Movement Disorders (MD)

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Anatomy of The Basal Ganglia

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

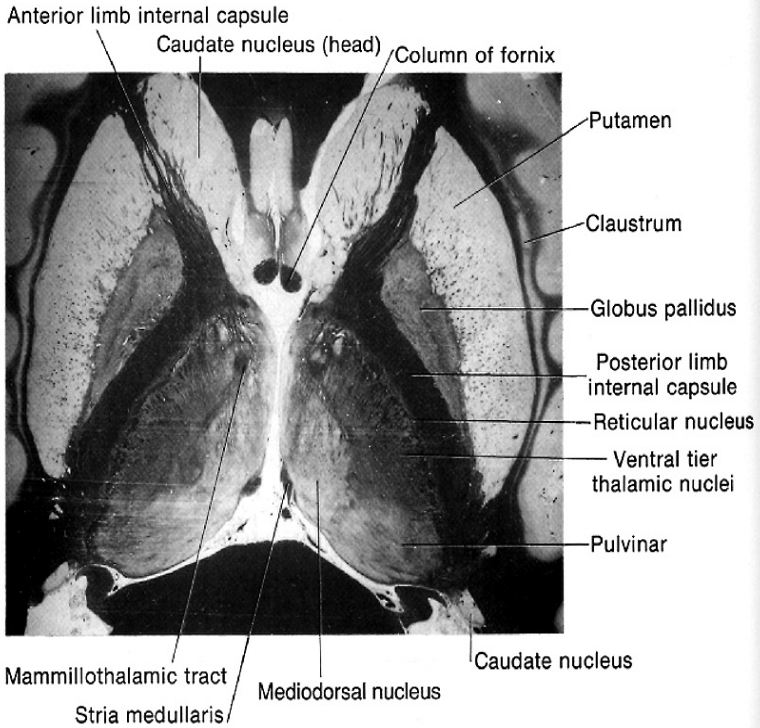


Figure 11.5. Horizontal section of the thalamus, internal capsule, and corpus striatum. Weigert's myelin stain. Photograph. (From Carpenter and Sutin, *Human Neuroanatomy*, 1983; courtesy of Williams & Wilkins.)

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

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

Pathology of Parkinson's Disease

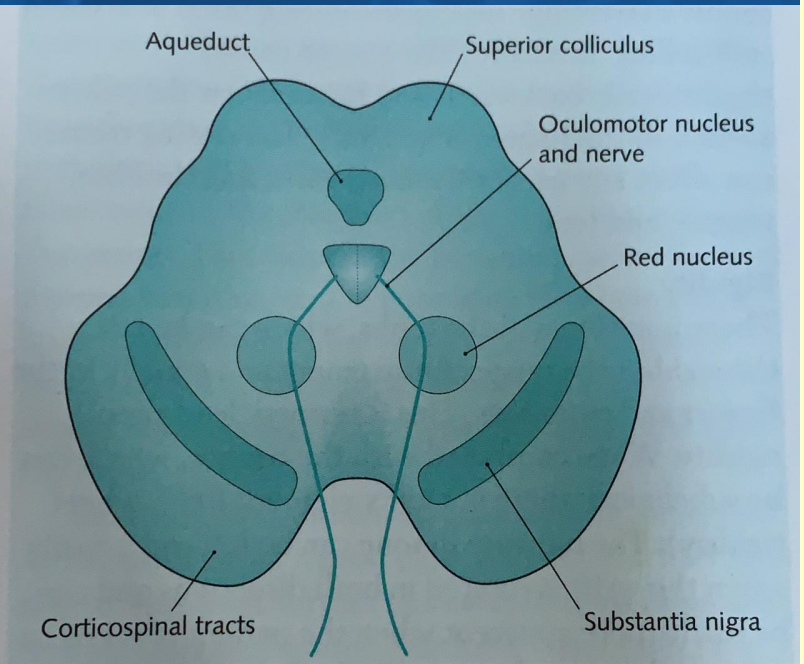
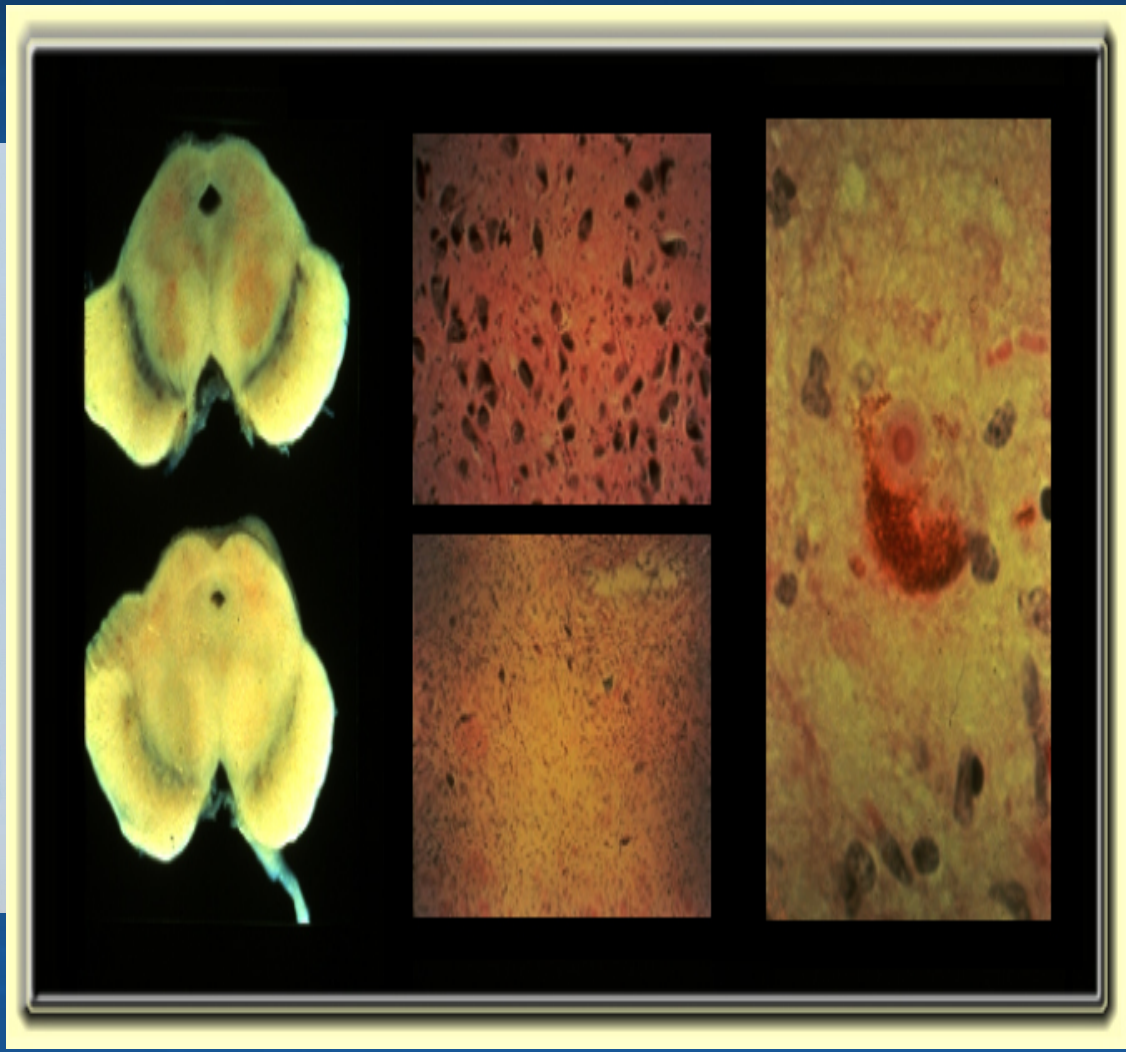


Fig. 18.1 Cross-section of the midbrain.



Risk Factors for PD

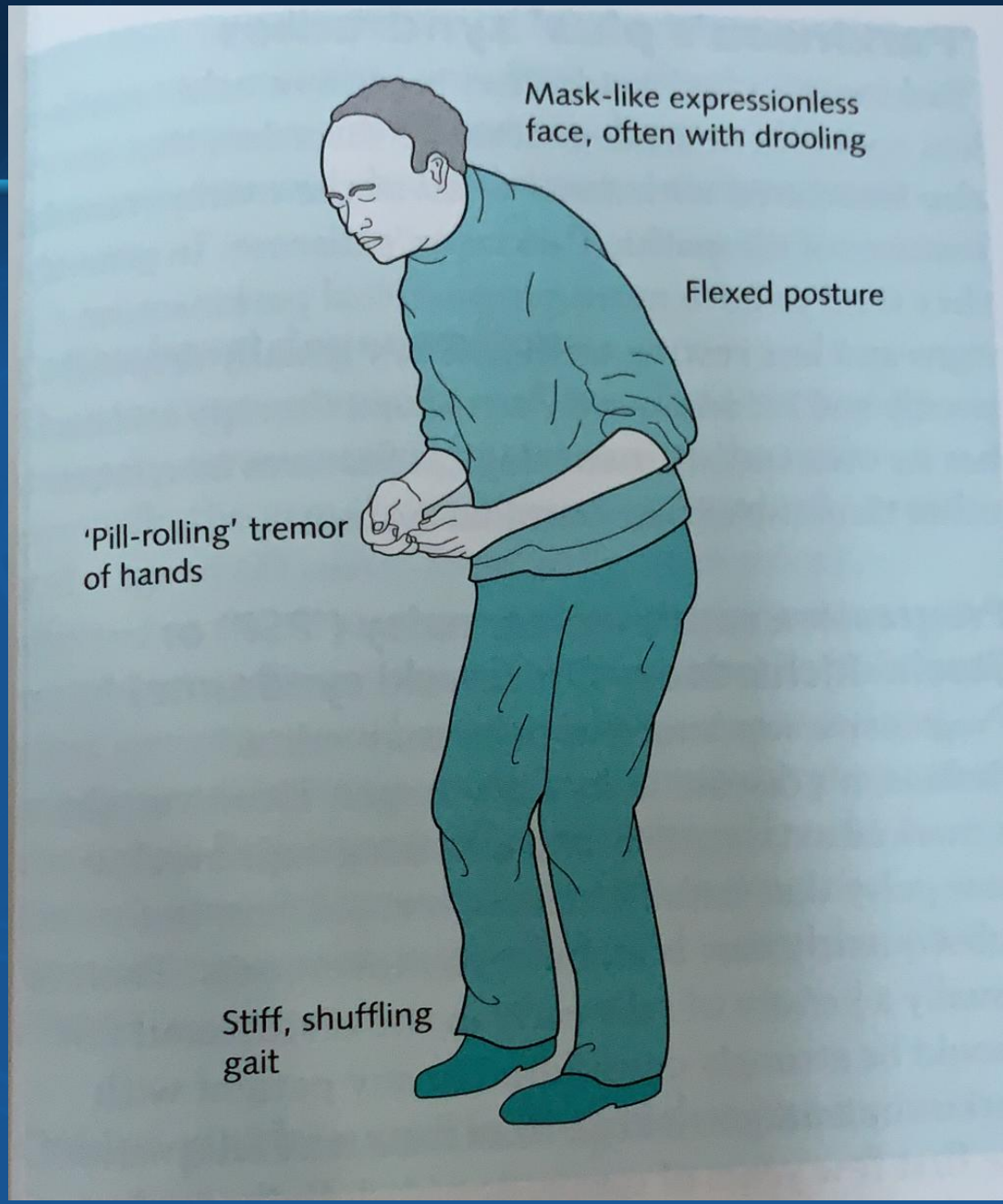
- Increased risk
  - Age
  - Family history
  - Exposure in early life to
    - Well water
    - Pesticides
  - Head injury
- Decreased risk
  - Caffeine
  - Cigarettes

Main Biochemical Abnormality

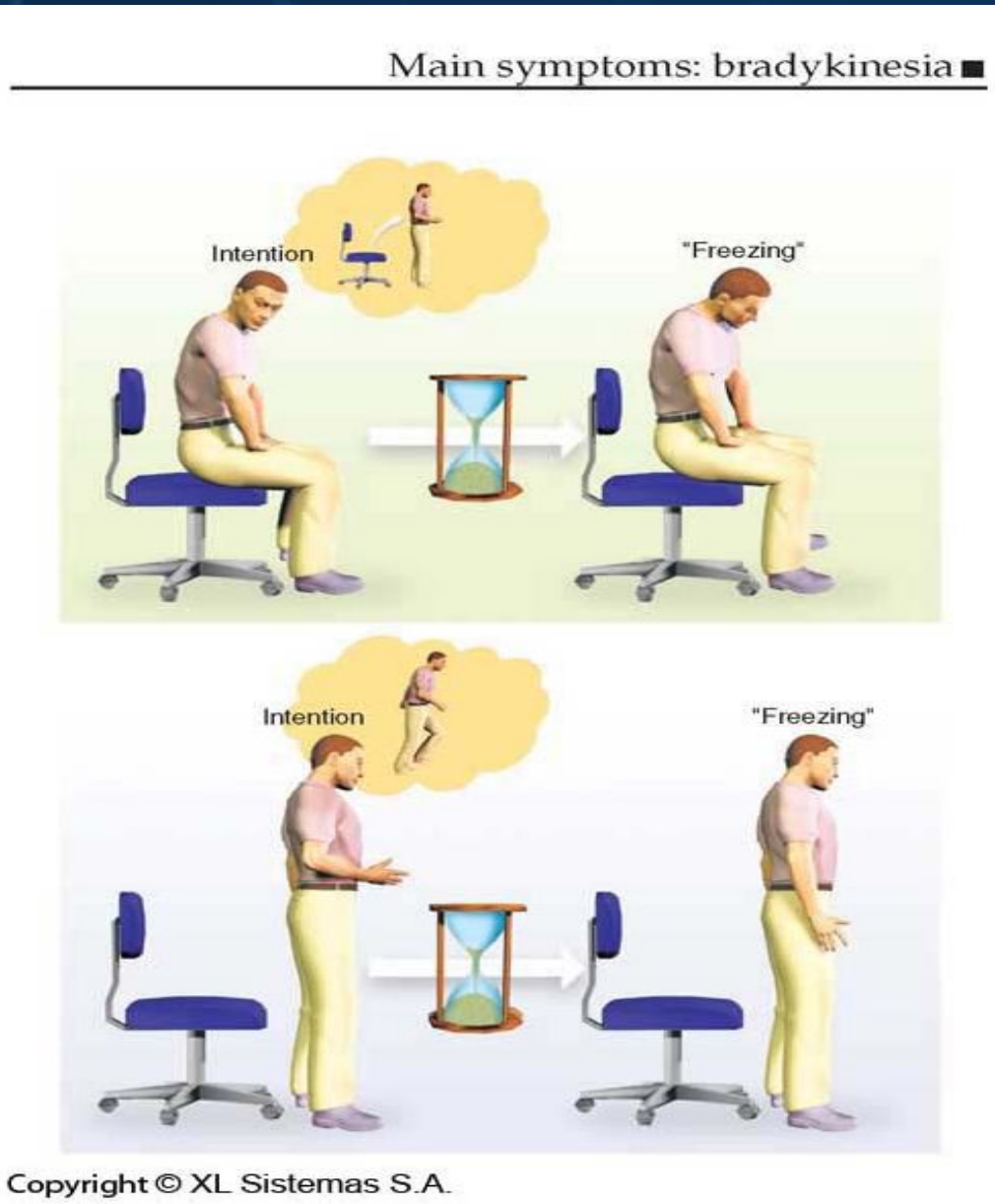
- Marked striatal Dopamine (DA) depletion
- <50% DA loss is asymptomatic
- ~70% DA loss for symptom manifestations
- At death, DA loss > 90%

Diagnosis / differential diagnosis

- Tremor
- Rigidity
- Akinesia
- Postural Instability

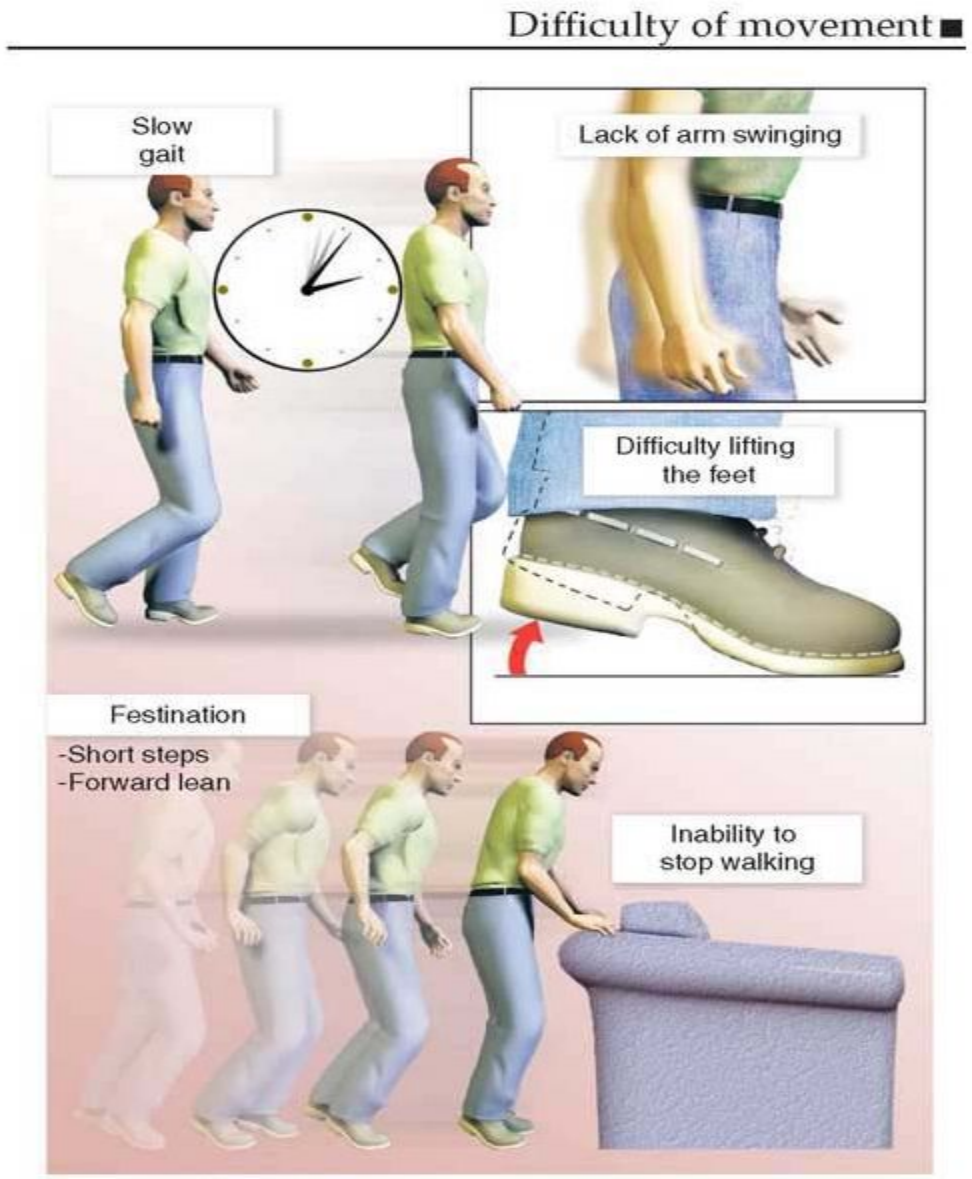


Bradykinesia

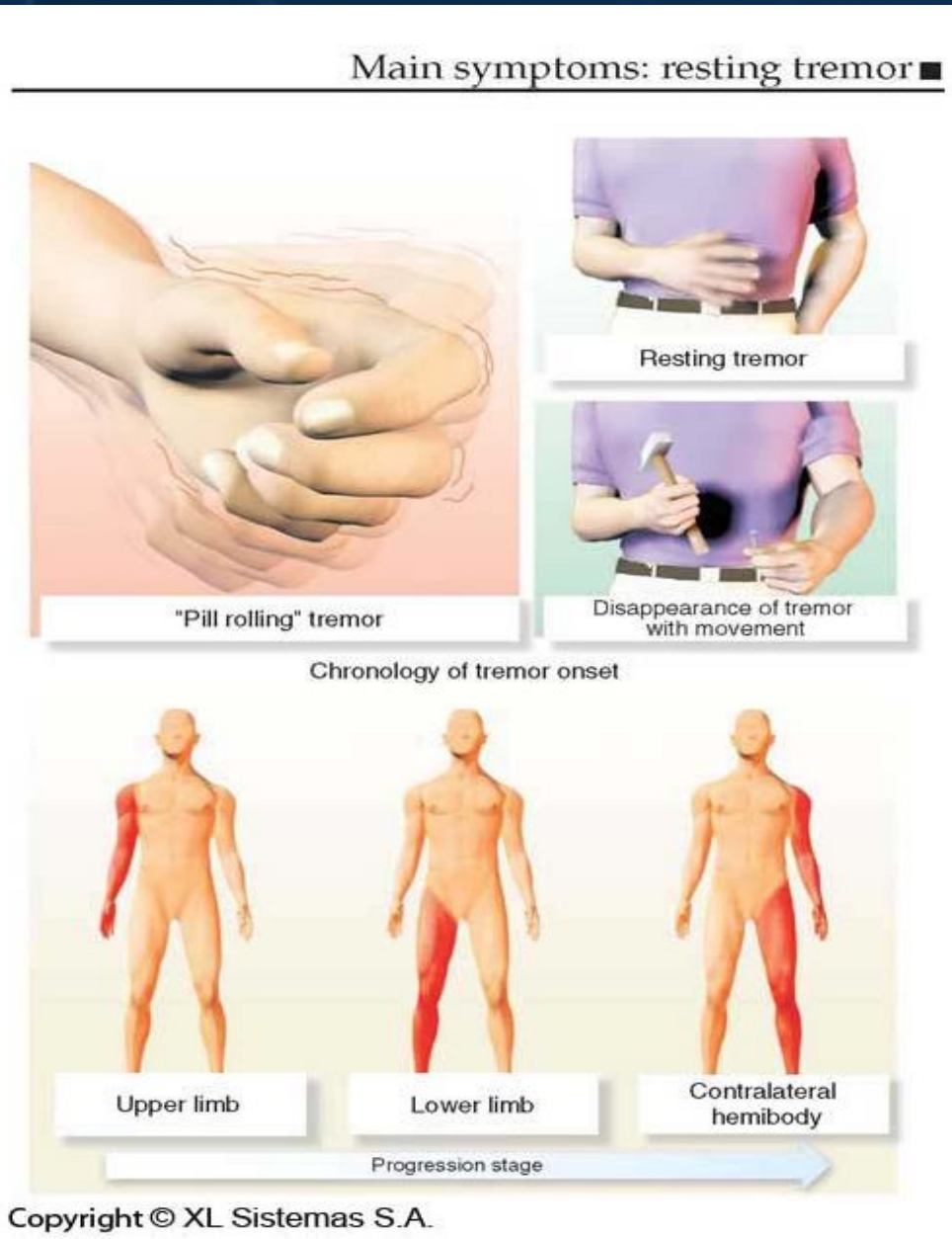


Bradykinesia includes such motor phenomena as delayed initiation, slow performance, low amplitude and intermittent arrests of voluntary movement.

Bradykinesia



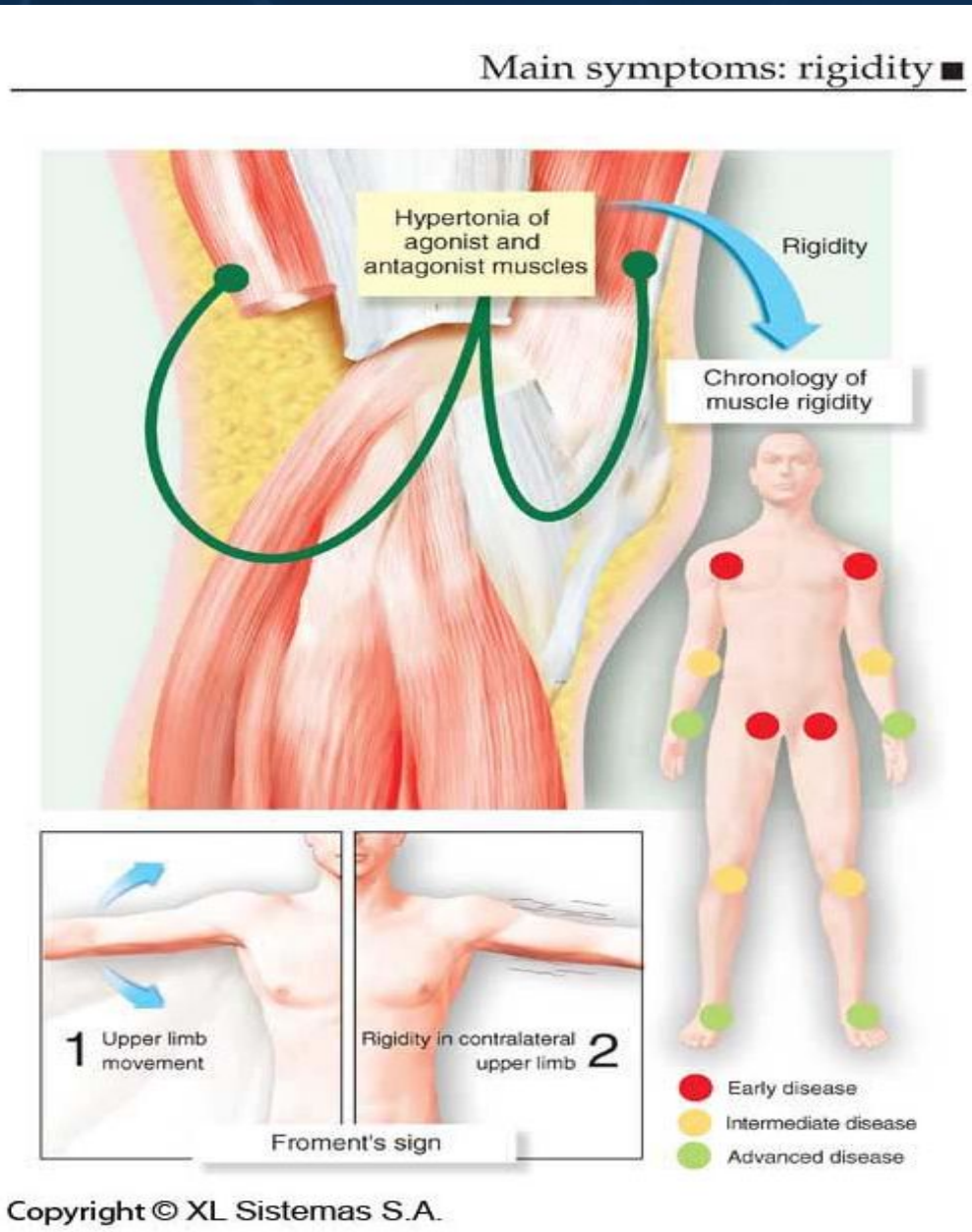
Tremor



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 neck or 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

Secondary Parkinsonism

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

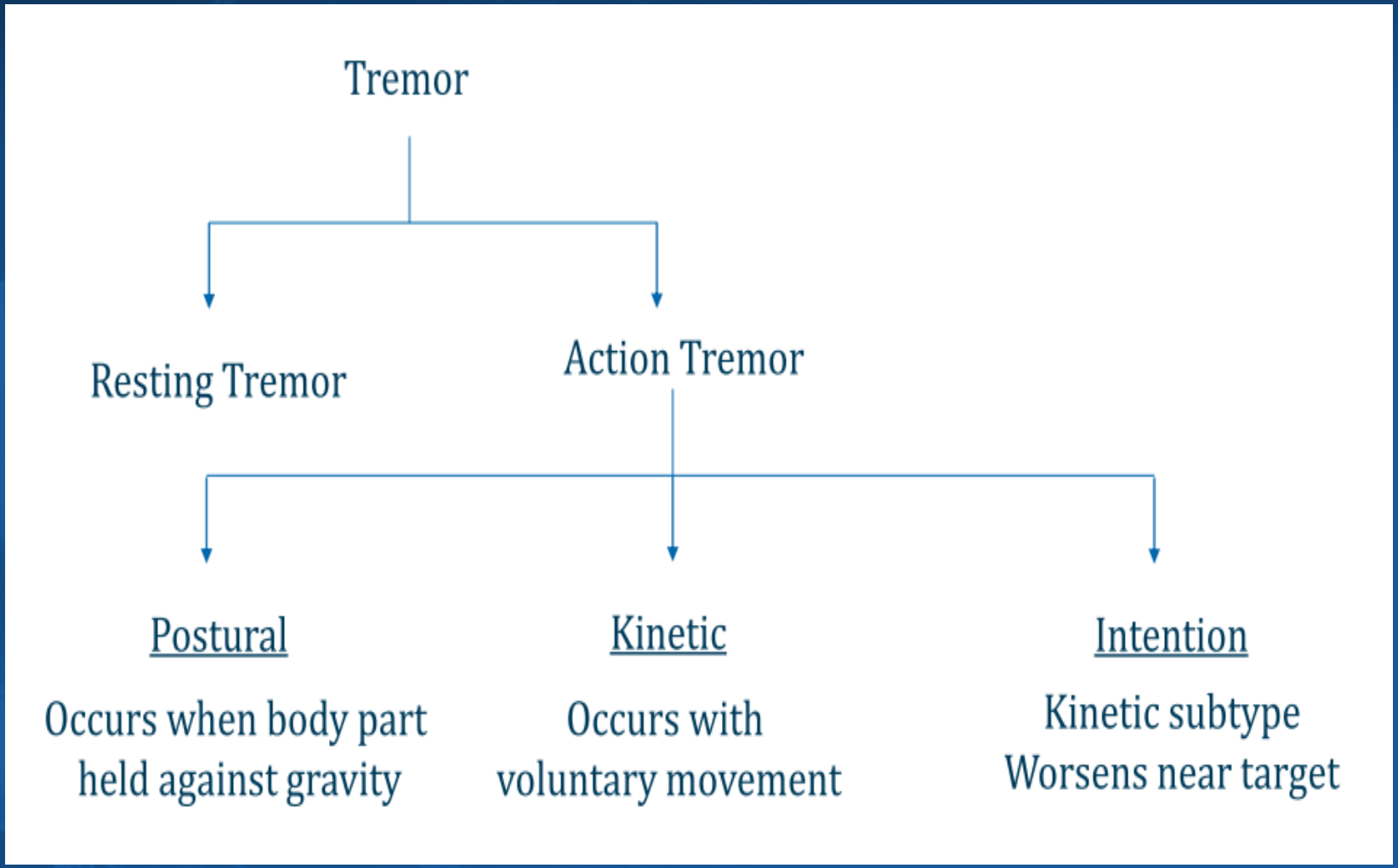
Hereditary PS

		locus	protein
PARK1	AD	4q21-23	□-synuclein
PARK2	AR	6q25.2-27	Parkin
PARK3	AD	2p13	?
PARK4	AD	4p15	?
PARK5	AD	4p14	UCH-L1
PARK6	AR	1p35-36	PINK1
PARK7	AR	1p36	DJ-1
PARK8	AD	12q12	LRRK2/dardarin
PARK9	AR	1p36	?
PARK10	AD	1p32	?
PARK11	AD	2q36-37	?

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

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:

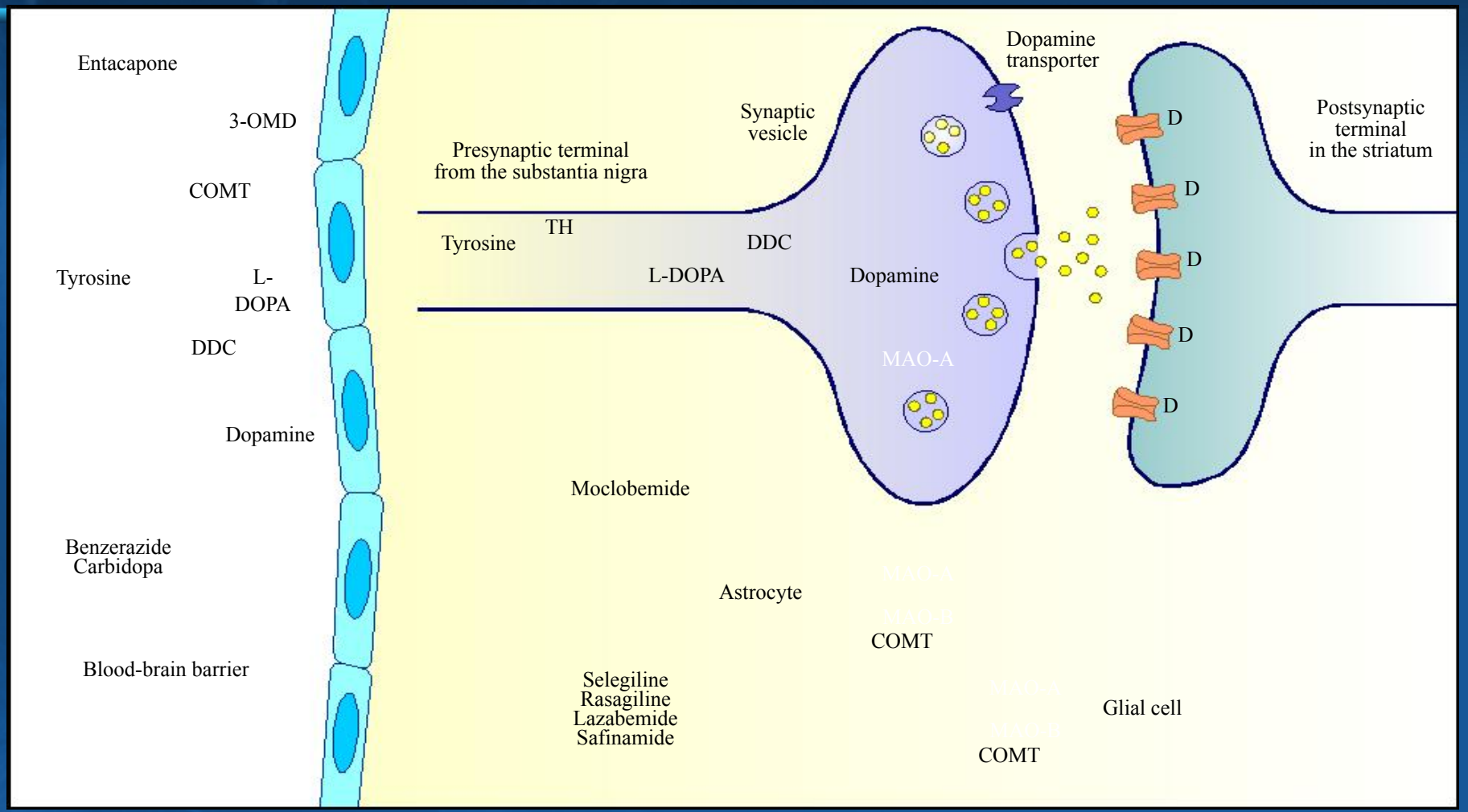
- Cerebellar disorders

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

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

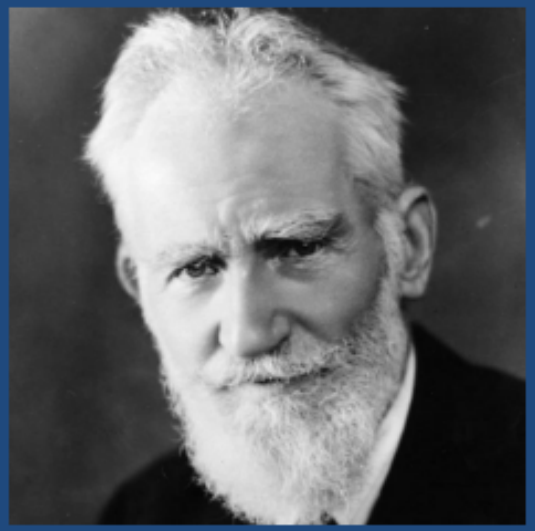
- Anticholinergic agents:
  - Trihexyphenidyl
  - Benztropine
- NMDA antagonists
  - Amantadine

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			

Science never solves a problem without creating ten more

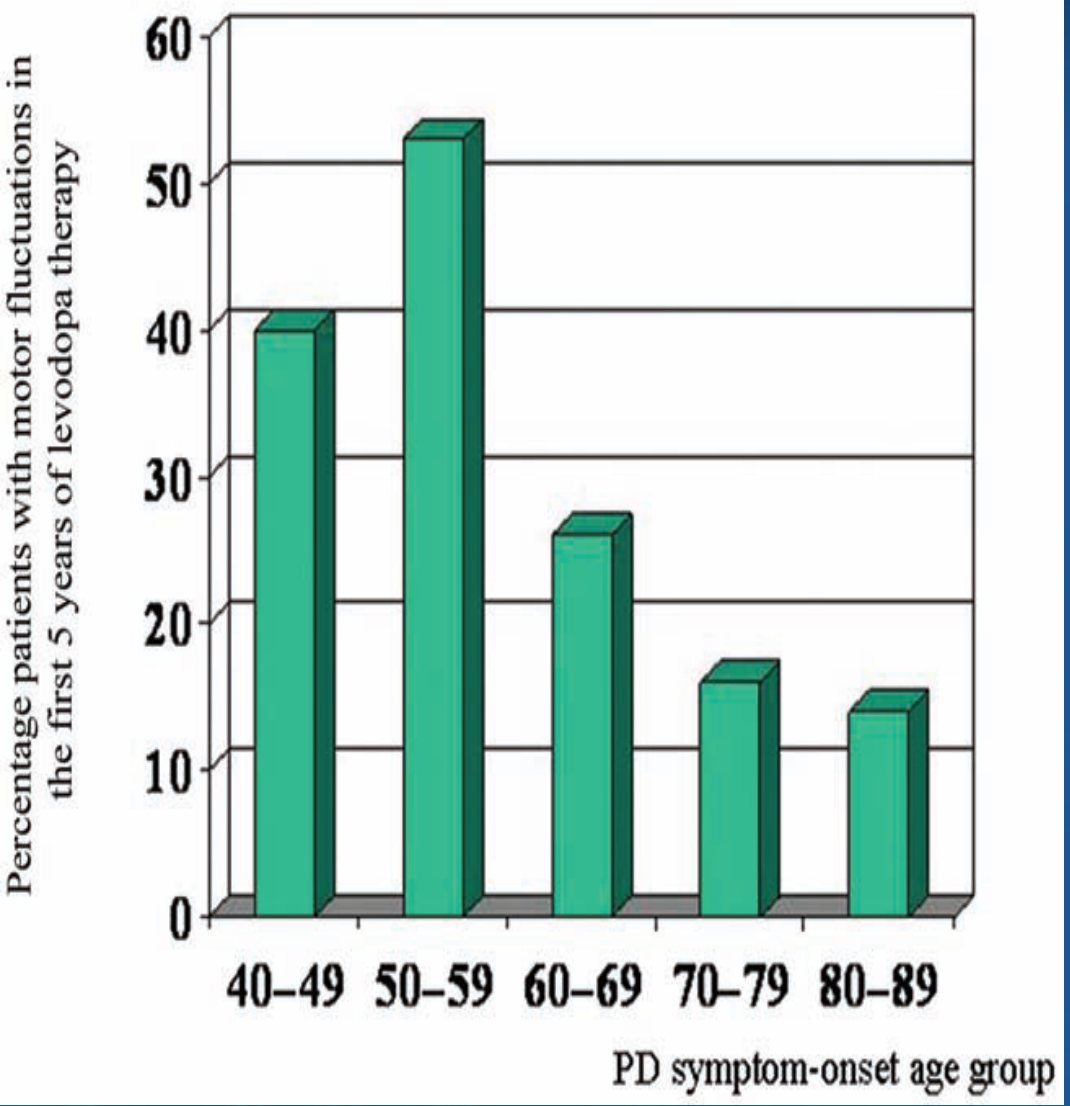
George Bernard Shaw



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

50 to 75% of patients develop motor fluctuations 3 to 6 years after initiating therapy

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

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.

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

- Focal
- Segmental
- Generalized

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

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

Wilson's disease

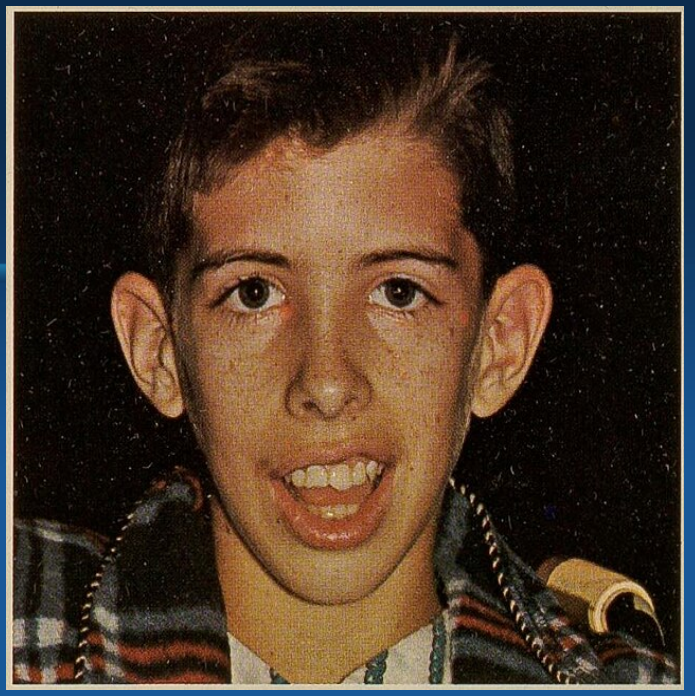
Clinical Presentation

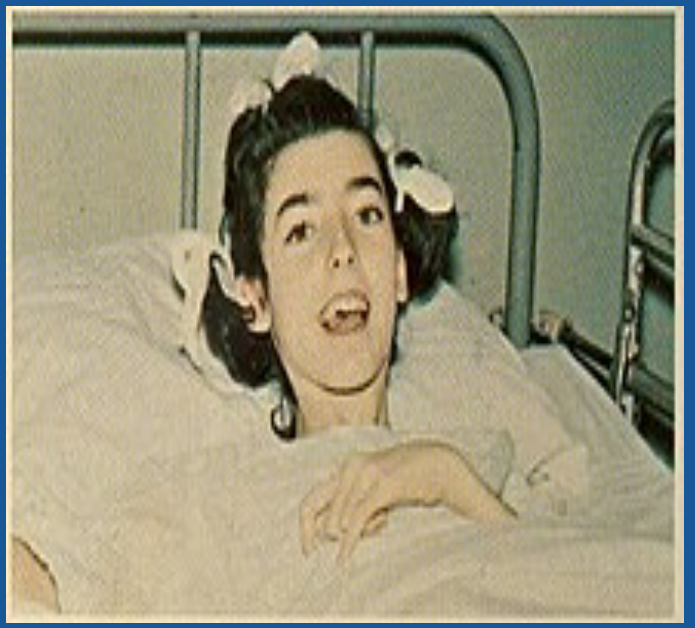
- Younger patients often develop hepatic manifestations
- Older patients with WD -neurological issues
- 20-30% of the patients have prominent psychiatric and behavioral issues
- Movement Disorders –often in combination
  - -dystonia
  - -parkinsonism
  - -tremor
  - -ataxia
  - -dysarthria
  - -rarely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

Dysphagia and drooling may occur

Wilsonian face/smile

Fig. 1 : Showing typical orofacial dystonia and carpopedal spasm

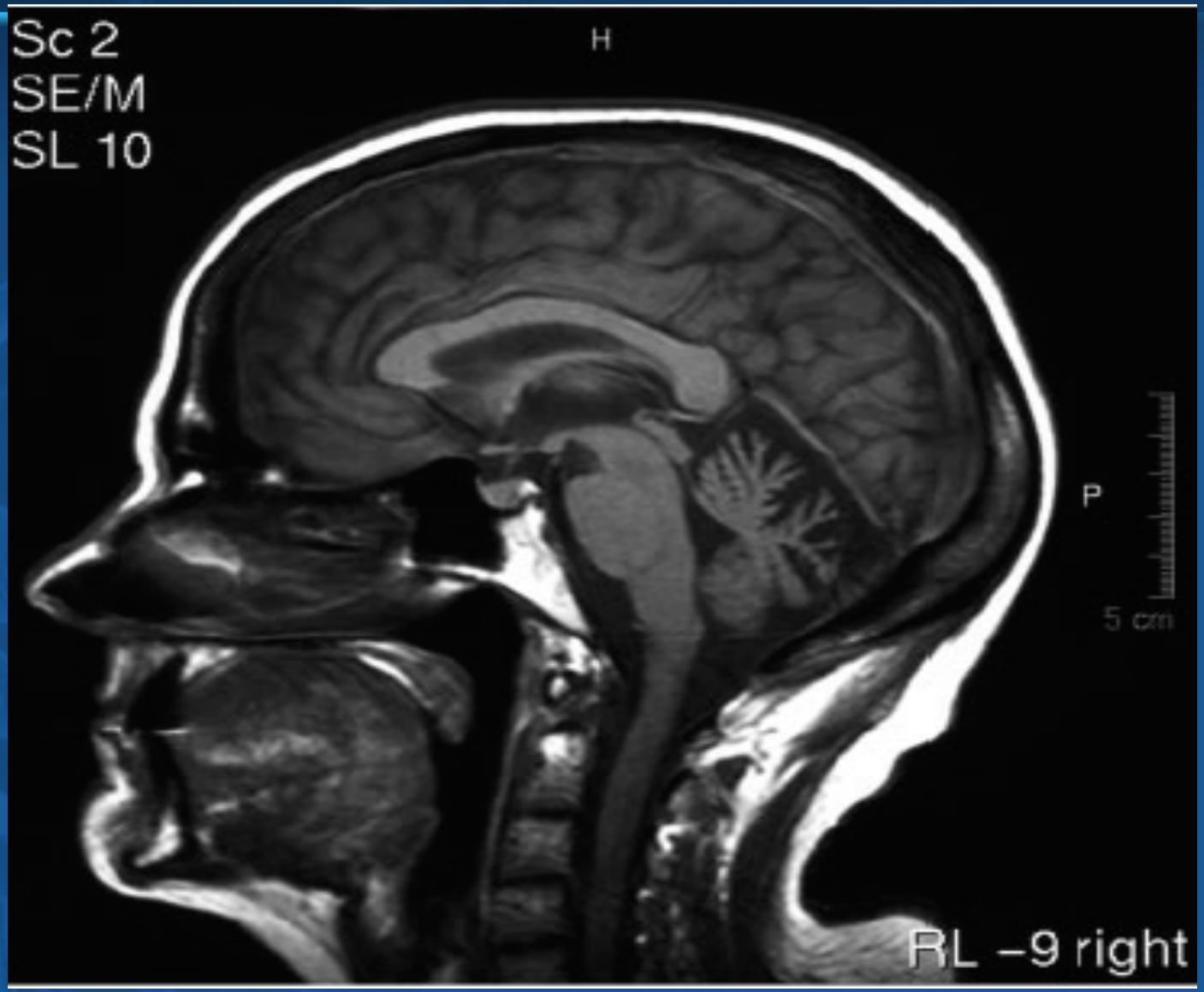




Dopa Responsive dystonia

- 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.*

Ataxias



Definition

- 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

- Neck tilt and 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. Sjogren's syndrome, cisplatin, CCNU, Para-neoplastic disorders, 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 postive
Pendular reflexes	Hypo to areflexia
Reeling, ataxic gait	Stamping gait

Dementia Made Easy !!

Clinical Definition of Dementia

- An acquired disorder of established mental function, defined as deterioration in more than one cognitive domain (Usually memory impairment) below the pre-morbid level, severe enough to impair normal daily functioning (DSM IV).

- Key principles
  - Patient has experienced a decline from some previous higher level of functioning, in contrast to developmental disorders of mental function in which normal mental function had never been achieved.
  - The dementia “significantly interferes with work or usual social activities”

Cognitive Domains

- Deficits apparent in > 1 Cognitive Domain
  - **Recent memory** – ability to learn, retain, and retrieve newly acquired information
  - **Language** – ability to comprehend and express verbal information
  - **Visuospatial function** – ability to manipulate and synthesize nonverbal, geographic, or graphic information
  - **Executive function** – ability to perform abstract reasoning, solve problems, plan for future events, mentally manipulate more than one idea at a time, maintain mental focus in the face of distraction, or shift mental effort easily

NORMAL AGING VS DEMENTIA

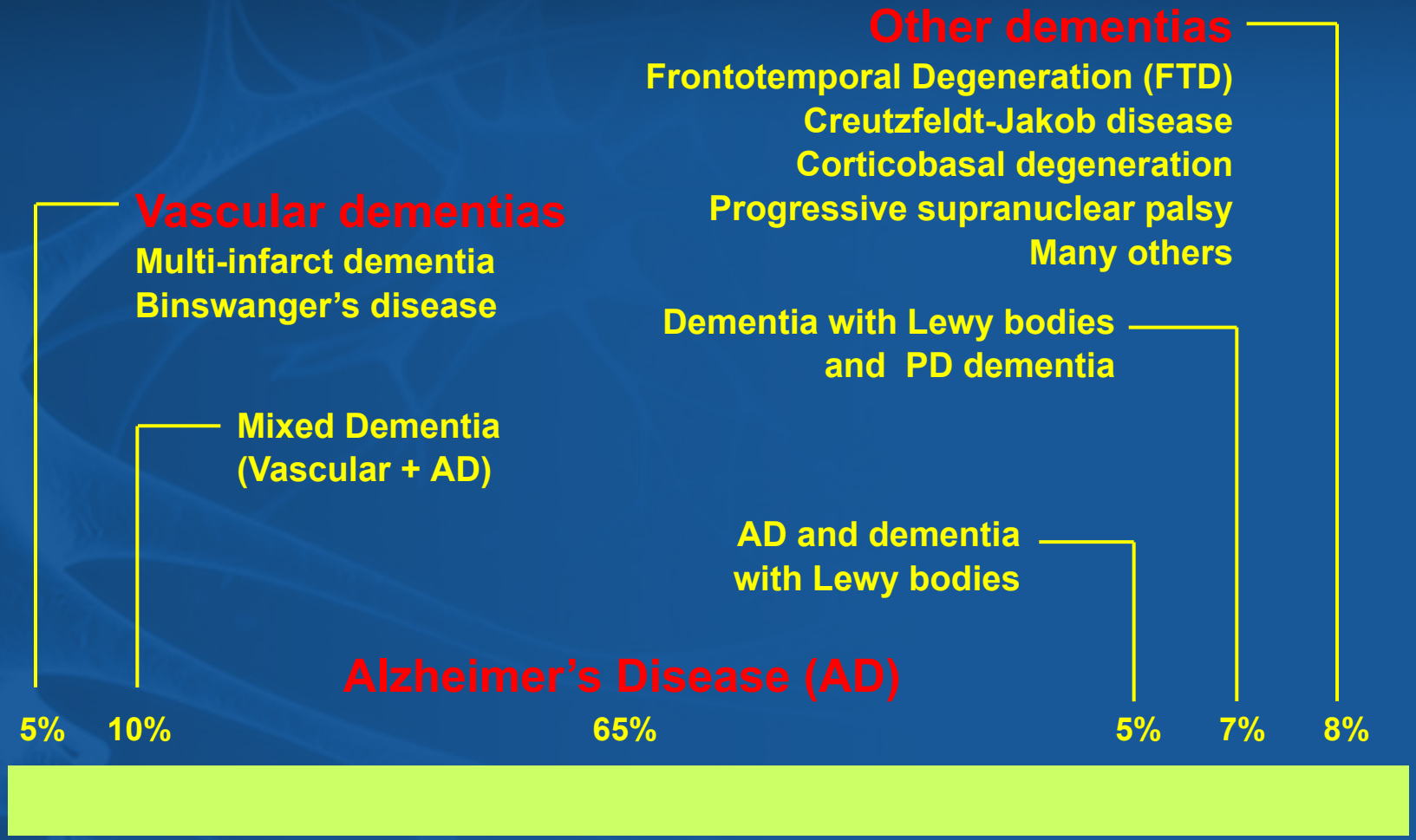
NORMAL AGING	DEMENTIA
Occasional trouble recalling people or places	Not remembering the names of close friends or relatives
Forgetting appointments or events occasionally	Frequently forgetting appointments and events
Taking longer to process information	Trouble verbalizing thoughts, frequent pauses in conversations and substituting common words
Sometimes losing track of a conversation	Regularly repeating statement or questions
Occasionally forgetting where an item is	Consistently misplacing items

OTHER DEMENTIA SYMPTOMS

- Frequent confusion or an inability to focus
- Becoming lost in familiar places
- Mood changes

THE BRIELLE
AT SEAVIEW

The common Dementias



Small et al, 1997; APA, 1997; Morris, 1994.

Classification of Dementias

- Primary degenerative dementias including pure dementia (AD , FTD) and dementia-plus syndromes (DLB …)

- Secondary forms of dementia such as vascular dementia, Infections, demyelination, Trauma , tumors, Subdural hematoma , hydrocephalus, Inborn errors of metabolism, metabolic-nutritional conditions, endocrine, toxic, and immune-mediated disorders – some of them may be reversible

Rapidly Progressive Dementias

- **Potentially reversible conditions**
  - Autoimmune encephalopathies.
  - CNS vasculitis.
  - Toxic
    - Medication misuse, overuse, adverse effects
    - Alcohol related
  - Metabolic disturbances
    - Thyroid, vitamin B12, electrolyte, hepatic, renal and calcium-based disturbances
  - Encephalitis
- **Fatal, irreversible conditions**

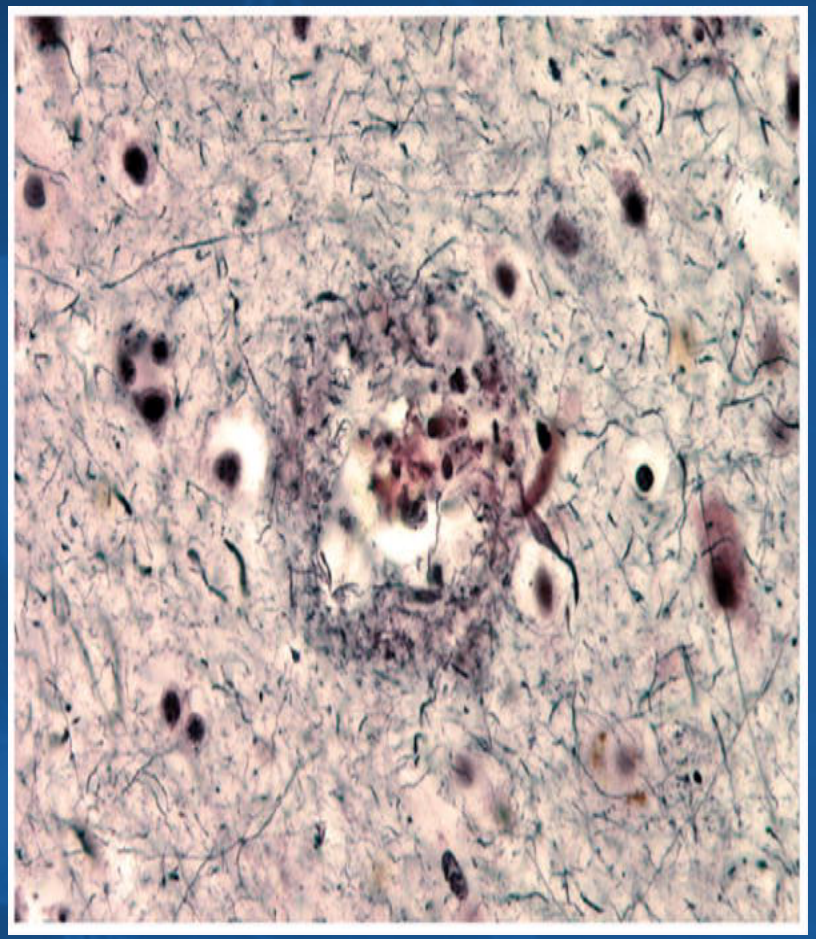
  - Creutzfeldt-Jakob Disease

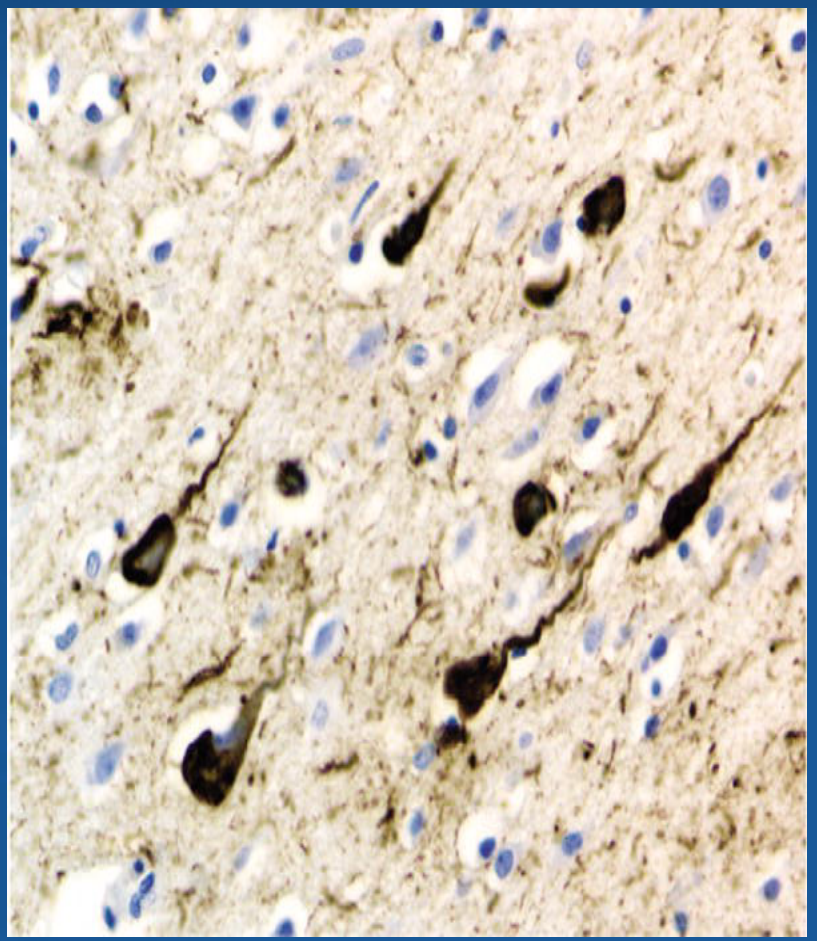
Pathology of Alzheimer's Disease

In patients with AD, atrophy starts in the entorhinal cortex and hippocampus, and as the illness worsens clinically, loss of brain volume increases and spreads more globally to involve most areas of the cortex.

Pathology of Alzheimer's Disease

Extracellular Amyloid Plaques and Intraneuronal Neurofibrillary Tangles



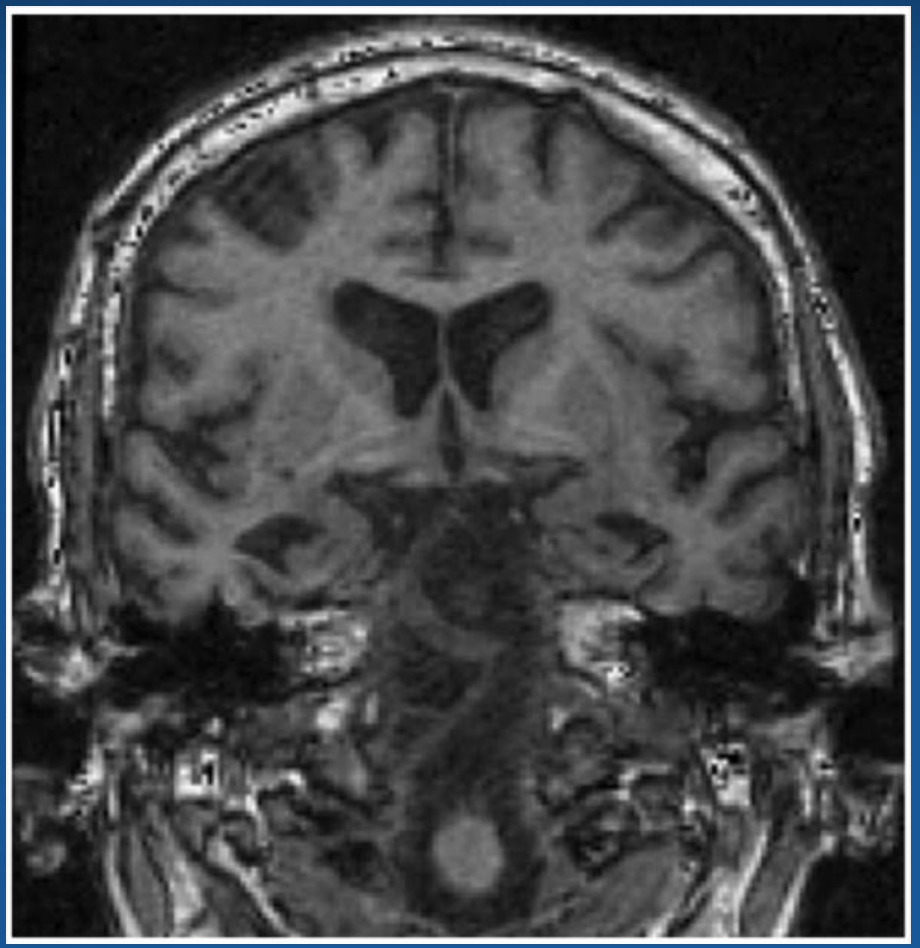


Warning signs of AD

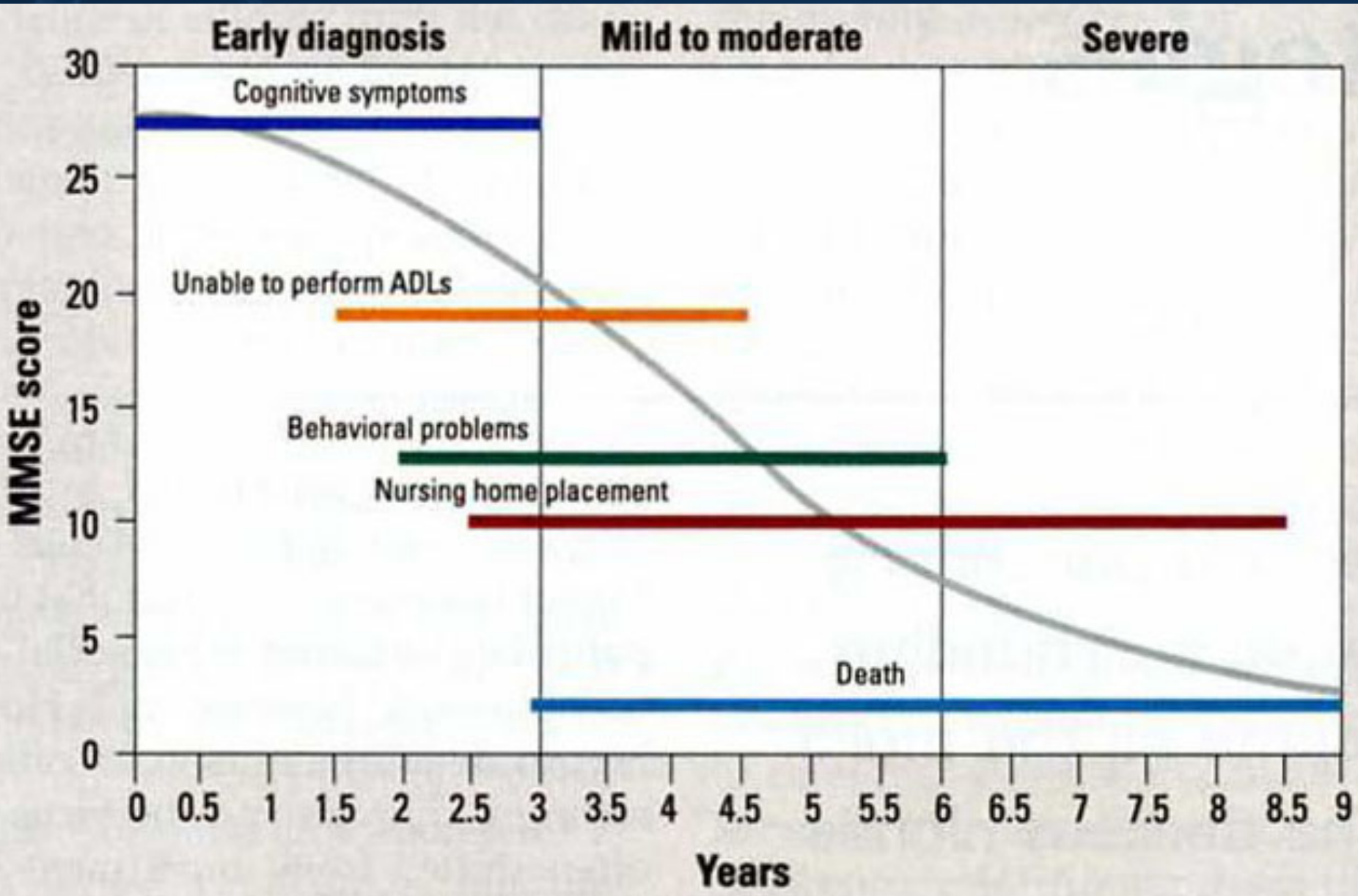
1. Memory loss that affects job skills
2. Difficulty performing familiar tasks
3. Problems with language
4. Disorientation to time and place
5. Poor or decreased judgment
6. Problems with abstract thinking
7. Misplacing things
8. Changes in mood or behavior
9. Changes in personality
10. Loss of initiative

MRI changes

- MRI study with coronal view through the hippocampal region illustrating moderately severe medial temporal atrophy and milder global atrophy typical for Alzheimer's disease



Alzheimer's Disease Progression



Management

- Died in 2004 @ 93 yrs of age

Treatment of AD-Symptomatic therapy
Cholinesterase Inhibitors

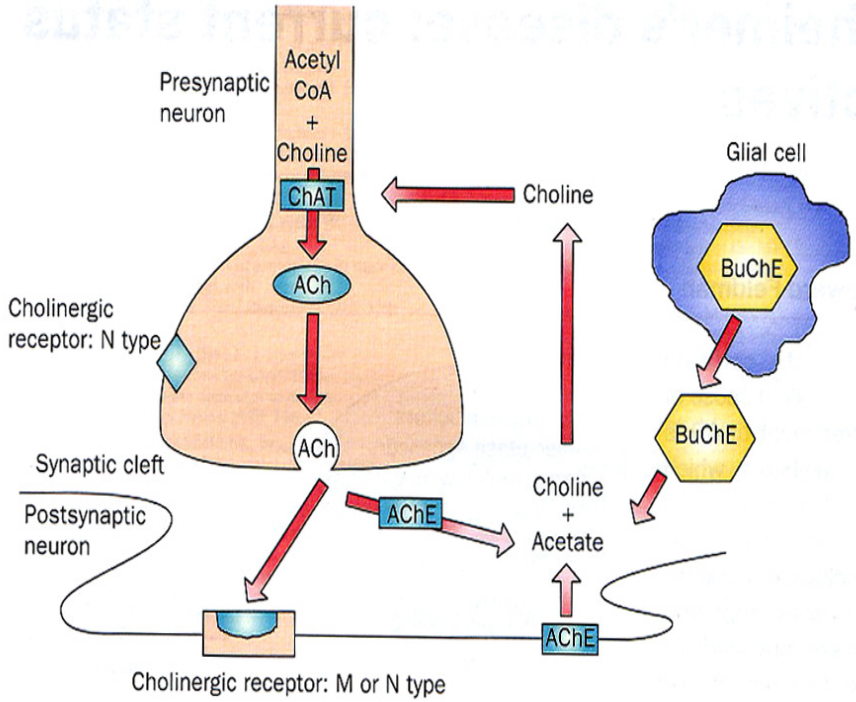


Figure 2. Functional features of the cholinergic system. ACh=acetylcholine; AChE=acetylcholinesterase; BuChE=butyrylcholinesterase; ChAT=choline acetyltransferase; CoA = coenzyme A.

Characteristic	Donepezil	Rivastigmine	Galantamine	Memantine
Chemical class	Piperidine	Carbamate	Phenanthrene alkaloid	Similar to amantadine
Primary mechanism	AChE-I	AChE-I	AChE-I	NMDA receptor antagonist
Other mechanism	None	BuChE-I	Nicotine modulator	HT3 receptor antagonist
Half-life	70 h	90 min	7 h	70 h
Metabolism	Hepatic CYP450 2D6 and 3A4	Synaptic, renal clearance	Hepatic	Partial hepatic

AChE-I = acetylcholinesterase inhibitor; BuChE-I = butyrylcholinesterase inhibitor; NMDA = *N*-methyl-D-aspartate.

Disease-Modifying Therapy

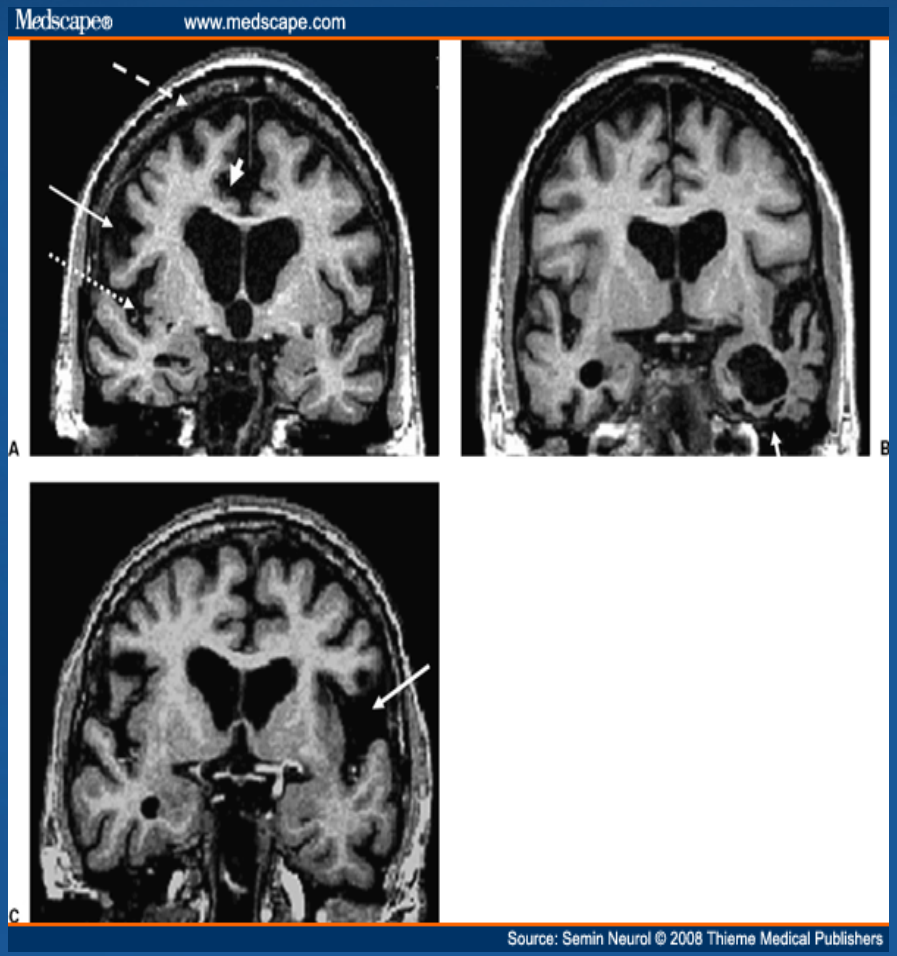
- New Monoclonal Anti-Amyloid Therapies

Treatment for Behavioral and psychiatric symptom

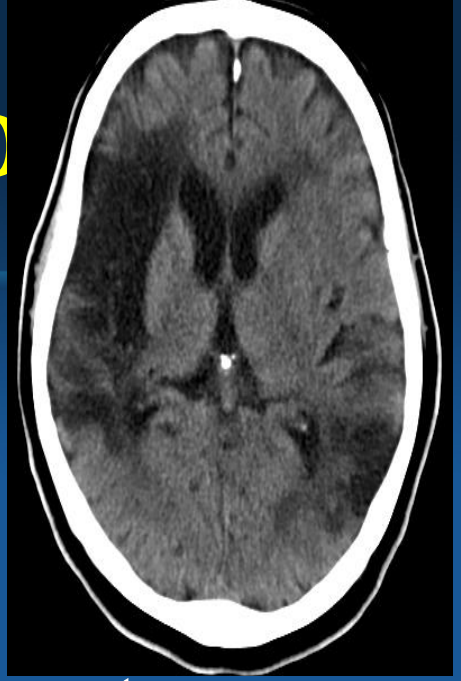
Behavioral	Psychiatric
Wandering	Delusions
Physical aggression	Hallucinations
Restlessness	Anxiety
Agitation	Depression
Pacing	Sleep disturbances
Screaming	Misidentifications
Disinhibition and social inappropriateness	

Frontotemporal Lobar Degeneration

- Uncommon
- Initially may be misdiagnosed as a psychiatric disorder
- Principal manifestations are changes in:
  - Personality
  - Behavior
  - Judgment
  - Impaired reasoning or impaired handling of complex tasks out of proportion to impairments of recent memory or to spatial abilities



Vascular Dementia (VaD



- Infarctions may be silent
  - More commonly non-dominant hemisphere
  - Lacunar infarctions
  - Severe white matter disease
- 1 in 10 to 1 in 5 patients with dementia have a VaD component
- Initial cognitive symptoms depend on location of infarction

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