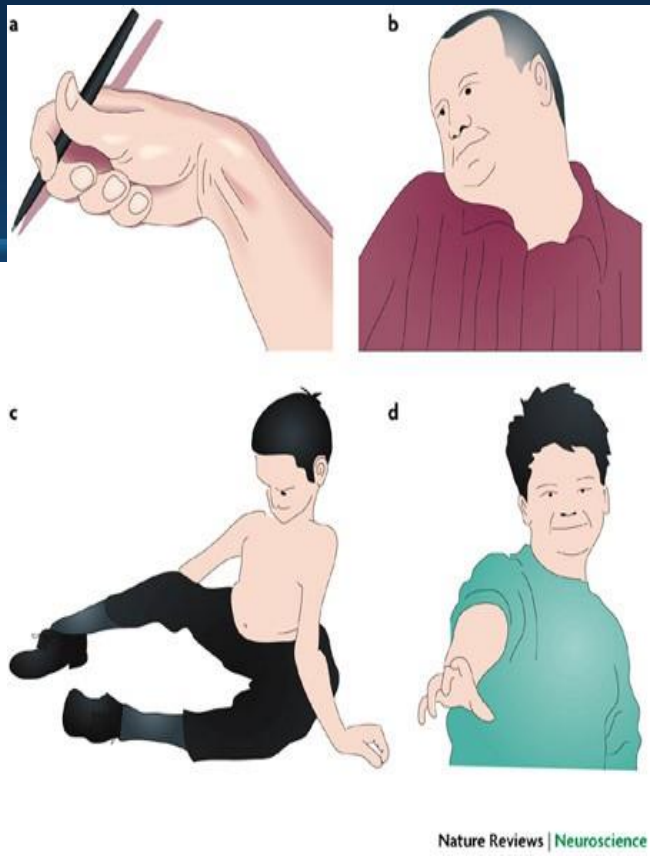
Primary dystonia:

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



Geste Antagoniste/sensory trick

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

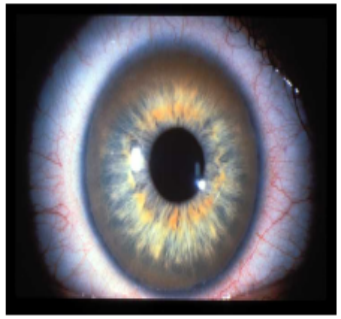


FIG. 1. Patient with hepatolenticular degeneration described by S. A. K. Wilson in 1912[6] (from *Brain*, vol. 34, page 327, with the courtesy of the Editor).

Wilson's disease

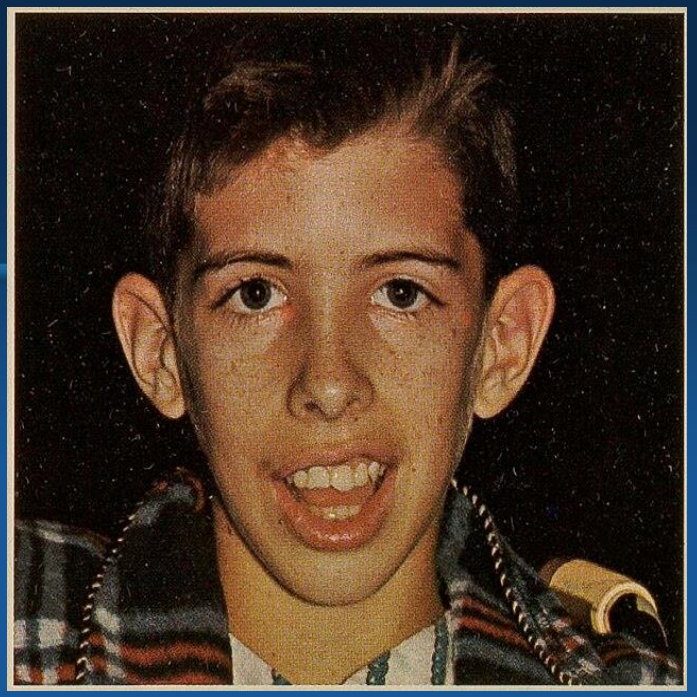
Clinical Presentation

- 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

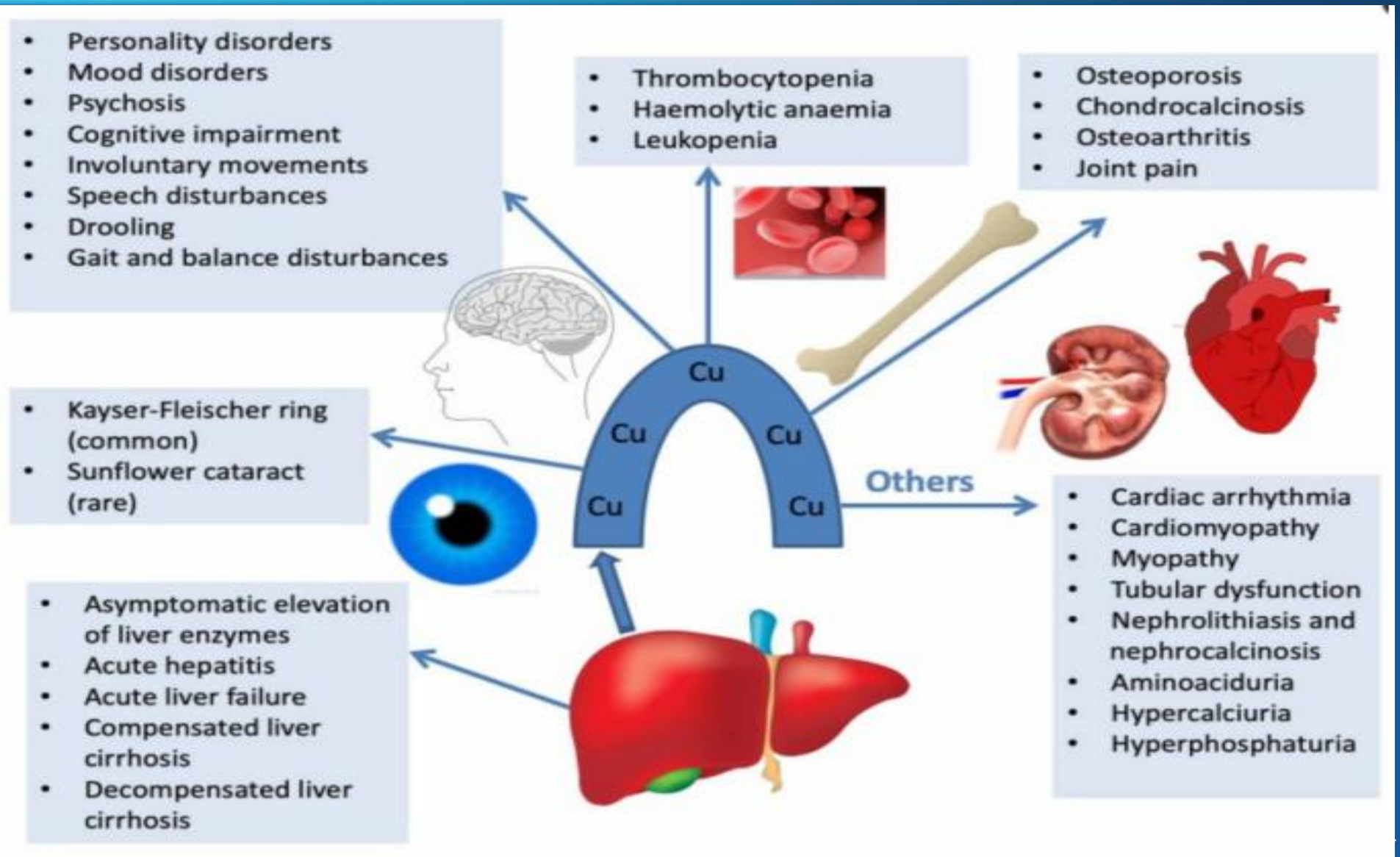
Dysphagia and drooling may occur

Wilsonian face/smile

Fig. 1 : Showing typical orofacial dystonia and carpopedal spasm



Wilson's disease



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