# CNS LECTURE 2

NEURODEGENERATIVE DISEASES

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# NEURODEGENERATIVE DISEASES

- Characterized by the progressive loss of neurons, typically affecting groups of neurons with functional interconnections.

- Diseases involving the hippocampus and associated cortices: cognitive changes (disturbances of memory, behavior, and language) and progress to dementia (ex. Alzheimer disease)
- Diseases that affect the basal ganglia: movement disorders (ex. hypokinetic, as with Parkinson disease) or (hyperkinetic, as with Huntington disease)
- Diseases that affect the cerebellum: ataxia, as seen in the spinocerebellar ataxias.

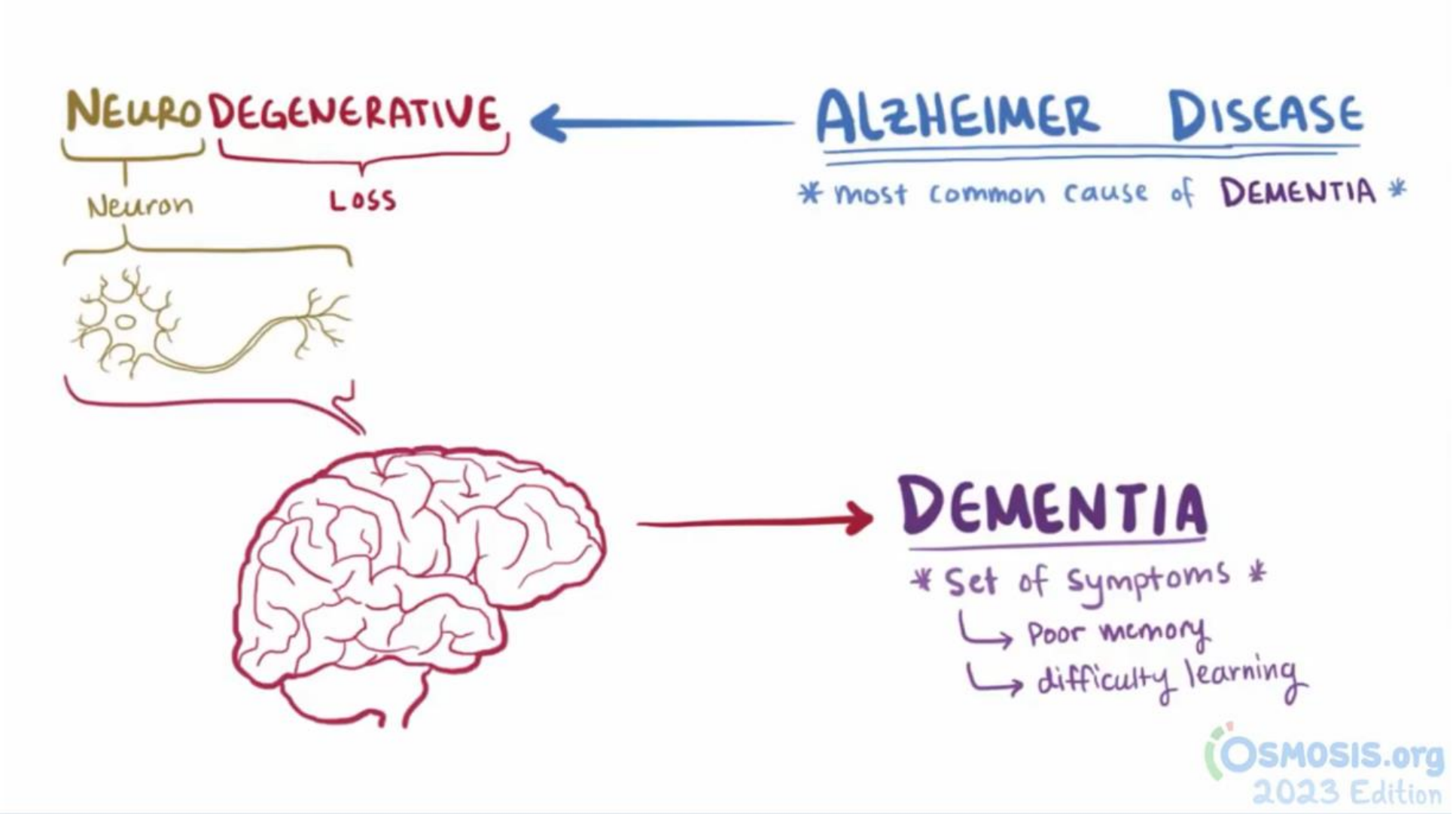
# NEURODEGENERATIVE DISEASES

- Characterized by loss of neurons in gray matter
- Accumulation of intra and/or extracellular proteins
- - Cortex degeneration: dementia;
  - Brainstem and basal ganglia degeneration: movement disorders
- Increased incidence with age

# NEURODEGENERATIVE DISEASES

- **Dementia:** is an overall term for diseases and conditions characterized by a decline in memory, language, problem-solving and other thinking skills that affect a person's ability to perform everyday activities.

Alzheimer's is the most common cause of dementia



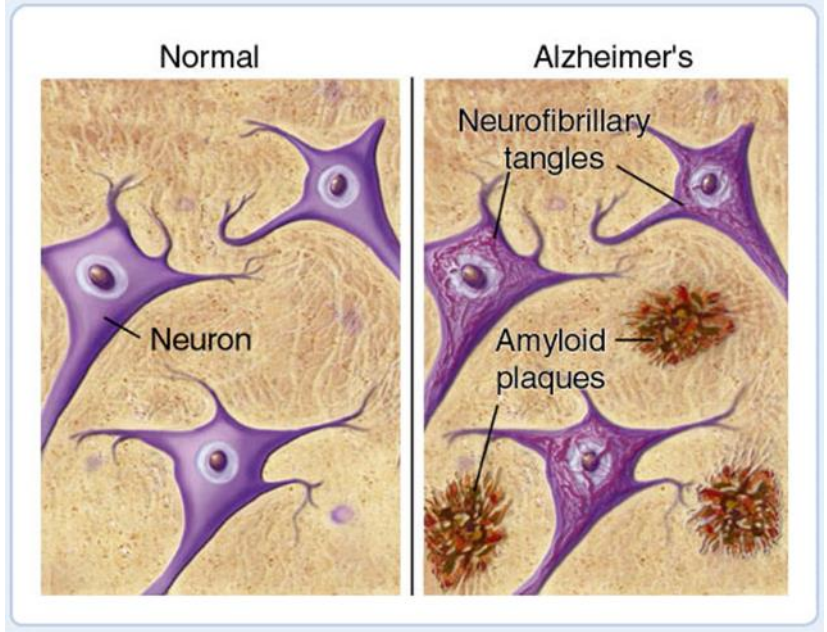

https://www.osmosis.org/learn/Alzheimer_disease

# ALZHEIMER DISEASE (AD)

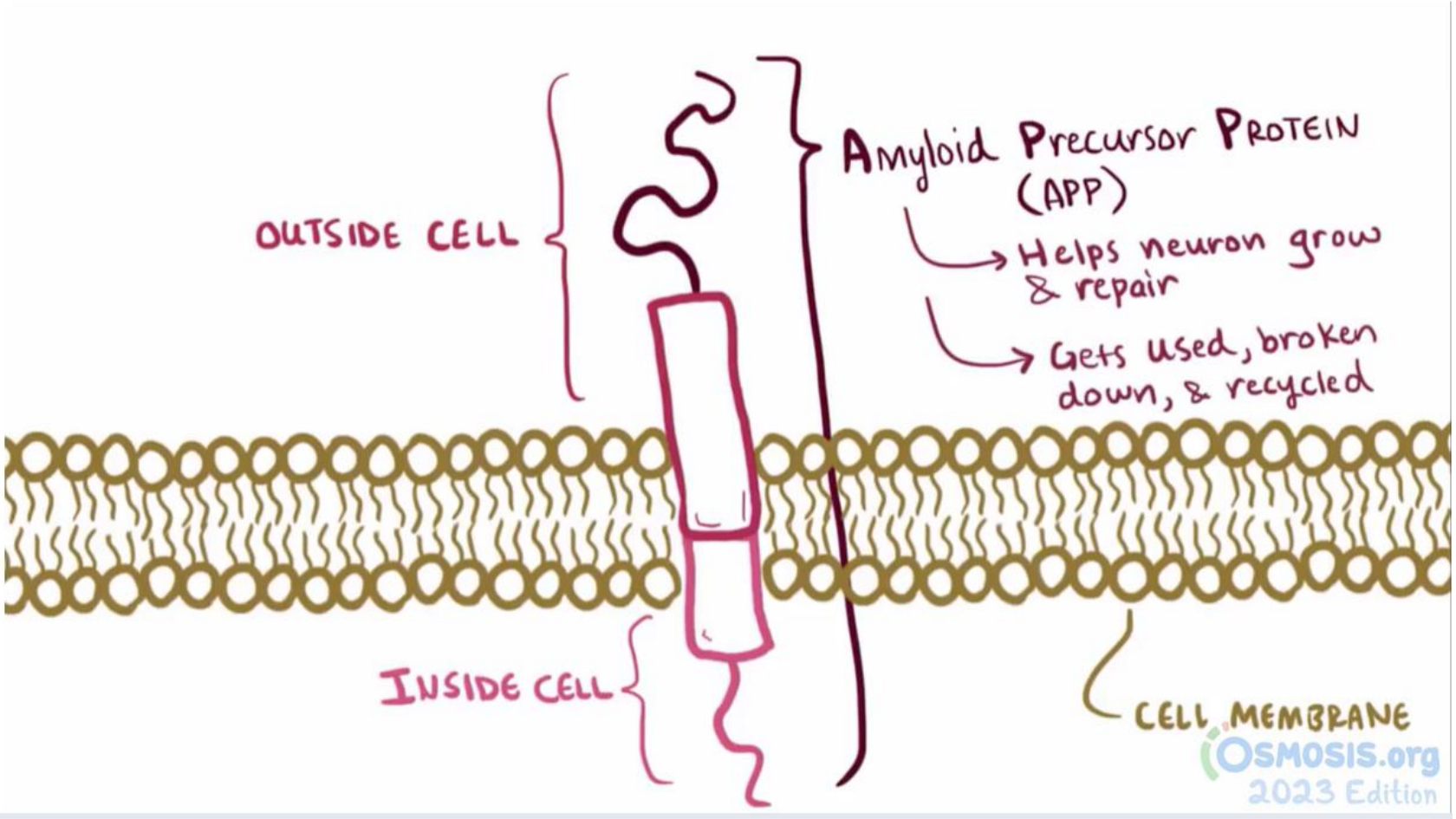

- The fundamental abnormality in AD is the accumulation of two proteins **(Aβ and tau) in the forms of plaques and tangles**, respectively;
- Resulting in secondary effects including <u>neuronal dysfunction, neuronal death, and inflammatory reactions.</u>

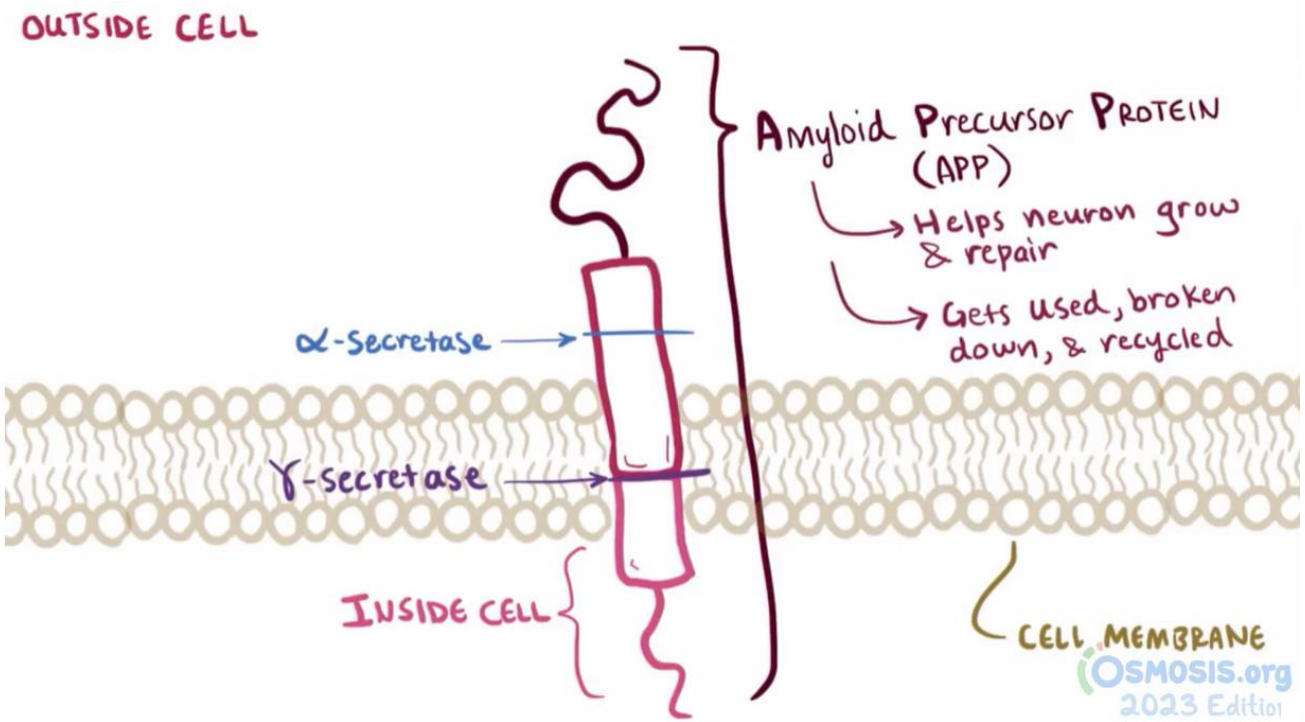
- **Microscopic findings in Alzheimer's disease** :

  **1- Extracellular AB amyloid deposits.**
  **2- Intracellular neurofibrillary tangles**
  (tuft of hyperphosphorylated tau protein)

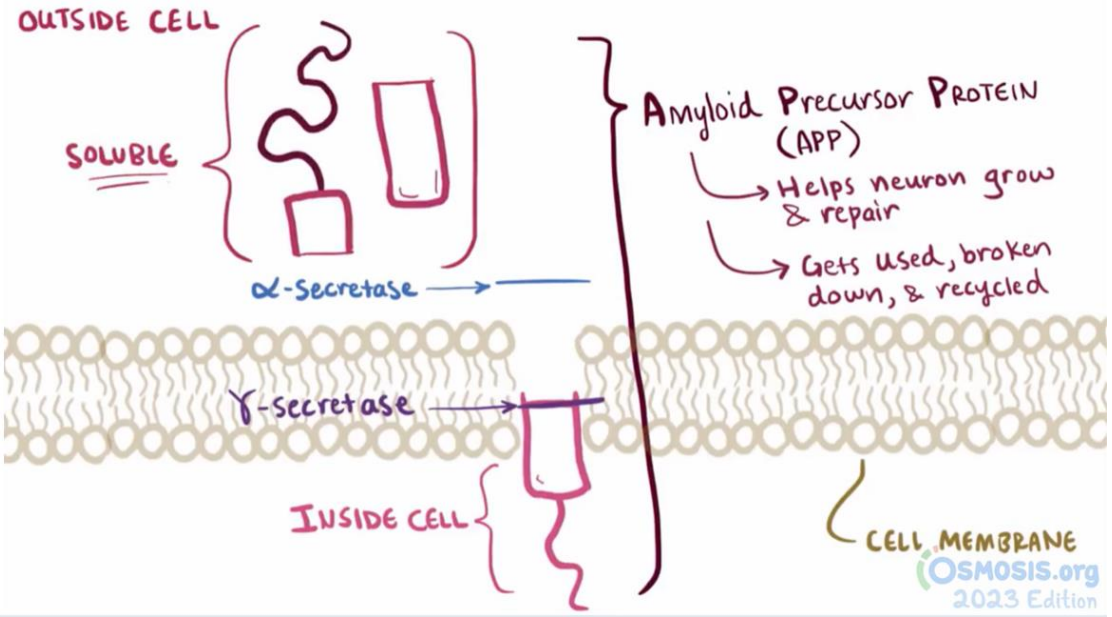


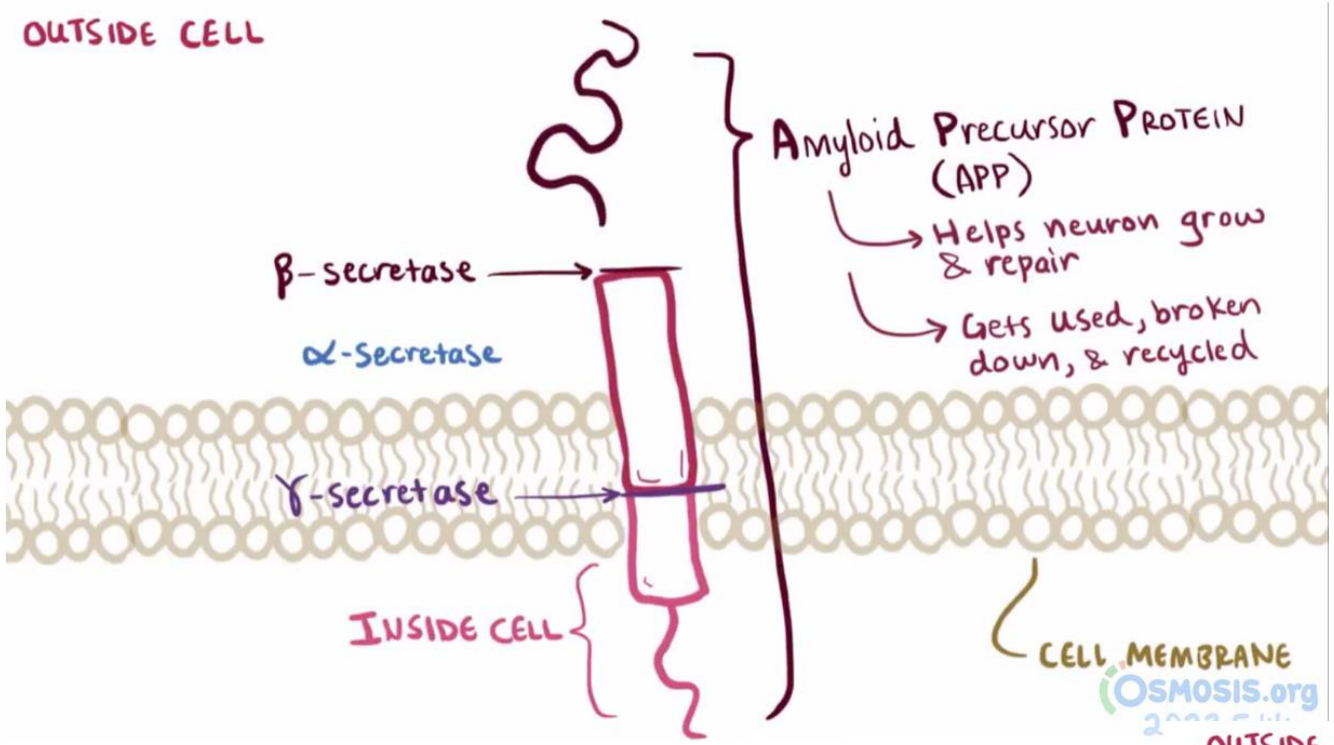
# EXTRACELLULAR AB AMYLOID PLAQUES






Normally, APP is degraded by alpha-secretase and gamma secretase. (Soluble)

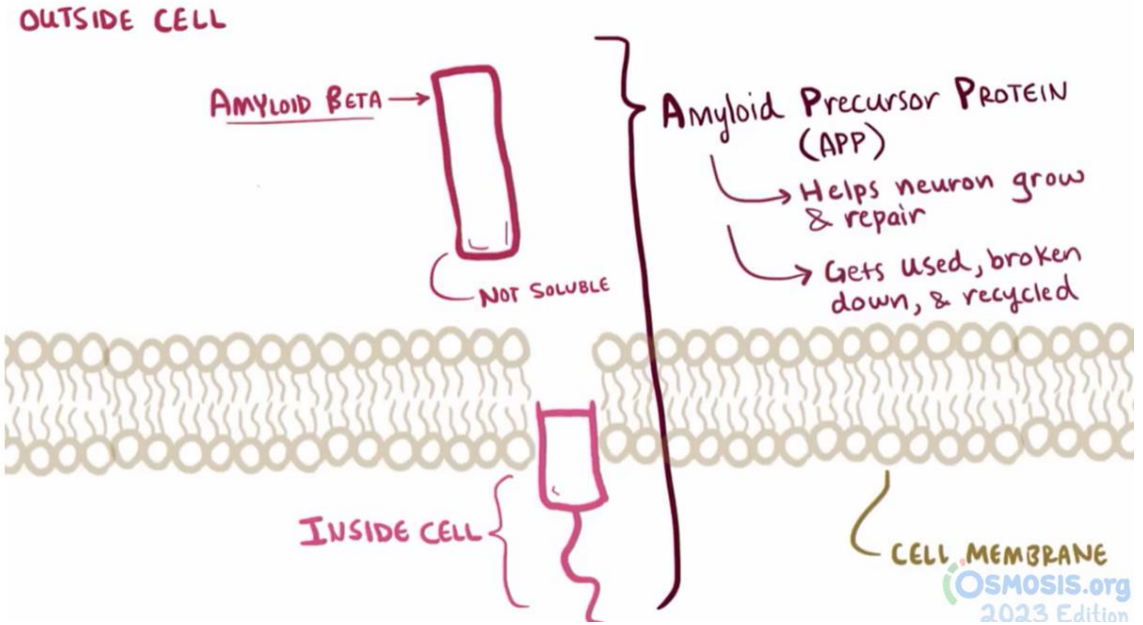


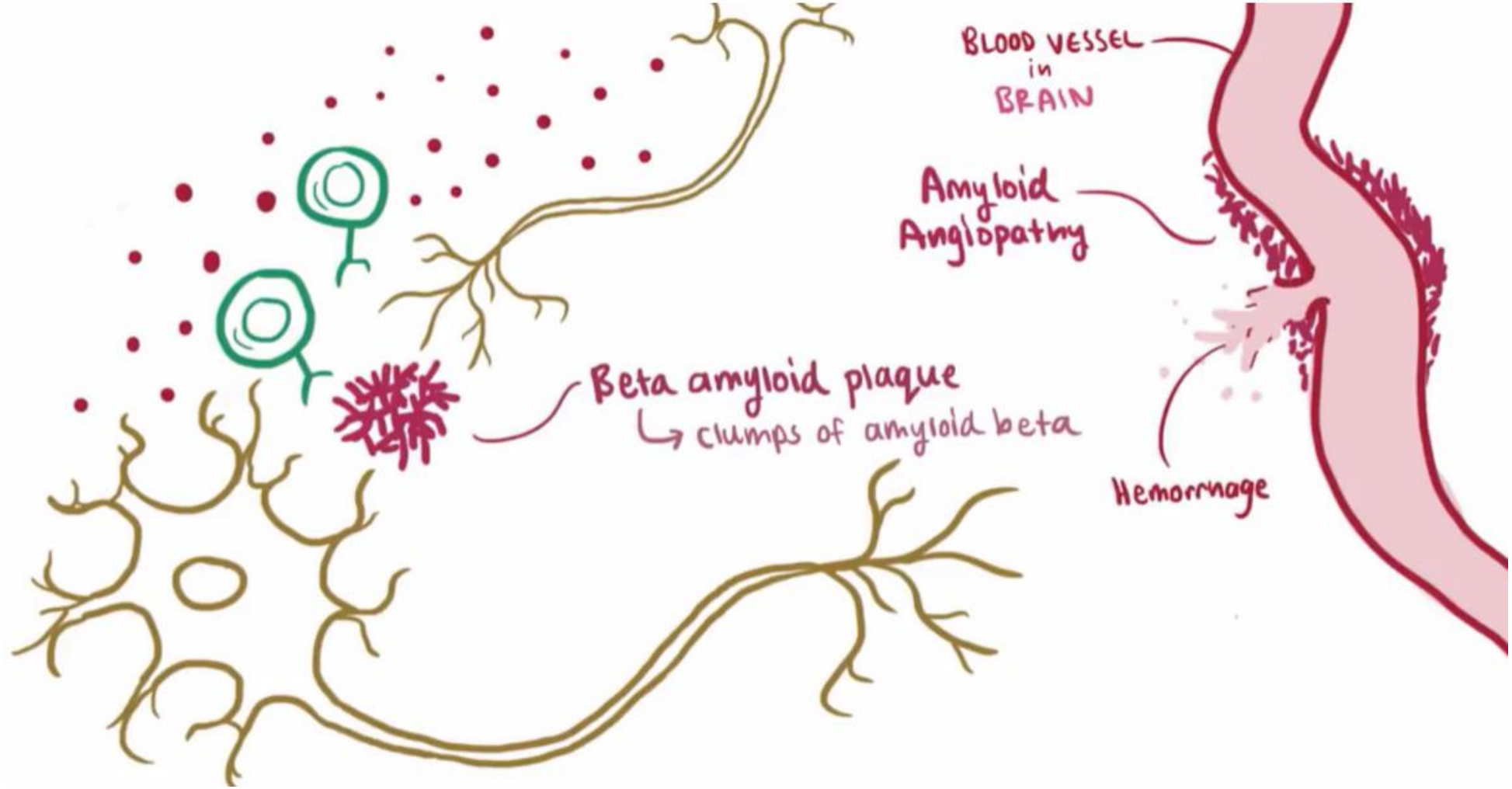



In Alzheimer disease:

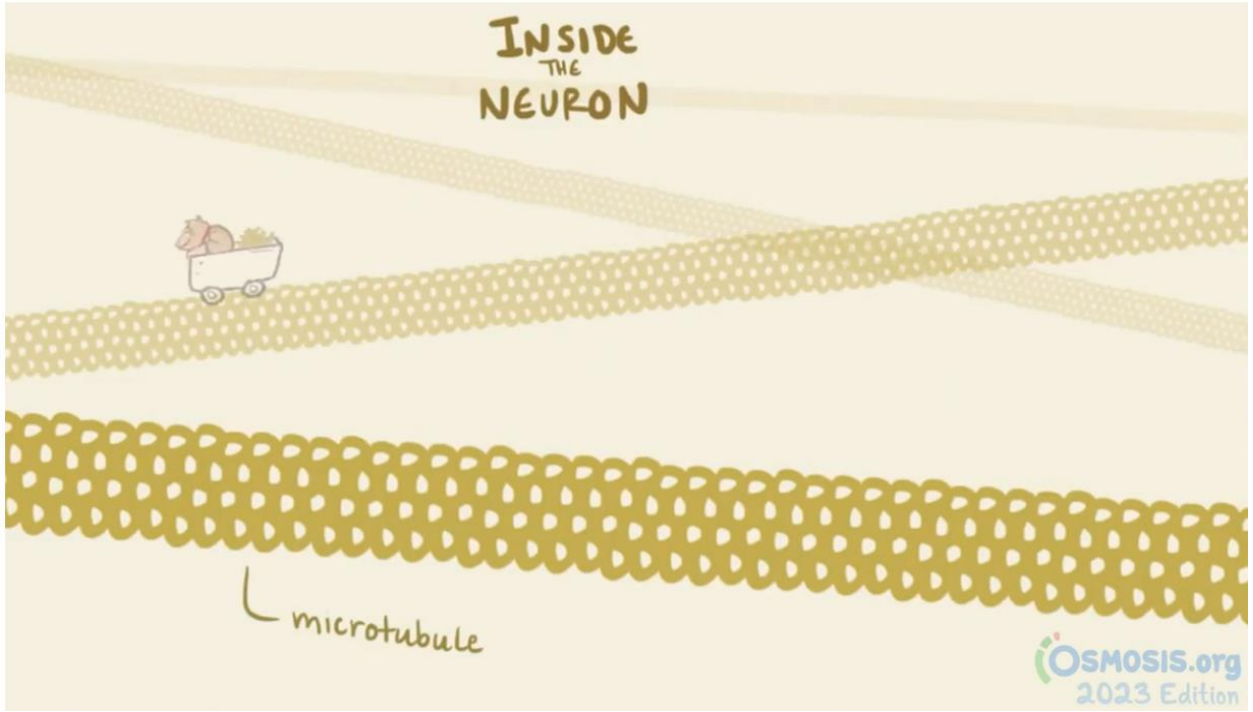
There is abnormal degradation via Beta-secretase (Not soluble)

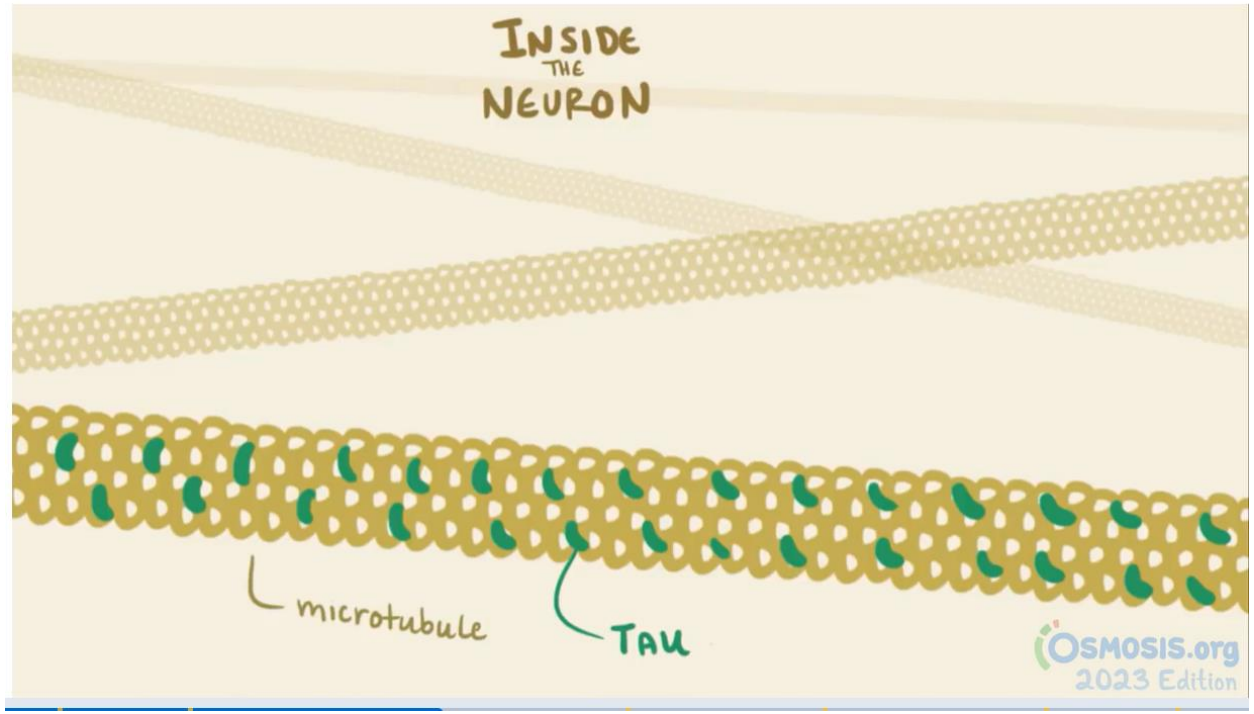
Leads to extracellular accumulation of AB amyloid plaques

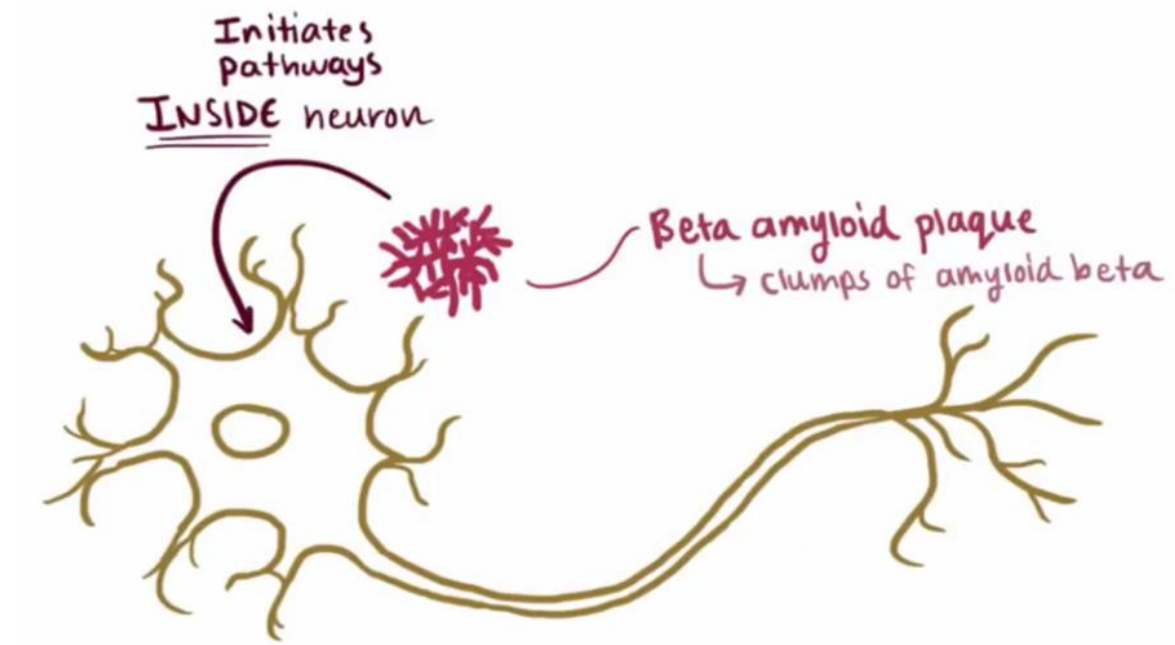



BLOOD VESSEL in BRAIN
Amyloid Angiopathy
Beta amyloid plaque
↳ clumps of amyloid beta
Hemorrhage

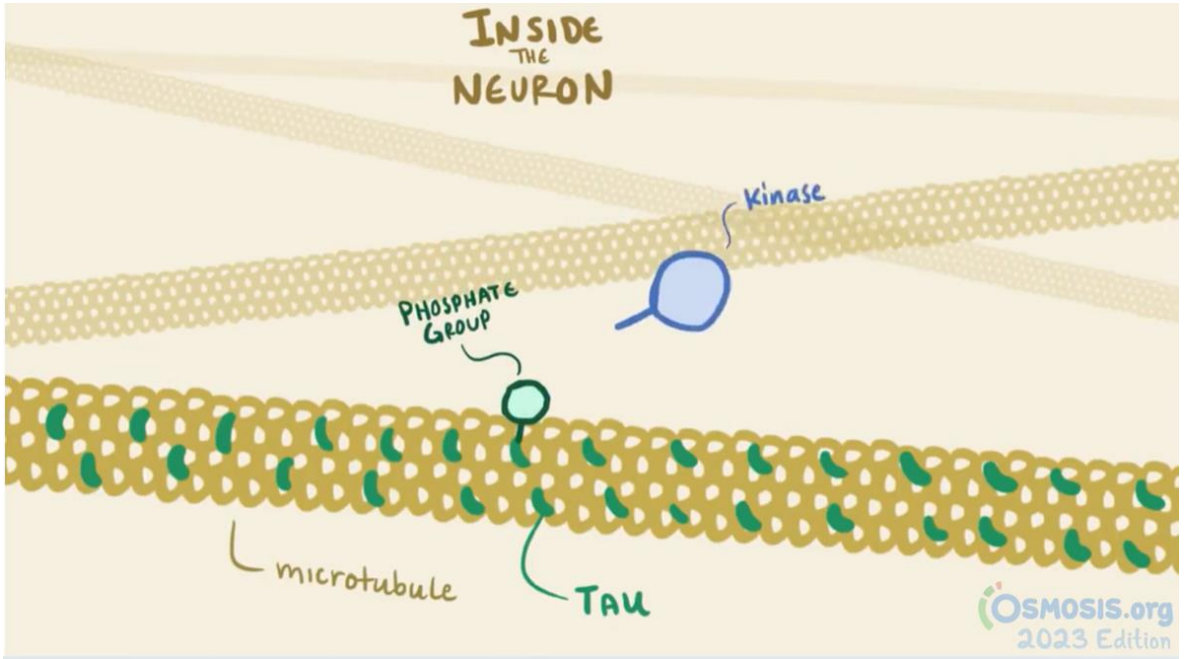
# INTRACELLULAR NEUROFIBRILLARY TANGLES

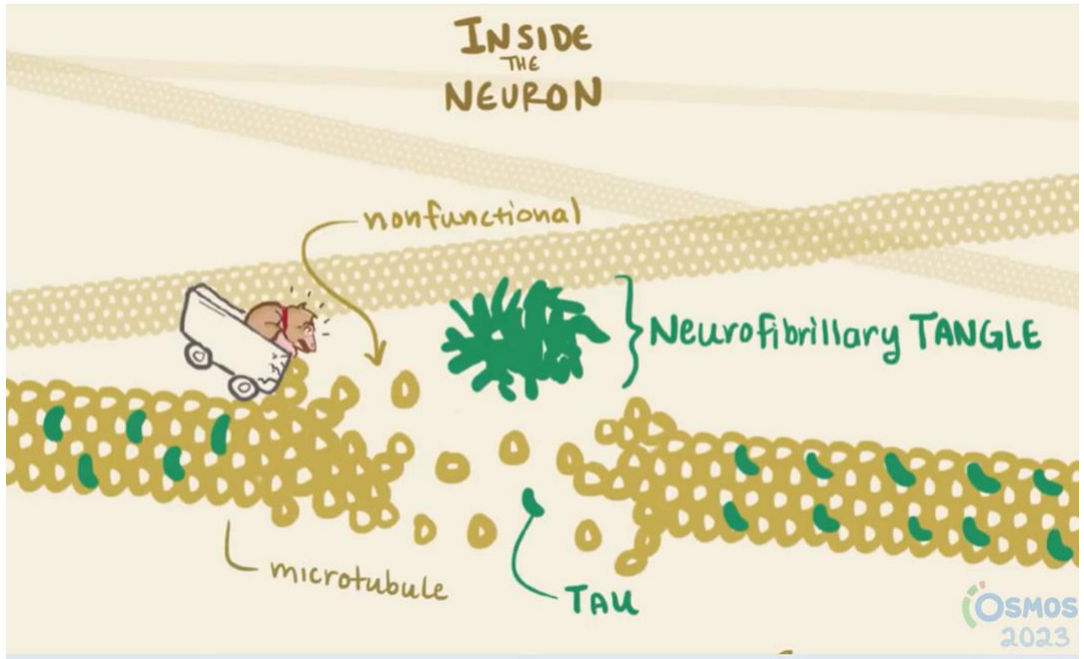





In Alzheimer disease:
Tau protein becomes pathologically hyperphosphorylated, leading to Tau aggregates >>> stop supporting microtubules>>>> forms neurofibrillary tangles >> obstruct neuronal signaling>> neuronal apoptosis



# ALZHEIMER DISEASE

**Alzheimer disease (AD) is the most common cause of dementia in older adults**

- The incidence: 65 to 74 years of age (3%), 75 to 84 years (19%) of age, and in those older than 84 years (50%)
- Most cases of AD are sporadic, but at least 5% to 10% are familial.

**Sporadic (95% of cases) Seen in elderly:** **(ApoE normally breakdown beta amyloid)**

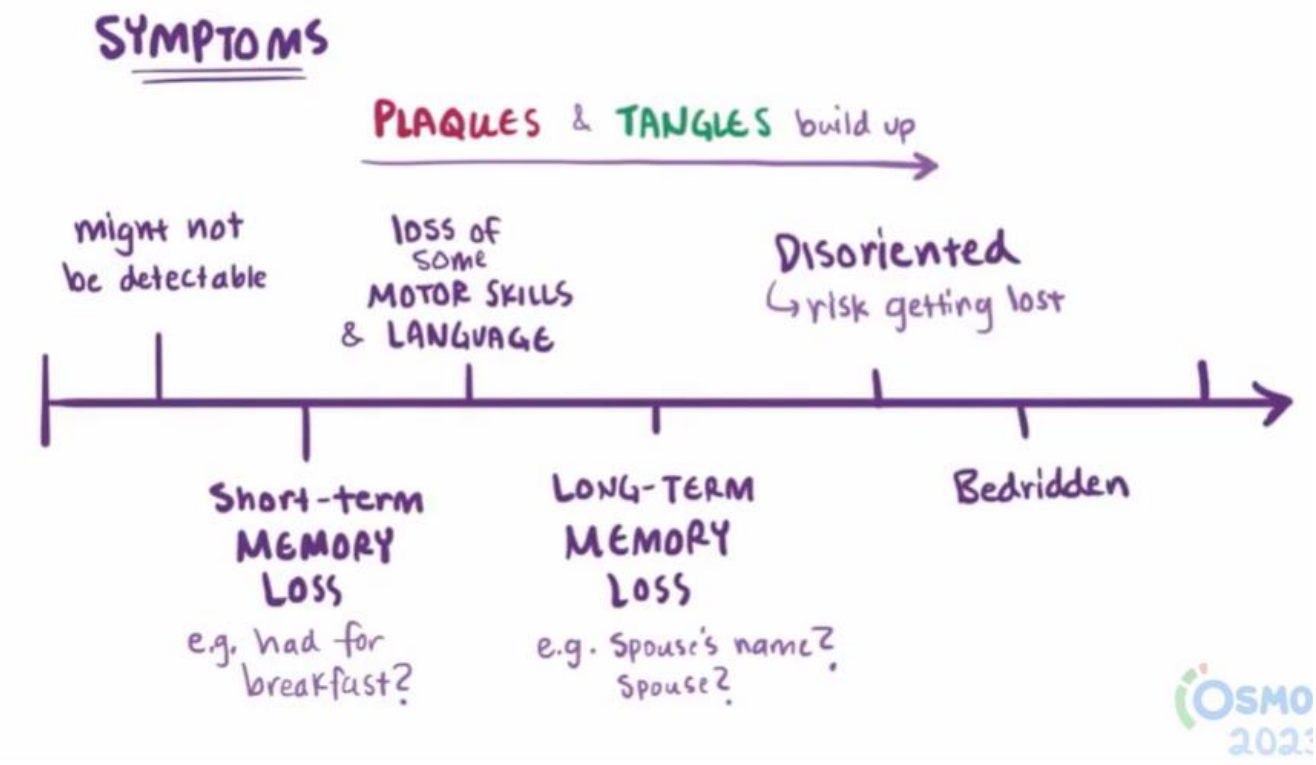
* e4 allele apolipoprotein E : increase risk
* e2 allele apolipoprotein E : decrease risk

**Familial cases (5% of cases) Early onset:**

* Presenilin 1 and 2 mutation (gamma-secretase subunits are mutated)
* Down's syndrome (dementia seen around 40) (APP gene is located on ch. 21)

# ALZHEIMER DISEASE

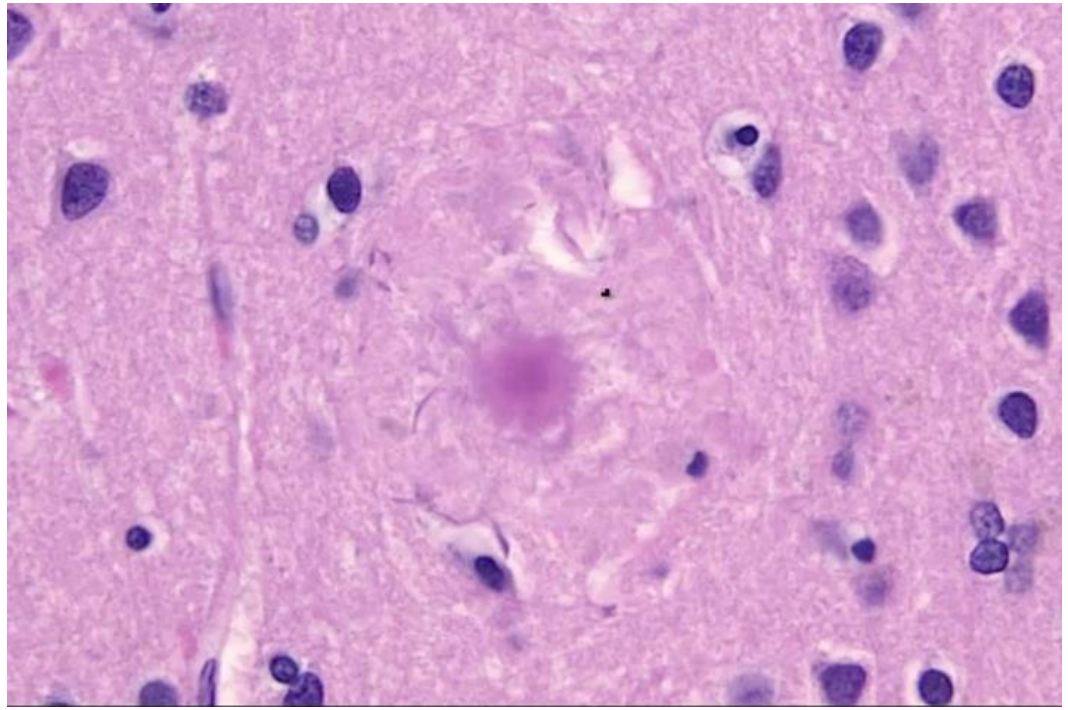
- Insidious onset of impaired higher intellectual function, memory impairment, and altered mood and behavior.
- Over time, disorientation and aphasia
- In the final phases: profoundly disabled, often mute and immobile.
- Death usually occurs from intercurrent pneumonia or other infections.



# MICROSCOPIC FINDINGS IN ALZHEIMER'S DISEASE

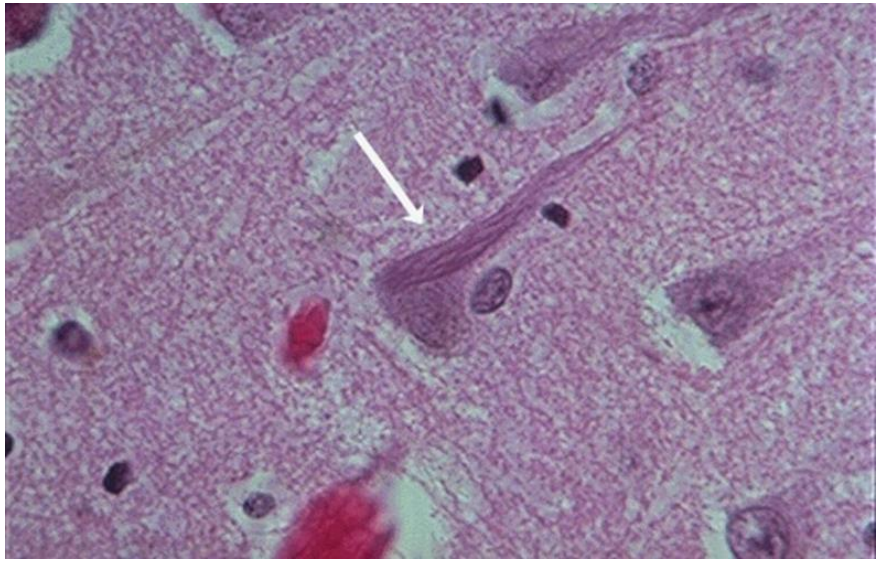
Extracellular AB amyloid deposits.

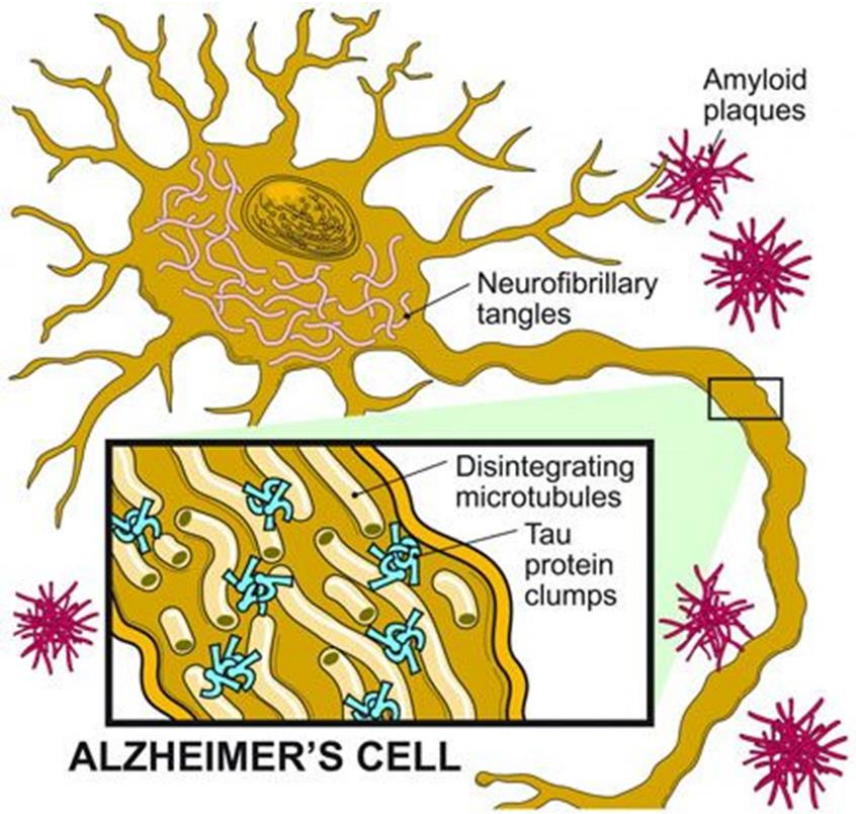
* Neuritic plaques ( A-Beta amyloid deposits with entangled neuritic process)



# MICROSCOPIC FINDINGS IN ALZHEIMER'S DISEASE

Intracellular neurofibrillary tangles (tuft of hyperphosphorylated tau protein):
Tau protein.





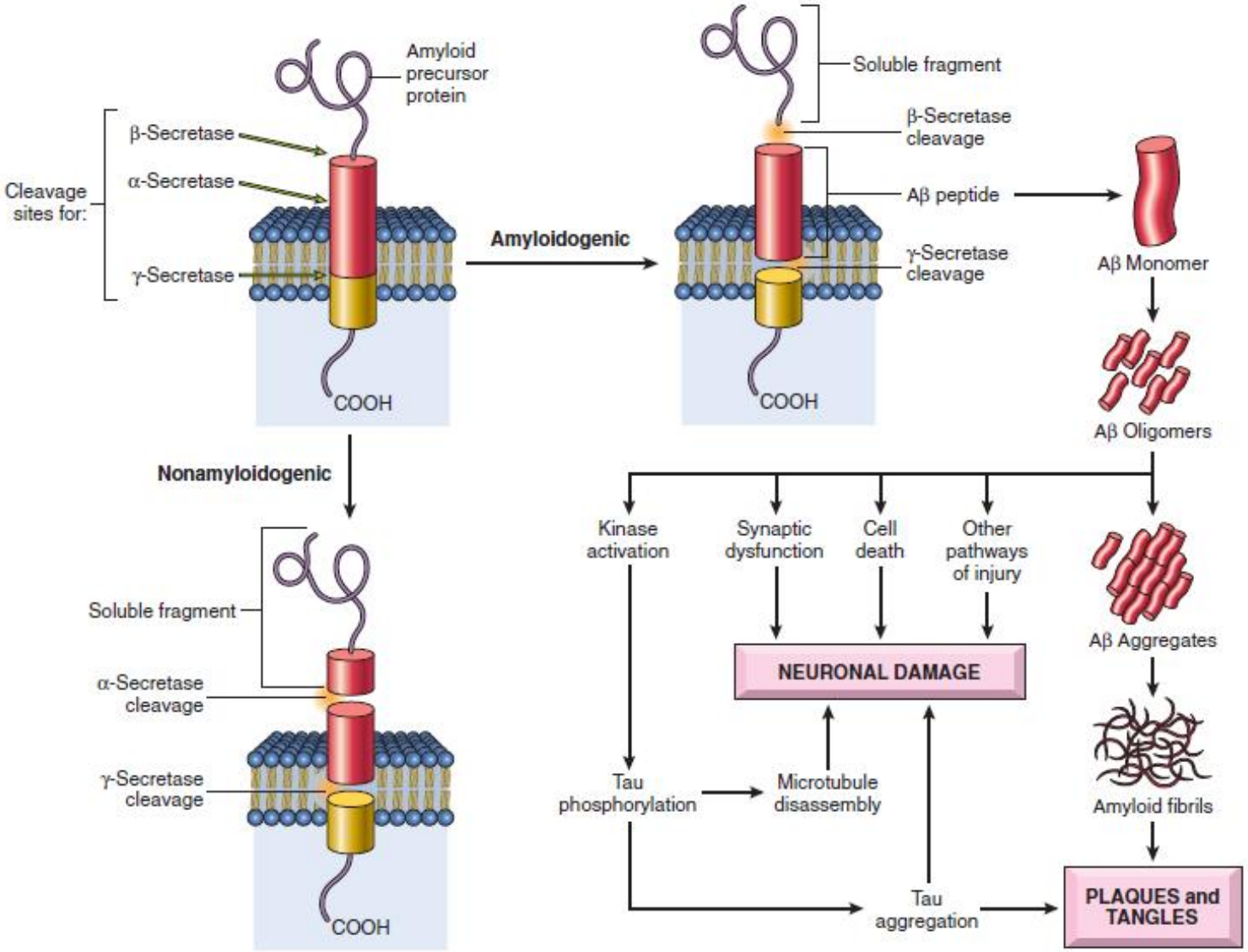
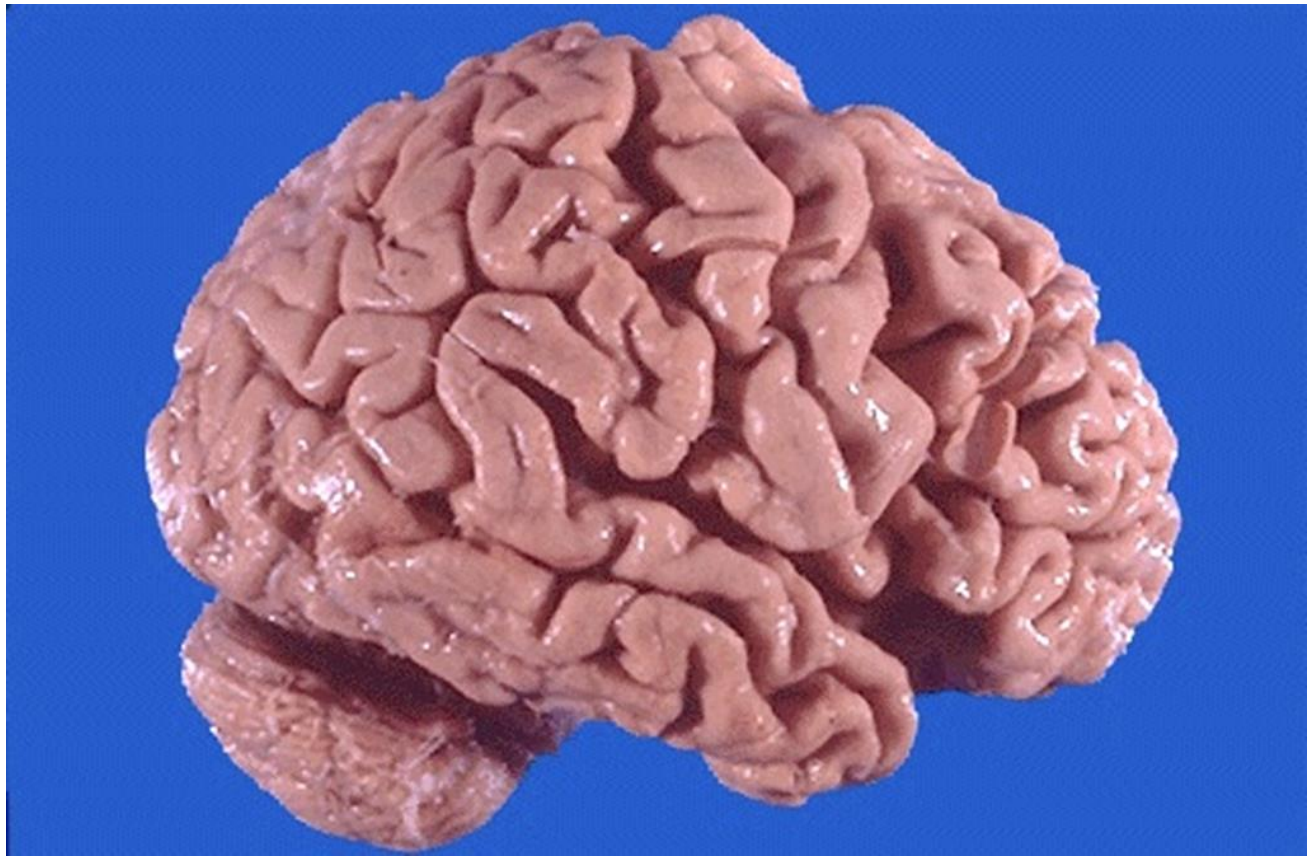


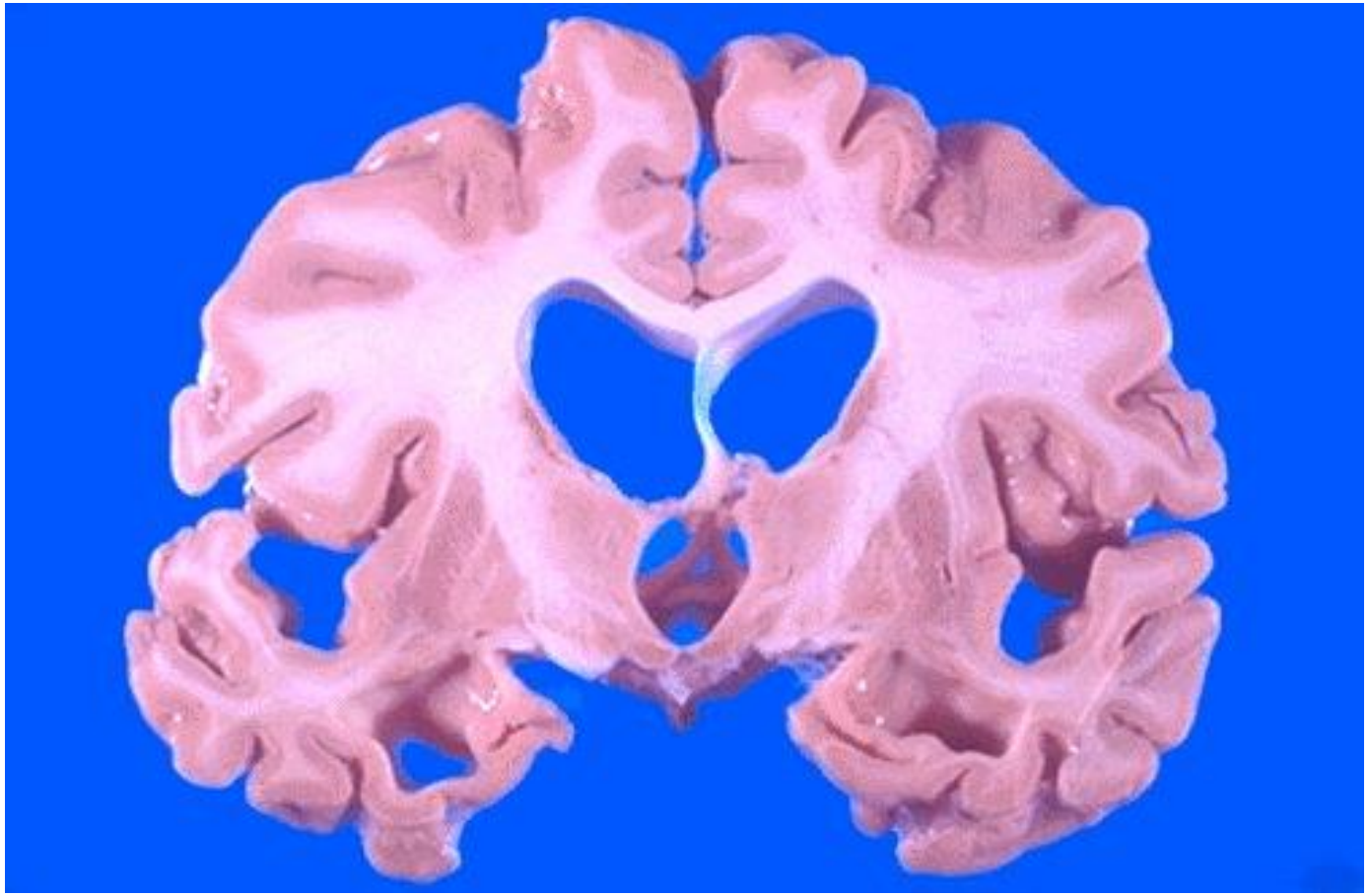

**Fig. 23.24** Aβ peptide genesis and consequences in Alzheimer disease. Amyloid precursor protein cleavage by α-secretase and γ-secretase produces a harmless soluble peptide, whereas amyloid precursor protein cleavage by β-amyloid–converting enzyme (BACE) and γ-secretase releases Aβ peptides, which form pathogenic aggregates and contribute to the characteristic plaques and tangles of Alzheimer disease.

# GROSS FINDINGS IN ALZHEIMER'S DISEASE



The cerebral atrophy seen here mainly in the frontal and parietal regions is characterized by narrowed gyri along with widened sulci.

# GROSS FINDINGS IN ALZHEIMER'S DISEASE



The progressive cortical atrophy with Alzheimer disease leads to compensatory dilation of the cerebral ventricles known as "hydrocephalus ex vacuo".

# FRONTOTEMPORAL LOBAR DEGENERATION (FTLD)

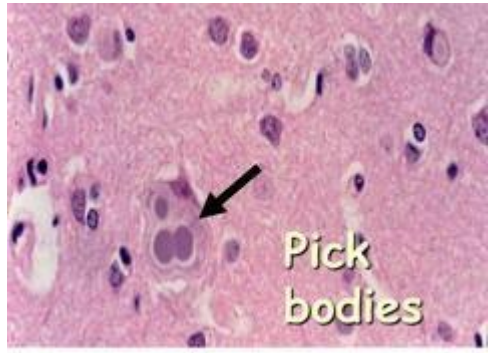
- FTLD: disorders that affect the frontal and/ or temporal lobes.
- Progressive deterioration of language and changes in personality.
- Also referred to as **frontotemporal dementias**.
- Depending on site affected (frontal or temporal), behavioral changes or language problems may dominate.
- Behavioral and language problems precede memory disturbances (a distinction between FTLD and AD).
- The onset of symptoms occurs at younger ages for FTLD than for AD.

# FRONTOTEMPORAL LOBAR DEGENERATION (FTLD)

Two pathologic subgroups exist (based on type of inclusions):

I. **FTLD-tau:** such as **Pick disease,** which is associated with smooth, round inclusions known as Pick bodies.

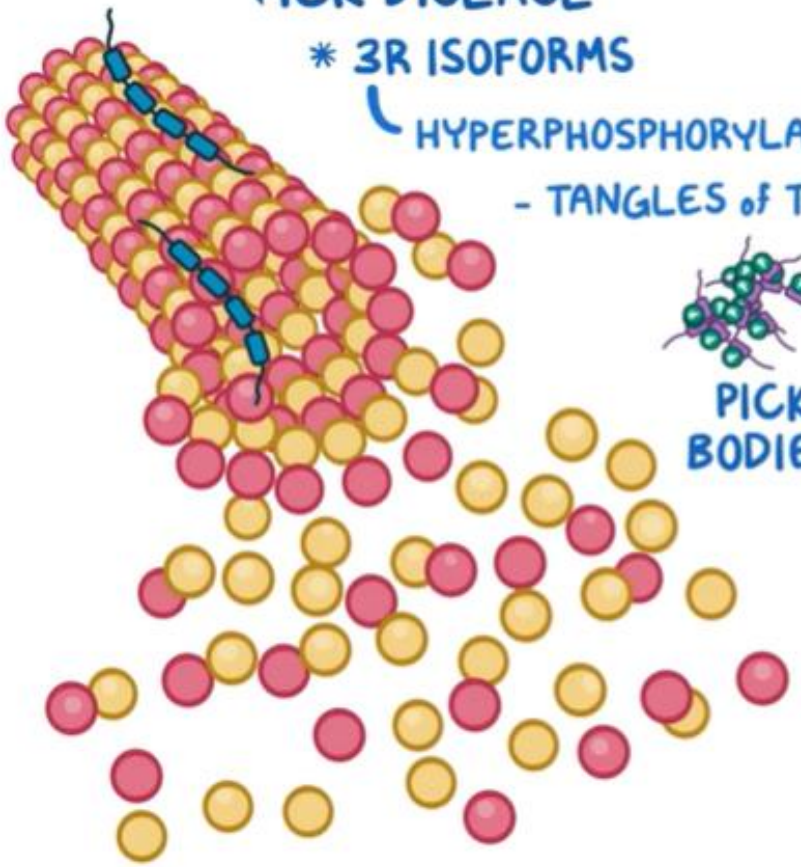
II. **FTLD-TDP43:** is characterized by aggregates containing the DNA/RNA-binding protein TDP43



# FRONTOTEMPORAL DEMENTIA

## PICK DISEASE

* 3R ISOFORMS
  - HYPERPHOSPHORYLATED
  - TANGLES of TAU PROTEINS



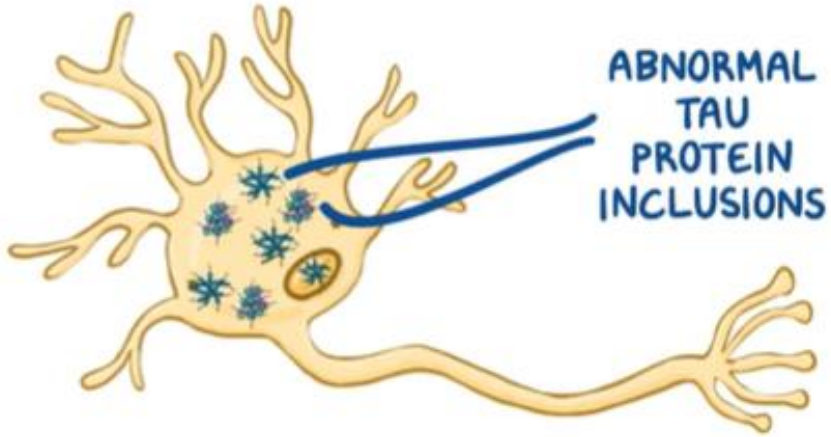


PICK BODIES

## TAUOPATHY

## ALZHEIMER'S DISEASE

* NEUROFIBRILLARY TANGLES
  - 3R and 4R TAU ISOFORMS



ABNORMAL TAU PROTEIN INCLUSIONS

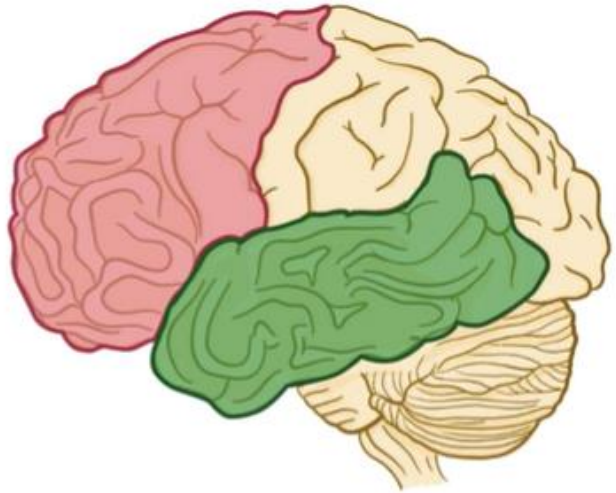
* INTRACELLULAR INCLUSIONS
  - TDP-43

# SYMPTOMS

* DETERMINED by PATTERN of BRAIN ATROPHY

## FRONTAL LOBE

* BEHAVIORAL VARIANT
  - PERSONALITY & BEHAVIOR CHANGES
  - MOST COMMON

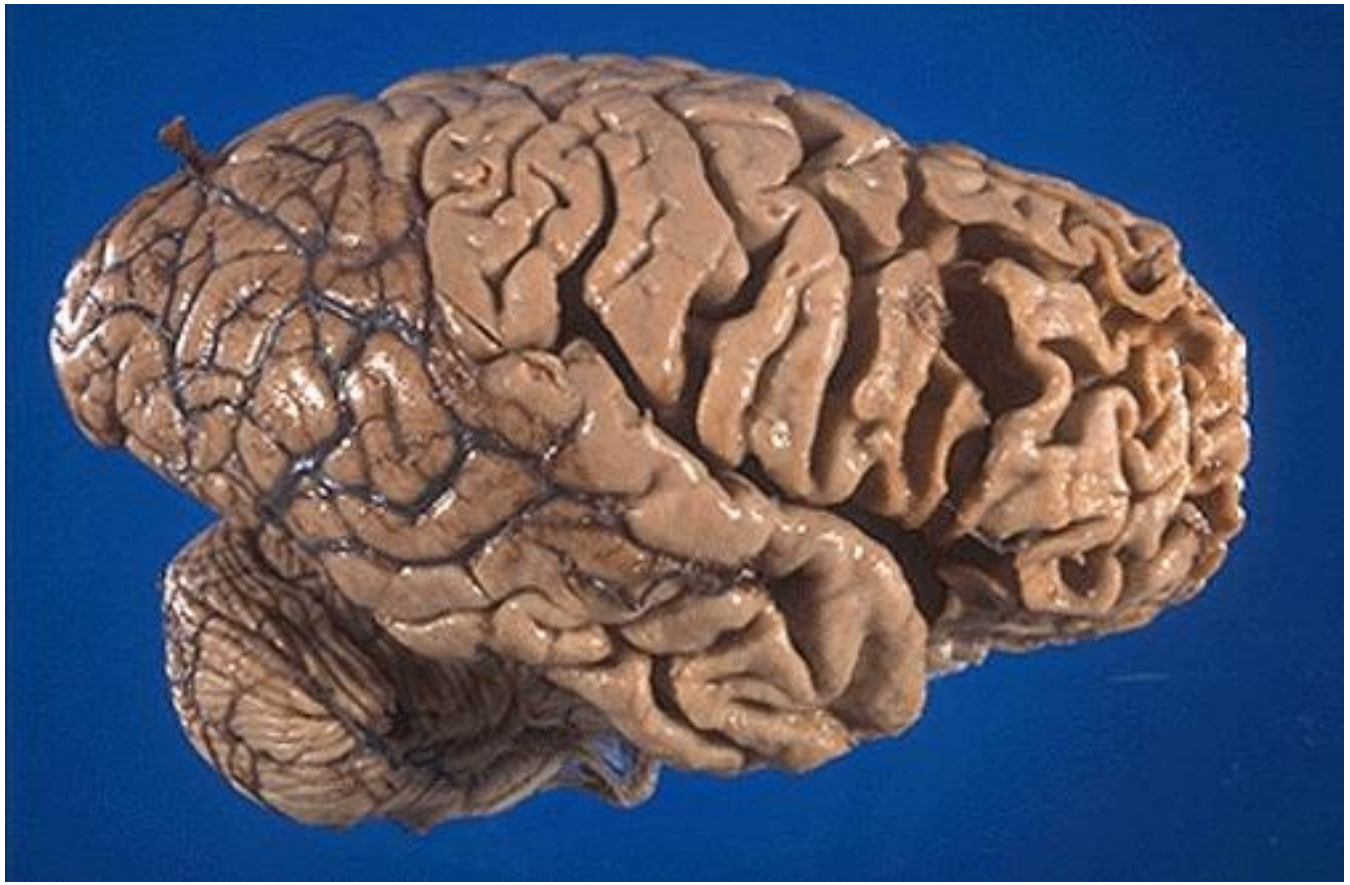


* ATROPHY PROGRESSES
  - DEMENTIA
  - STRUGGLE with:
    - MEMORY
    - CONCENTRATION
    - ABILITY to LEARN NEW THINGS

## TEMPORAL LOBE

* SEMANTIC VARIANT PRIMARY PROGRESSIVE APHASIA
  - DIFFICULTY FINDING the RIGHT WORDS
* NONFLUENT VARIANT PRIMARY PROGRESSIVE APHASIA
  - DIFFICULTY SPEAKING WHILE KNOWING the MEANINGS of INDIVIDUAL WORDS

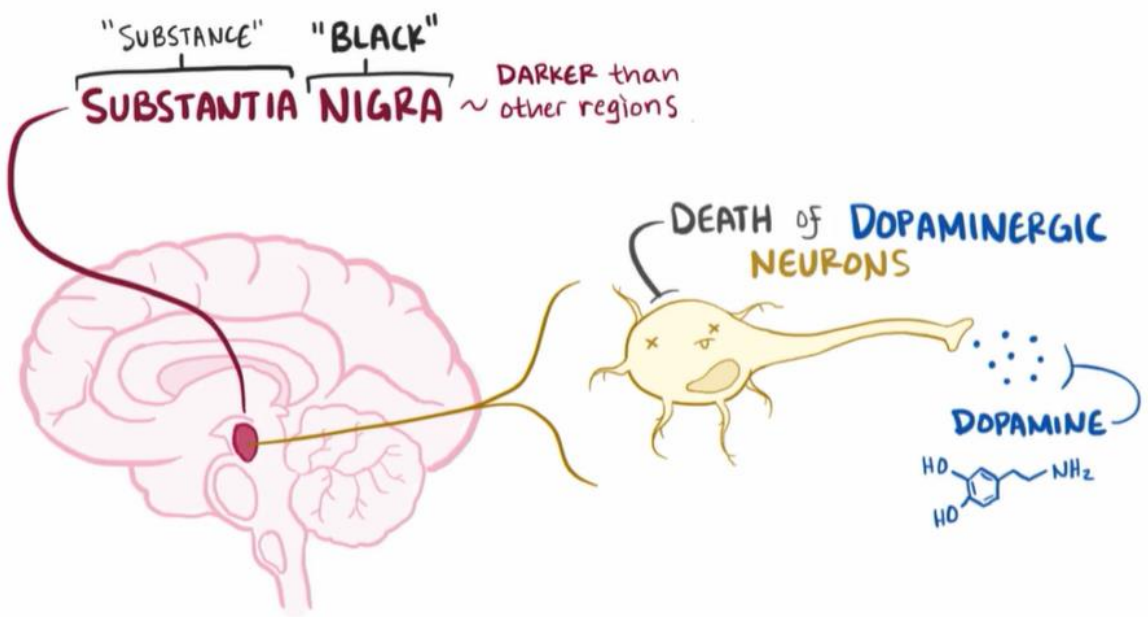
# PICK DISEASE

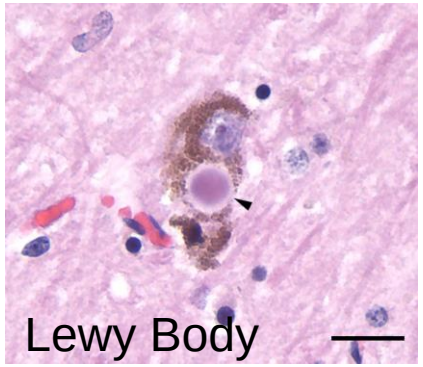


The very marked frontal lobe atrophy and temporal lobe atrophy seen here in sagittal view is due to another much less common type of dementia known as Pick disease.

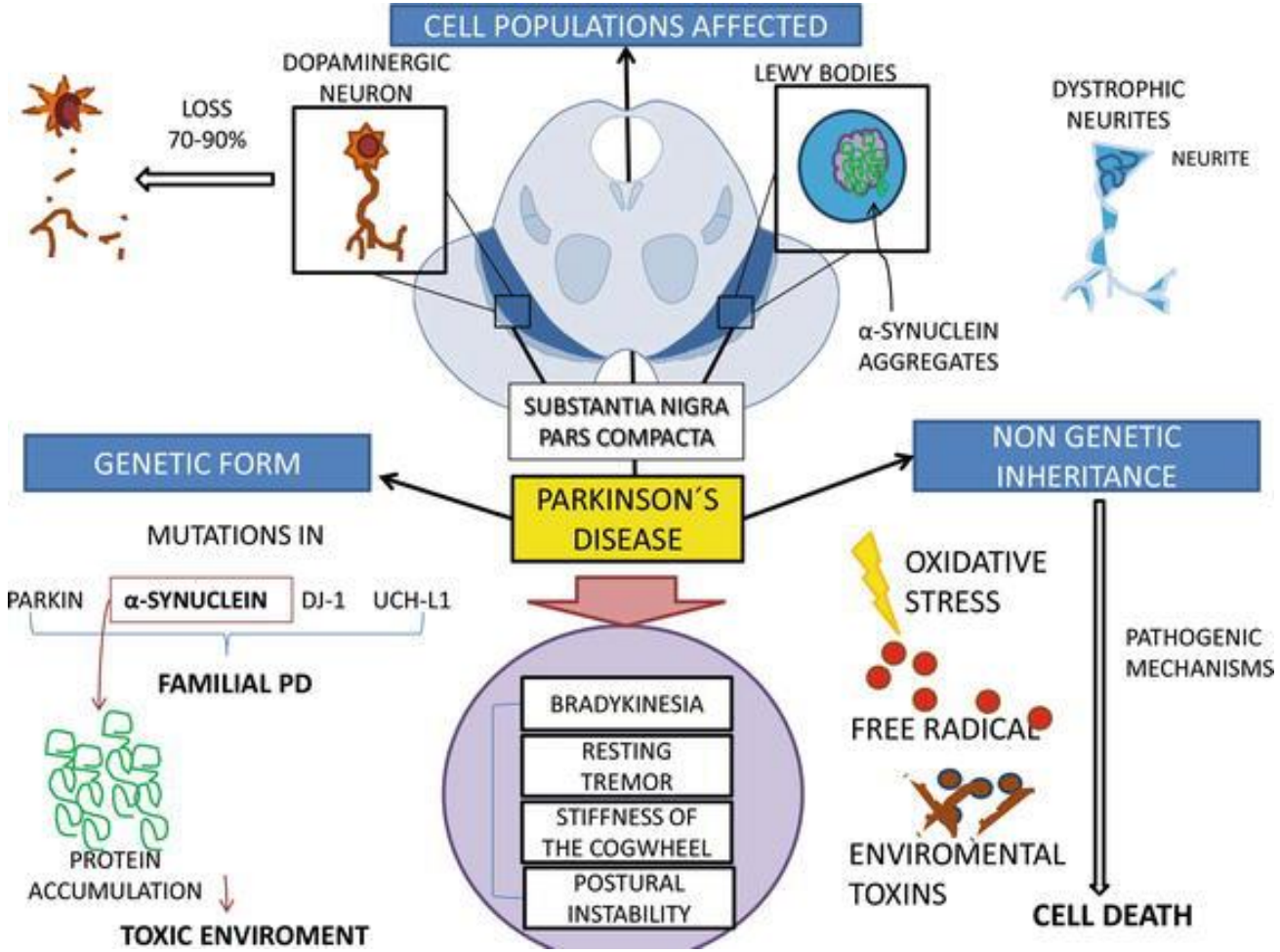
# PARKINSON DISEASE (PD)

- A neurodegenerative disease marked by **a hypokinetic movement disorder** that is caused by **loss of dopaminergic neurons from the substantia nigra.**
- Can be induced by drugs such as dopamine antagonists or toxins that selectively injure dopaminergic neurons.
- PD is associated with characteristic neuronal inclusions Lew bodies **containing α-synuclein.**



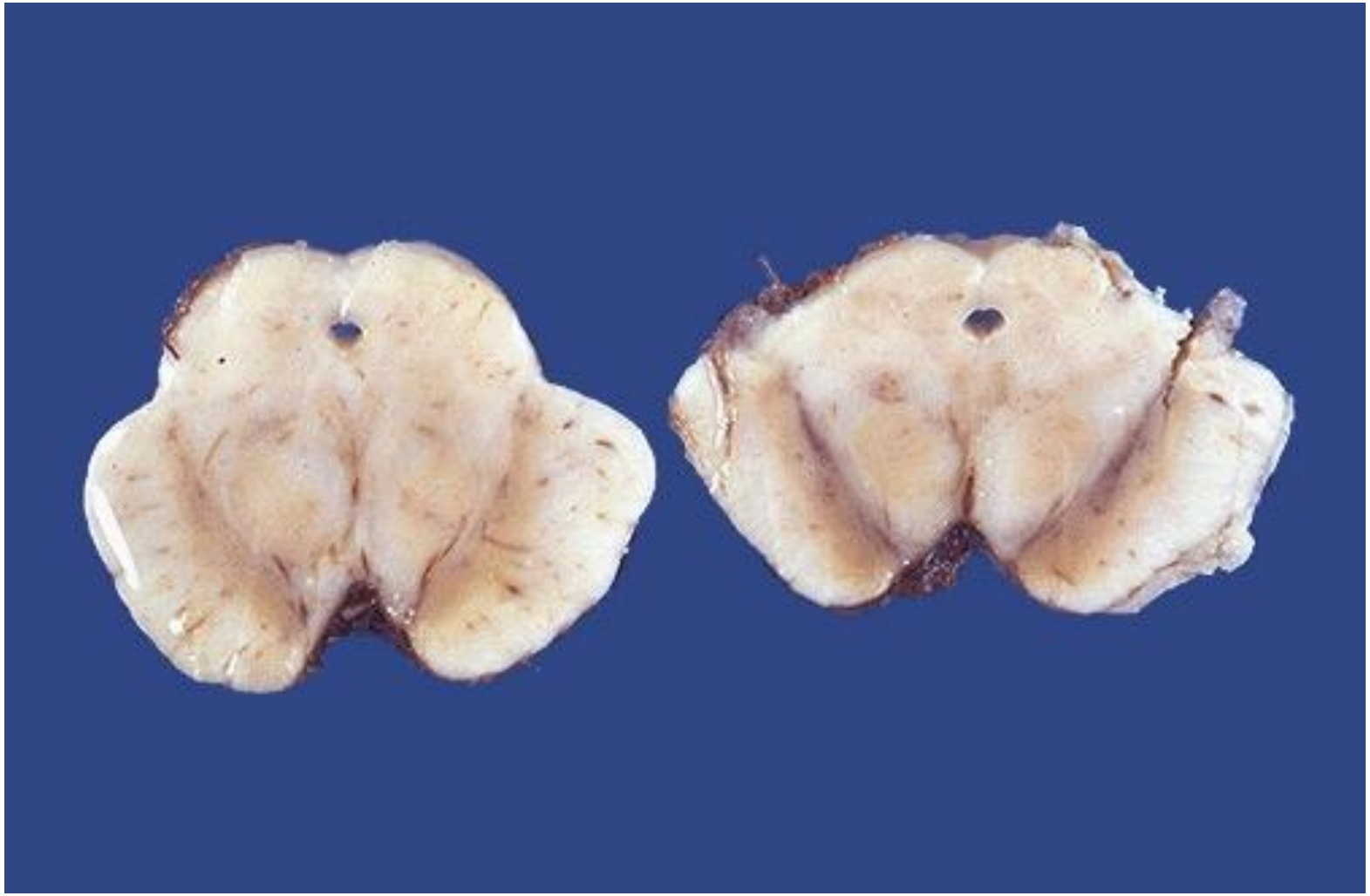


Lewy Body

# PARKINSON DISEASE (PD)

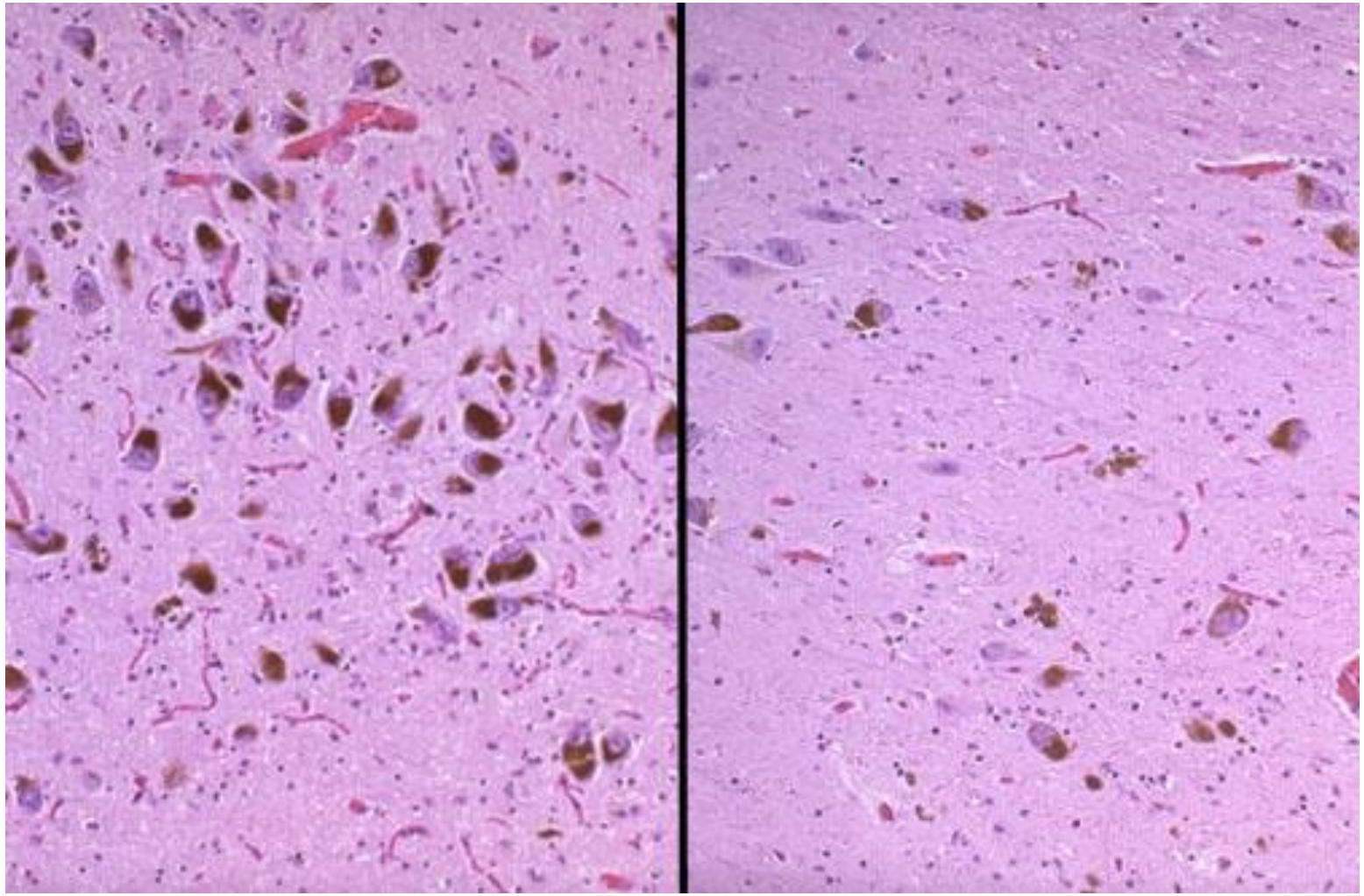


# PARKINSON DISEASE (PD) PATHOGENESIS

- ✓Protein accumulation and aggregation, mitochondrial abnormalities, and neuronal loss, mainly in the substantia nigra
- ✓Synuclein aggregates are cleared by autophagy
- ✓Defects in autophagy and lysosomal degradation
- ✓Lewy body, inclusion containing α-synuclein, a protein involved in synaptic transmission.
- ✓While PD in most cases is sporadic, mutations of the gene encoding α-synuclein cause autosomal dominant PD.

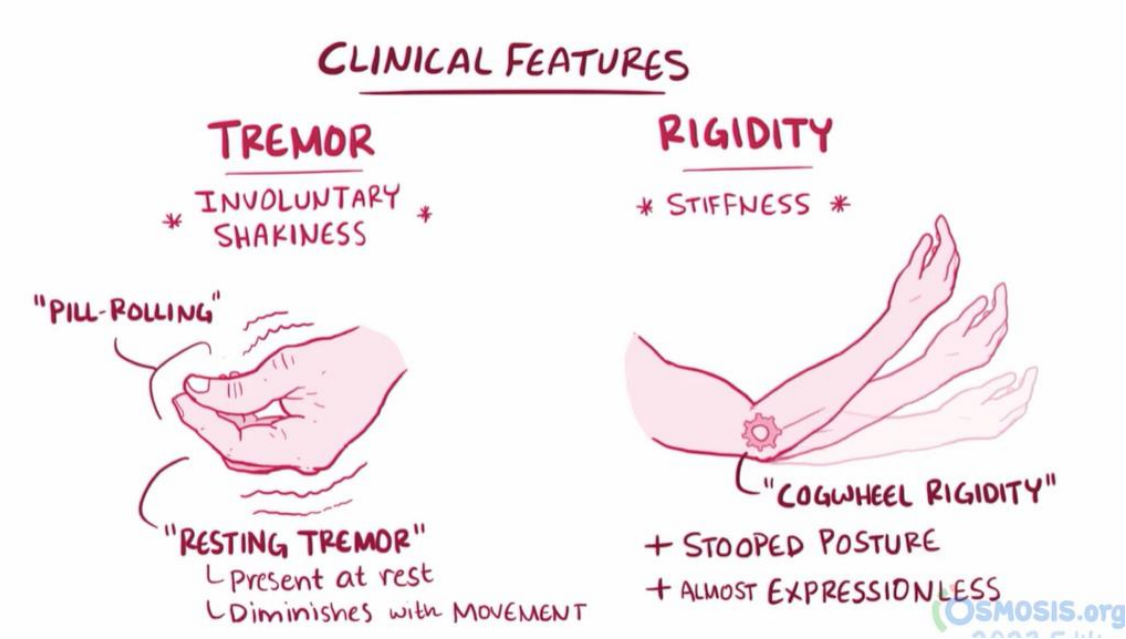


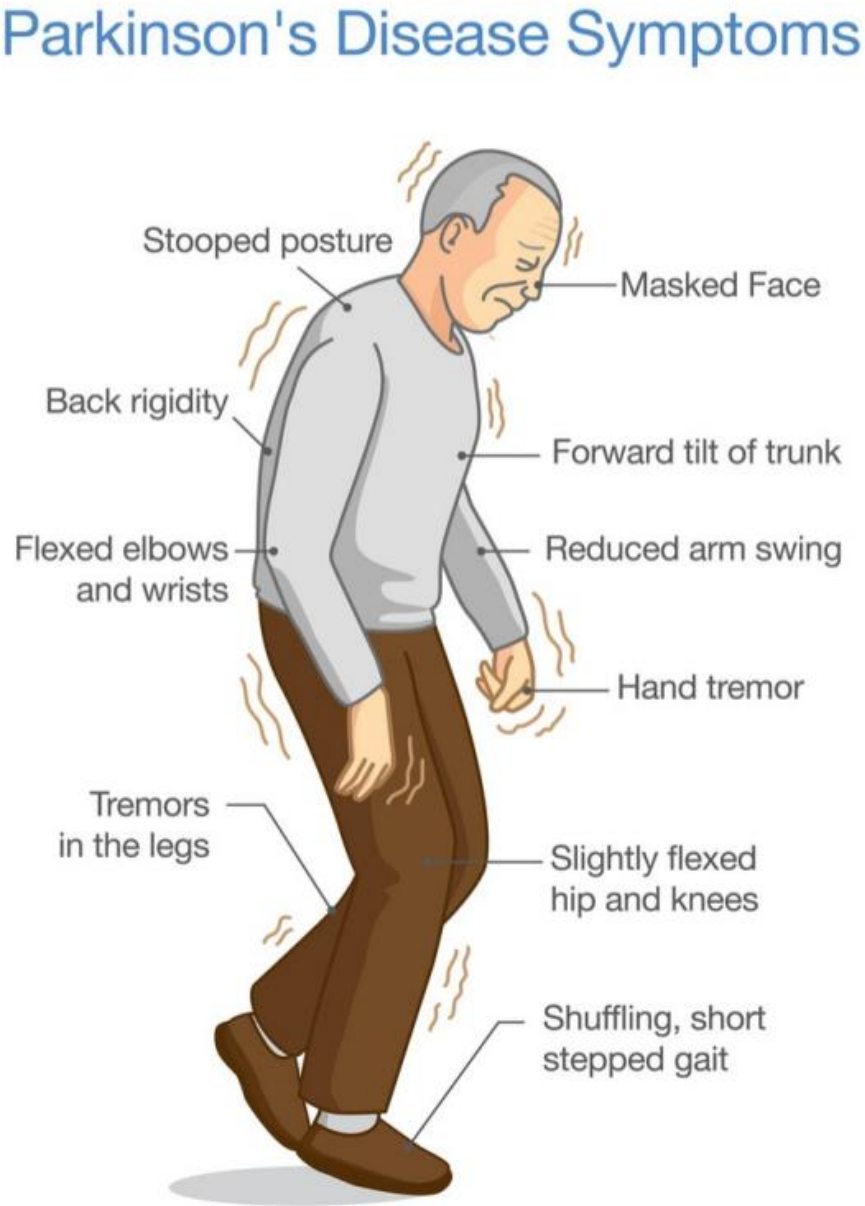
The loss of pigmentation in the substantia nigra of the midbrain at the left in a patient with Parkinson disease is contrasted with a normal midbrain at the right in which dark pigmentation appears in the region of the substantia nigra above the cerebral peduncles.



At the left, normal numbers of neurons in the subtantia nigra are pigmented. At the right, there is loss of neurons and loss of pigmentation with Parkinson's disease

# PARKINSON DISEASE (PD) CLINICAL FEATURES



# PARKINSON DISEASE (PD)
# CLINICAL FEATURES

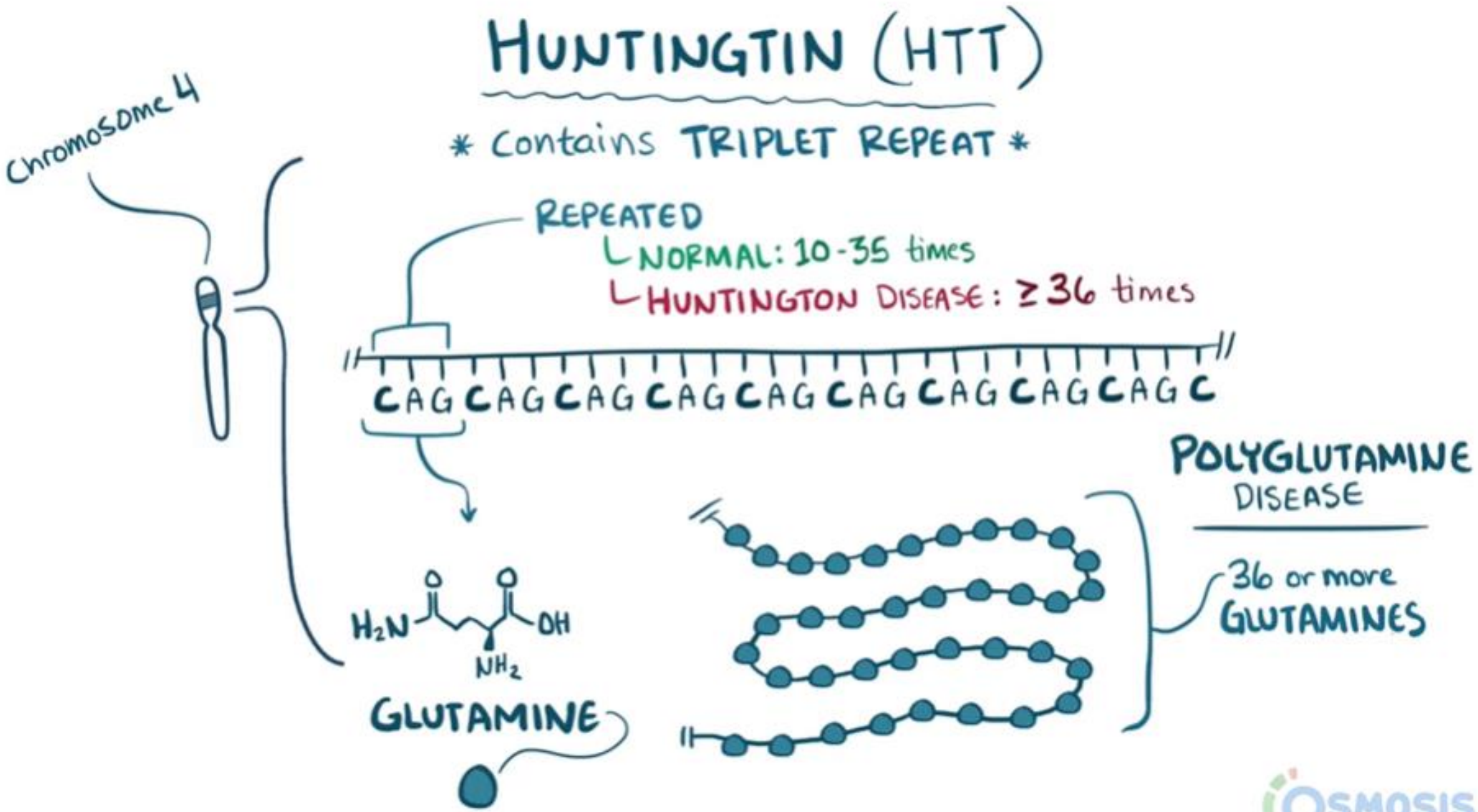
- PD commonly manifests as a movement disorder.
- Progresses over 10 to 15 years, eventually producing severe motor and near immobility.
- Death usually is the result of aspiration pneumonia or trauma from falls caused by postural instability.
- Involvement of the cerebral cortex might occur causing dementia. If dementia arises within 1 year of the onset of motor symptoms, it is referred to **Lewy body dementia (LBD).**

**Treatment:**

- PD initially respond to L-DOPA, but does not slow disease progression.
- Over time, L-DOPA becomes less effective

# HUNTINGTON DISEASE (HD)

- Huntington disease (HD) is an autosomal dominant movement disorder associated with degeneration of the striatum (caudate and putamen).
- HD is characterized by involuntary jerky movements of all parts of the body; writhing movements of the extremities are typical.
- The disease is progressive, resulting in death after approx.15 years.
- Early cognitive symptoms occur, and may be a progression to severe dementia.
- As a part of these early behavioral changes, HD carries an increased risk for suicide.

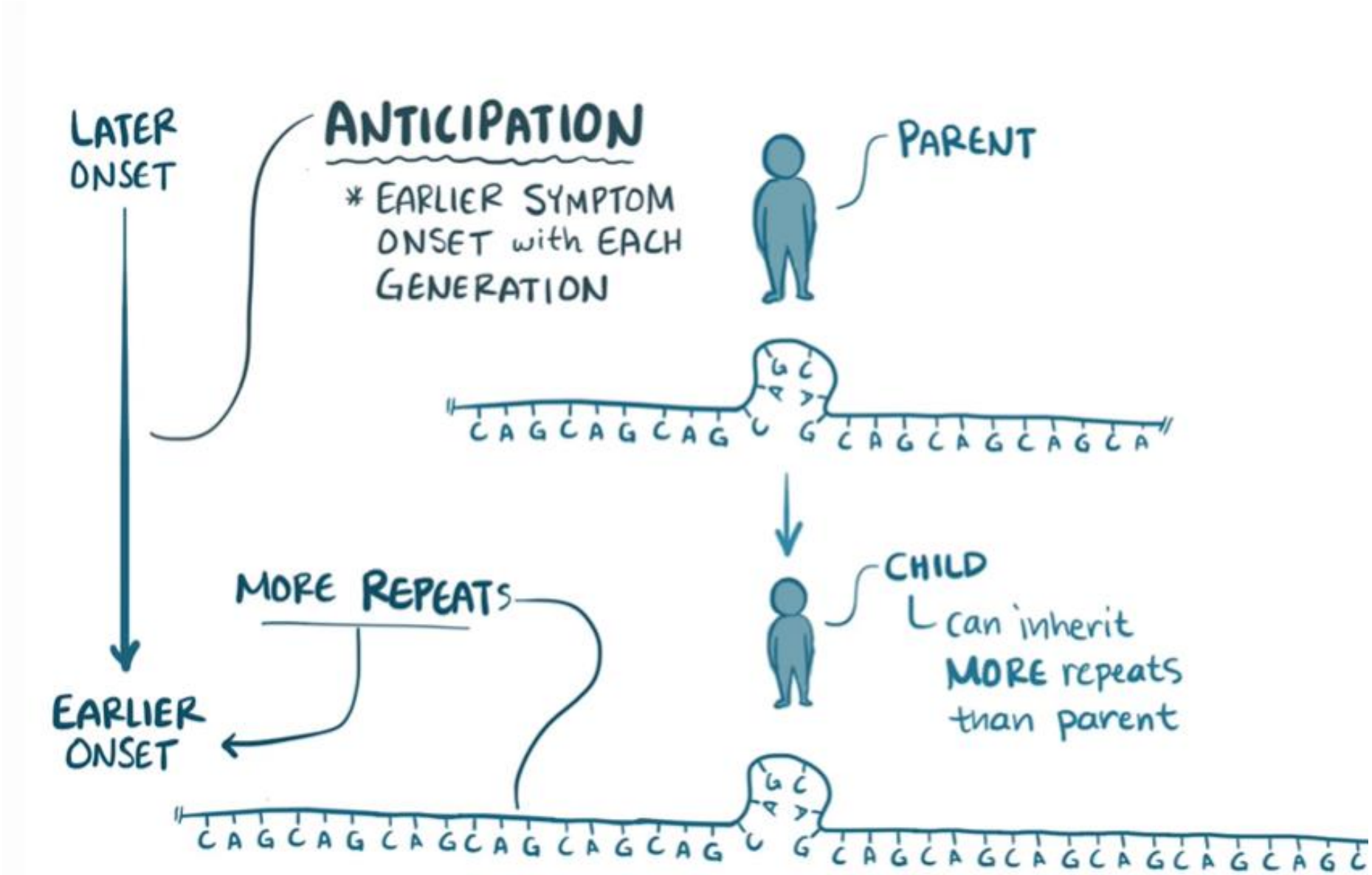


# HUNTINGTON DISEASE (HD) PATHOGENIES

- HD is caused by CAG trinucleotide repeat expansions in a gene located on 4p16.3 encoding Huntington protein. Normal alleles contain 11 to 36 copies of the repeat; in disease-causing alleles, the number of repeats is increased, sometimes into the hundreds

- There is a strong genotype-phenotype correlation, with larger numbers of repeats resulting in earlier-onset disease.

- The mutant protein aggregates, causing abnormal protein fragments that are toxic.


LATER ONSET
ANTICIPATION
* EARLIER SYMPTOM ONSET with EACH GENERATION
PARENT
CAGCAGCAG
GCAGCAGCAGCA
CHILD
can inherit MORE repeats than parent
MORE REPEATS
EARLIER ONSET
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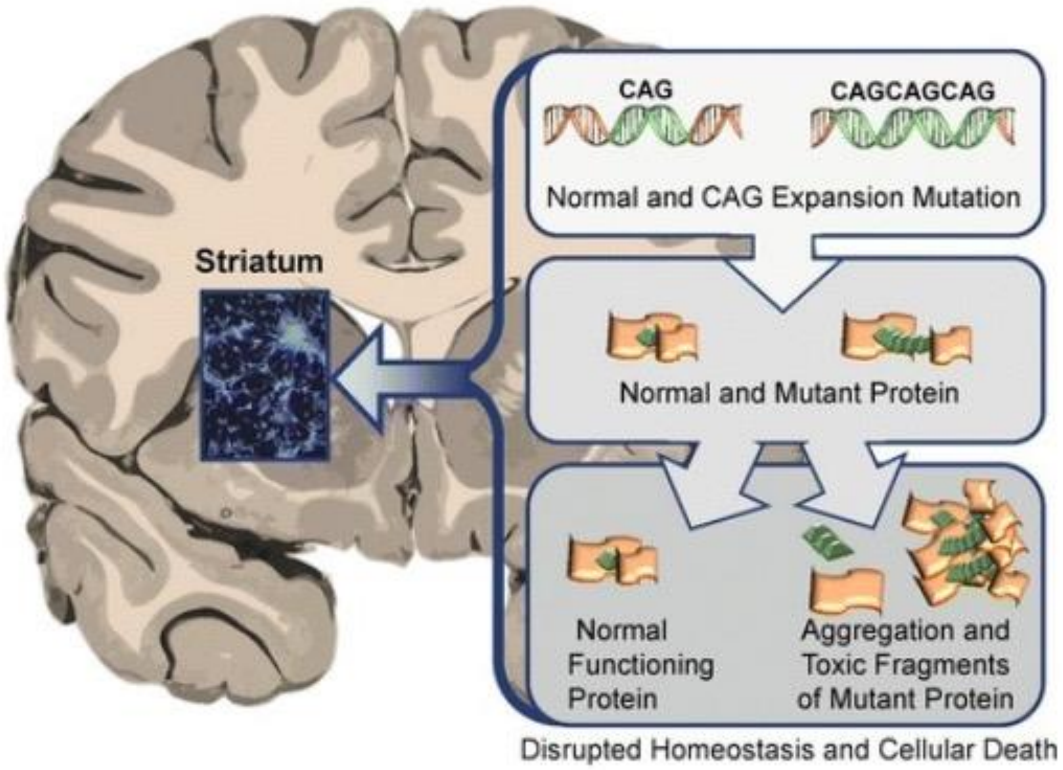
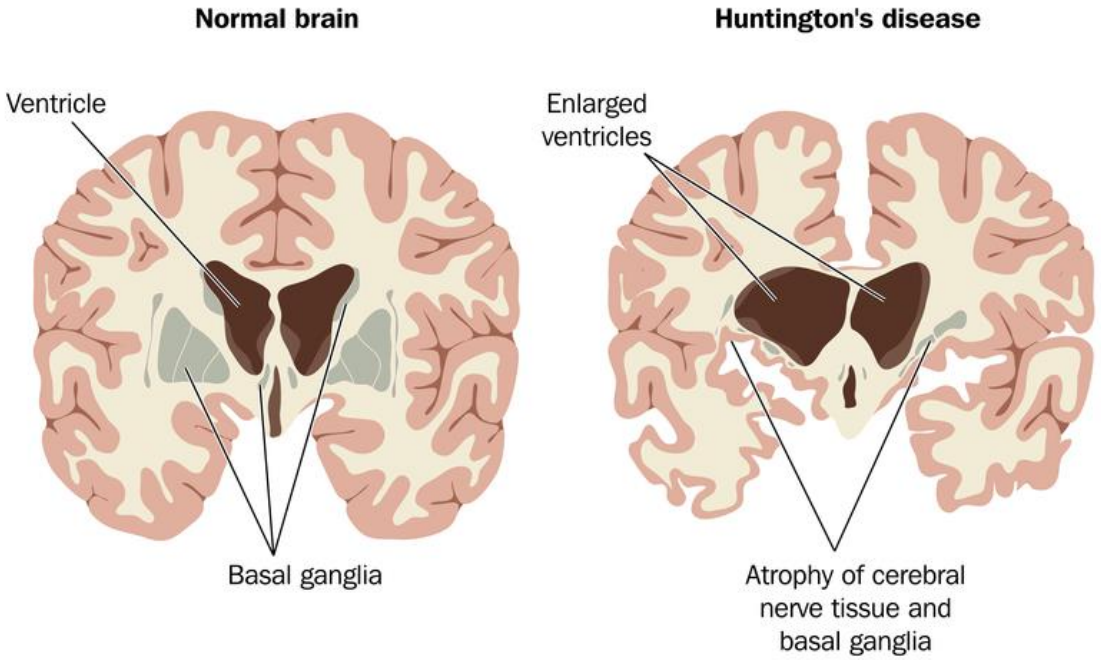
# HUNTINGTON DISEASE (HD) MORPHOLOGY

- Grossly, the brain is small and shows striking atrophy of the caudate nucleus and, sometimes the putamen
- The globus pallidus may be atrophied secondarily, and the lateral and third ventricles are dilated.
- Histology: severe loss of neurons from affected regions of the striatum along with gliosis.
- In remaining striatal neurons and in the cortex, there are intranuclear inclusions that contain aggregates of abnormal huntingtin protein

# HUNTINGTON DISEASE (HD)

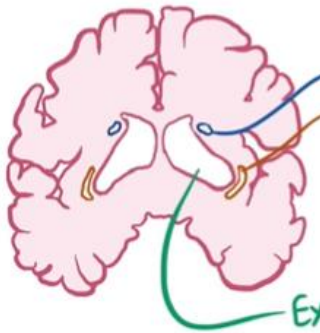


# SYMPTOMS

Depends on REPEATS

* Progressive CNS involvement *
  - MOVEMENT, COGNITIVE, MOOD
* ONSET ~ 40 years old



DORSAL STRIATUM
- CAUDATE
- PUTAMEN
- ↓ TISSUE LOSS

EXPANSION of LATERAL VENTRICLES

## MOVEMENT (INHIBITION) PROBLEMS

* CHOREA ~ purposeless, dance-like
* ATHETOSIS ~ slow, "snake-like"
- CAN'T SUPPRESS; STOPS with SLEEP
* ABNORMAL EYE MOVEMENTS
* POOR COORDINATION

## PSYCHOLOGICAL PROBLEMS

* DEMENTIA
* PERSONALITY CHANGES
* DEPRESSION

Chorea is a medical condition and a type of movement disorder

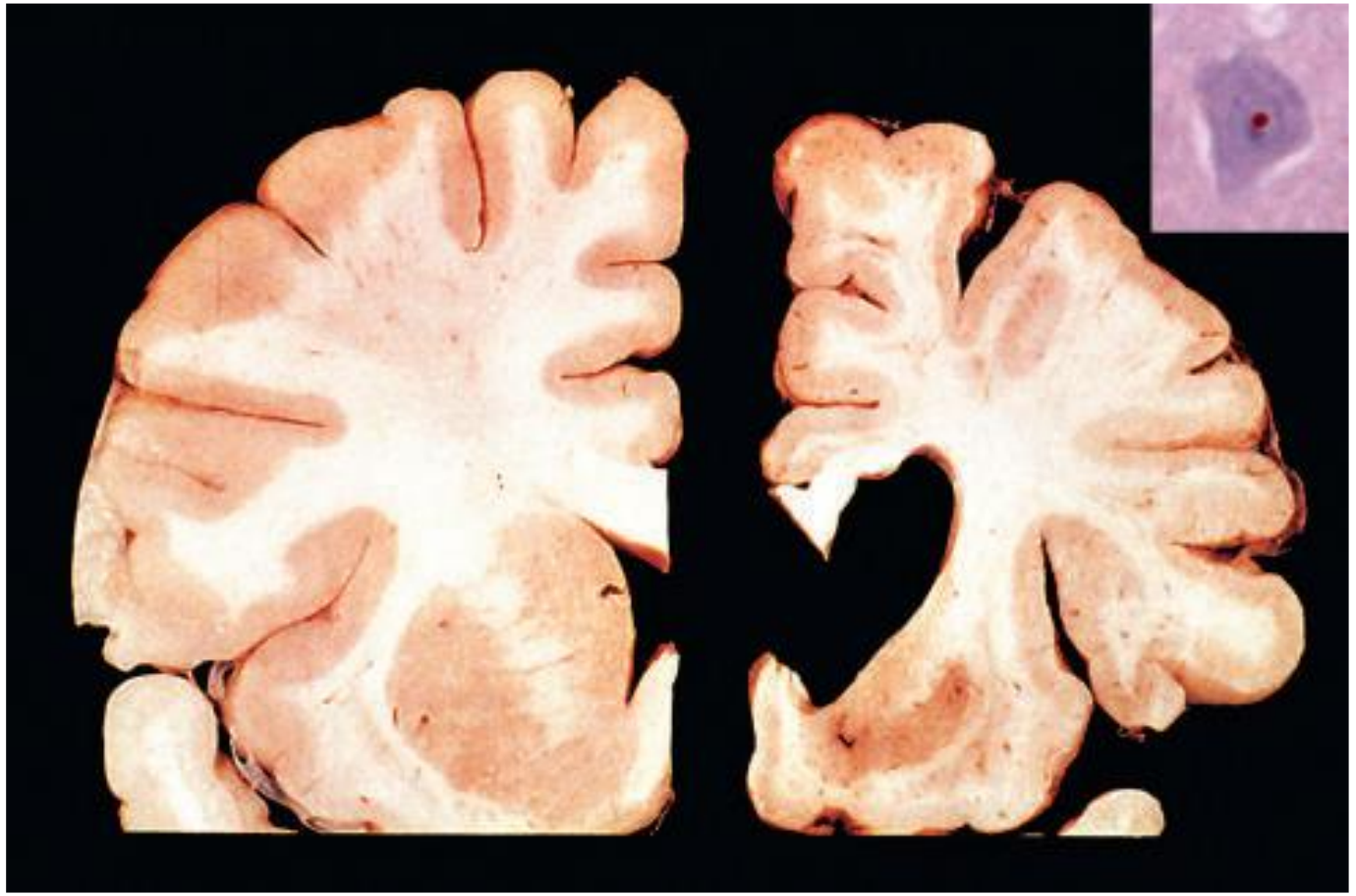
# DIAGNOSIS

PERSON'S HISTORY

GENETIC TESTING

PHYSICAL ASSESSMENT

CT SCAN or MRI
↳ ATROPHY of BASAL GANGLIA



**Huntington disease.** Normal hemisphere (left) compared with a hemisphere with Huntington disease (right) showing atrophy of the striatum and ventricular dilation. Inset, An intranuclear inclusion in a cortical neuron.

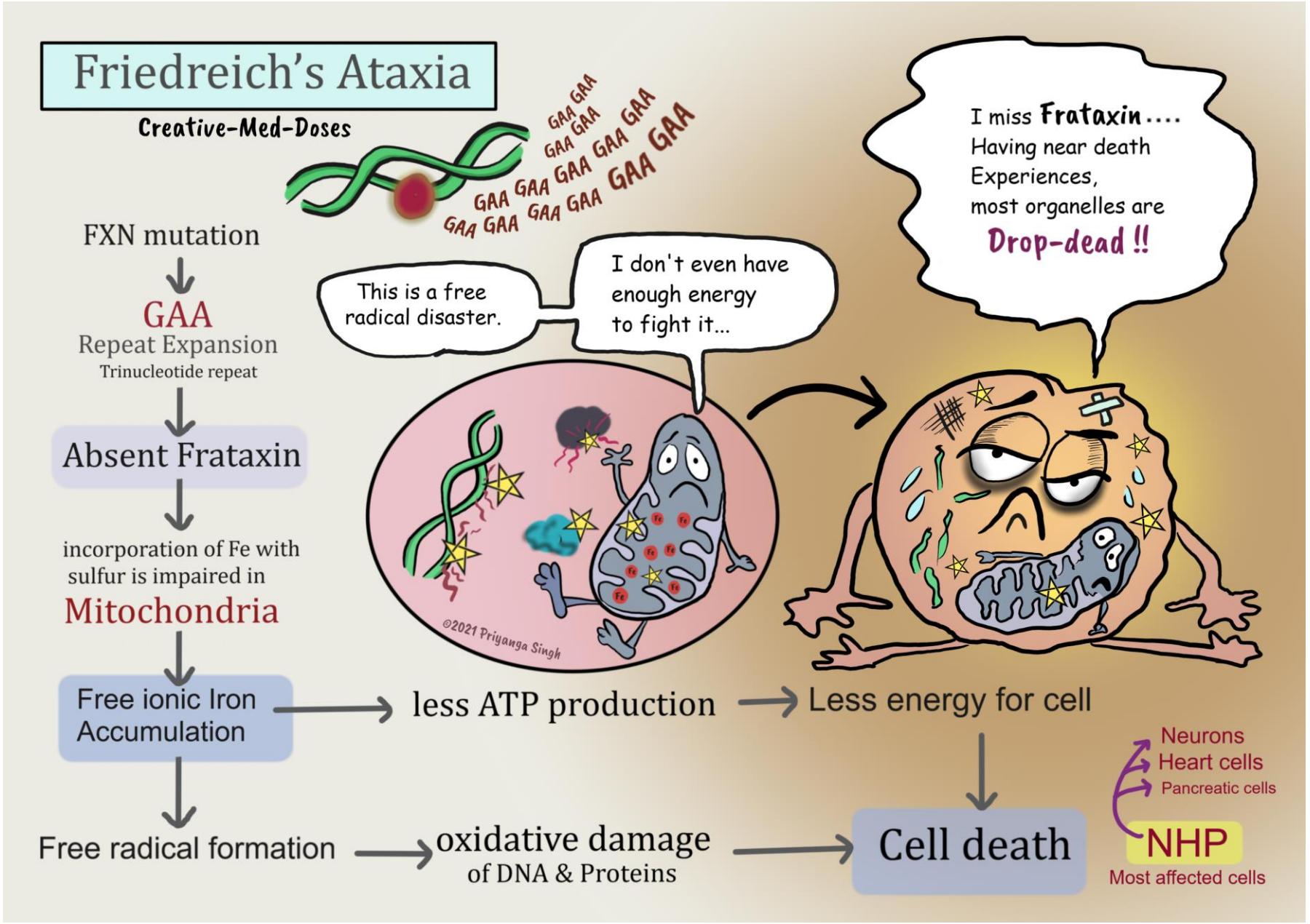
# SPINOCEREBELLAR ATAXIAS (SCAS)

- Heterogeneous group of diseases with clinical findings that include a combination of cerebellar and sensory ataxia, spasticity, and sensorimotor peripheral neuropathy.
- They have different mutations, patterns of inheritance, age at onset, and signs and symptoms.
- This group of diseases affects the cerebellar cortex, spinal cord, other brain regions, and peripheral nerves.
- The affected area shows degeneration of neurons with mild gliosis.

# SPINOCEREBELLAR ATAXIAS (SCAS)

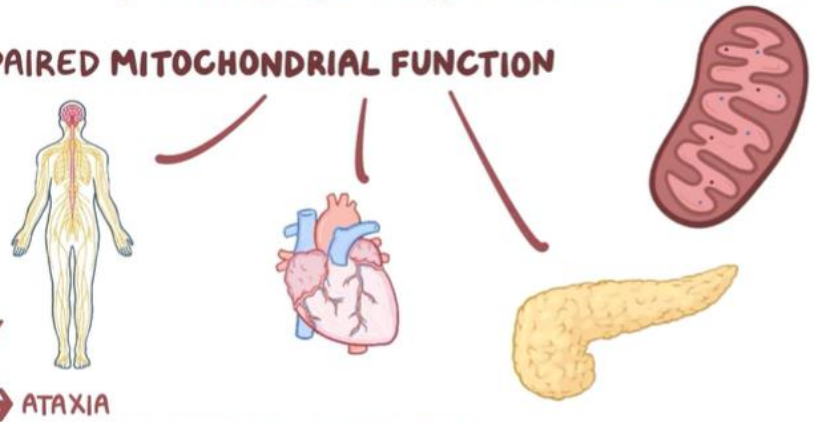
## FRIEDREICH ATAXIA

- ✓Friedreich ataxia is an **AR disorder**
- ✓Manifests in the first decade of life with gait ataxia, followed by hand clumsiness and dysarthria.
- ✓There is a high incidence of cardiac disease and diabetes.
- ✓Caused by a **GAA trinucleotide repeat expansion in the gene encoding frataxin,** a protein that regulates cellular iron levels, particularly in the mitochondria.
- ✓The repeat expansion results in decreased protein levels; decreased frataxin leads to mitochondrial dysfunction as well as increased oxidative damage.


Friedreich's Ataxia
Creative-Med-Doses
GAA GAA
GAA GAA
GAA GAA GAA GAA
GAA GAA GAA GAA
FXN mutation
GAA
Repeat Expansion
Trinucleotide repeat
Absent Frataxin
incorporation of Fe with sulfur is impaired in
Mitochondria
Free ionic Iron Accumulation
less ATP production
Less energy for cell
Free radical formation
oxidative damage of DNA & Proteins
Cell death
This is a free radical disaster.
I don't even have enough energy to fight it...
I miss Frataxin....
Having near death Experiences, most organelles are
Drop-dead !!
©2021 Priyanga Singh
Neurons
Heart cells
Pancreatic cells
NHP
Most affected cells

# FRIEDREICH'S ATAXIA

* IMPAIRED MITOCHONDRIAL FUNCTION




* **NIKOLAUS FRIEDREICH:** FIRST DESCRIBED IT > 150 YRS ı

# FRIEDREICH'S ATAXIA

## REPEAT EXPANSION

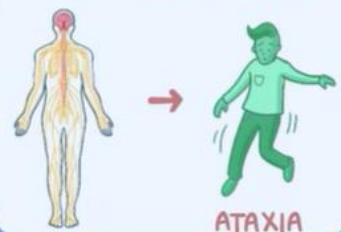
* FXN GENE (CHROMOSOME 9)

NORMAL < 34 REPEATS
PATHOGENIC > 100 REPEATS

* PANCREAS

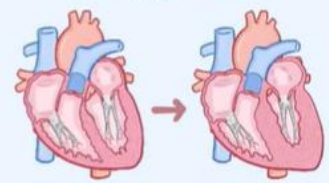

## AFFECTS

* NERVOUS SYSTEM



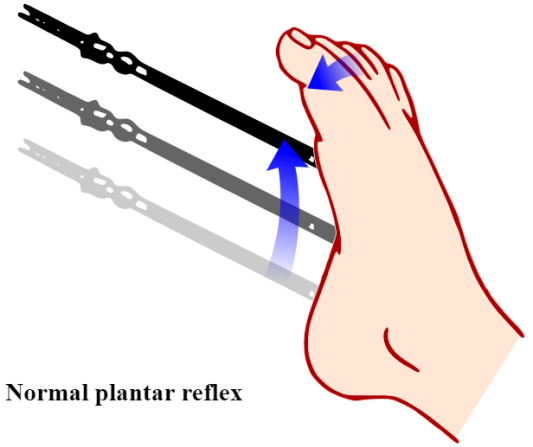

DEFECTIVE MITOCHONDRIAL FUNCTION
OXIDATIVE DAMAGE

* HEART

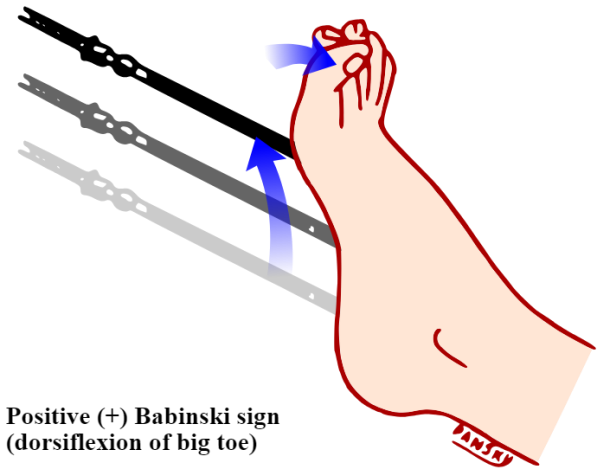


# AMYOTROPHIC LATERAL SCLEROSIS (ALS)

- ALS results from the death of lower motor neurons in the spinal cord and brain stem as well as upper motor neurons in the cortex.
- The loss of lower motor neurons results in denervation of muscles, muscular atrophy (the “amyotrophy” of the condition), weakness, and fasciculations,
- While the loss of upper motor neurons results in paresis, hyperreflexia, and spasticity, along with a + Babinski sign.
- Clinically manifest in the fifth decade or later.



Normal plantar reflex

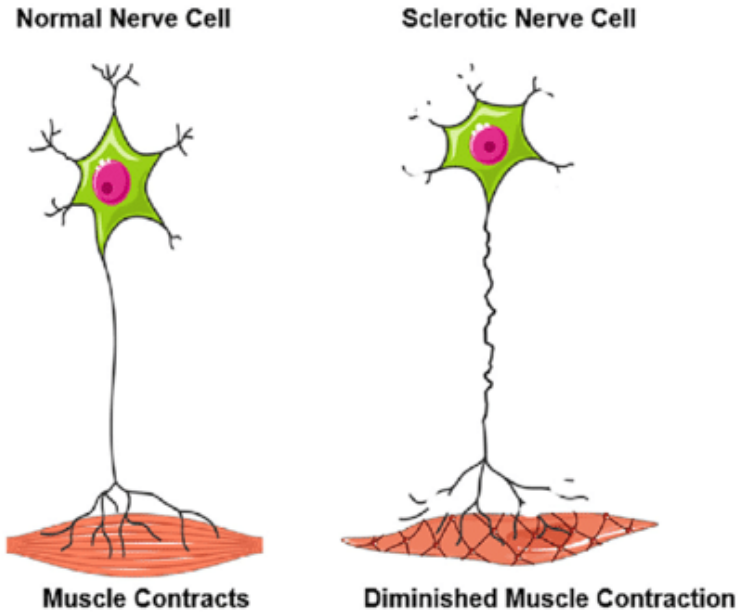


Positive (+) Babinski sign
(dorsiflexion of big toe)

# AMYOTROPHIC LATERAL SCLEROSIS (ALS)

- ALS is the most common form of motor neuron disease, with diverse genetic causes as well as sporadic forms.
- The disease eventually involves the respiratory muscles, leading to recurrent bouts of pulmonary infection, which is the usual cause of death.
- The balance between upper and lower motor neuron involvement can vary, although most patients exhibit involvement of both.

# Amyotrophic Lateral Sclerosis (ALS)




**(A) UMN Symptoms**

Spasticity

Hyperreflexia

Cognitive & behavioral changes (ALS-FTD)

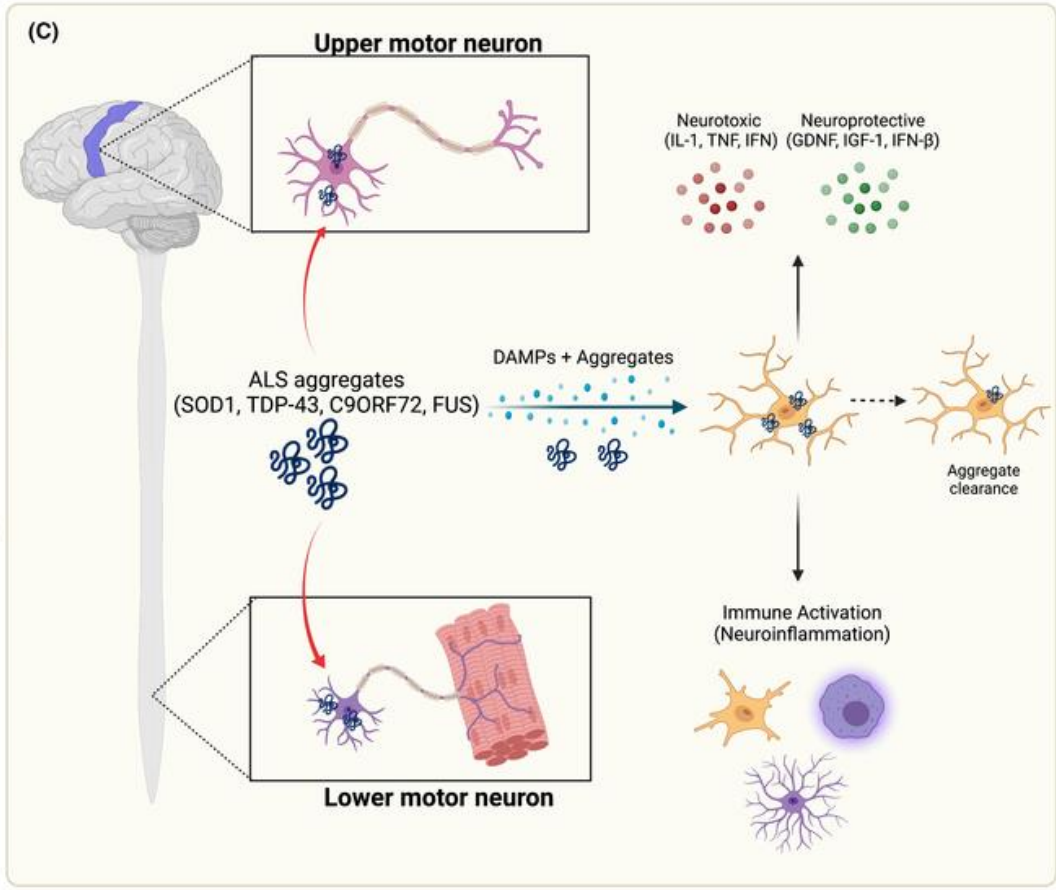
Slow speech, jaw-jerk reflex (bulbar onset)

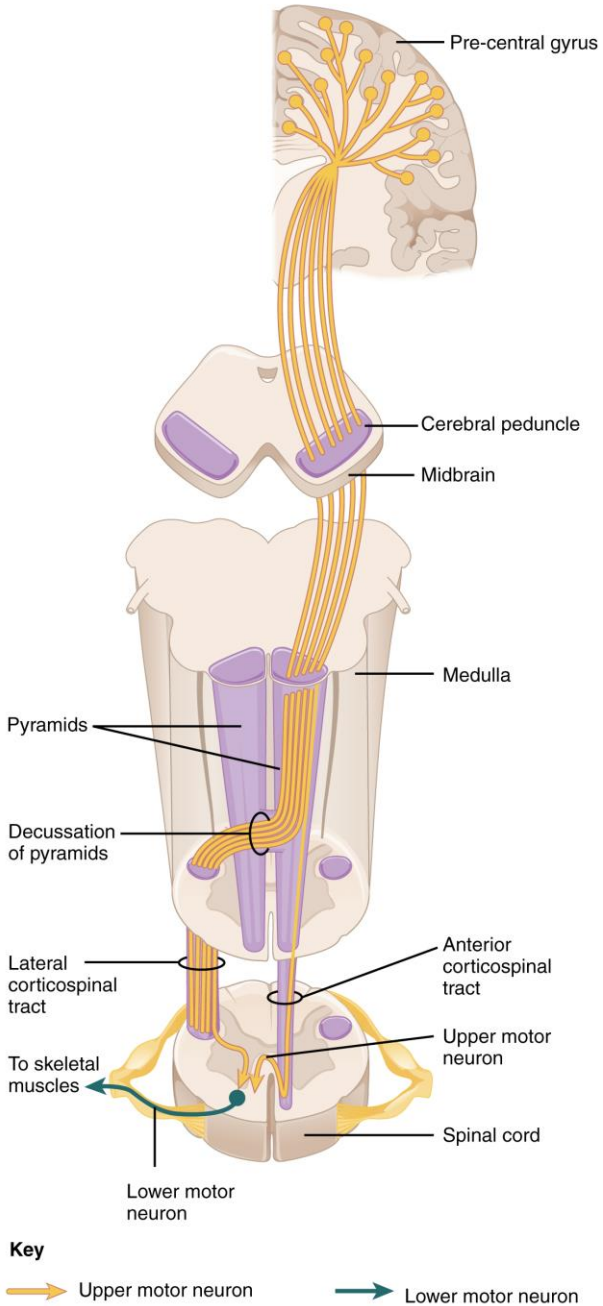
**(B) LMN Symptoms**

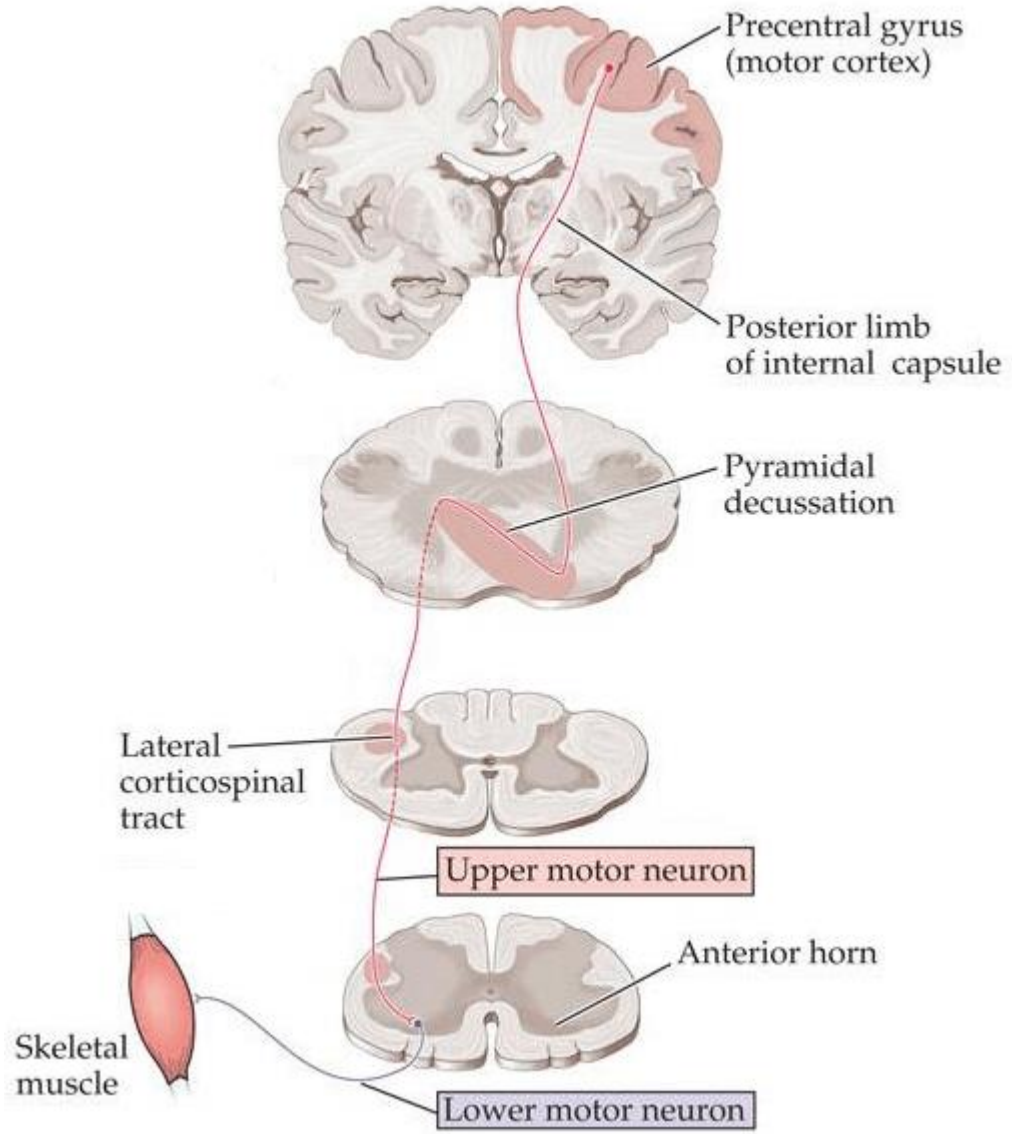
Muscle atrophy, weakness, fasiculations

Respiratory insufficiency

Dysarthria, tounge atrophy, facial weakenes (bulbar onset)




Pre-central gyrus
Cerebral peduncle
Midbrain
Medulla
Pyramids
Decussation of pyramids
Lateral corticospinal tract
Anterior corticospinal tract
Upper motor neuron
To skeletal muscles
Spinal cord
Lower motor neuron
Key
Upper motor neuron
Lower motor neuron


Precentral gyrus (motor cortex)
Posterior limb of internal capsule
Pyramidal decussation
Lateral corticospinal tract
Upper motor neuron
Anterior horn
Skeletal muscle
Lower motor neuron