Neurodegenerative disorders-1

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MODIFIED 1

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Classic features:

Neurodegenerative means degenaration of cells
(death of cells)

- Progressive loss of neurons.
- Typically affects groups of neurons with functional interconnections.

↪ For the disese to happen , it must affect group of neurons

- Different diseases involve different neural systems, so different symptoms.
- The histologic hallmark for ALL diseases is the ACCUMULATION OF PROTEIN AGGREGATES. Either inside cells or outside (neuropil).
- Same protein may aggregate in different diseases, BUT AT DIFFERENT DISTRIBUTION.. Disease and Symptoms related to site of accumulation
- Proteins resist degradation, accumulate within the cells, elicit inflammatory response, and is toxic to neurons. Then cause neuronal cell death

Depending on location of the brain that is affected

☆ why they accumulate ?
Misfolding of protein that result in nonfunctional protein formation, which resist degeneration .

Causes of protein accumulation

- Mutations that alter protein conformation.
- Mutations disrupting the processing and clearance of proteins.
- Subtle imbalance between protein synthesis and clearance (genetic or environmental factors)

Increased synthesis
Or decreased clearance

Different diseases

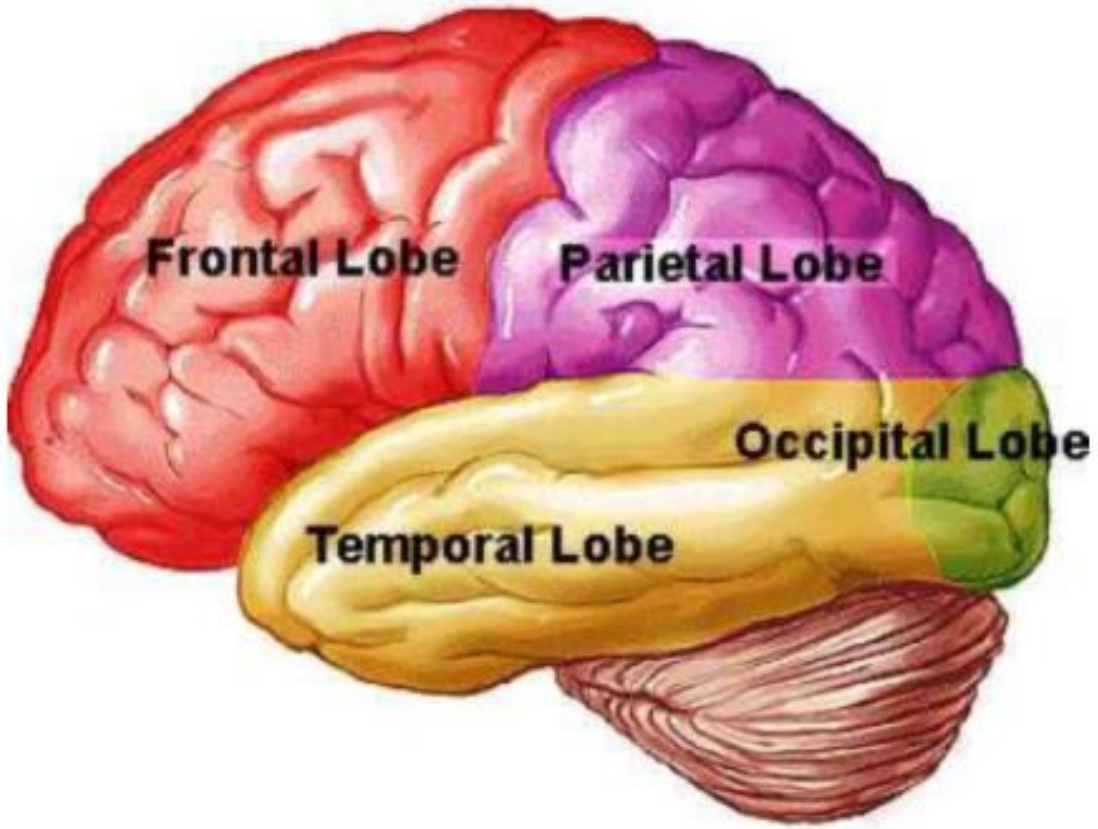
☆ Divided according to the site of brain that is affected :

- **Involving the hippocmpus and cortex** (Higher intellectual function of brain) >>>> cognitive changes (memory disturbances, behavior and language) >>>> dementia >>>>>ALZHEIMER DISEASE (AD) , FRONTOTEMPORAL DEMENTIA (FTD), PICK DISEASE (SUBTYPE OF FTD) (الخرف) (The most common)

- **Involving the basal ganglia** (Which has motion control function) >>>>> movement disorders >>>>hypokinesia (PARKINSON DISEASE) or hyperkinesia (HUNTINGTON DISEASE)

- **Involving the cerebellum** (Which has coordination function) >>>> ataxia >>> (SPINOCEREBELLAR ATAXIA, FRIEDRICH ATAXIA, ATAXIA TELANGECTASIA) (Loss of balance)

- **Involving the motor system** >>> difficulty swallowing and respiration with muscle weakness >> (AMYOTROPHIC LATERAL SCLEROSIS)


Frontal Lobe
Parietal Lobe
Occipital Lobe
Temporal Lobe

Common features to many neurodegenerative diseases:

- Protein aggregates can seed the development of more aggregates.
- Protein aggregates can spread from one neuron to another in **Prion-like pattern.**
- No evidence of person-to-person transmission.
- Activation of the innate immune system is a common feature of neurodegenerative diseases.

Immune system recognize the accumulated protein as a foreign body , result in inflammatry rxn and microglial proliferation , and as a result : death of neurons

DEMENTIA الخرف

- *Development of memory impairment and other cognitive deficits severe enough to decrease the person's capacity to function at **his previous** level **despite** normal level of consciousness.*⇾ Patient is not comatose
- Cognitive deficit *must affect the person's performance in his daily life activities.*
- There is no standard NORMAL COGNITION, always compared to previous level.

SYMPTOMS OF DEMENTIA

Some cognitve
Some psycological and behavioral changes

Cognitive changes	• Memory loss, which is usually noticed by a spouse or someone else	• Difficulty communicating or finding words	• Difficulty reasoning or problem-solving	• Difficulty handling complex tasks	• Difficulty with planning and organizing
• Difficulty with coordination and motor functions	• Confusion and disorientation	**Psychological changes**	• Personality changes	• Depression	• Anxiety
Late symptom	• Inappropriate behavior	• Paranoia	• Agitation	• Hallucinations	

Psycological Symptoms are related to frontal lobe cortex involvement .

Causes of dementia

Not all patients with dementia have neurogenerative disorder , there is other causes :

- Neurodegenerative diseases.
- Infections.
- Nutritional deficiencies.
- Metabolic and endocrine abnormalities
- Drugs.
- Subdural hematoma.
- Poisons.
- Tumours.
- Anoxia and ischemia.

Ischemia to the brain , can cause memory loss, and the cause is accumulating infarcts , not alzheimer disease .
Its mainly with young patients .

الدكتورة حكت مش كتير تركزو عليهم

COMPLICATIONS OF DEMENTIA

- **Inadequate nutrition.** Many people with dementia eventually reduce or stop their intake of nutrients.
- **Inability to perform self-care tasks.** As dementia progresses, it can interfere with bathing, dressing, brushing hair or teeth, using the toilet independently and taking medications accurately.
- **Personal safety challenges.** Some day-to-day situations can present safety issues for people with dementia, including driving, cooking and walking alone.
- **Death.** Late-stage dementia results in coma and death, often from infection

  ↳ Death is usually as a result of recurrent infections .

Alzheimer disease:

- Most common cause of dementia in older adults.
- Increase incidence with age (47% in those over 84 years).
- Most cases are sporadic.
- 5-10% are familial (onset before 50)
- Gradual onset.
- Impaired higher intellectual functions, memory impairment and altered mood and behavior.
- Severe cortical dysfunction with time (disorientation and aphasia, profound disability, mute and immobile)
- Death usually due to infections (pneumonia)

We think of familial cases with patient < 50 years , specially with family history

Can't talk

- **The most commonly recognized symptom of Alzheimer is an inability to acquire new memories and difficulty in recalling recently observed facts.**
- As the disease advances, symptoms include confusion, irritability and aggression, mood swings, language breakdown, long term memory loss, and ultimately a gradual loss of bodily functions and death.

Pathogenesis:

Alpha beta amyloid result in Tau protein accumulation , so any mutation affect AB amyloid precursor protein will increase the risk alzehimer disease .

- Accumulation of two proteins (AB amyloid and Tau)
- In the form of plaques and neurofibrillary tangles, respectively.
- This leads to neuronal dysfunction, death and inflammation.
- Plaques deposit in the neuropil. Neuropil means outside the neurons , in the matrix
- Tangles develops intracellularly.
- Aβ generation is the critical initiating event for the development of AD.
- Mutations of the gene encoding the precursor protein for Aβ >>> elevated risk of AD.
- Mutations of Tau gene do NOT increase risk of AD.

AB amyloid forms neurotic plaques , and Tau protein form neurofibrillary tangles .

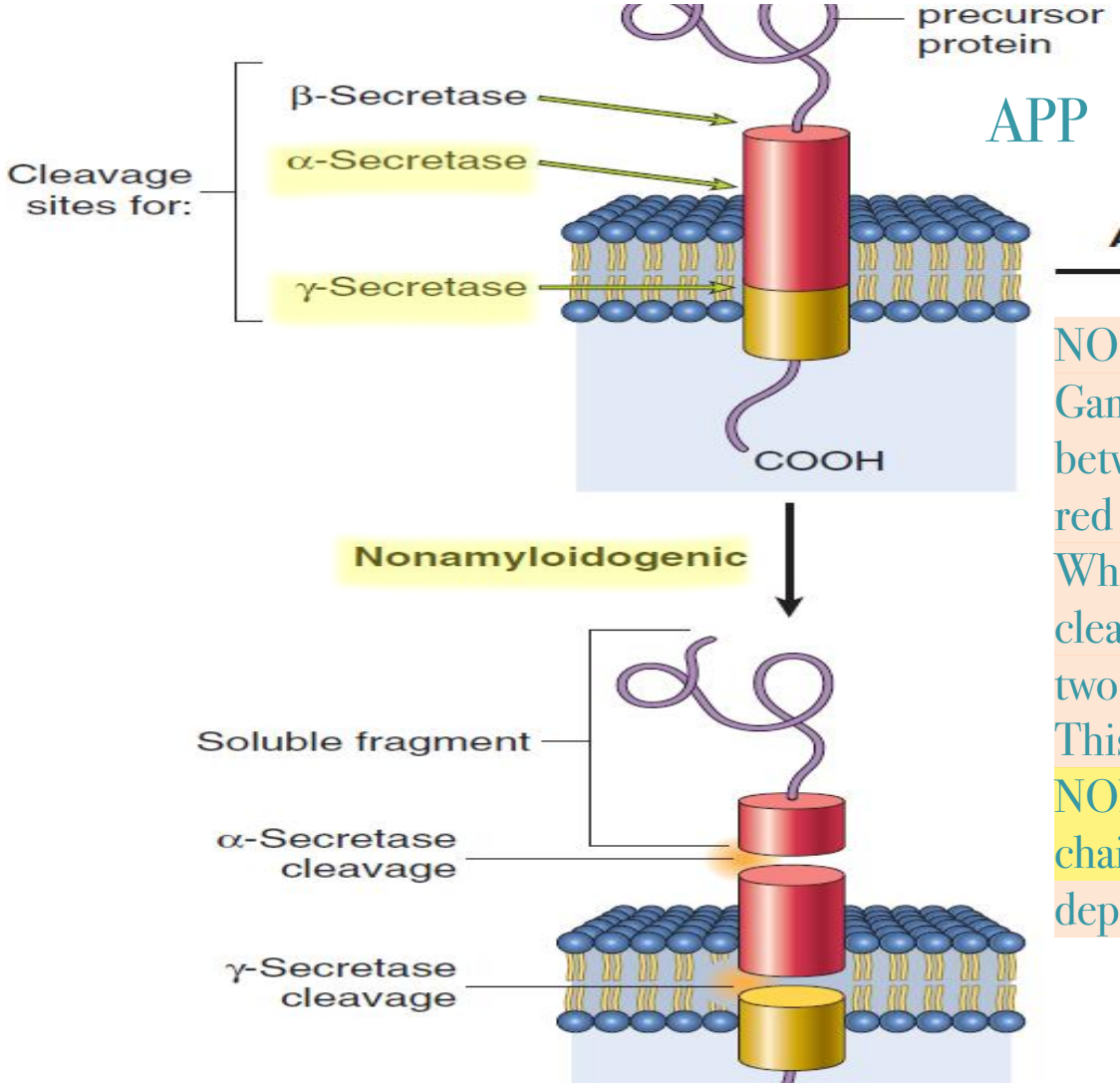
Role of Aβ

the way of cleavge determine if it will form amyloidoginic chain of AB amyloid (pathogenic peptide) or not.

- AD results when the transmembrane protein (amyloid precursor protein APP) is sequentially cleaved by the **enzymes β-amyloid–converting enzyme (BACE) (B-secretase) and γ-secretase** creating Aβ. Amyloidoginic chains
- Normally, APP can be cleaved by **α-secretase and γ-secretase**, liberating a nonpathogenic peptide.
- Mutations in APP or in components of γ-secretase lead to familial AD.
- The A*PP* gene is located on chromosome 21, increased risk in down syndrome
- Once generated, Aβ is highly prone to aggregation >>>> PLAQUES FORMATION >>> decreased number of synapses and alter their function >>> memory disruption.

Slow transmission of signals

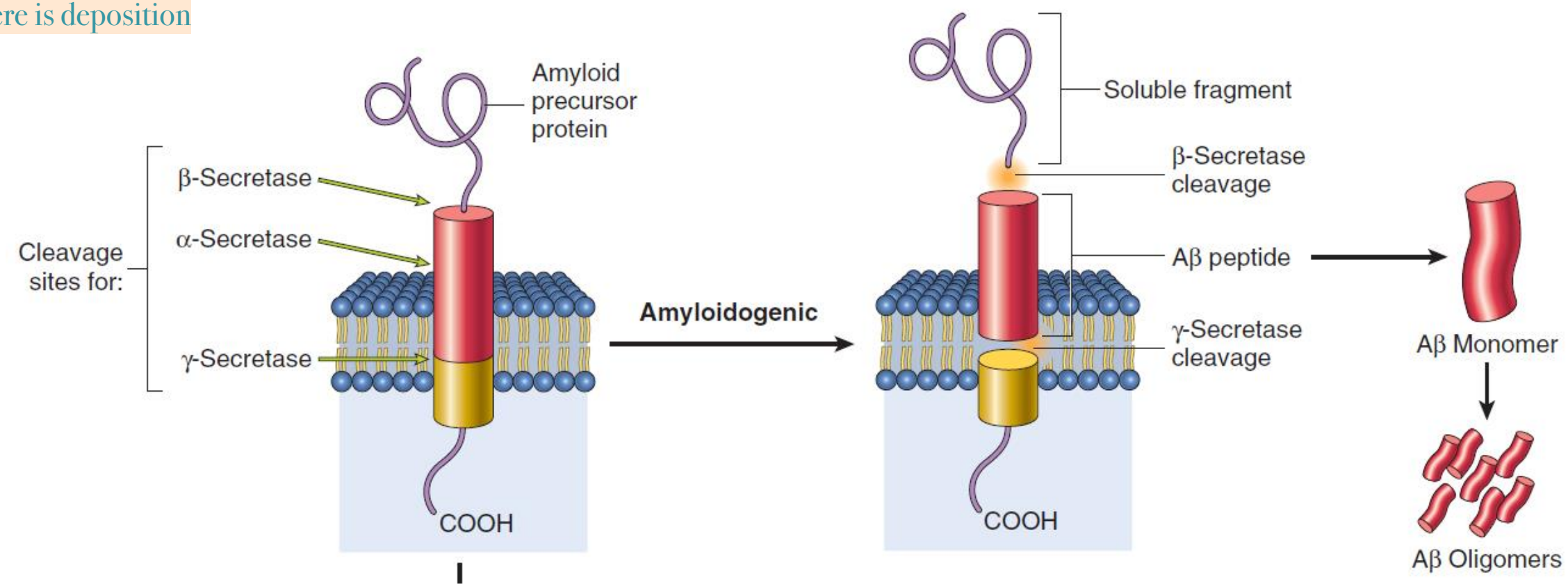
Because down syndrome have extra copy of chromosome 21 , they are at higher risk of alzheimr disease

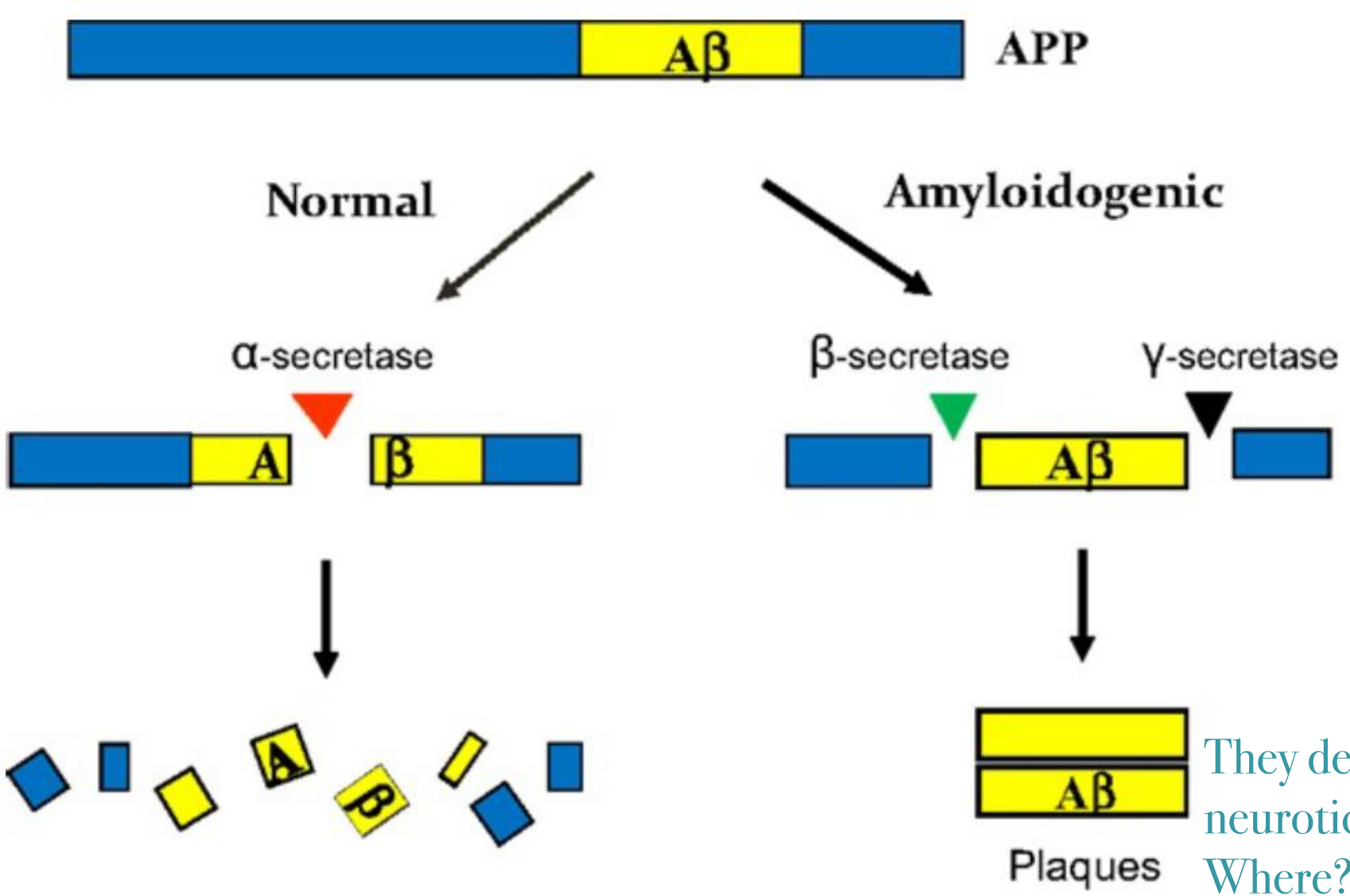


APP

NORMALLY
Gamma secretase cleave between the yellow and red parts.
While alpha secretase cleave the red part into two parts.
This result in NONamyloidogenic chain, and there is no deposition

BUT in PATHOLOGIC conditions :
Red part (AB amyloid) will be seperated alone, which result on AMYLOIDOGENIC chain, there is deposition

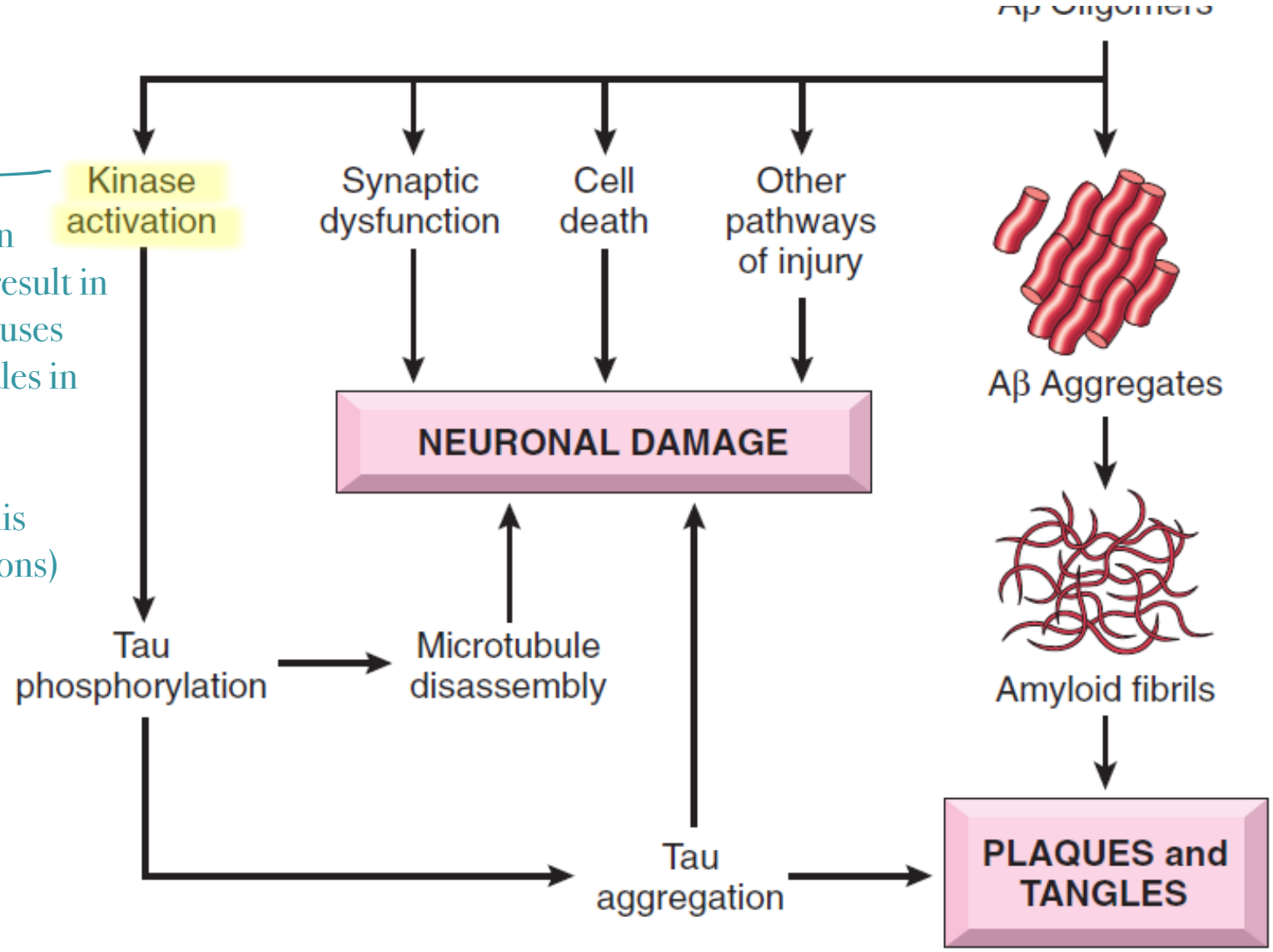




They deposit to form neurotic plaques
Where? In neuropil

Normally Tau protein is responsable for axons microtubules assembly

Kinases cause Tau protein phosphorylation , which result in nonfunctional Tau and causes disassembly of microtubules in axons , and Tau protein accumulation to form neurofibrillary tangles (this happen INSIDE the neurons)



Role of tau:

- Tau is a microtubule-associated protein.
- Present in axons in association with the microtubular network.
- Responsible for tangles in AD >>> Tau aggregates leads to cell death
- Hyperphosphorylated and loses the ability to bind to microtubules >>>> loss of microtubule stability >>> neuronal toxicity and death.

- Tau aggregates can be passed across synapses from one neuron to the next >>> spread of lesions.

Role of inflammation

- Innate immune system responds to Aβ and tau.
- Deposits of Aβ elicit an inflammatory response from microglia and astrocytes.
- Clearance of the aggregated peptide, and secretion of mediators that cause neuronal injury over time.

Basis for cognitive impairment

- Deposits of Aβ and tangles appear long before cognitive impairment
- In familial AD, deposition of Aβ and the formation of tangles precede cognitive impairment by as much as 15 to 20 years.
- Large burden of plaques and tangles is strongly associated with severe cognitive dysfunction.
- **The number of neurofibrillary tangles correlates better with the degree of dementia than does the number of neuritic plaques.**

Severity of symptoms depend on the magnitude of depositioned plaques and tangles , and this severity is more correlated with number of tau protein neurofibrillary tangles .

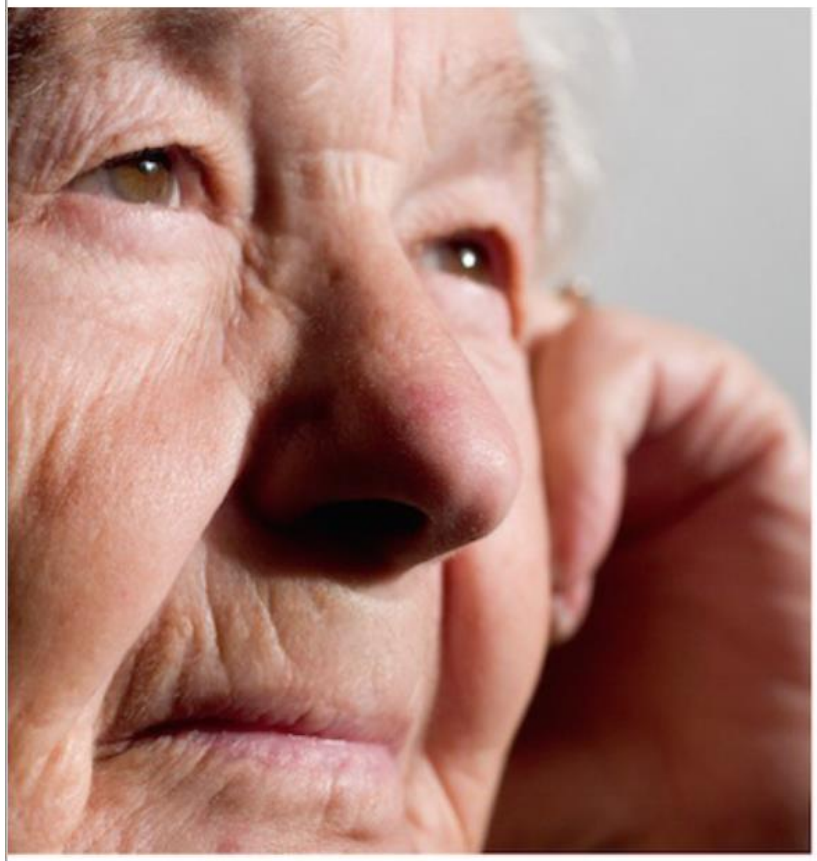
Morphology

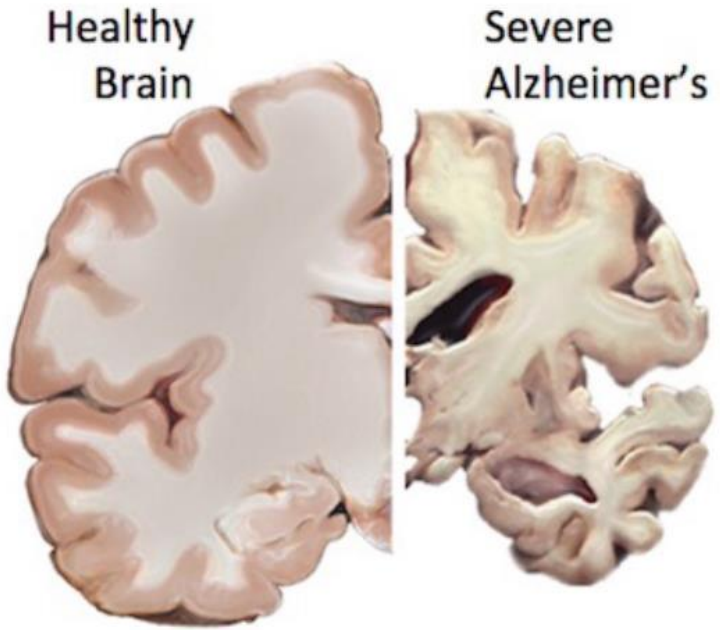
This is a characteristic of neurodegenerative disorders because of loss of neuron , gyri getting smaller while sulci will be wider.

- Cortical atrophy,
- Widening of the cerebral sulci
- Most pronounced in the frontal, temporal, and parietal lobes.
- Compensatory ventricular enlargement (hydrocephalus ex vacuo).

It's hydrocephalus but without an increase in Intrcranial pressure , because it's a compensatory mechanism to atrophy.

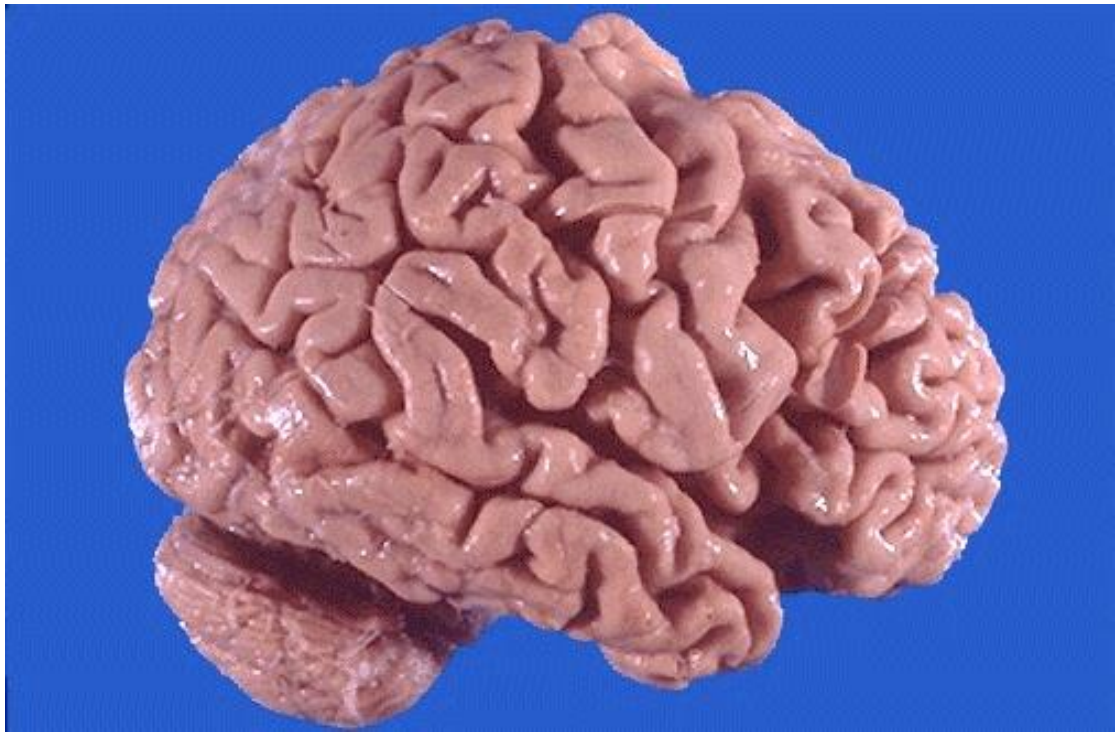
Notice the diffrence





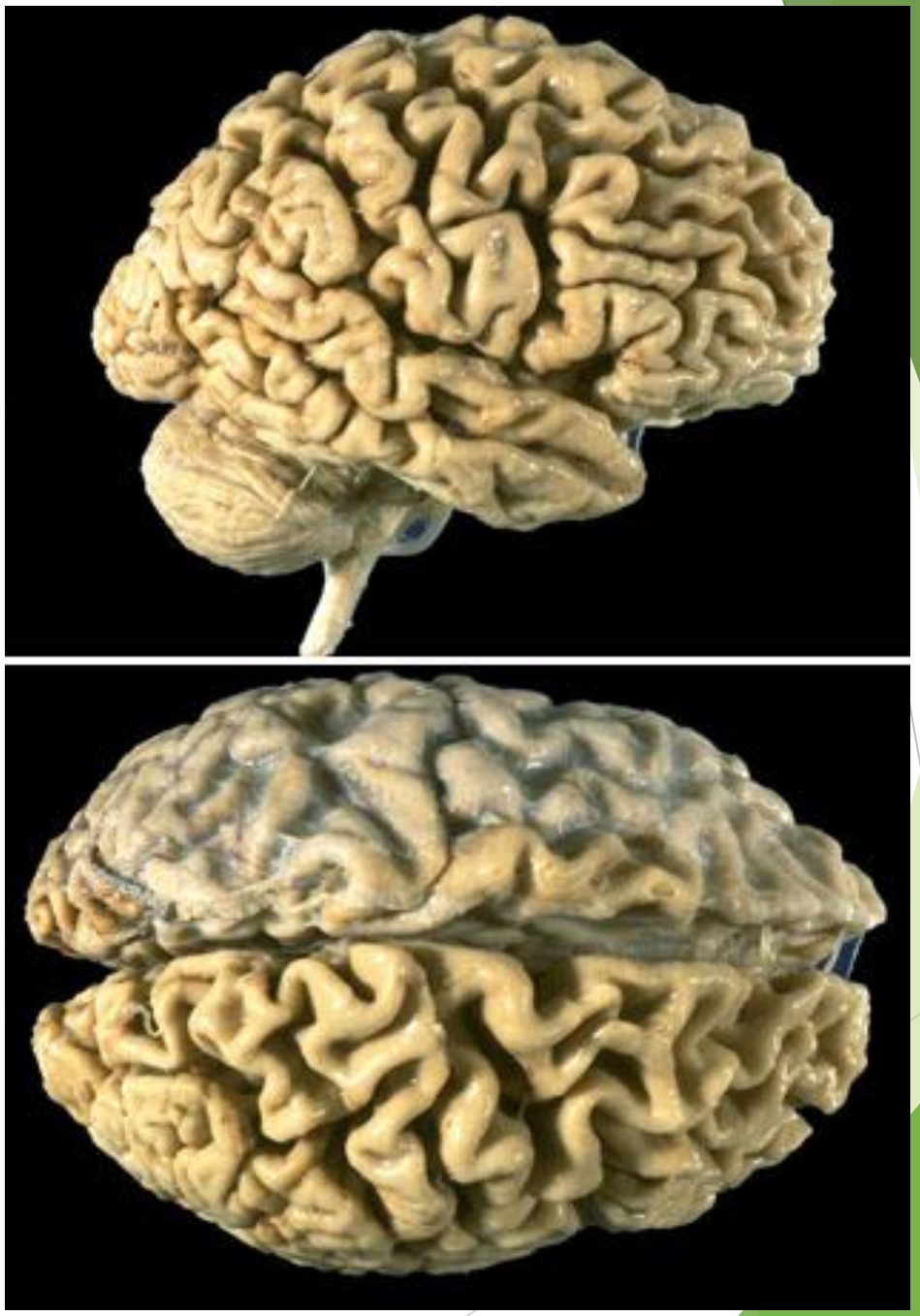
Neuronal cell loss leading to extensive shrinkage in an Alzheimer's brain (right), as compared to a healthy human brain (left).

Notice how the occipetal lobe is not affected.
REMEMBER: with alzheimer disease FRONTAL, PARIETAL , and TEMPORAL lobes are affected .
most in temporal and parietal , frontal comes later on (personality and behavioral changes symptoms occur late in disease).

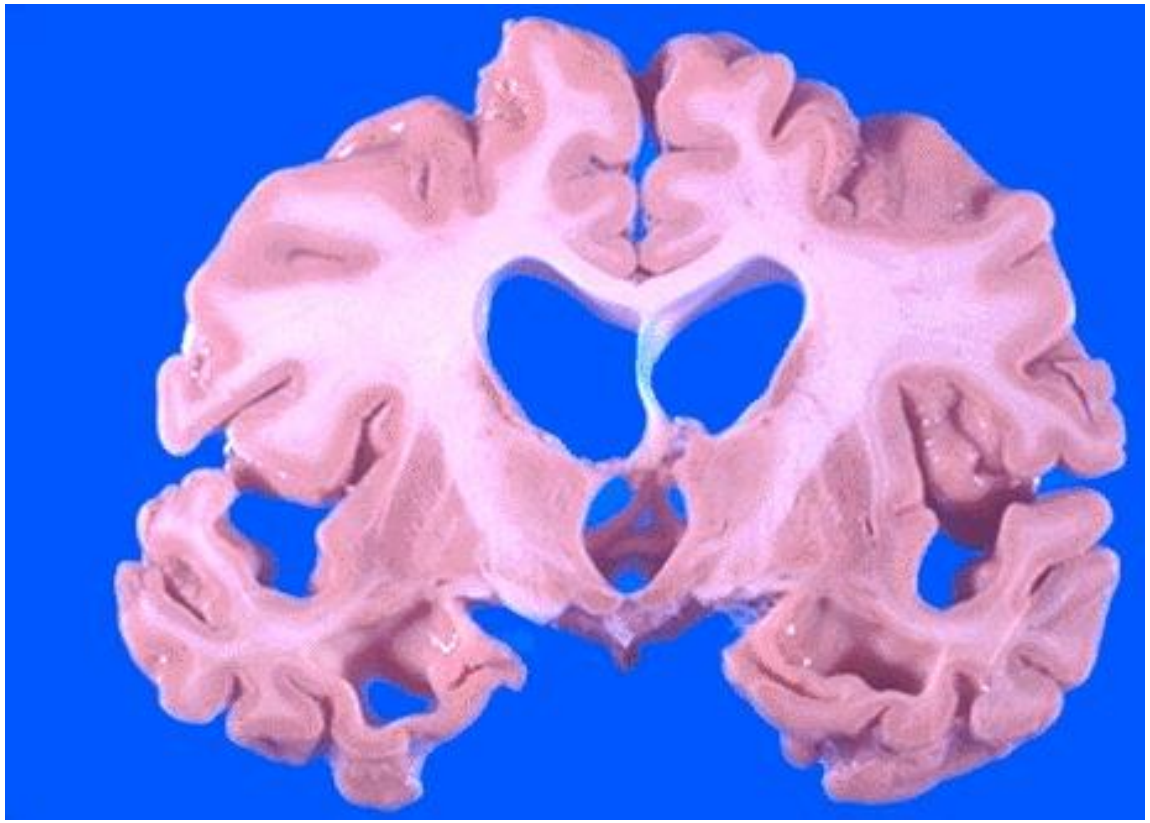


- Mainly in the frontal and parietal regions, characterized by **narrowed gyri** along with **widened sulci**.

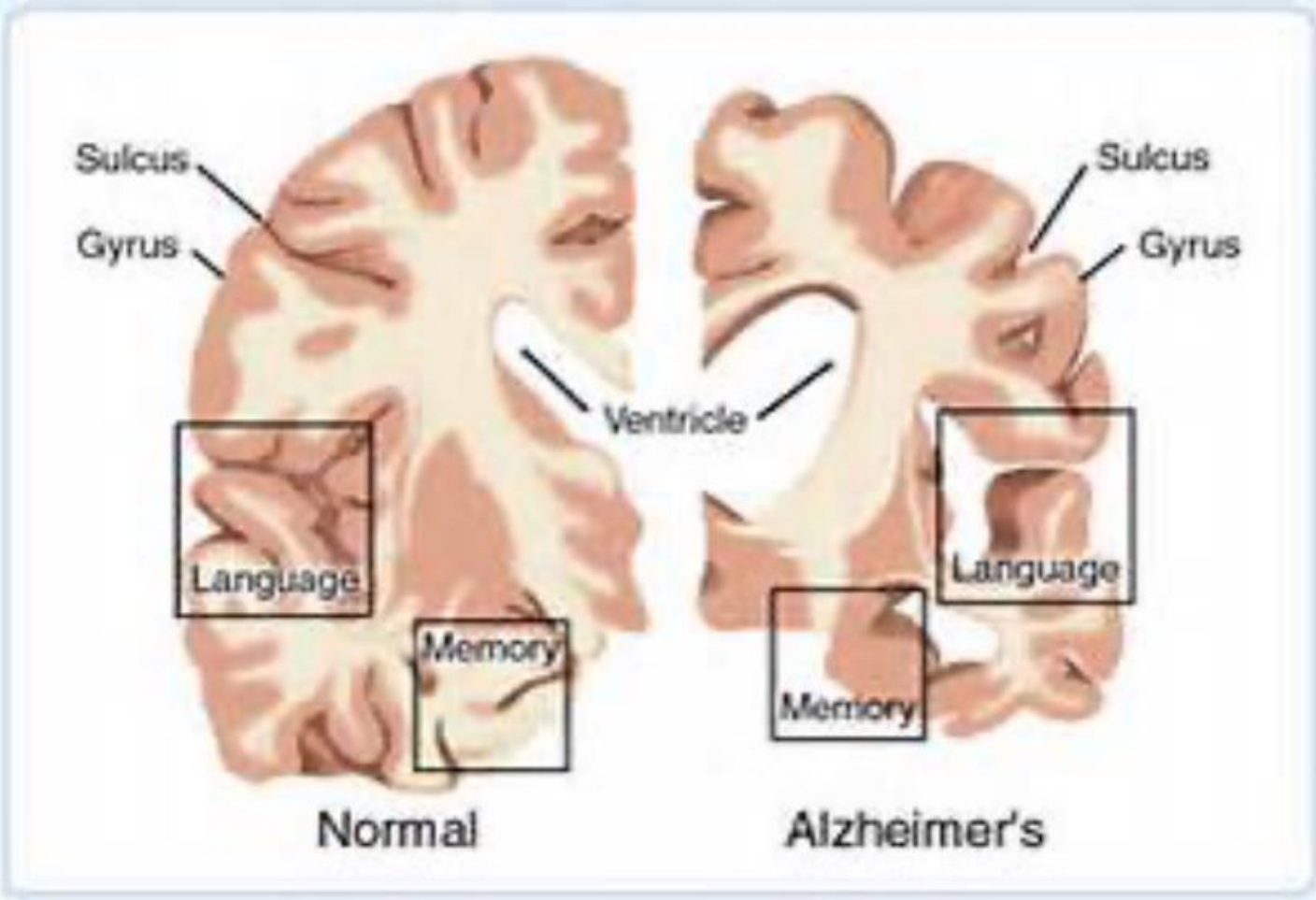
- More marked atrophy seen superiorly and laterally, with sparing of the occipital region.



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



Notice the enlargement of the ventricles


Sulcus
Gyrus
Ventricle
Language
Memory
Sulcus
Gyrus
Language
Memory
Normal
Alzheimer's

Alzheimer disease neuropathologic changes.

↝That deposit in the neuropil (outside neurons)

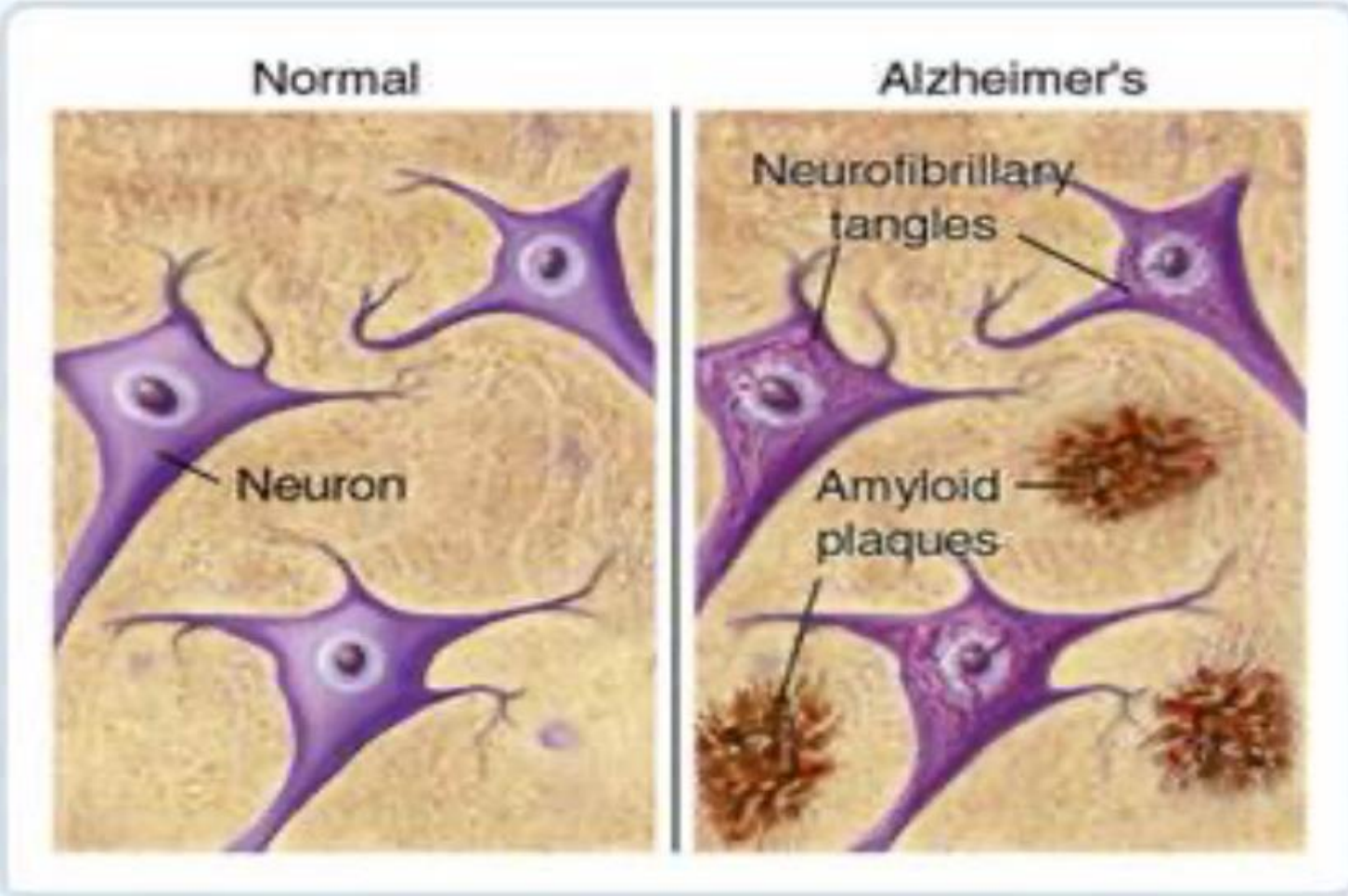
- **Neuritic plaques** (an extracellular lesion): central amyloid core surrounded by collections of dilated, tortuous, processes of dystrophic neurites.
- Hippocampus and amygdala and neocortex, (sparing of primary motor and sensory cortices until late)
- The amyloid core contains Aβ

AB amyloid is surrounded by dystrophic neurites, which is adjacent neurons processes.

↝That deposit in the neurons cytoplasm

- **Neurofibrillary tangles**, basophilic fibrillary structures in the cytoplasm of neurons, displace or encircle the nucleus; persist after neurons die, becoming extracellular.
- Cortical neurons, pyramidal cells of hippocampus, the amygdala, the basal forebrain, and the raphe nuclei.
- Hyperphosphorylated tau

They promote cell death , and when it happens the neurofibrillary tangles resist degredation, and we will see them in neuropil later on

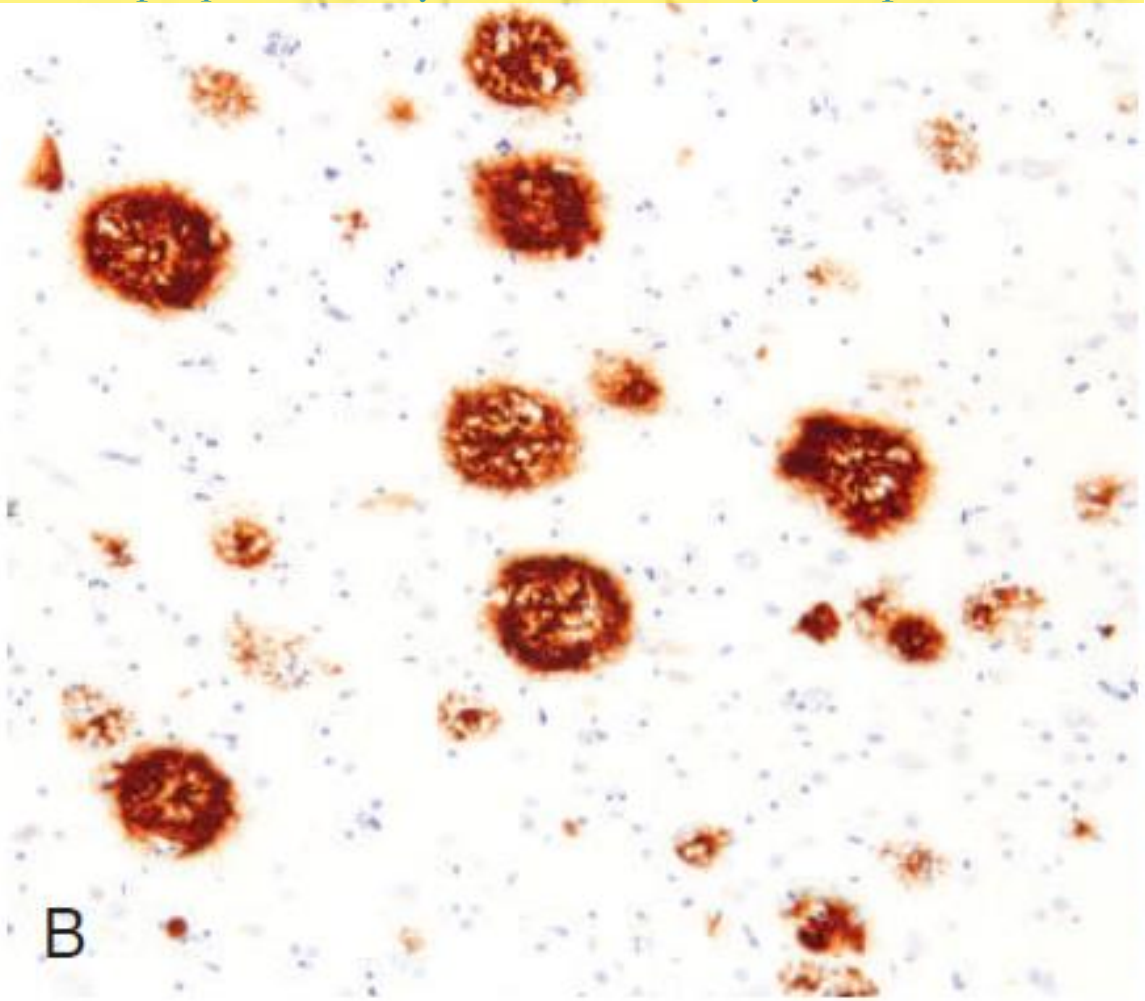


Notice brown color plaques in neuropil And the tangles around the nucleus

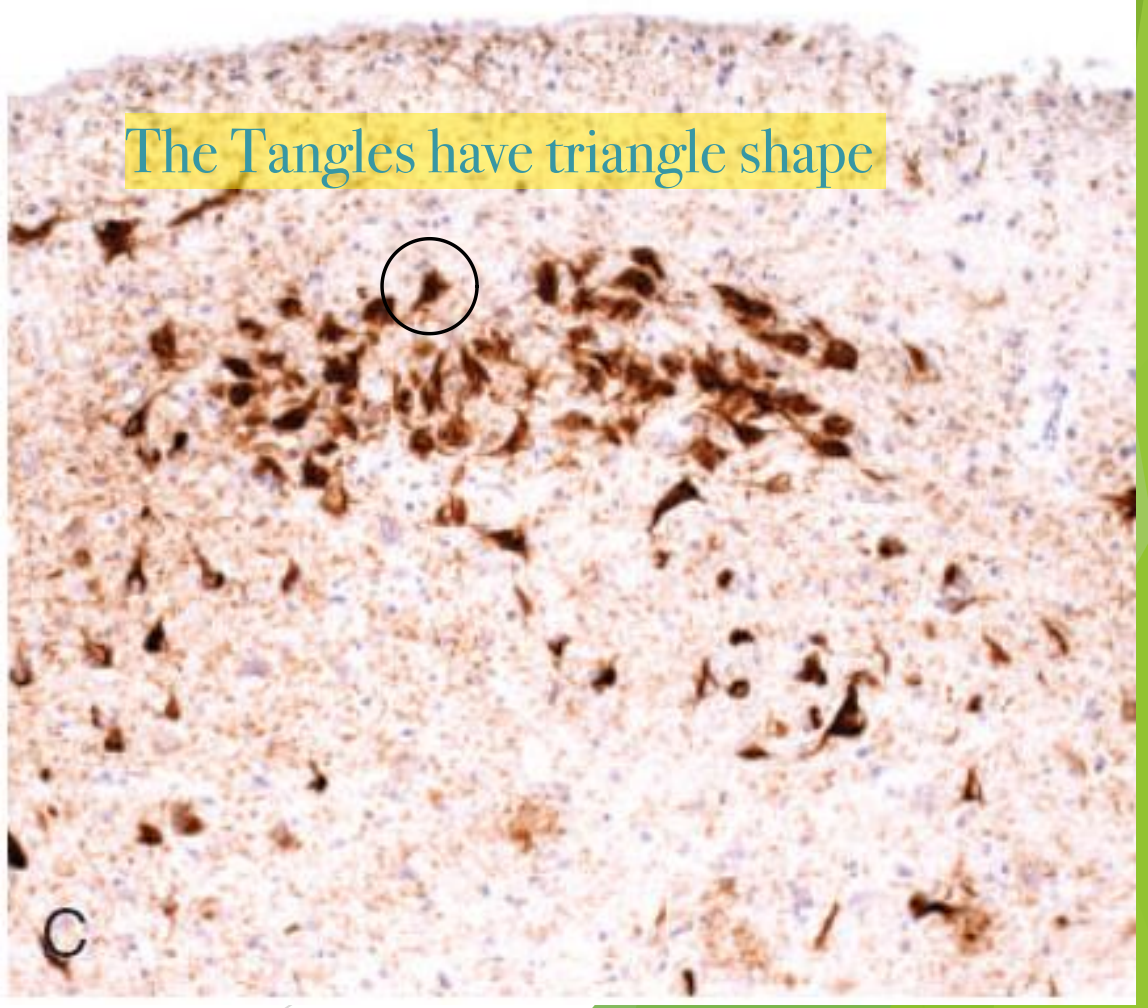
Immuno Stain

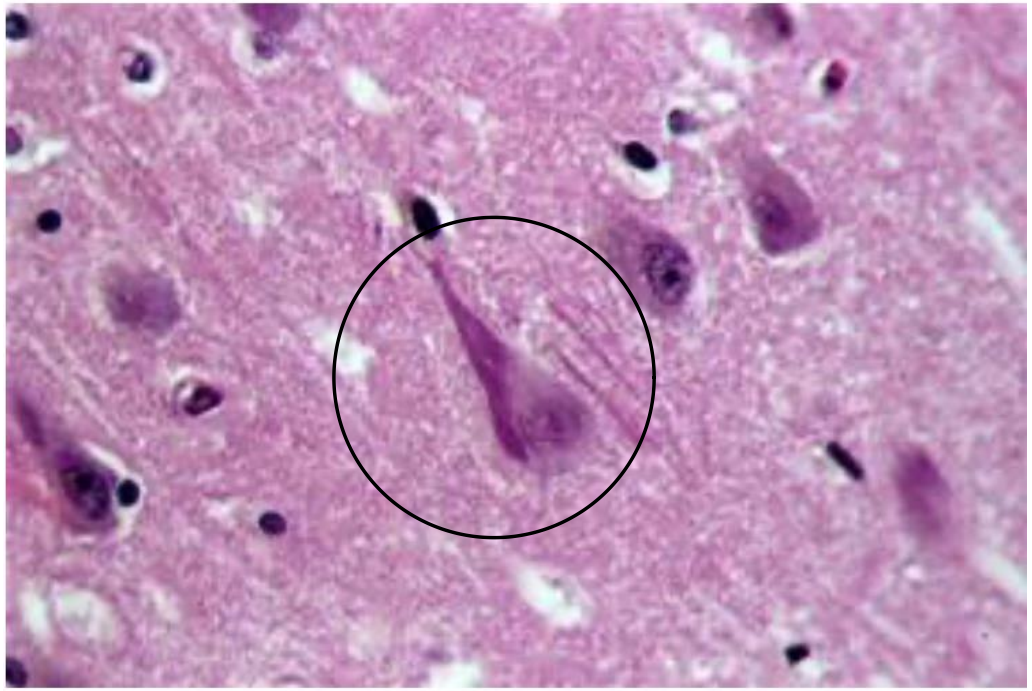
Plaques and tangles

Neurotic plaques (AB amyloid surrounded by distrophic neurites)

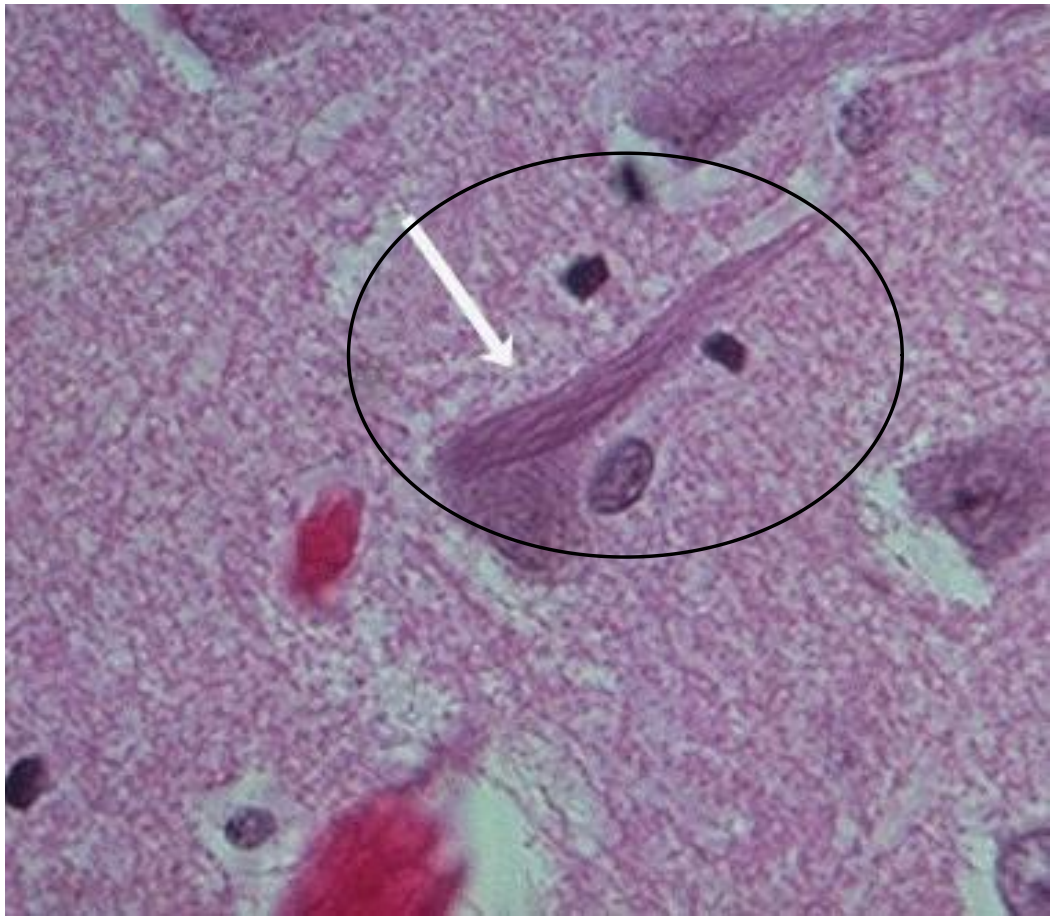


The Tangles have triangle shape



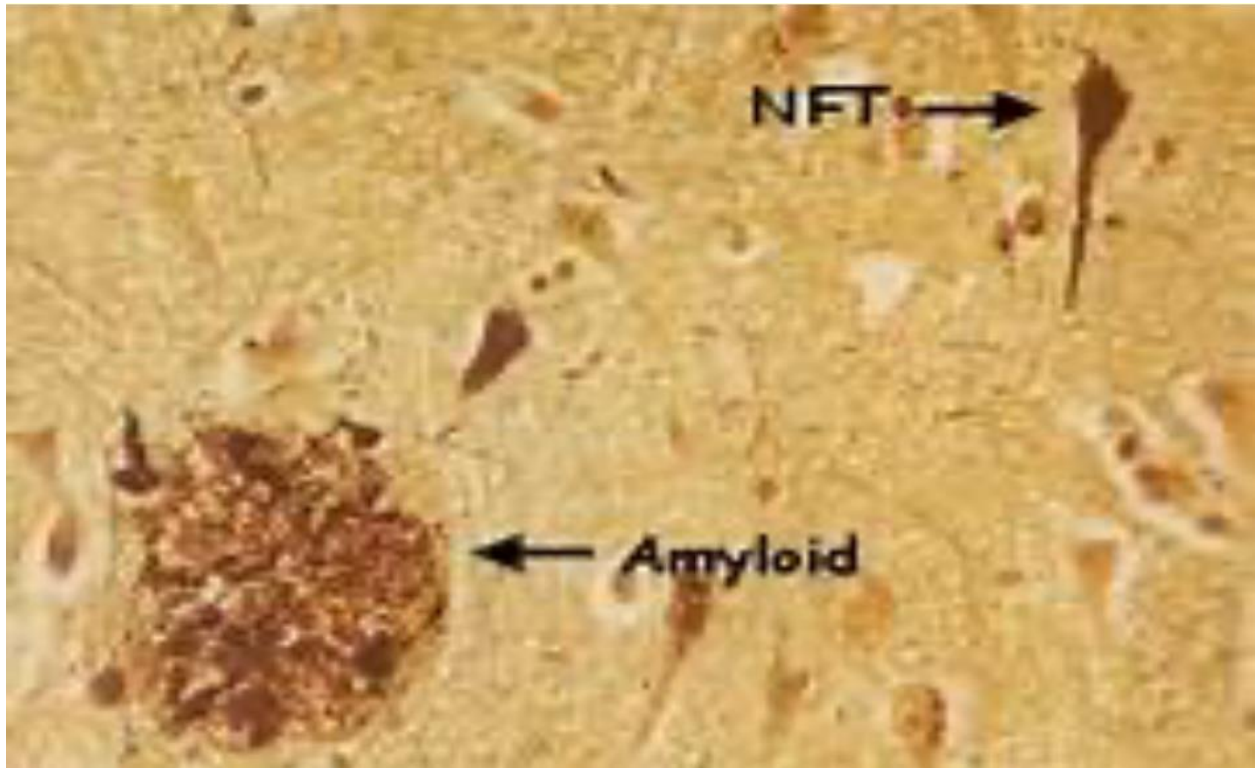


NEUROFIBRILLARY TANGLES

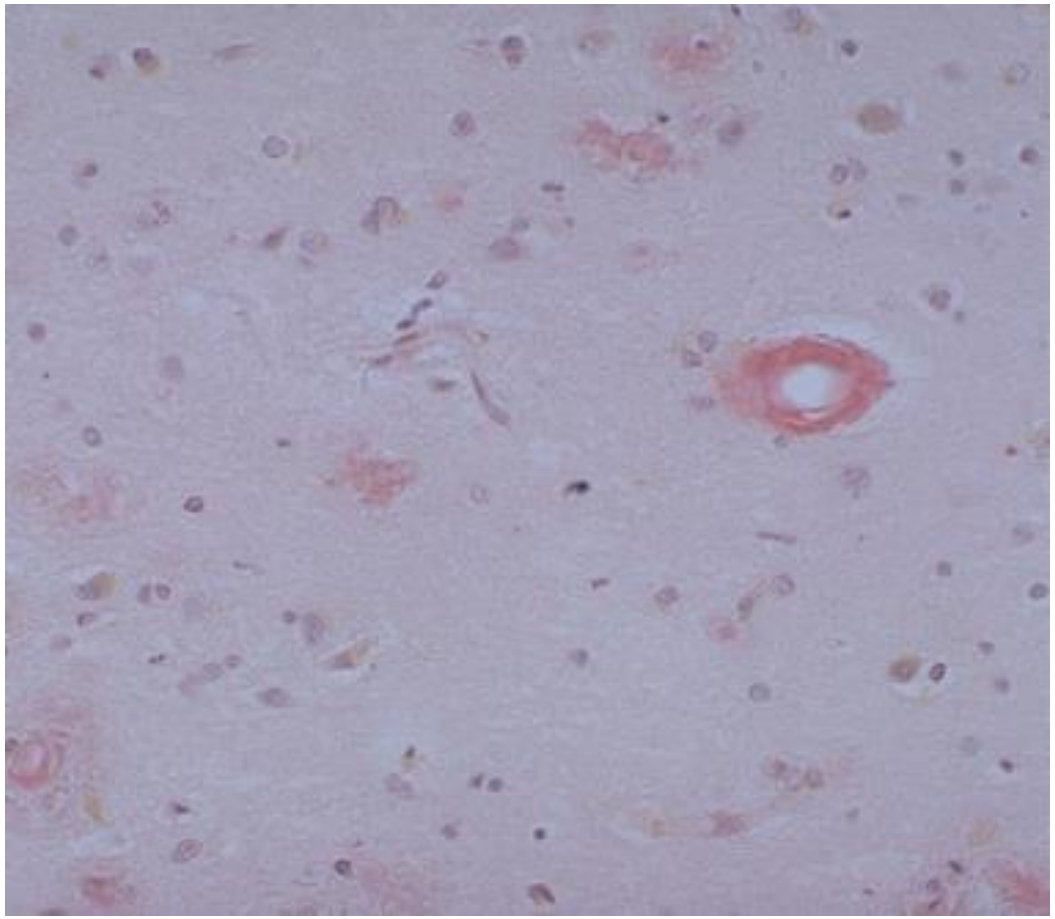


Notice how it's fibrillary

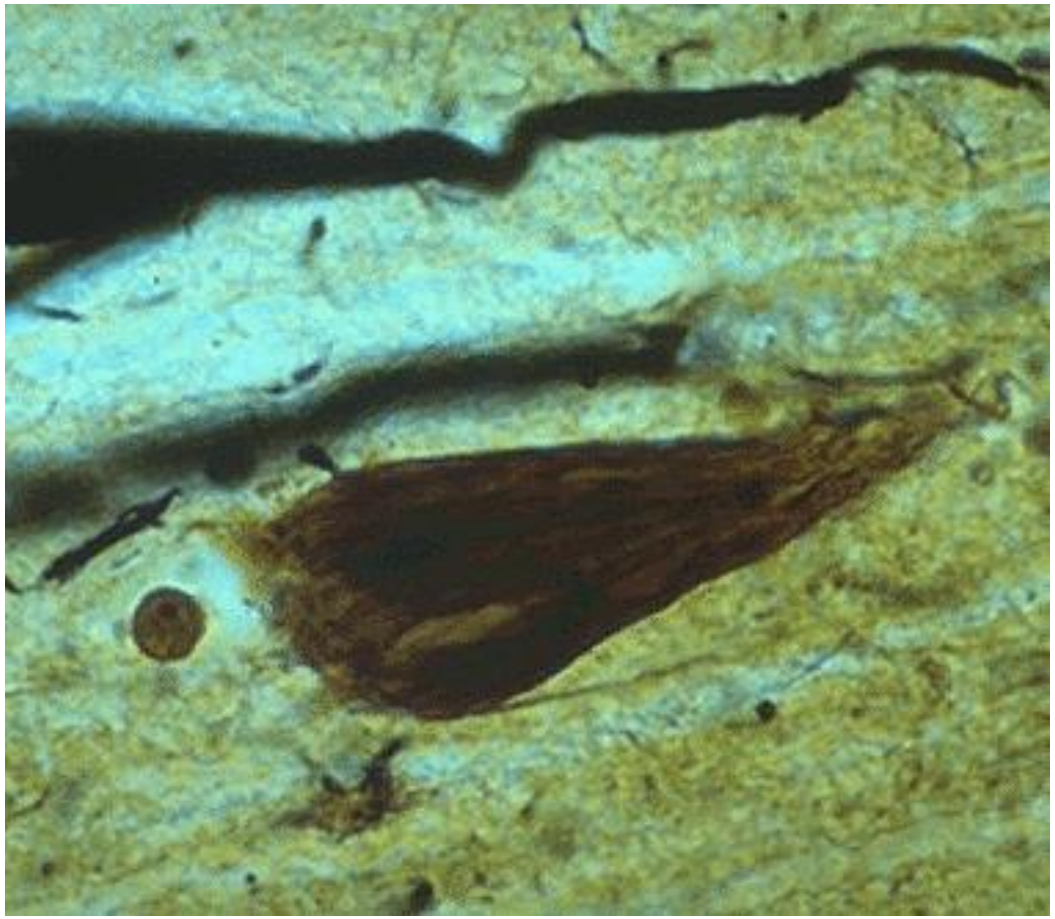
Neurofibrillary tangles



By immuno stain



Congo red stain for (Amyloid stain) amyloid core of plaques.



Silver stain for NFT

THIS IS ANOTHER TYPE OF DEMENTIA :

Frontotemporal Lobar Degeneration

Frontotemporal dementias

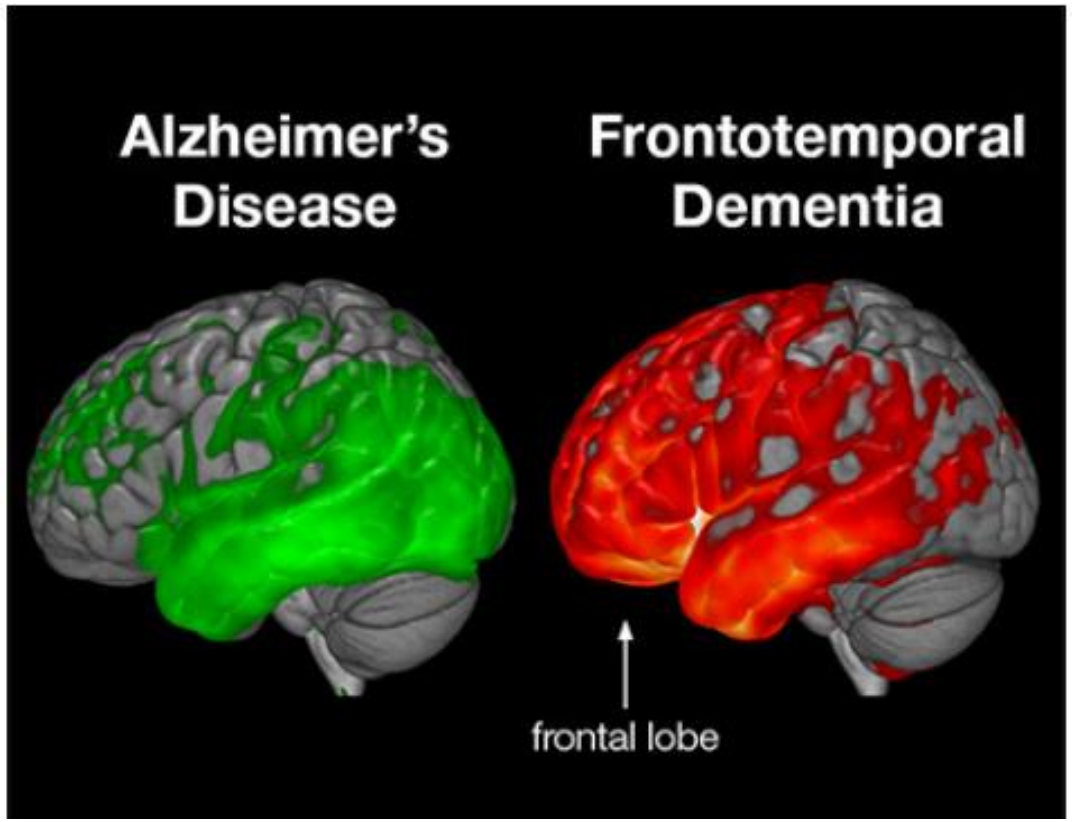
They differ from alzheimer disease by the involvement of frontal lobe early on (start with behaviral changes before memory changes)
Another difference is on deposition of proteins

- Several disorders, preferentially affect the frontal and/or temporal lobes.
- Progressive deterioration of language and changes in personality
- **Behavioral and language problems precede memory disturbances, in contrast to AD.**
- The onset of symptoms occurs at younger ages than for AD.
- Neuronal inclusions, which may contain **tau or TDP43. (two forms of disease)**
- ***Pick disease*** *(subtype of* FTLD-tau*)*, associated with smooth, round inclusions known as *Pick bodies*
- ***TDP34 subtype*** *(also deposited in ALS)*

Here the deposition is neuronal inclusions

(or Pick inclusions contain tau, different than neurofibrillary tangles in their rounded shape .)

(Ametrophic lateral sclerosis, which we will descuss in another lecture)

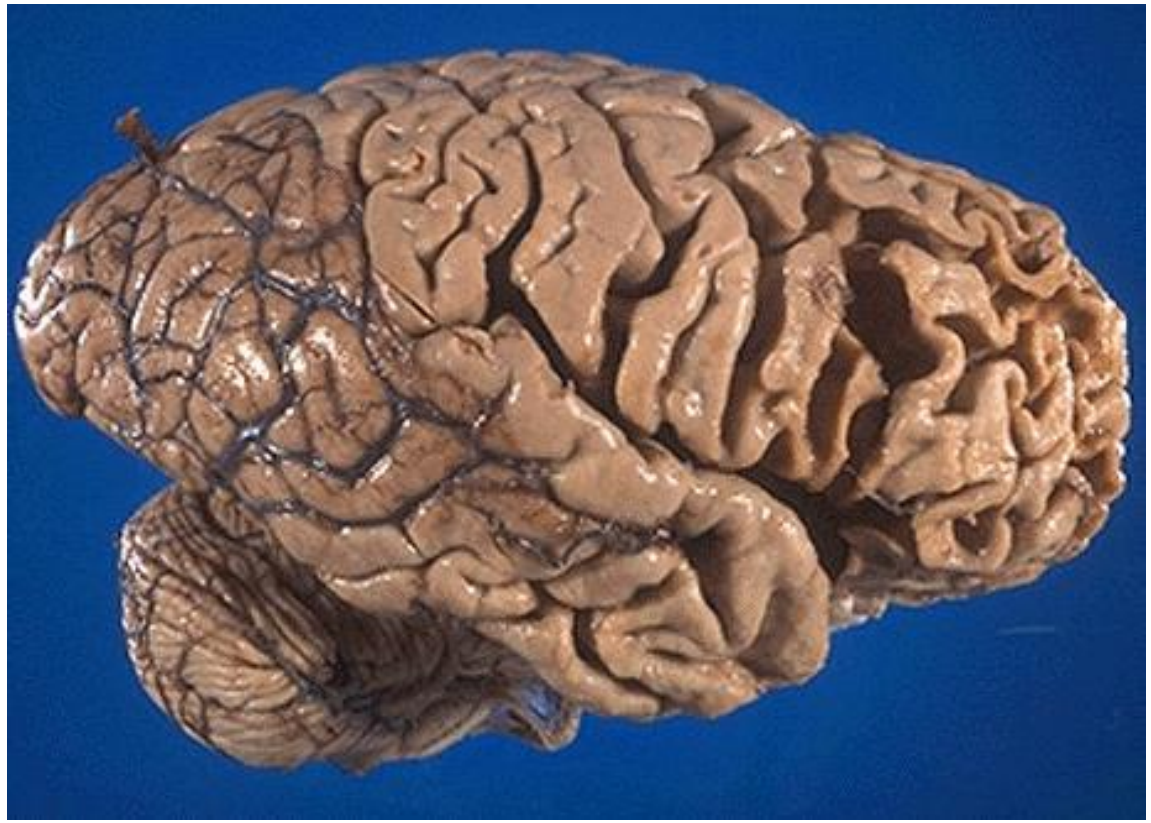


- In AD there is sparing of the frontal lobe, at least at the beginning so behavioural changes are a late manifestation.
- In FTLD frontal is affected from the beginning so patients present with behavioural problems first.

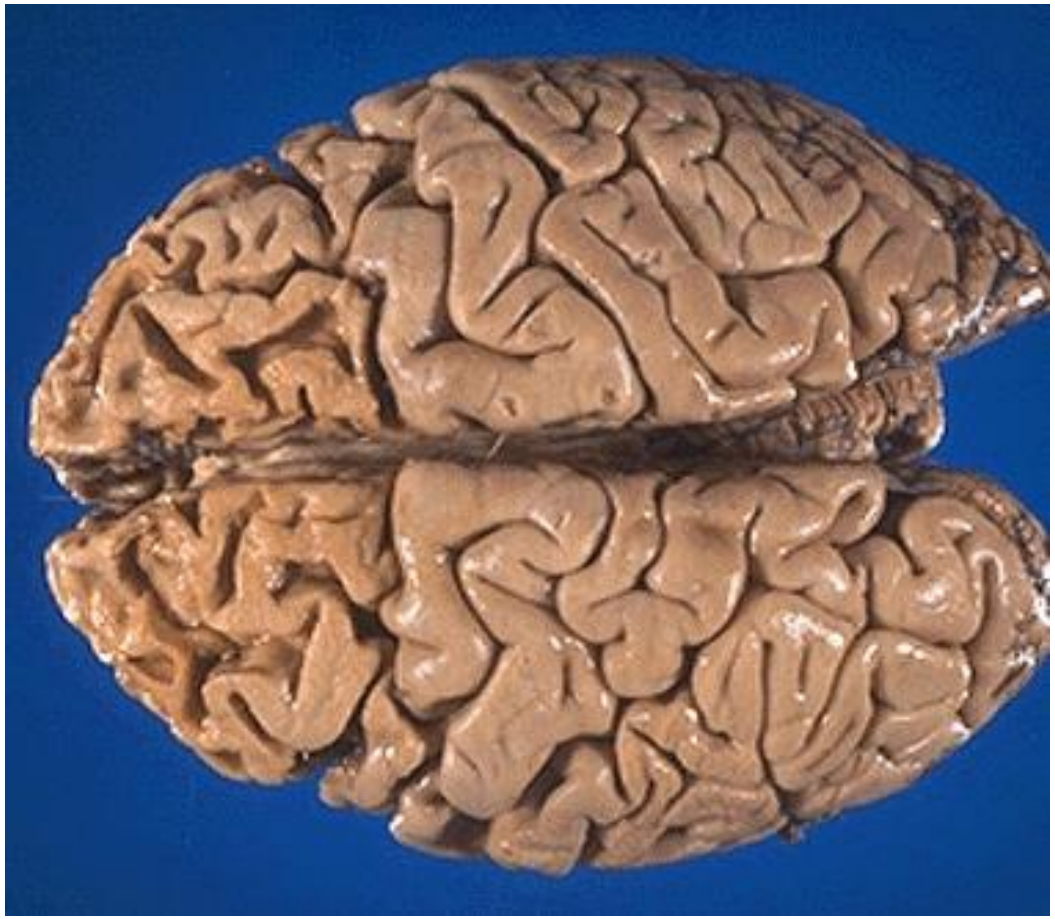
MORPHOLOGY

- Atrophy of frontal and temporal lobes.
- Neuronal loss and gliosis
- In FTLD-tau, the characteristic neurofibrillary tangles, similar to AD
- Pick bodies in pick Disease.

  Again , pick bodies is a rounded inclusions inside the neurons that contain tau protein .

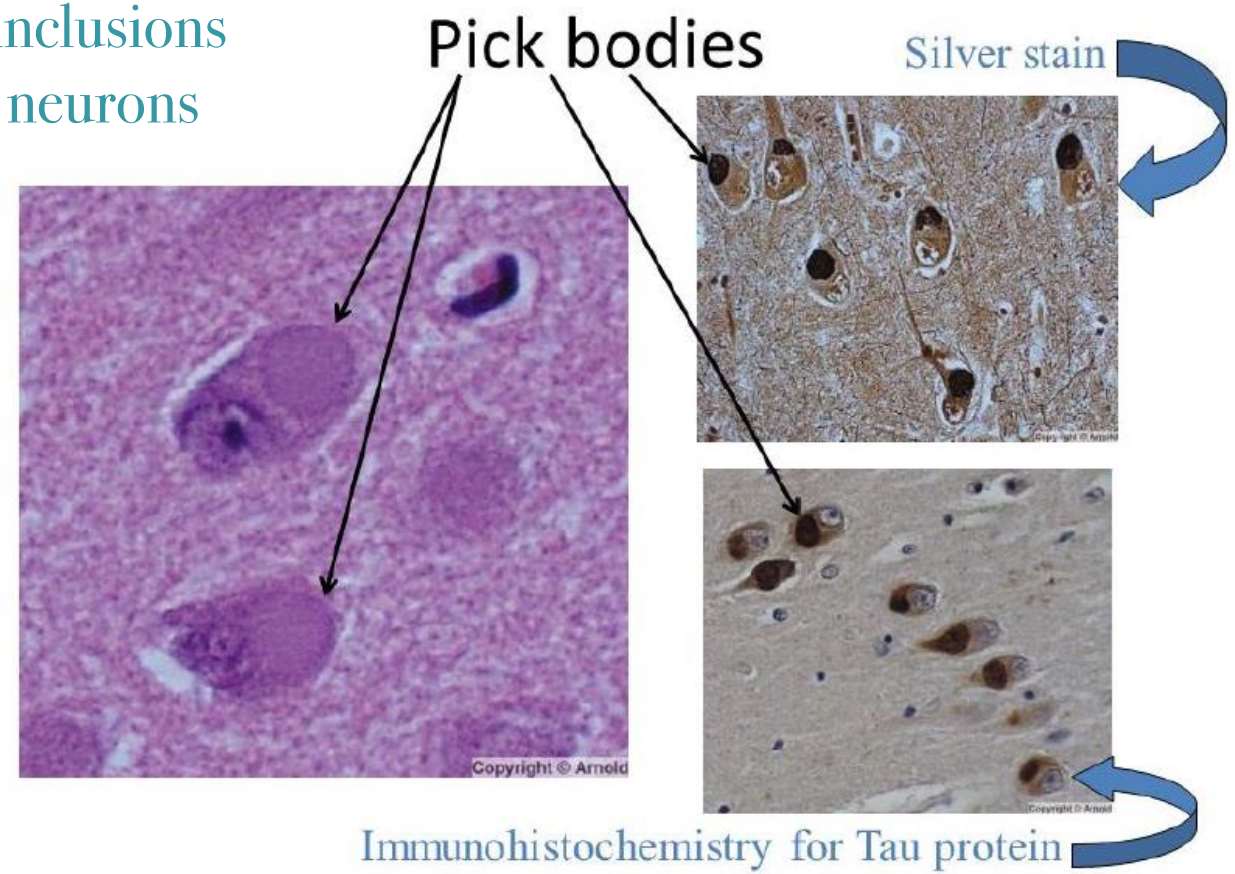


- Very marked **frontal lobe atrophy** and **temporal lobe atrophy**



Frontal lobes are markedly thinned

Rounded inclusions within the neurons



In this lecture we discussed :
Neurodegenerative diseases affecting cerebral cortex

1.Alzheimer disease

2.Frontotemporal lobar degeneration

✨THANK YOU ✨