Neurodegenerative disorders-1

Manar Hajeer, MD, FRCPath

University of Jordan, School of medicine

Classic features:

- Progressive loss of neurons.
- Typically affects groups of neurons with functional interconnections.
- Different diseases involve different neural systems, so different symptoms.
- The histologic hallmark for ALL diseases is the ACCUMULATION OF PROTEIN AGGREGATES.
- Same protein may aggregate in different diseases, BUT AT DIFFERENT DISTRIBUTION..
- Proteins resist degradation, accumulate within the cells, elicit inflammatory response, and is toxic to neurons.

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)

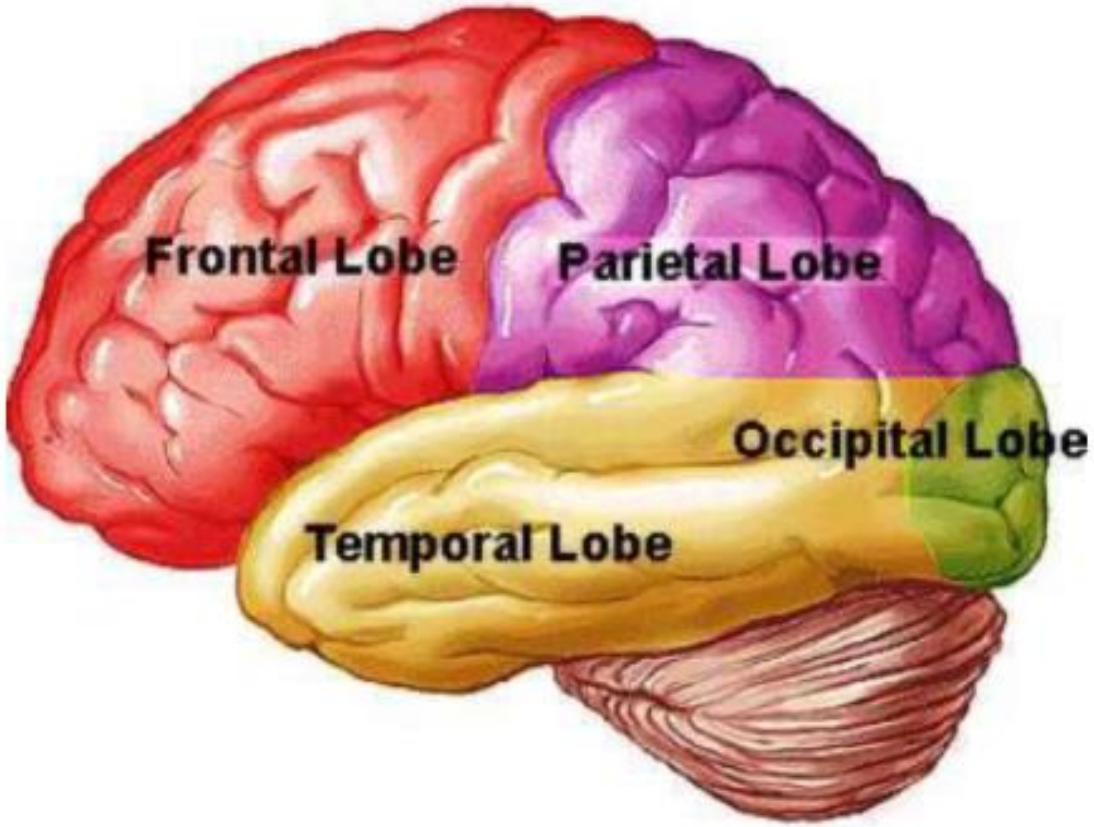
Different diseases

- **Involving the hippocampus and cortex**>>>> cognitive changes (memory disturbances, behavior and language) >>>> dementia >>>>>ALZHEIMER DISEASE (AD) , FRONTOTEMPORAL DEMENTIA (FTD), PICK DISEASE (SUBTYPE OF FTD)

- **Involving the basal ganglia** >>>>> movement disorders >>>>hypokinesia (PARKINSON DISEASE) or hyperkinesia (HUNTINGTON DISEASE)

- **Involving the cerebellum** >>>> ataxia >>> (SPINOCEREBELLAR ATAXIA, FRIEDRICH ATAXIA, ATAXIA TELANGECTASIA)

- **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.

DEMENTIA

- 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.
- Cognitive deficit must affect the person's performance in his daily life activities.
- There is no standard NORMAL COGNITION, always compared to previous level.

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
- Inappropriate behavior
- Paranoia
- Agitation
- Hallucinations

Causes of dementia

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

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

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)

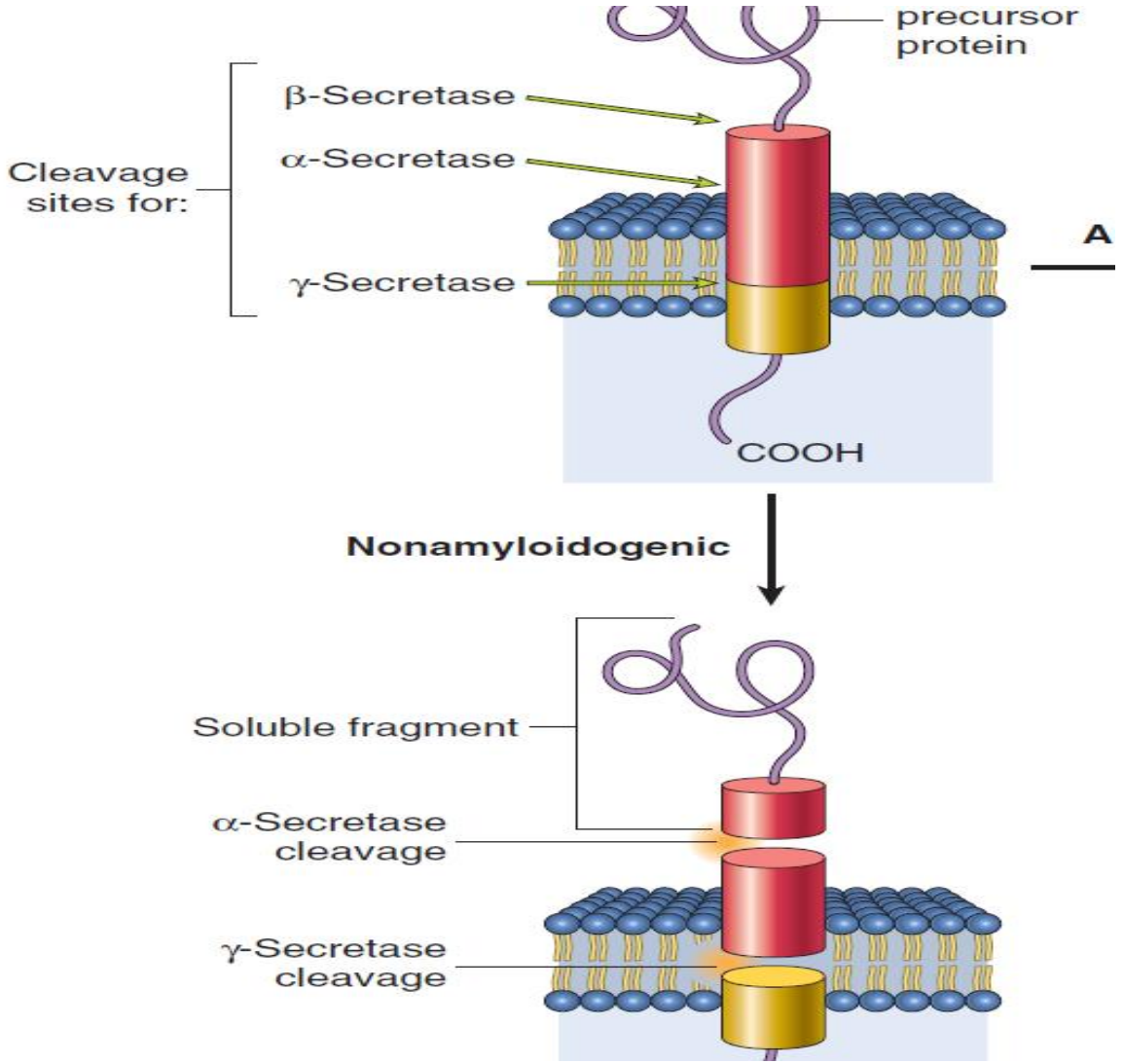
- **The most recognized symptom of Alzheimer is an inability to acquire new memories and difficulty in recalling recently observed facts.**
- As the disease advances, symptoms include confusion, irritability and aggression, mood swings, language breakdown, long term memory loss, and ultimately a gradual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

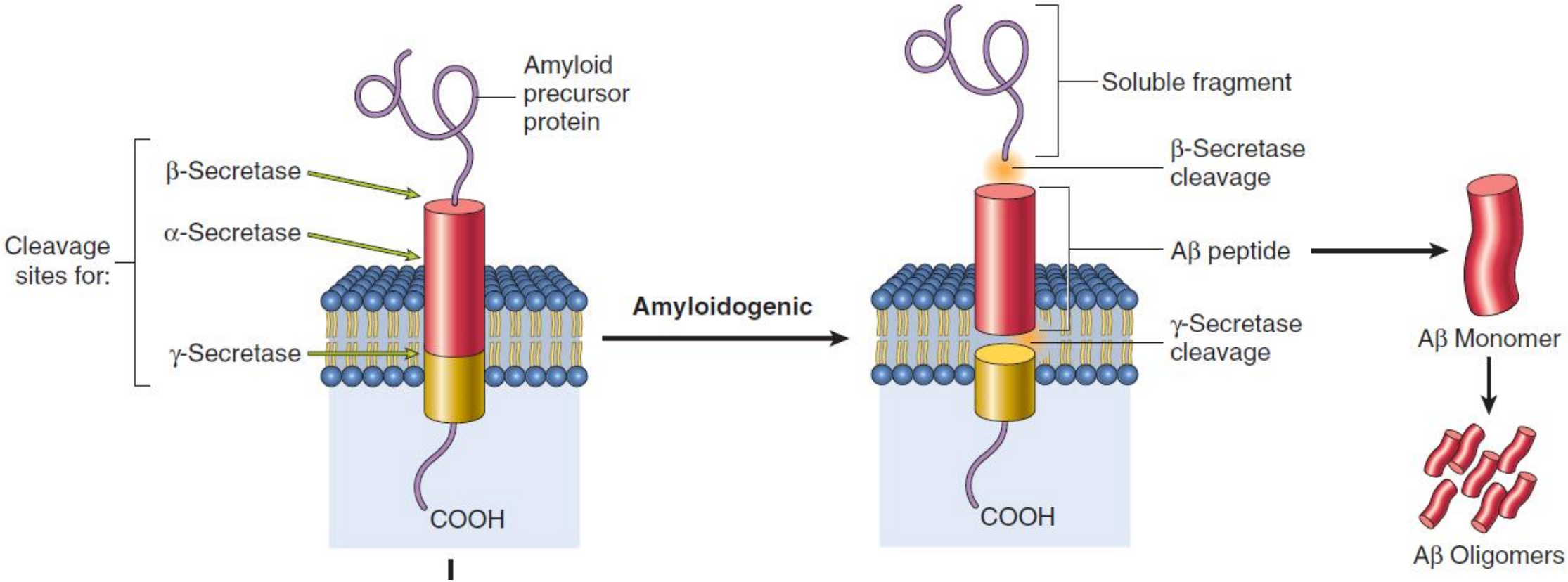
Pathogenesis:

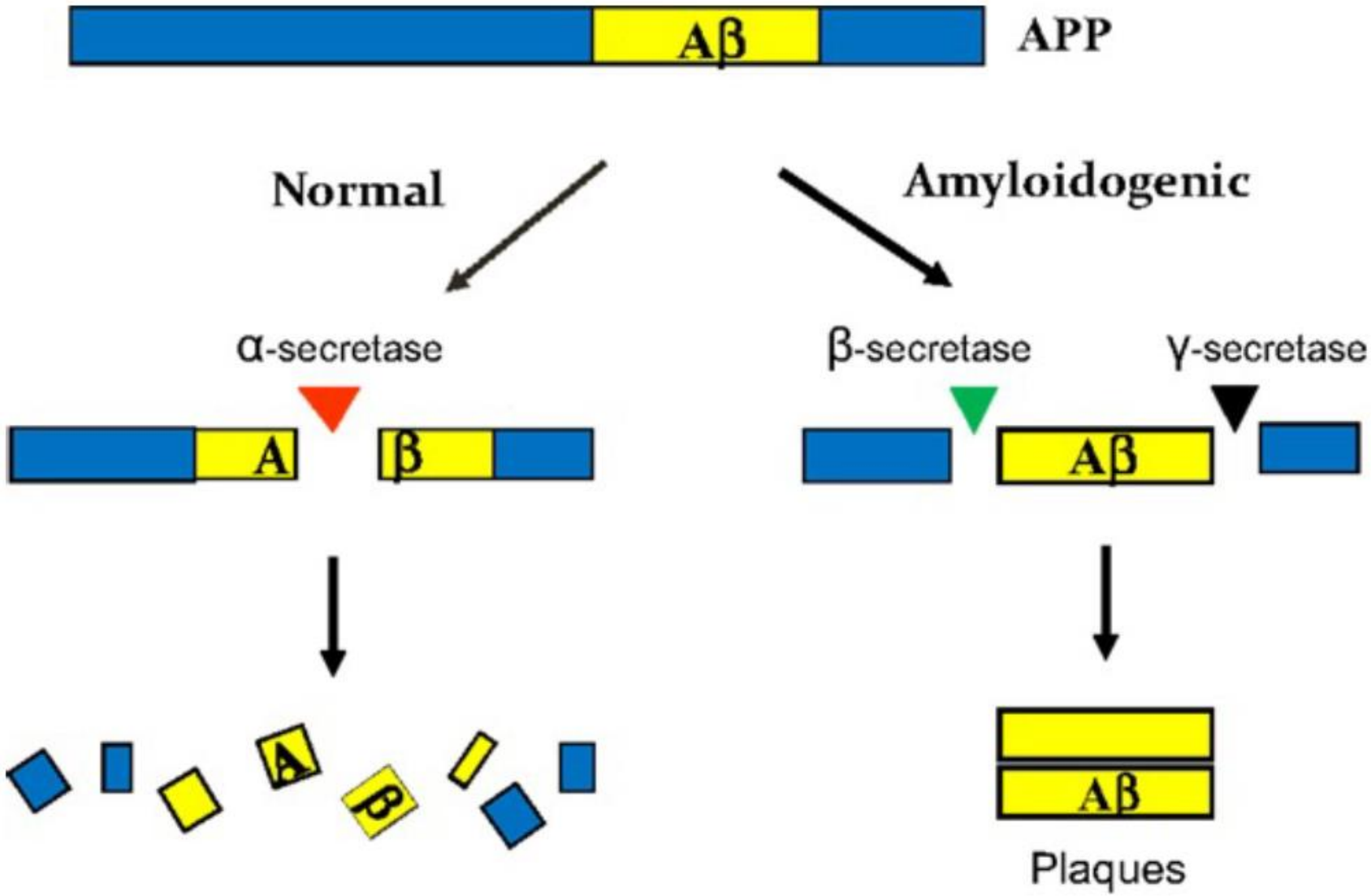
- Accumulation of two proteins (AB amyloid and Tau)
- In the form of plaques and neurofibrillary tangles, respectively.
- This leads to neuronal dysfunction, death and inflammation.
- Plaques deposit in the neuropil.
- Tangles develops intracellularly.
- Aβ generation is the critical initiating event 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.

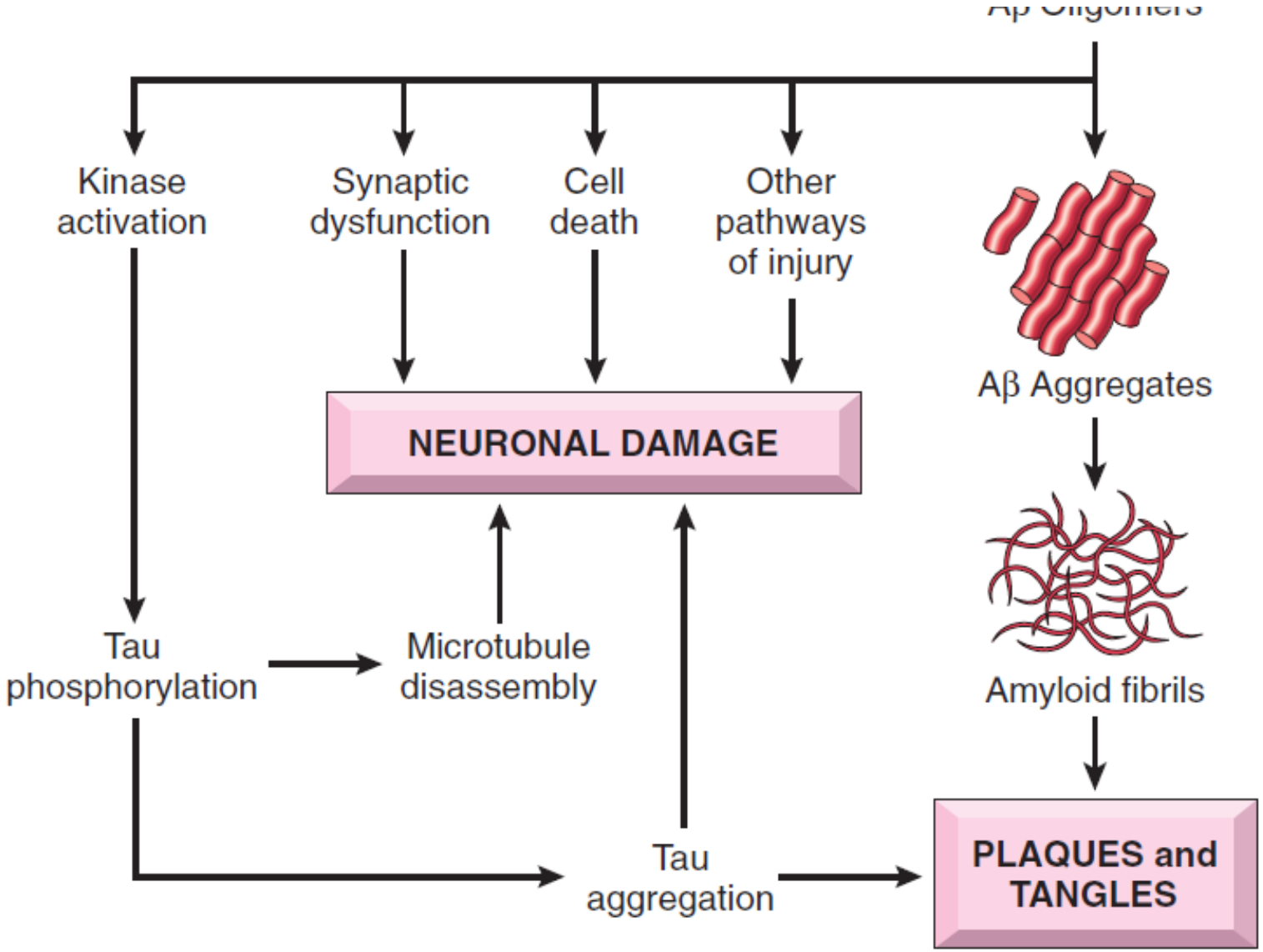
Role of Aβ

- 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.
- Normally, APP can be cleaved by **α-secretase and γ-secretase**, liberating a nonpathogenic peptide.
- Familial AD: Mutations in APP or in components of γ-secretase.
- 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.


precursor protein
β-Secretase
α-Secretase
Cleavage sites for:
γ-Secretase
A
COOH
Nonamyloidogenic
Soluble fragment
α-Secretase cleavage
γ-Secretase cleavage


Amyloid
precursor
protein
β-Secretase
α-Secretase
γ-Secretase
Cleavage
sites for:
COOH
Amyloidogenic
Soluble fragment
β-Secretase
cleavage
Aβ peptide
γ-Secretase
cleavage
COOH
Aβ Monomer
Aβ Oligomers


Aβ
APP
Normal
Amyloidogenic
α-secretase
β-secretase
γ-secretase
A
β
Aβ
Aβ
Plaques


Aβ Oligomers
Kinase activation
Synaptic dysfunction
Cell death
Other pathways of injury
Aβ Aggregates
NEURONAL DAMAGE
Tau phosphorylation
Microtubule disassembly
Amyloid fibrils
Tau aggregation
PLAQUES and TANGLES

Role of tau:

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

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

Role of inflammation

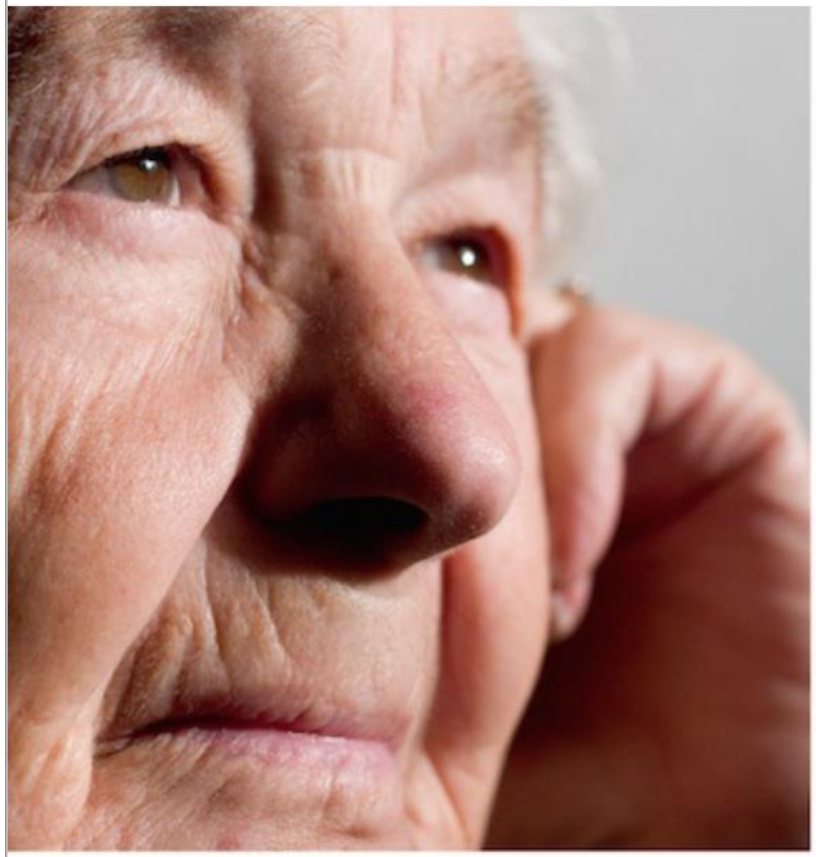
- Innate immune system responds to Aβ and tau.
- Deposits of Aβ elicit an inflammatory response from microglia and astrocytes.
- Clearance of the aggregated peptide, and secretion of mediators that cause neuronal injury over time.

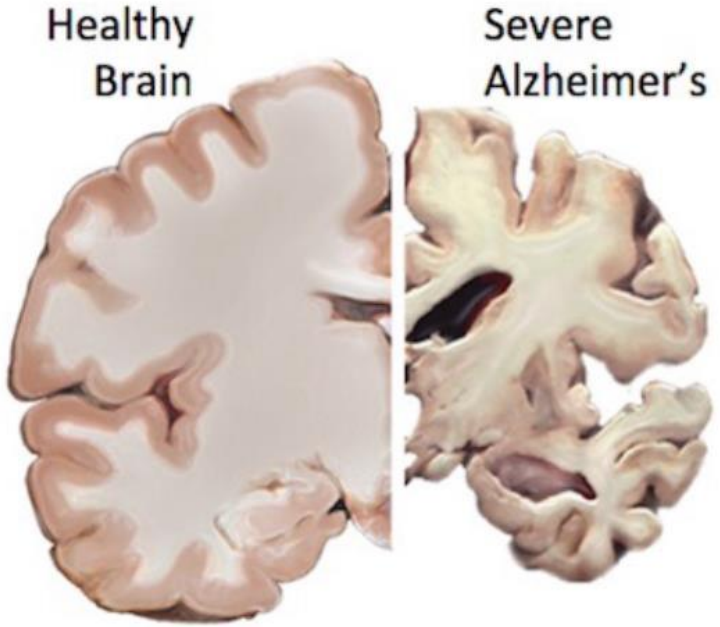
Basis for cognitive impairment

- 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.**

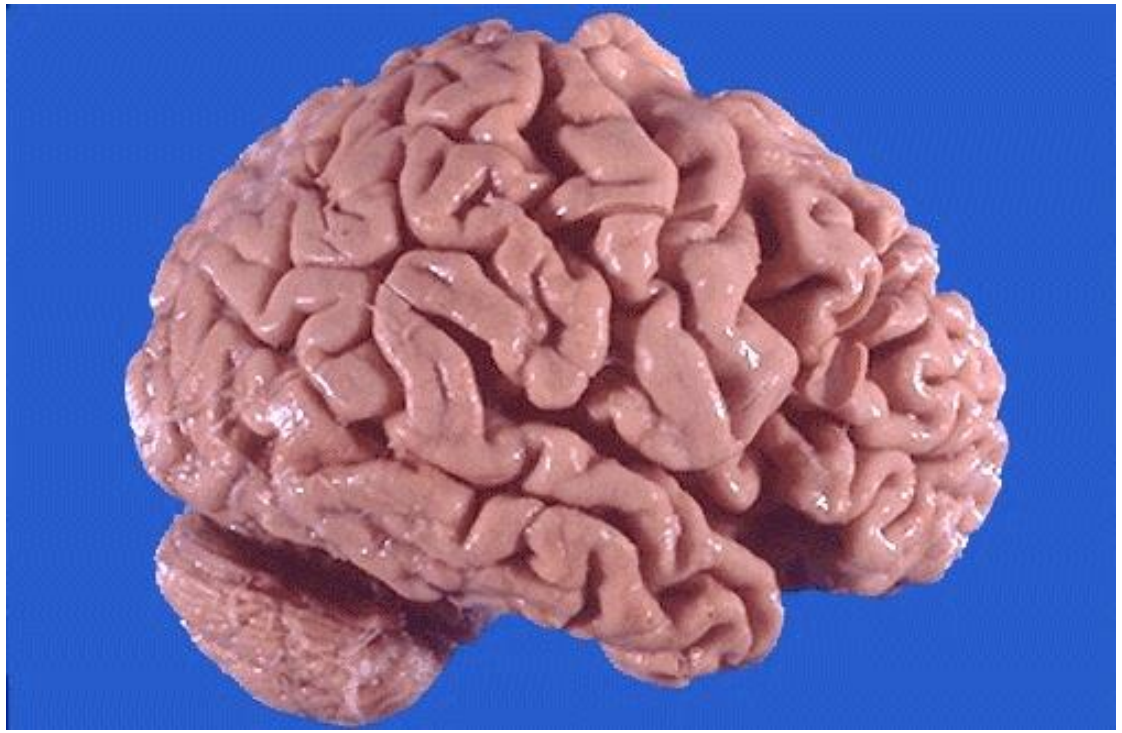
Morphology

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



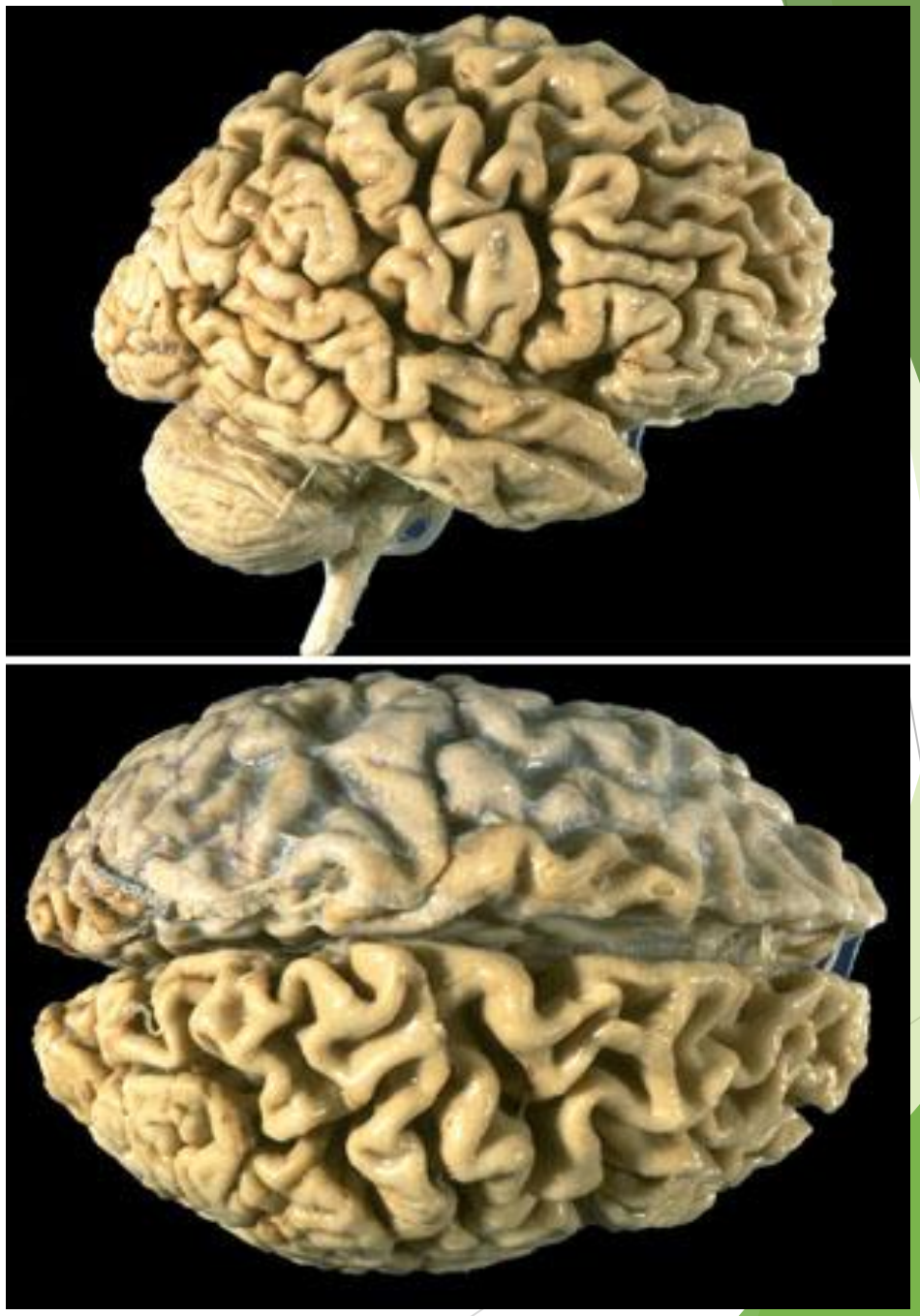


Neuronal cell loss leading to extensive shrinkage in an Alzheimer's brain (right), as compared to a healthy human brain (left).

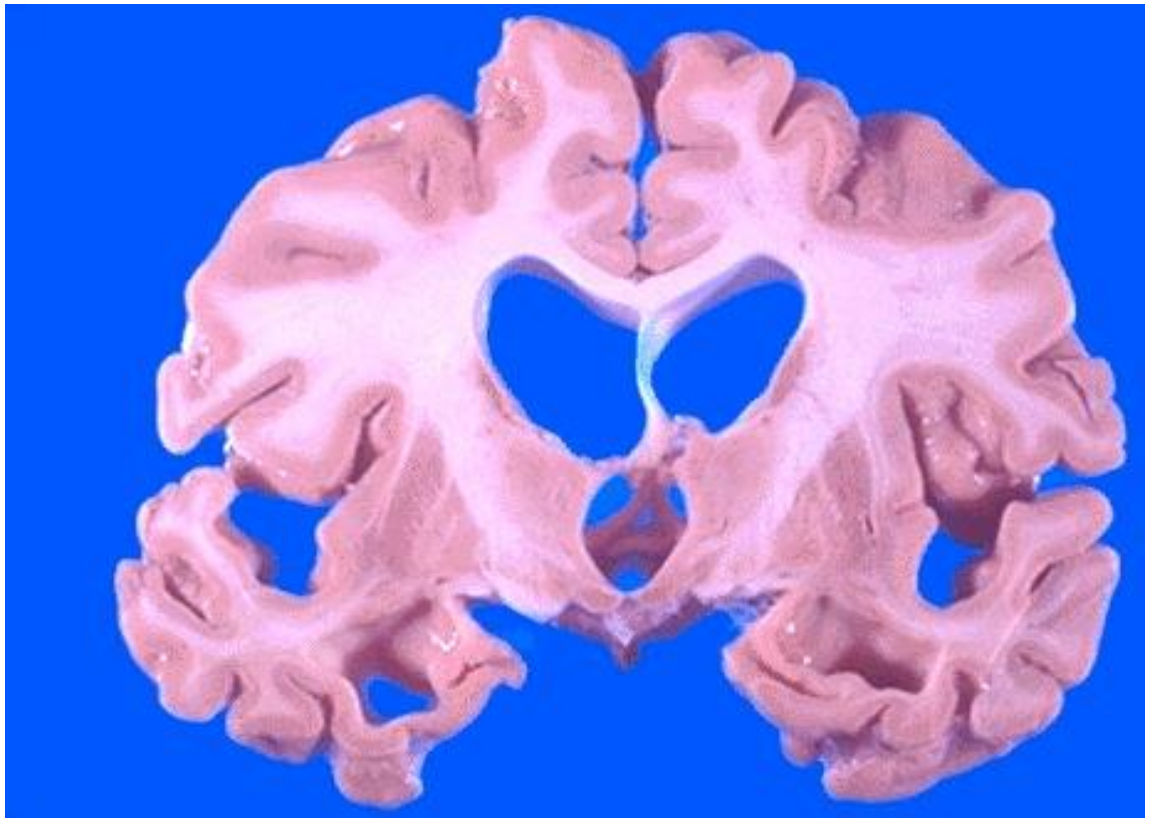


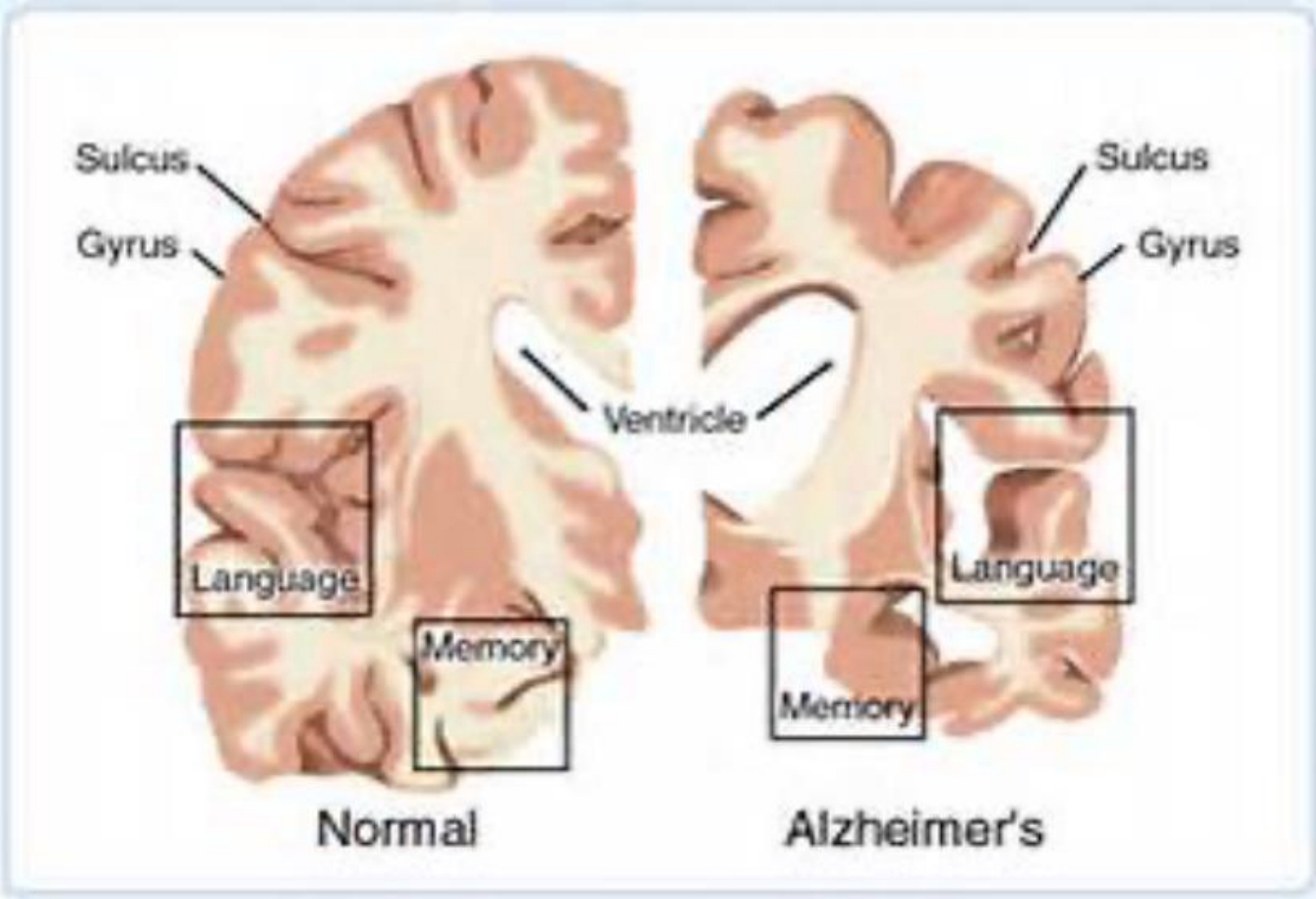
- Mainly in the frontal and parietal regions, characterized by **narrowed gyri** along with **widened sulci**.

- 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".

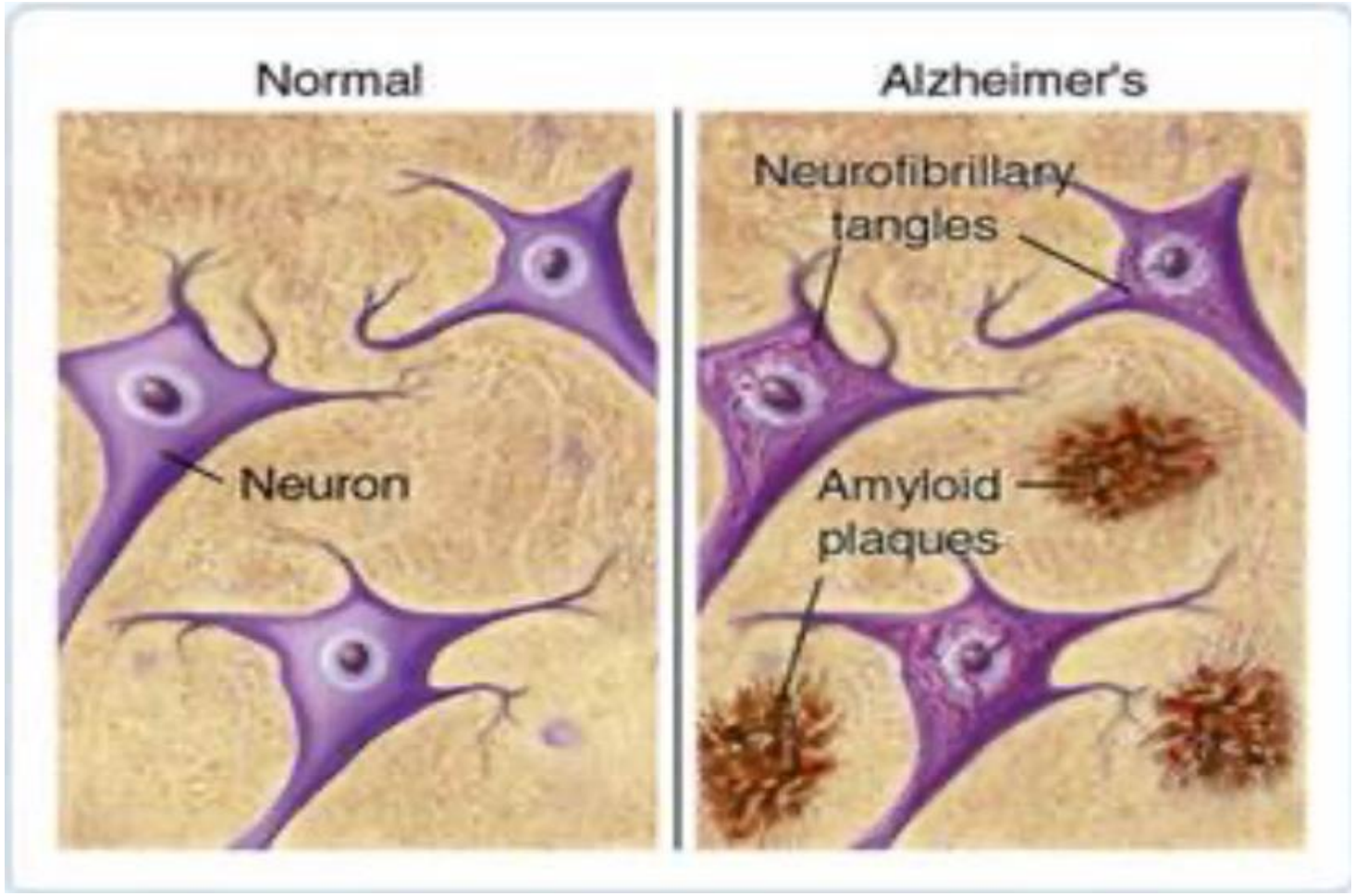



Sulcus
Gyrus
Ventricle
Language
Memory
Sulcus
Gyrus
Language
Memory
Normal
Alzheimer's

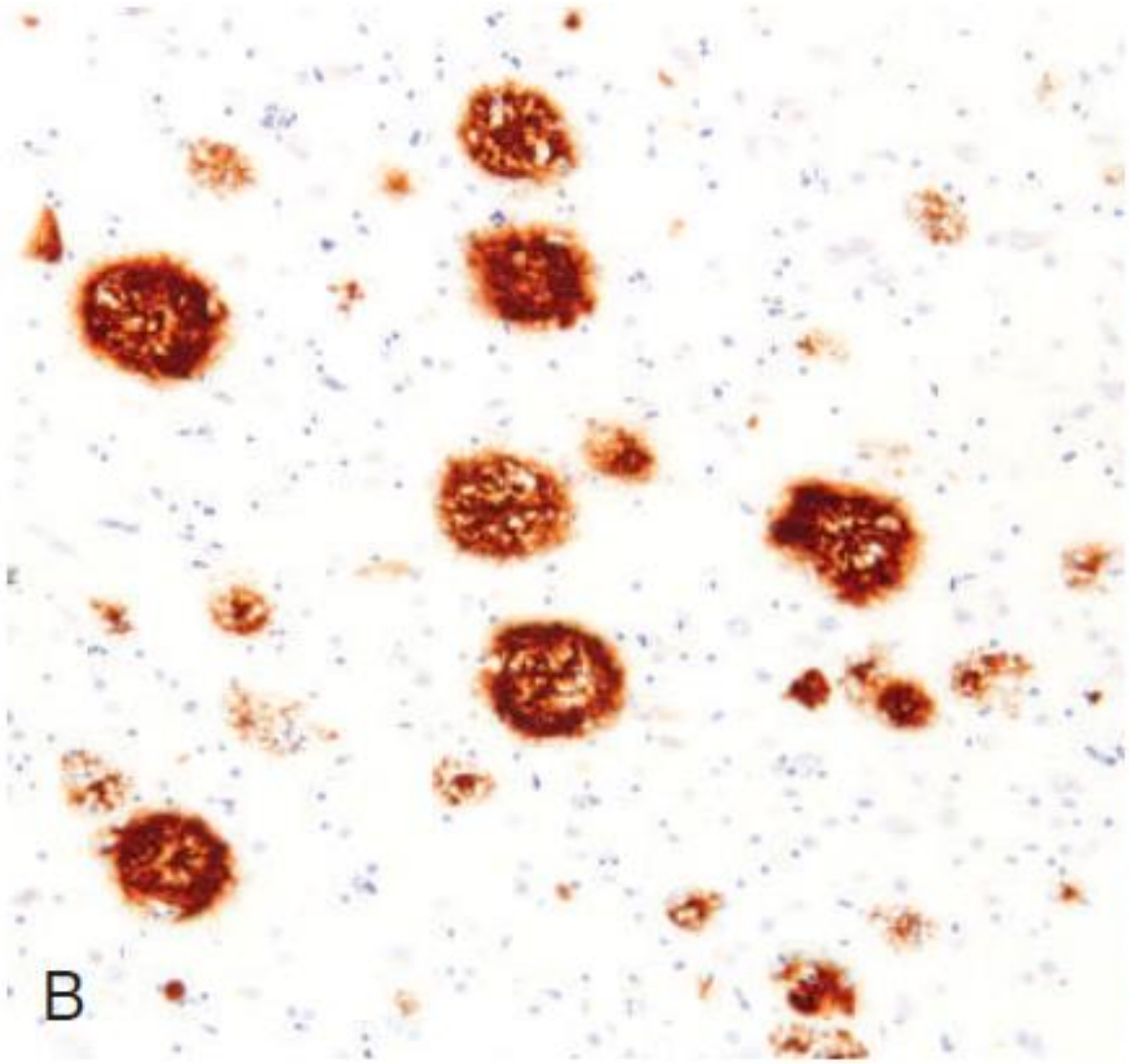
Alzheimer disease neuropathologic changes.

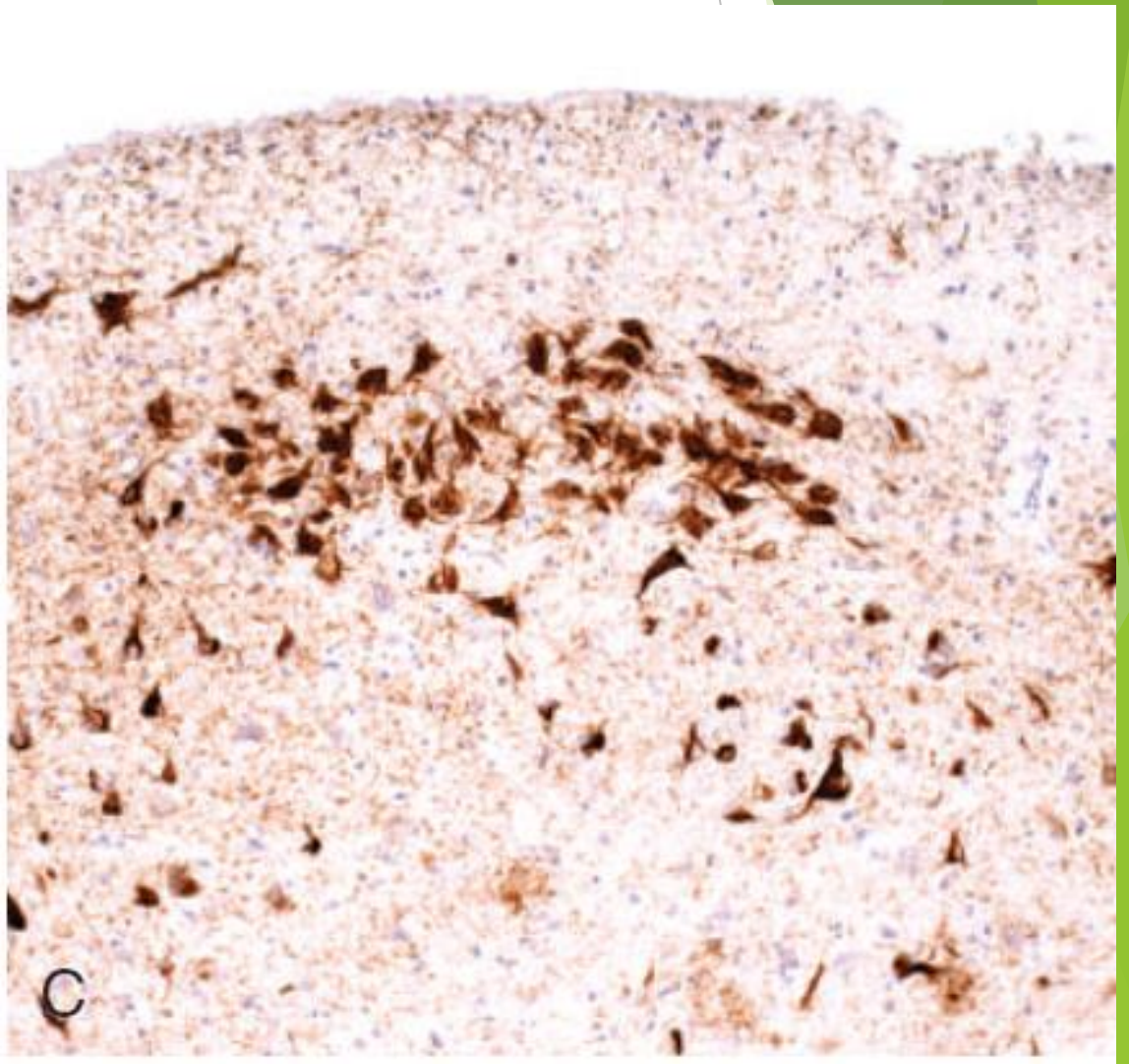
- **Neuritic plaques** (an extracellular lesion): central amyloid core surrounded by collections of dilated, tortuous, processes of dystrophic neurites.
- Hippocampus and amygdala and neocortex, (sparing of primary motor and sensory cortices until late)
- The amyloid core contains Aβ

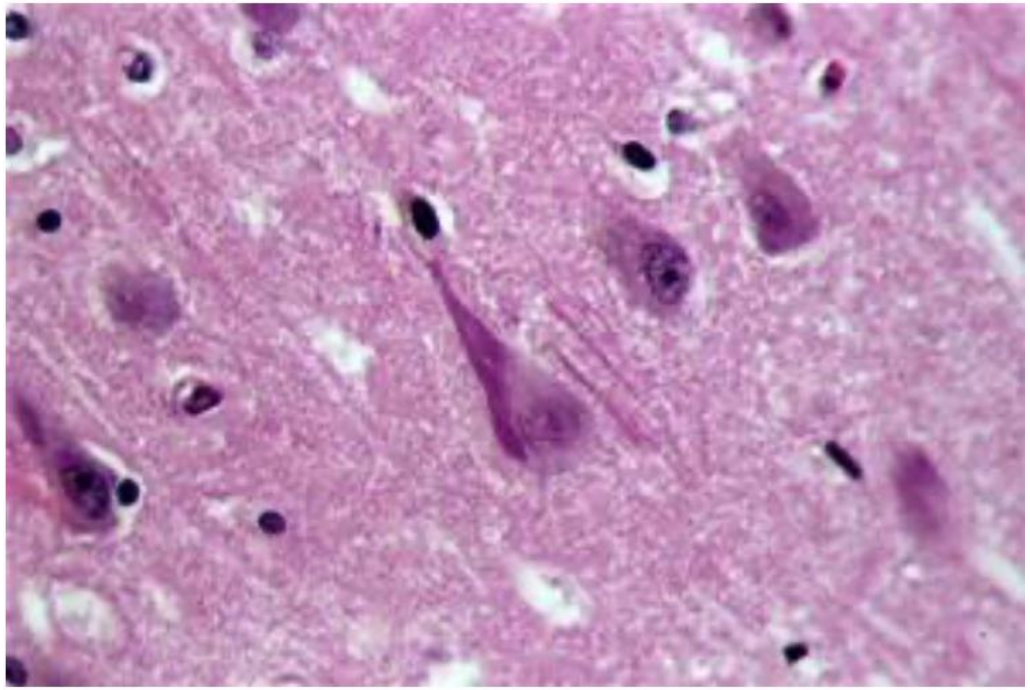
- **Neurofibrillary tangles**, basophilic fibrillary structures in the cytoplasm of neurons, displace or encircle the nucleus; persist after neurons die, becoming extracellular.
- Cortical neurons, pyramidal cells of hippocampus, the amygdala, the basal forebrain, and the raphe nuclei.
- Hyperphosphorylated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


Normal
Alzheimer's
Neuron
Neurofibrillary tangles
Amyloid plaques

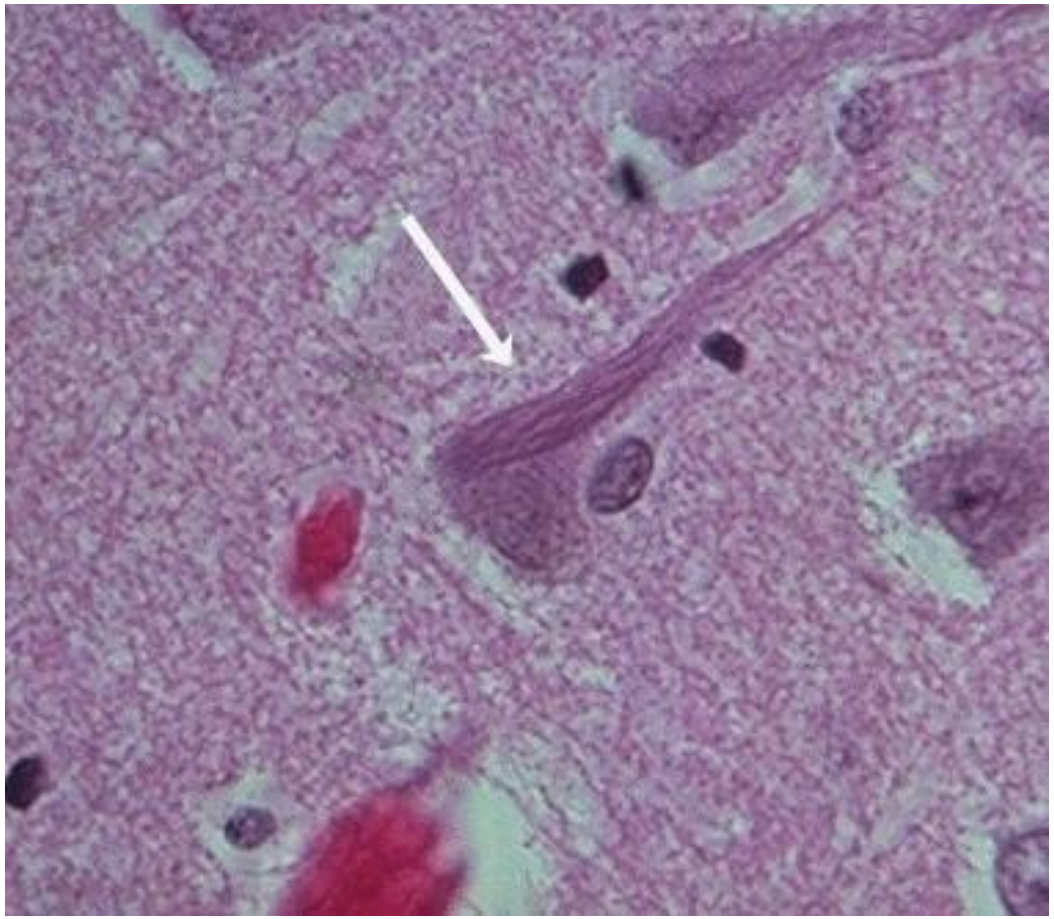
Plaques and tangles



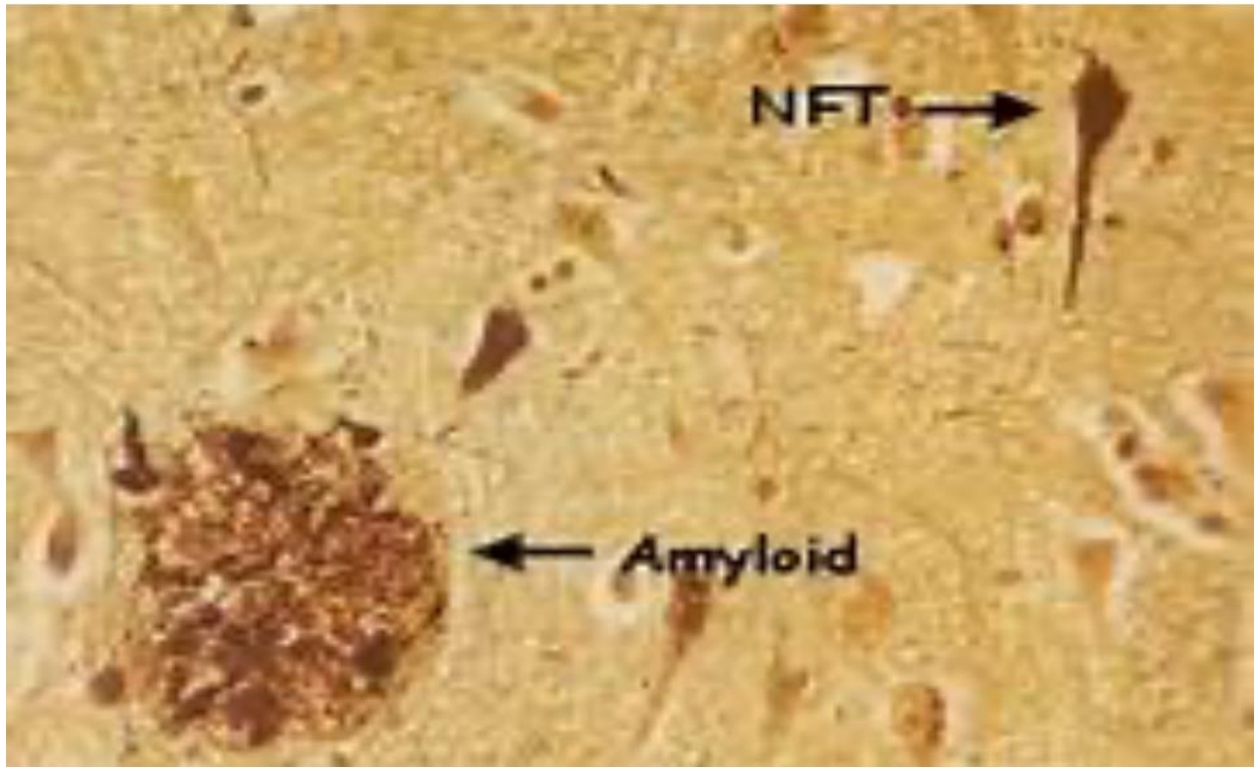


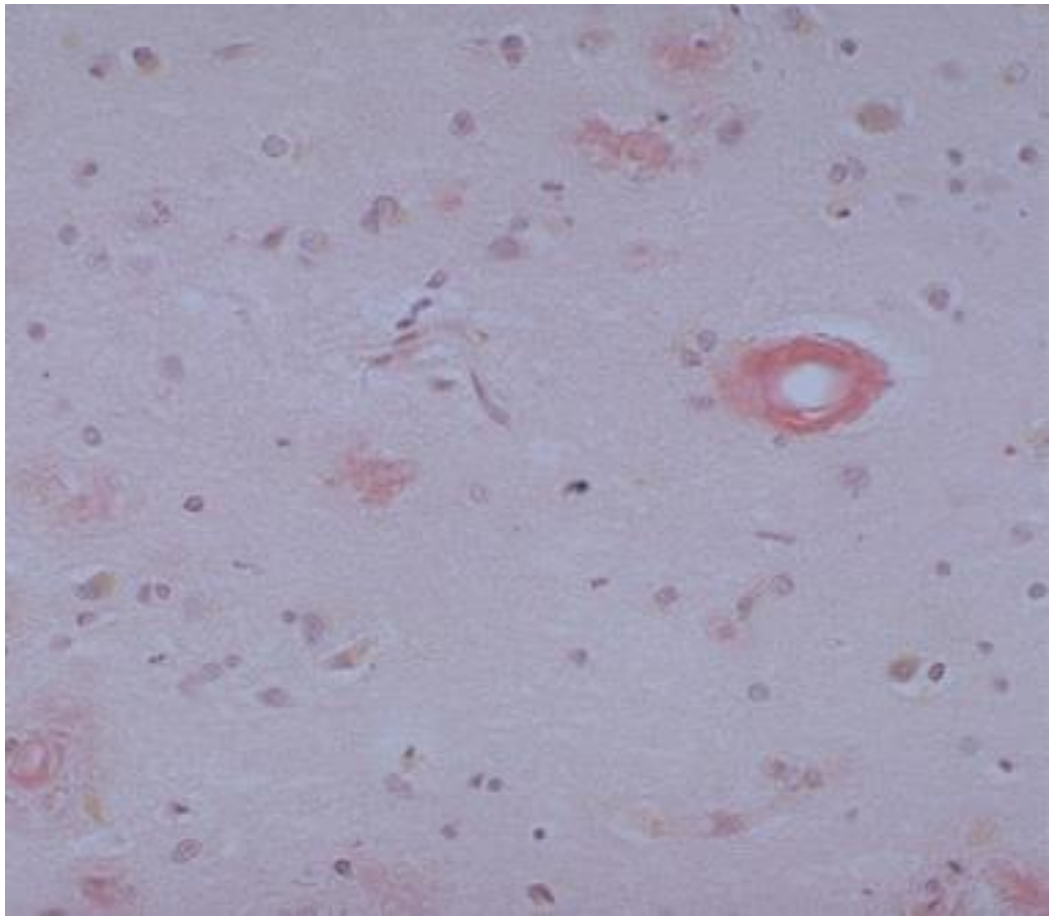


NEUROFIBRILLARY TANGLES

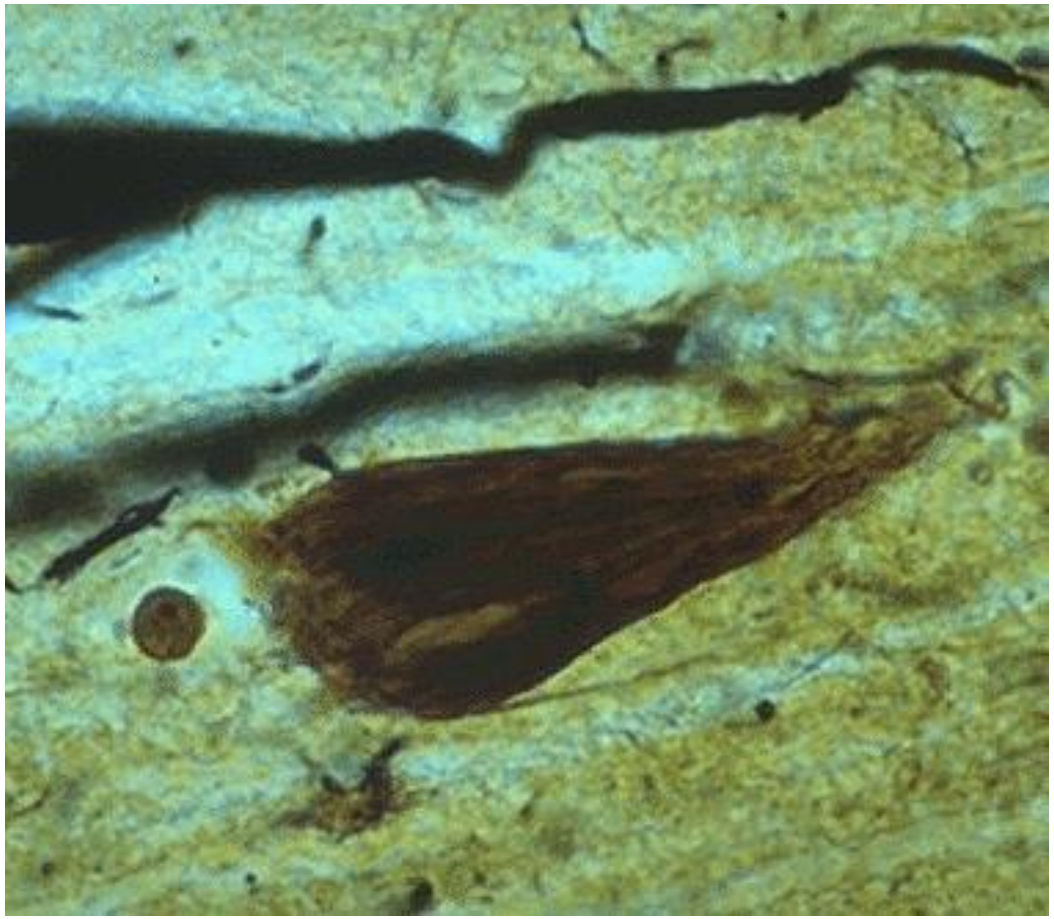


Neurofibrillary tangles


NFT
Amyloid



Congo red stain for amyloid core of plaques.

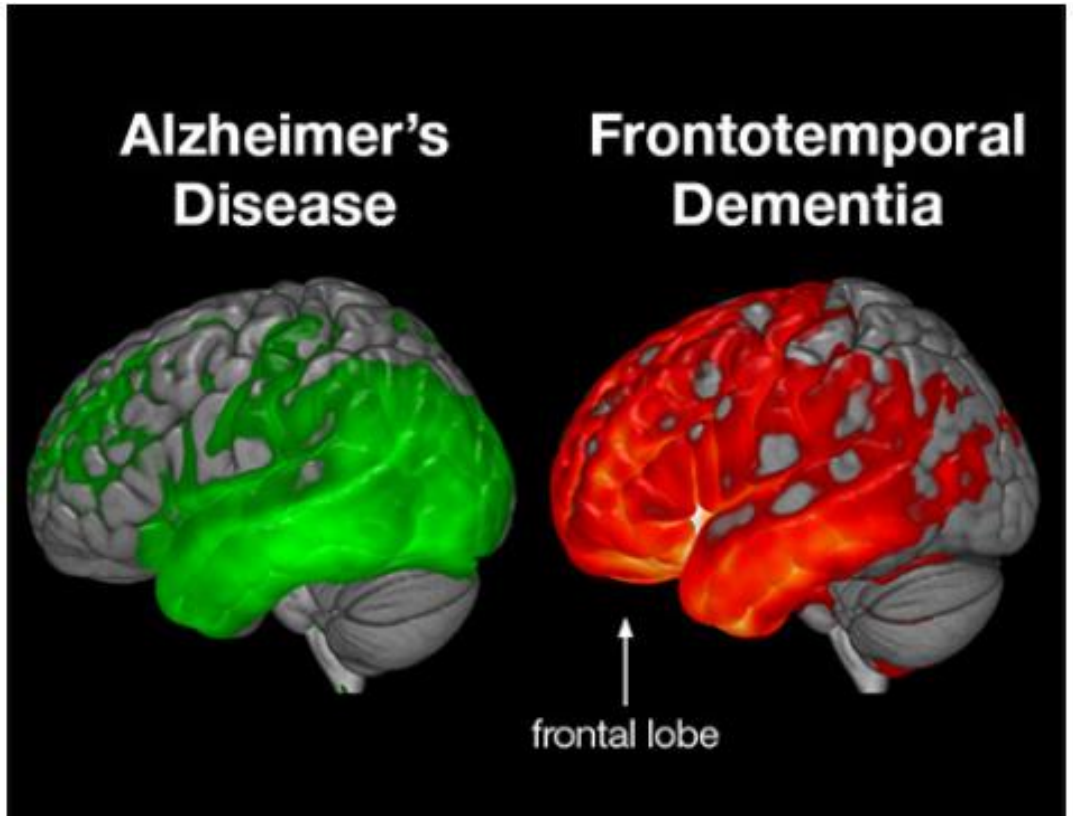


Silver stain for NFT

Frontotemporal Lobar Degeneration
Frontotemporal dementias

- 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.
- **Two forms of disease:** Neuronal inclusions may contain **tau or TDP43.**
- **Pick disease** (subtype of FTLD-tau), associated with smooth, round inclusions known as Pick bodies
- **TDP34 subtype** (also deposited in ALS)

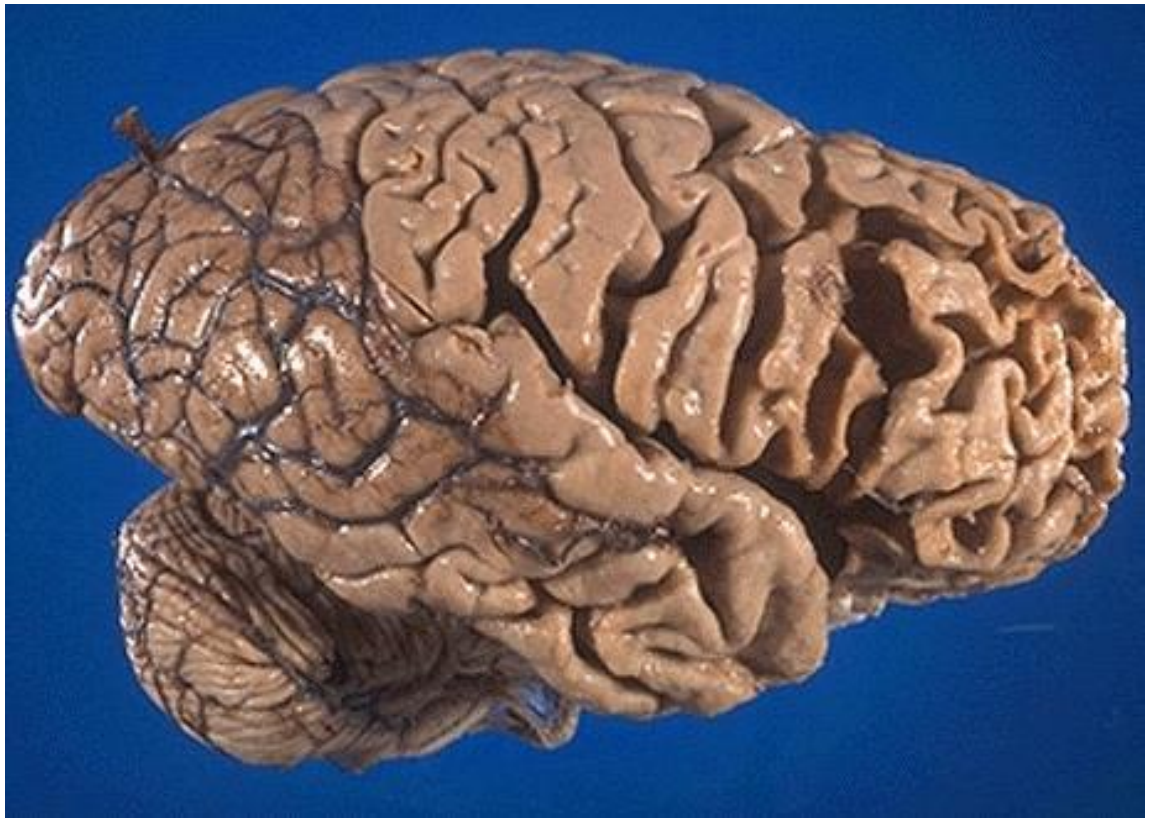
In FTLD, frontal lobe is affected from the beginning, so patients present with behavioral problems first.



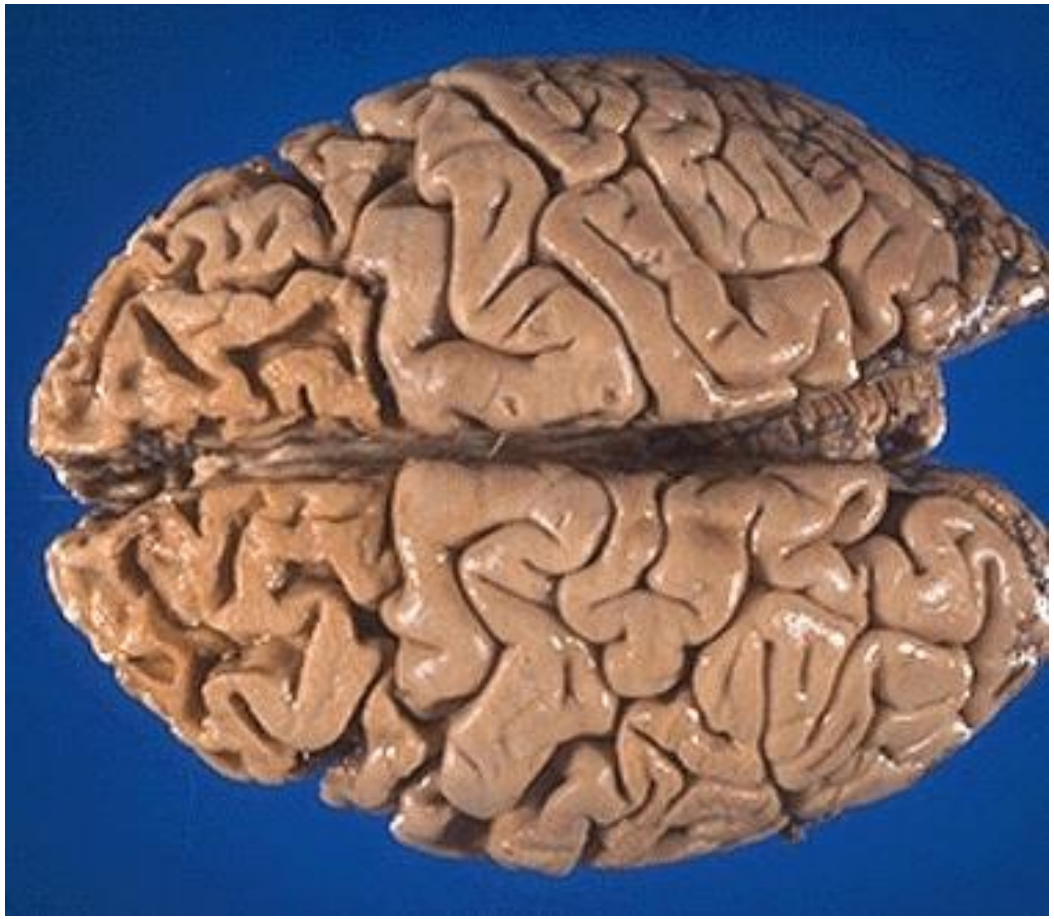
- In AD there is sparing of the frontal lobe, at least at the beginning so behavioral changes are a late manifestation.

MORPHOLOGY

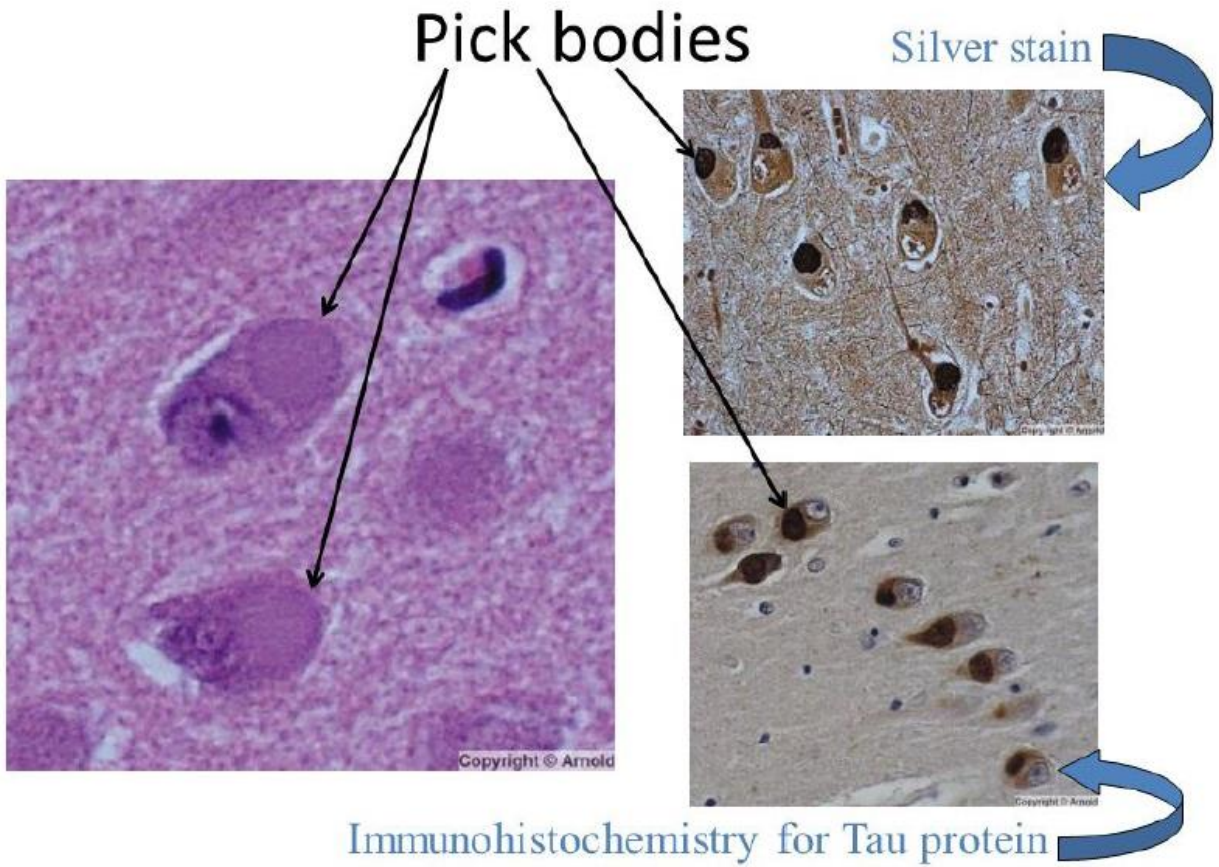
- Atrophy of frontal and temporal lobes.
- Neuronal loss and gliosis
- In FTLD-tau, the characteristic neurofibrillary tangles, similar to AD
- Pick bodies in pick Disease.



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



Frontal lobes are markedly thinned


Pick bodies
Silver stain
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Immunohistochemistry for Tau protein