
# Pathology

## Modified no. 5

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# Neurodegenerative disorders-1

Neurodegenerative disease = degeneration in the neural material = progressive neuronal loss

**Color code**

- Slides
- Doctor
- Additional info
- Important

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# Classic features:

- **Progressive** loss of neurons, once they start, they won't stop.
- Typically affects **groups** of neurons with functional interconnections.
- Different diseases involve different neural systems, so different symptoms.

The distribution of neuronal loss will influence the clinical symptoms, which leads to divide the neurodegenerative diseases into 4 types:

1)affecting the cortex 2)basal ganglia 3)cerebellum 4)motor system

- The histologic hallmark for ALL diseases is the ACCUMULATION OF PROTEIN AGGREGATES, but the type and distribution of the protein will differ between them.
- Same protein may aggregate in different diseases, BUT AT DIFFERENT DISTRIBUTION..
- Proteins **resist degradation**, accumulate within the cells, or within the neuropil which is the matrix that surrounding the neurons , elicit inflammatory response, and is toxic to neurons.

# Causes of protein accumulation

- **Mutations** that alter protein **conformation,** misfolding proteins will accumulate.
- **Mutations** disrupting the **processing and clearance** of proteins, so they resist the clearance.

It could be a mixture of both

- Subtle imbalance between protein synthesis and clearance (genetic or environmental factors)

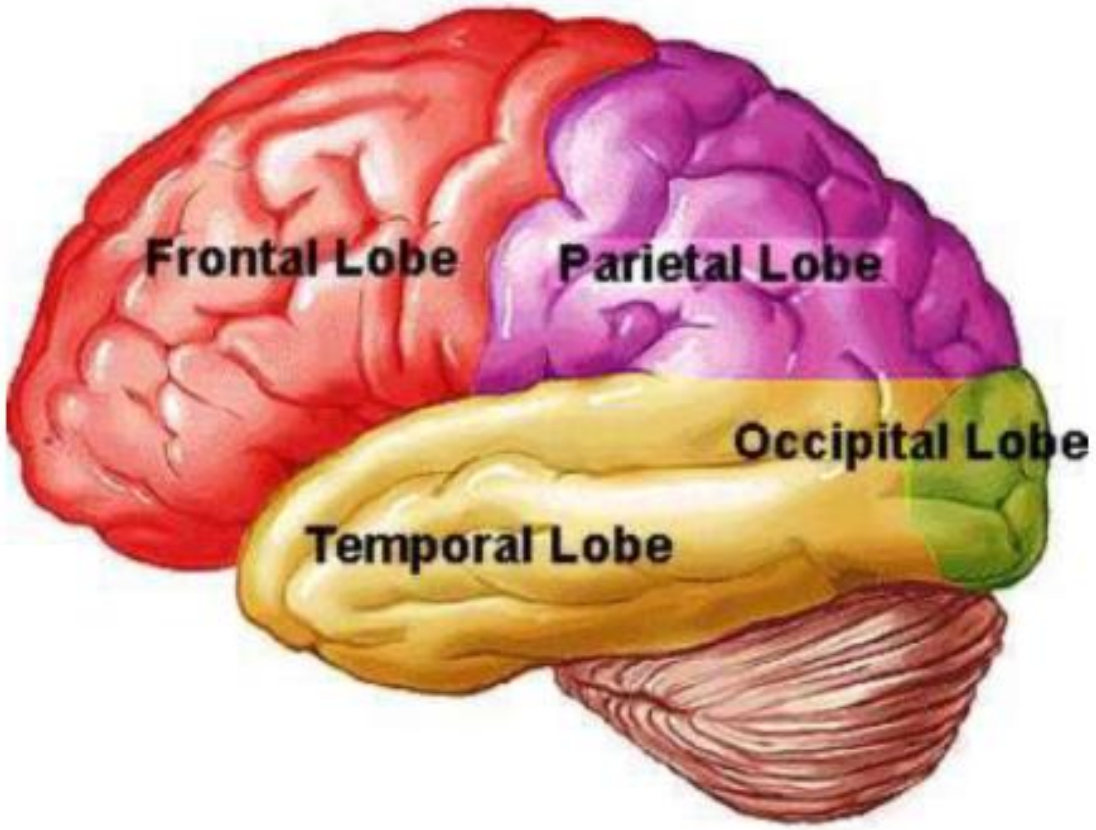
# Different diseases, again according to different distribution

- **Involving the hippocampus and cortex** leading to 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)
- Hyperkinesia = excessive movement

- **Involving the cerebellum** [responsible for the balance] >>> ataxia >>> (SPINOCEREBELLAR ATAXIA, FRIEDRICH ATAXIA, ATAXIA TELANGECTASIA)

- **Involving the motor system** [spinal or cranial nerves roots] >>> difficulty swallowing and respiration with muscle weakness >> (AMYOTROPHIC LATERAL SCLEROSIS)




- The brain is divided into lobes:
Frontal, parietal, temporal, occipital.

- Each area is responsible for a specific function called the higher cortical functions.

# Common features to many neurodegenerative diseases, regardless of the distribution:

- Protein aggregates can seed the development of more aggregates. Again, it's progressive, and will become more severe.
- Protein aggregates can spread from one neuron to another in **Prion-like pattern.**
- No evidence of person-to-person transmission, it's not contagious.
- Activation of the innate immune system is a common feature of neurodegenerative diseases, because it considers the protein accumulation as foreign bodies, making more & more neuronal loss.

# DEMENTIA

That's why dementia should not be limited to memory; it is only a part of it.

- Development of memory impairment and other cognitive deficits or behavioral or phycological severe enough to decrease the person's capacity to function at **his previous** level **despite** a 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 the **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, like doing two tasks at the same time, brushing hair, tying shoes, cooking or driving.
- Difficulty with planning and organizing.
- Difficulty with coordination and motor functions, which happens later, in the early stages, the motor system is spared.
- Confusion and disorientation.

# Psychological changes as part of the disease, not due to psychological problems

- Personality changes.
- Depression.
- Anxiety.
- Inappropriate behavior.
- Paranoia.
- Agitation.
- Hallucinations.
- Irritable, aggressive, mood changes.

# Causes of dementia

- Neurodegenerative diseases.
- Infections, meningitis or encephalitis.
- Nutritional deficiencies, pernicious anemia or Vit B12 deficiency.
- Metabolic and endocrine abnormalities, like hypothyroidism.
- Drugs.
- Subdural hematoma.
- Poisons.
- Tumours, compress the CNS.
- Anoxia and ischemia.

- **We must exclude other causes before saying it's a neurodegenerative disease, especially if the patient is young, and symptoms appear suddenly, we should think about ischemia or stroke for example.**

- Alzheimer's disease affects **the elderly and progressively appears, over the years**.

# COMPLICATIONS OF DEMENTIA

- **Inadequate nutrition.** Many people with dementia eventually reduce or stop their intake of nutrients.

  This leads to other diseases like **cachexia.**

- **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.

  **Remember it's not only cognitive impairment.**

- **Personal safety challenges.** Some day-to-day situations can present safety issues for people with dementia, including driving, cooking and walking alone.

  They should not be alone!

- **Death.** Late-stage dementia results in coma and death, often from **infection, especially aspiration pneumonia.**

# Alzheimer disease:

- Most common cause of dementia in older adults.
- Increase incidence with age (47% in those over 84 years), it's a disease of aging.
- Most cases are sporadic.
- 5-10% are familial (onset before 50), even the disease that occurs in advanced age indicates the presence of a familial tendency.
- 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.
- The old memory is spared until later stages.

- 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.

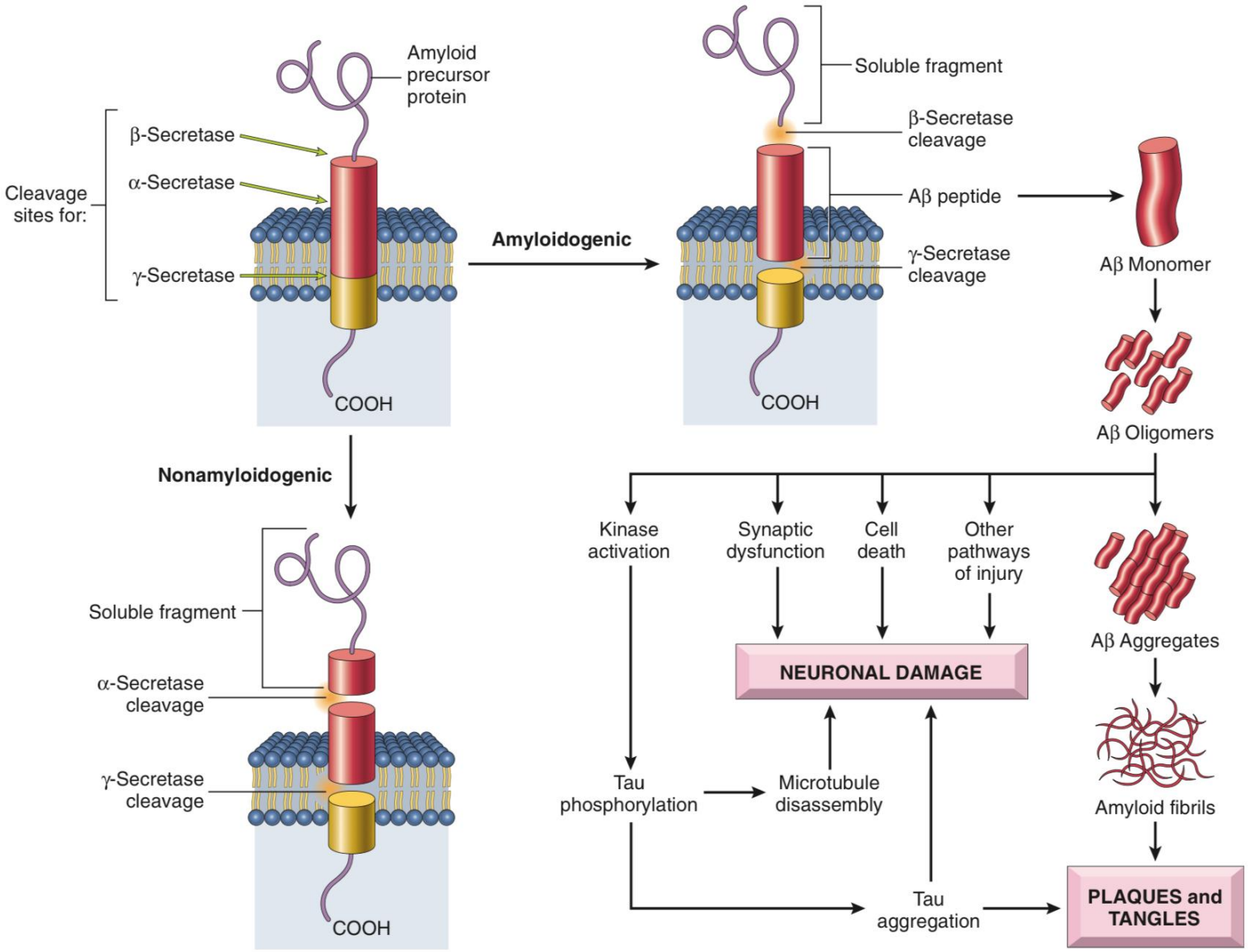
# Pathogenesis:

- Accumulation of two proteins (AB amyloid( the most essential one ) and Tau ( as a consequence ). it's start as AB amyloid deposition later on, as a consequence Tau protein will be accumulated .
- 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.

- Alpha beta amyloid result from amayloid precursor protein , so any mutation affect AB amyloid precursor protein will increase the risk alzehimer disease .

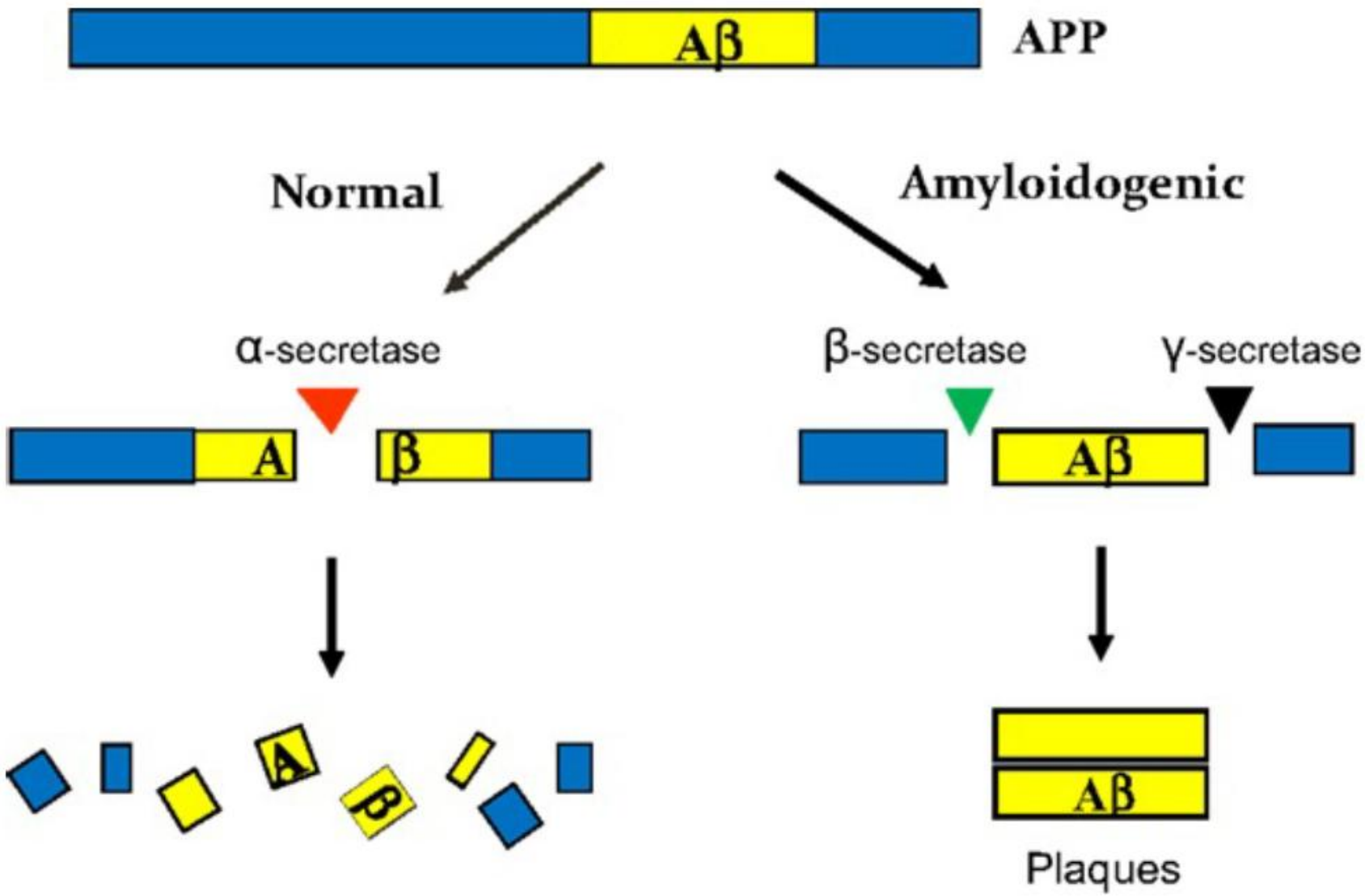
# Role of Aβ

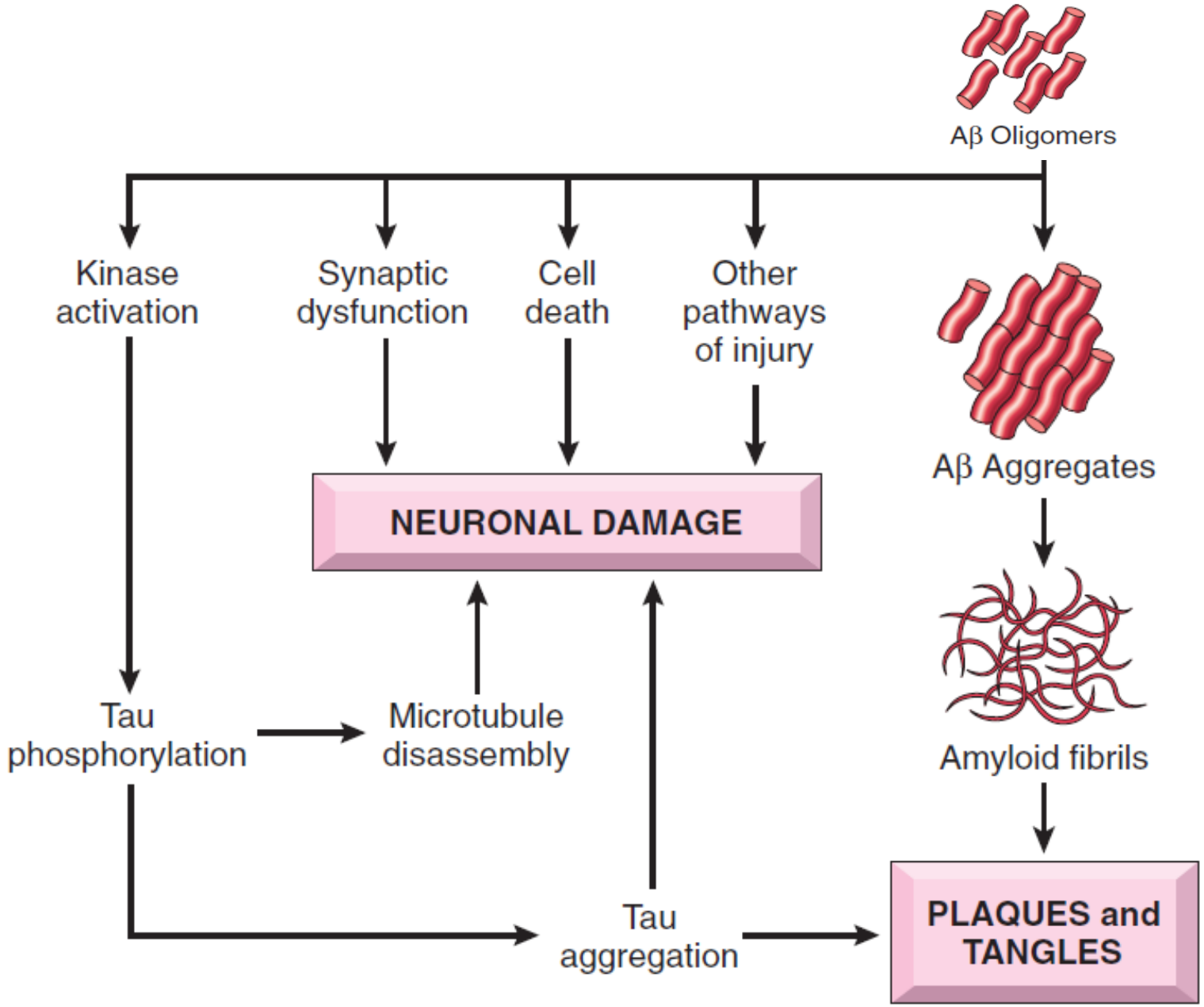
- AD results when the transmembrane protein (amyloid precursor protein APP) is sequentially cleaved by the **enzymes β-amyloid–converting enzyme (BACE) (B-secretase) and γ-secretase** creating Aβ.
- Normally, APP can be cleaved by **α-secretase and γ-secretase**, liberating a nonpathogenic peptide.
- 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.




- Aβ peptide genesis and consequences in Alzheimer disease. Amyloid precursor protein cleavage by α-secretase and γ-secretase produces a harm-less 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..

- Aβ peptides aggregate and form plaques in the brain.
- Leads to synaptic dysfunction, neuroinflammation, and neuronal loss.
- Disrupts memory and cognitive function.
- Aβ accumulation is linked to tau pathology, which further contributes to neurodegeneration.


Aβ
APP
Normal
Amyloidogenic
α-secretase
β-secretase
γ-secretase
A
β
Aβ
A
β
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.**

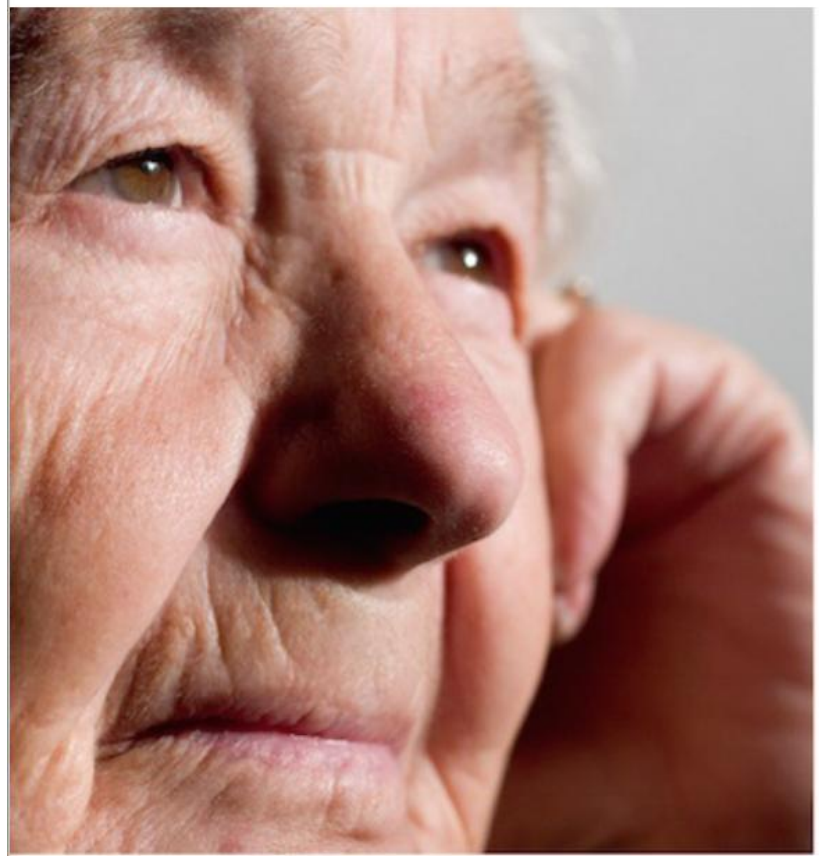
# Morphology

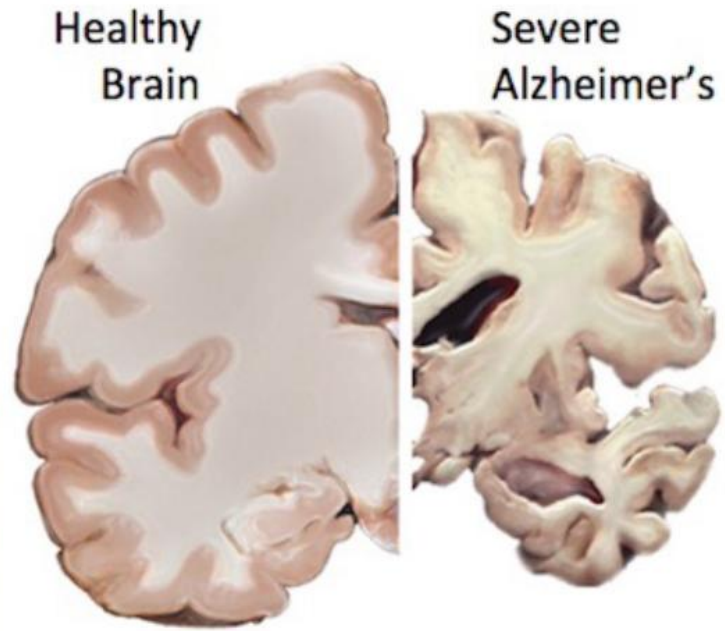
- Cortical ( brain ) atrophy ( brain size is decreased ) , gyri getting smaller while sulci will be wider.
- Widening of the cerebral sulci
- Most pronounced in the frontal, temporal, and parietal lobes.
- Compensatory ventricular enlargement (hydrocephalus ex vacuo).It’s hydrocephalus but without an increase in Intracranial pressure , because it’s a compensatory mechanism to atrophy.

Here is an extra table to revise Ur information. U can skip them

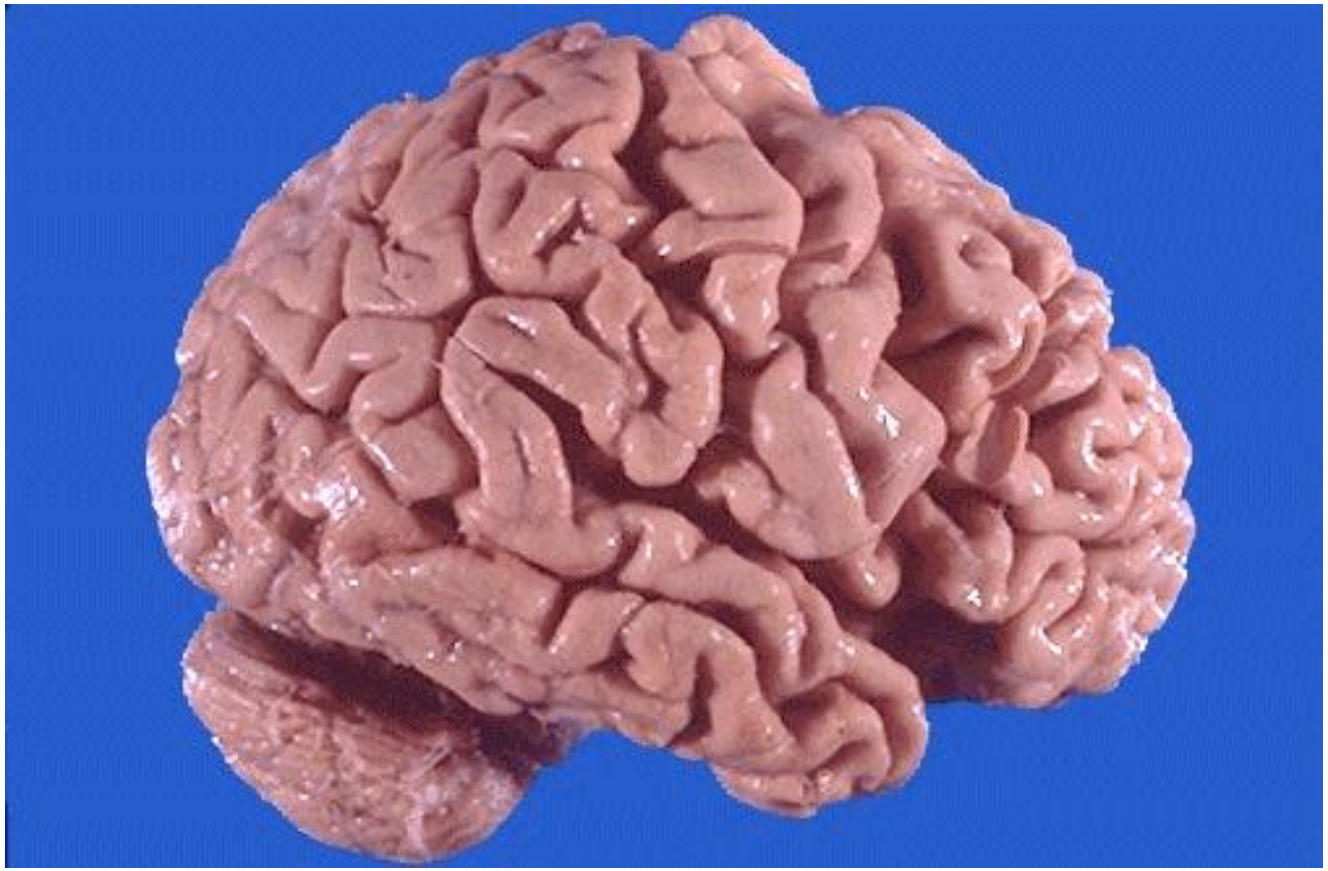
| Category | Details |
| --- | --- |
| Prevalence & Risk Factors | - Most common cause of dementia in older adults. - Incidence increases with age (47% in those over 84 years). - Most cases are sporadic. - 5-10% are familial (onset before 50). - Even late-onset cases suggest a familial tendency. |
| Onset & Progression | - Gradual onset. - Impaired higher intellectual functions, memory impairment, and altered mood and behavior. - Severe cortical dysfunction over time (disorientation, aphasia, profound disability, mute and immobile). - Death usually due to infections (e.g., pneumonia). |
| Memory Impairment | - Most recognized symptom: inability to acquire new memories and difficulty recalling recent facts. - Old memory is spared until later stages. |
| Advanced Symptoms | - Confusion, irritability, aggression, mood swings, language breakdown, and long-term memory loss. - Gradual loss of bodily functions leading to death. |
| Pathophysiology | - Accumulation of two proteins: Aβ amyloid (most essential) and Tau (as a consequence). - Aβ deposition starts first → later Tau protein accumulates. - Plaques (Aβ) form in the neuropil (extracellular matrix). - Neurofibrillary tangles (Tau) develop intracellularly. - Leads to neuronal dysfunction, death, and inflammation. |
| Role of Aβ | - Aβ generation is the critical initiating event. - Mutations in the APP gene increase AD risk. - Once generated, Aβ aggregates → plaque formation → decreased synapses and altered function → memory disruption. |

| Category | Details |
| --- | --- |
| Role of Tau | - Tau is a microtubule-associated protein, present in axons.<br>- Hyperphosphorylation causes Tau to lose its ability to bind microtubules.<br>- Loss of microtubule stability leads to neuronal toxicity and death.<br>- Responsible for tangles in AD, leading to cell death.<br>- Tau aggregates spread across synapses, worsening lesions. |
| Immune Response | - Innate immune system responds to Aβ and Tau.<br>- Aβ deposits trigger inflammation from microglia and astrocytes.<br>- Inflammatory response leads to neuronal injury over time. |
| Timeline of Deposits & Symptoms | - Aβ and Tau deposits appear long before cognitive impairment. In familial AD, plaques and tangles appear 15-20 years before symptoms.<br>- Large plaque and tangle burden strongly correlates with severe cognitive dysfunction.<br>- The number of neurofibrillary tangles correlates more with dementia severity than the number of plaques. |
| Brain Structural Changes | - Cortical atrophy: brain size decreases, gyri shrink, and sulci widen.<br>- Most pronounced in the frontal, temporal, and parietal lobes.<br>- Compensatory ventricular enlargement (hydrocephalus ex vacuo) without increased intracranial pressure. |



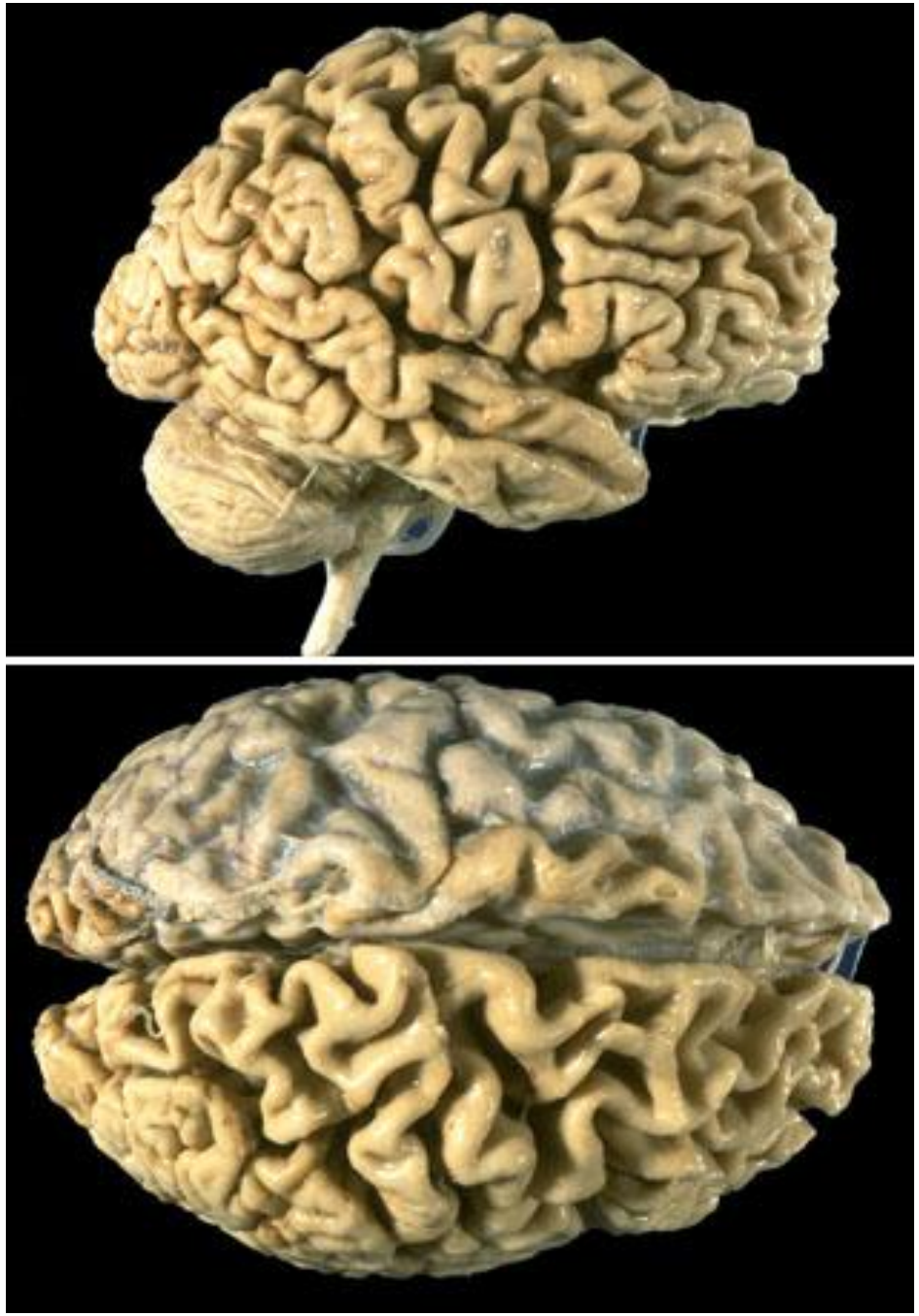


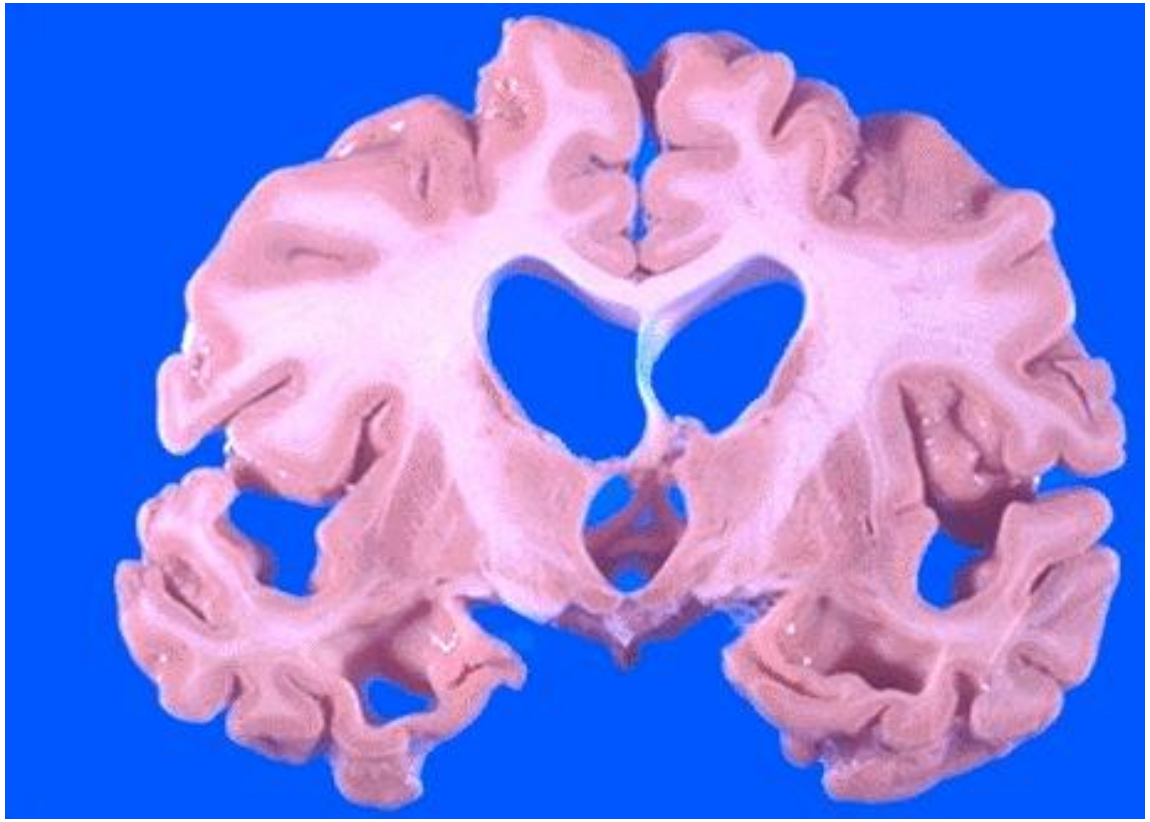

Neuronal cell loss leading to extensive shrinkage in an Alzheimer's brain (right), as compared to a healthy human brain (left).



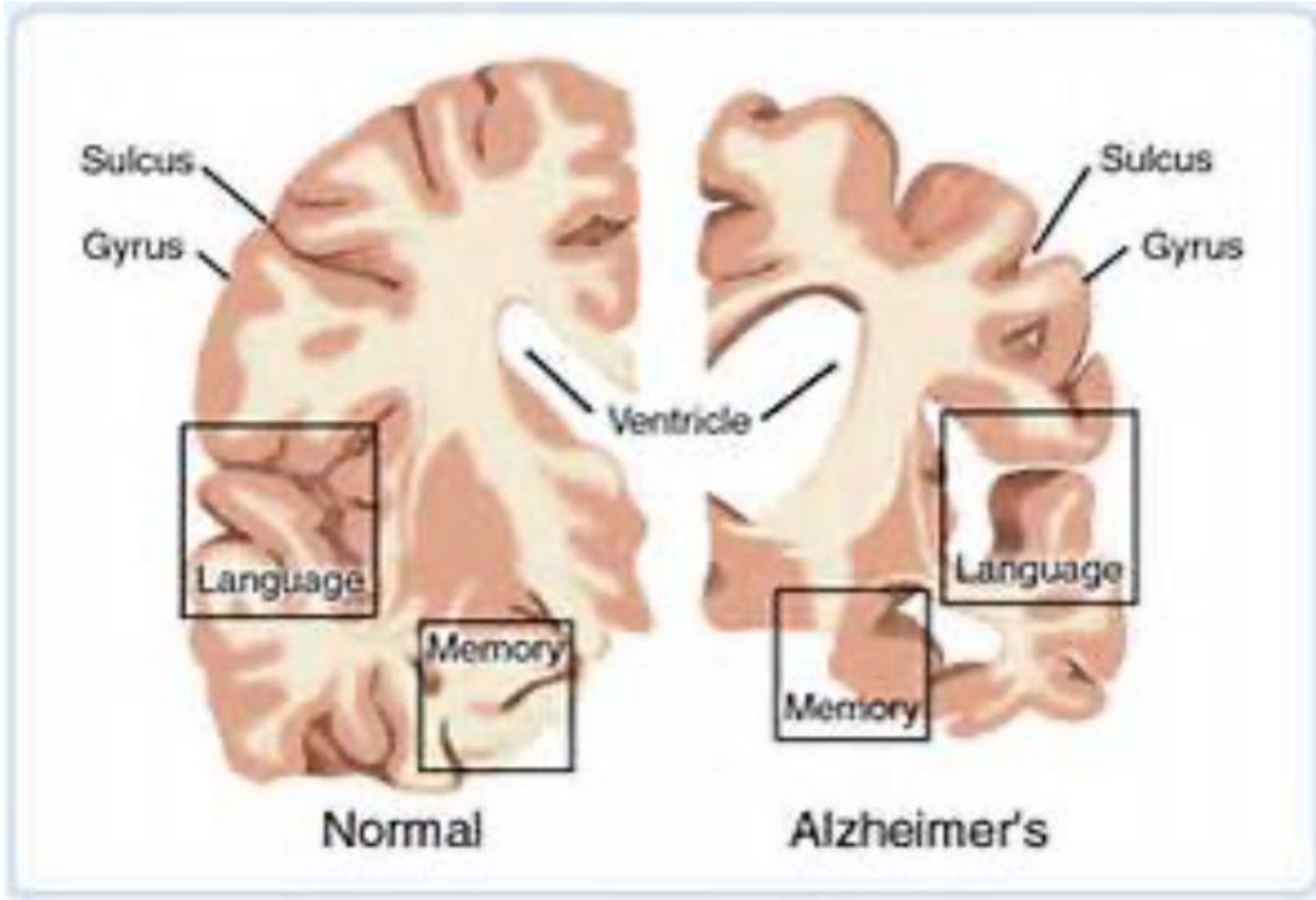
- Mainly in the frontal and parietal regions, characterized by **narrowed gyri** along with **widened sulci**.

- More marked atrophy seen superiorly and laterally, with sparing ( not affected ) 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

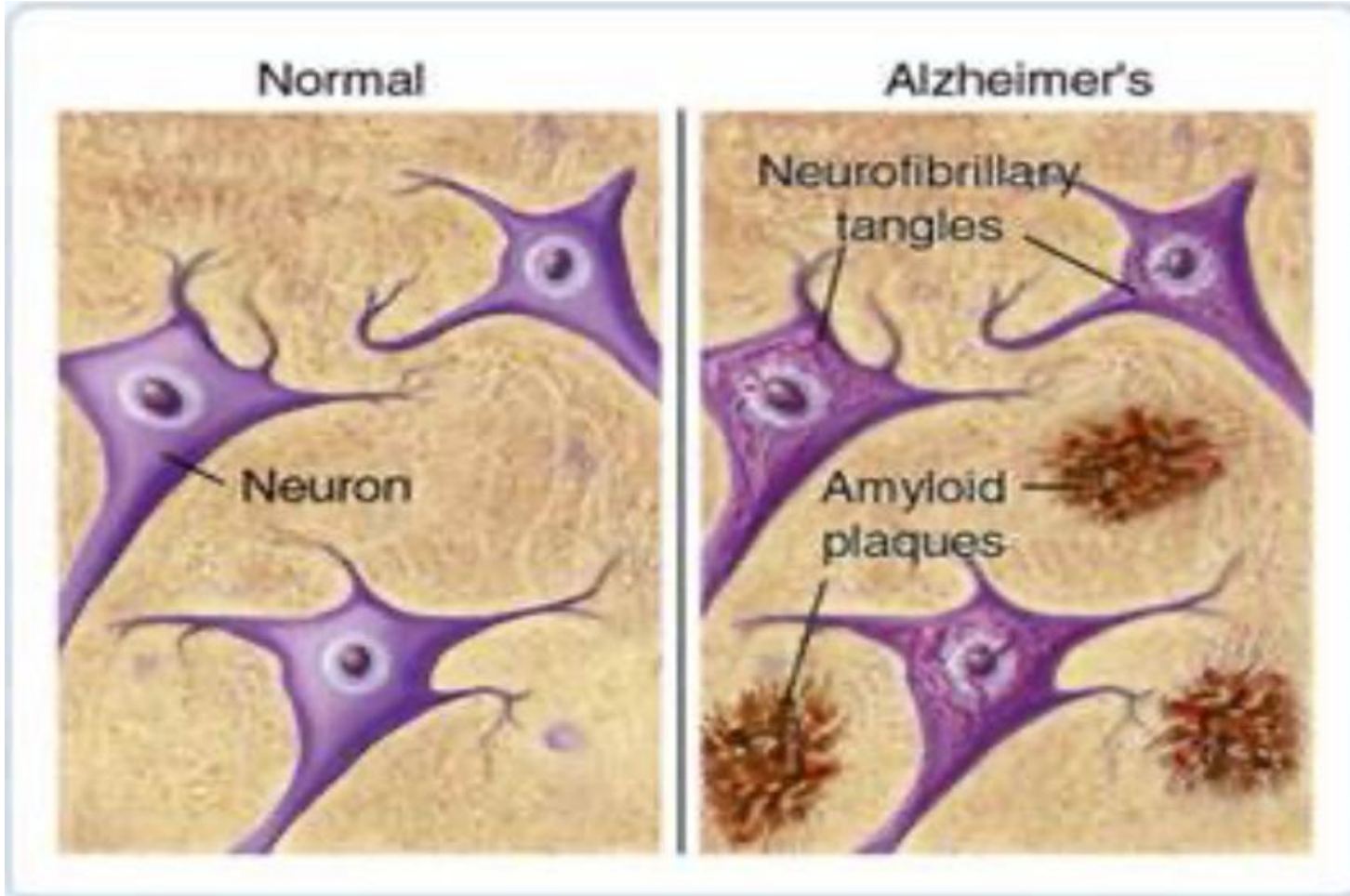
- **Neurofibrillary tangles**, basophilic fibrillary structures in the cytoplasm of neurons, displace or encircle the nucleus; persist after neurons die, becoming extracellular.
- Cortical neurons, pyramidal cells of hippocampus, the amygdala, the basal forebrain, and the raphe nuclei.
- Hyperphosphorylated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

From Robbins book

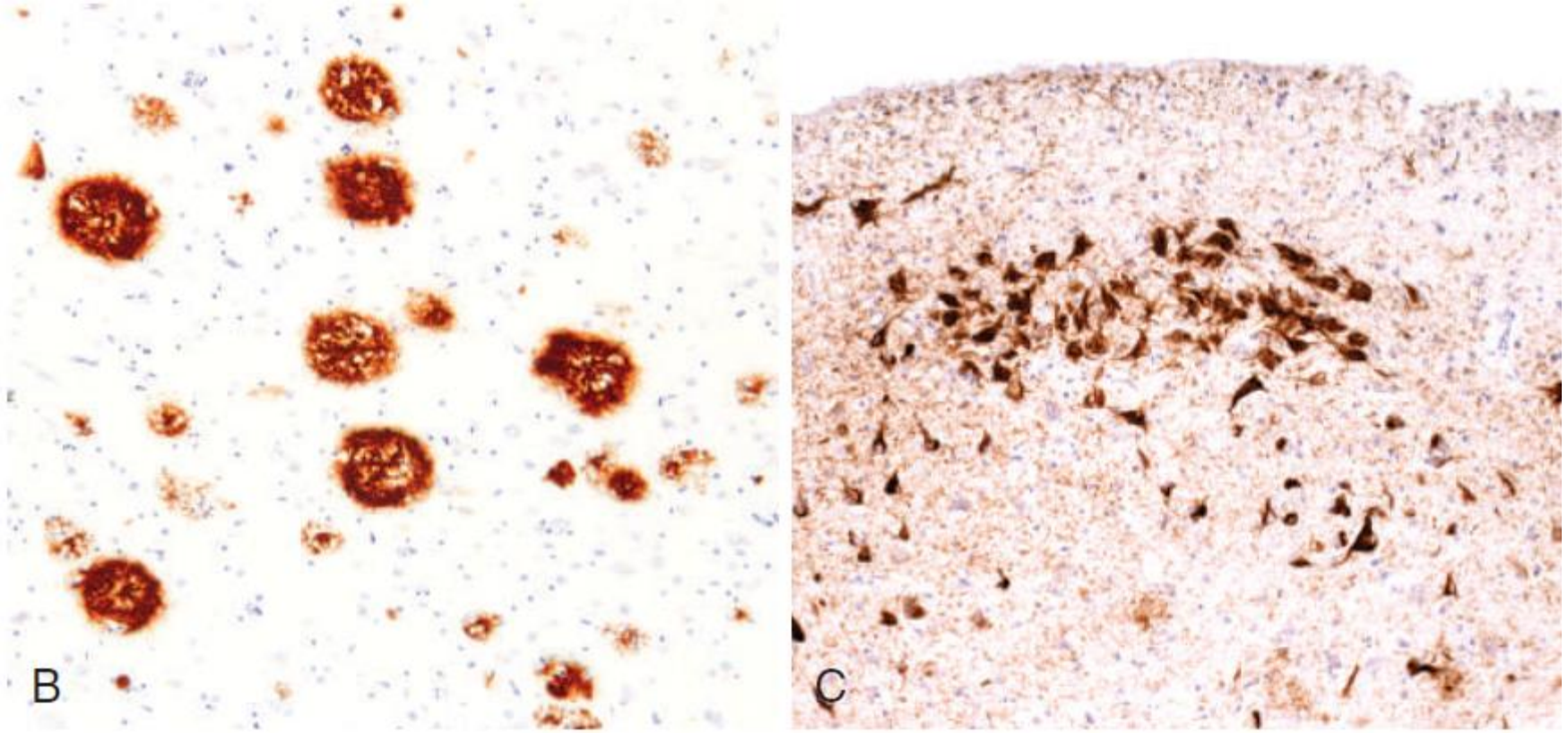
**Neuritic plaques** are focal, spherical collections of dilated, tortuous, processes derived from dystrophic neurites, often around a central amyloid core (see Fig. 23.25A). Neuritic plaques range in size from 20 to 200 μm in diameter; microglial cells and reactive astrocytes are present at their periphery. Plaques can be found in the hippocampus and amygdala as well as in the neocortex, although there is relative sparing of primary motor and sensory cortices until late in the disease course. The amyloid core contains Aβ (see Fig. 23.25B). Aβ deposits also can be found that lack the surrounding neuritic reaction, termed **diffuse plaques;** these are found in the superficial cerebral cortex, the basal ganglia, and the cerebellar cortex and may represent an early stage of plaque development.

**Neurofibrillary tangles** are bundles of paired helical filaments visible as basophilic fibrillary structures in the cytoplasm of the neurons that displace or encircle the nucleus; tangles can persist after neurons die, becoming a form of extracellular pathology. They are commonly found in cortical neurons, especially in the entorhinal cortex, as well as in the pyramidal cells of the hippocampus, the amygdala, the basal forebrain, and the raphe nuclei. A major component of paired helical filaments is **hyperphosphorylated tau** (see Fig. 23.25C).

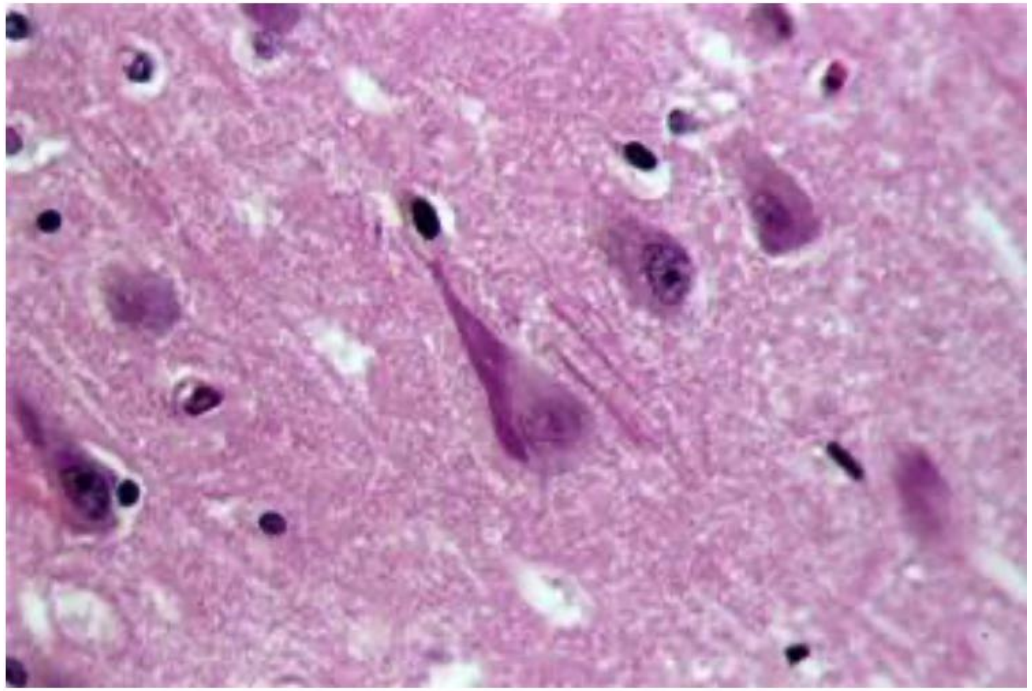
In individuals harboring autosomal dominant mutations that cause AD, deposition of Aβ and the formation of tangles precede the emergence of cognitive impairment by as much as 15 to 20 years. For this reason, the current diagnostic criteria consider the burden and distribution of amyloid deposits, tangles, and neuritic plaques—a constellation known as **Alzheimer disease neuropathologic changes.** The staging of each of these processes, which has a fairly consistent pattern across individuals, is then used to assess the likelihood that the observed lesions resulted in cognitive impairment.


Normal
Neuron
Alzheimer's
Neurofibrillary tangles
Amyloid plaques

# Plaques and tangles

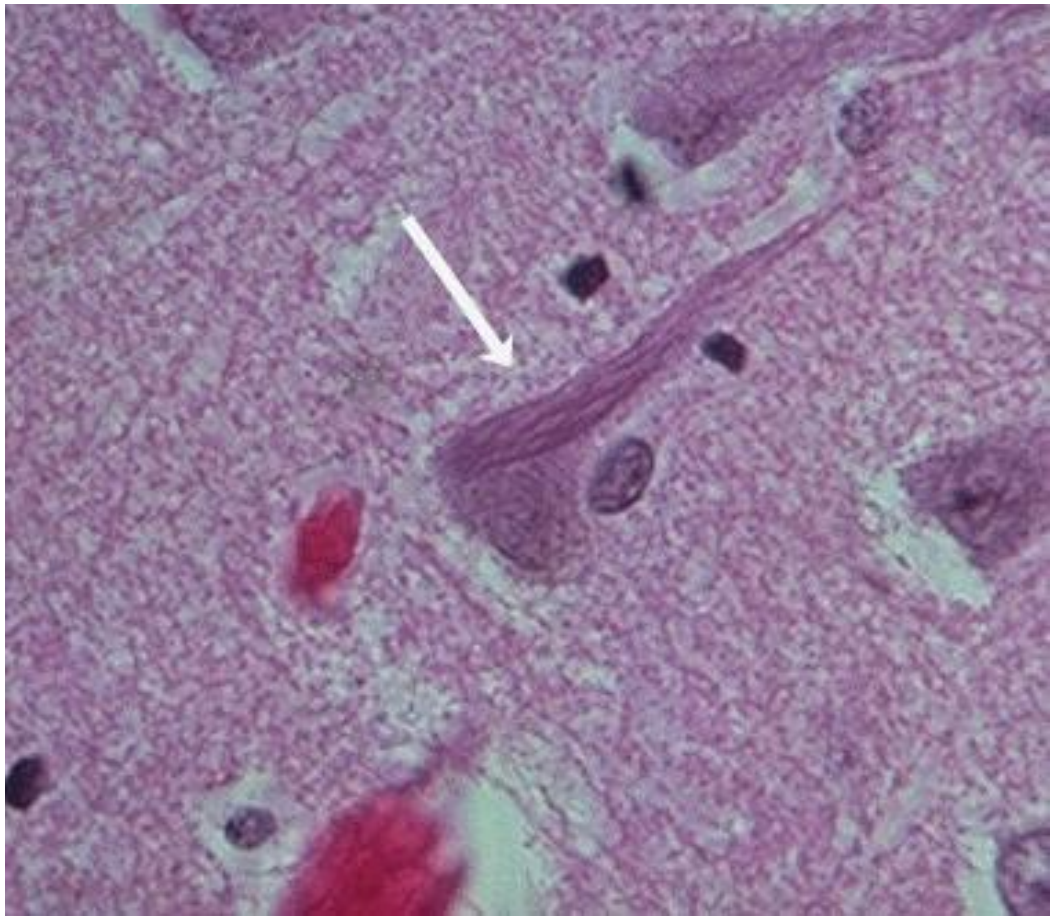



(B) Immunohistochemical stain for Aβ. Peptide is present in the core of the plaques as well as in the surrounding region. (C) Neurons containing tanglesstained with an antibody specific for tau.

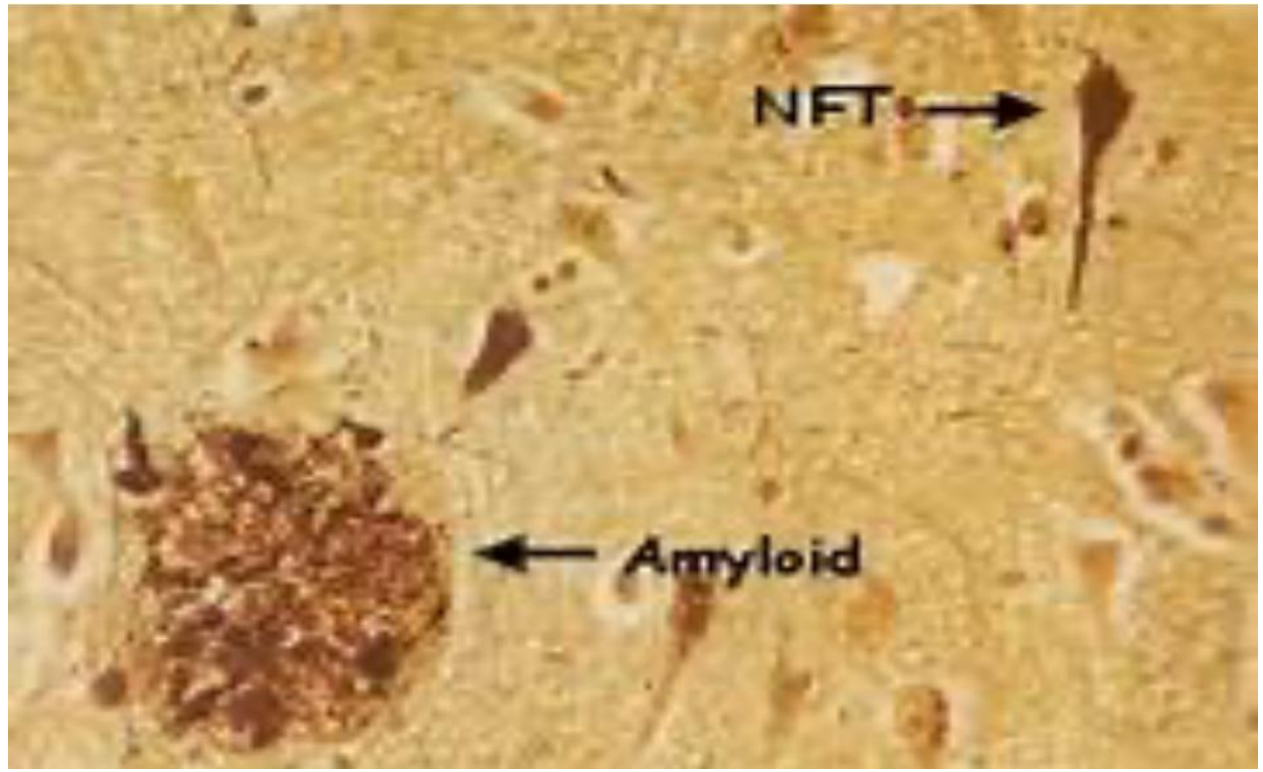


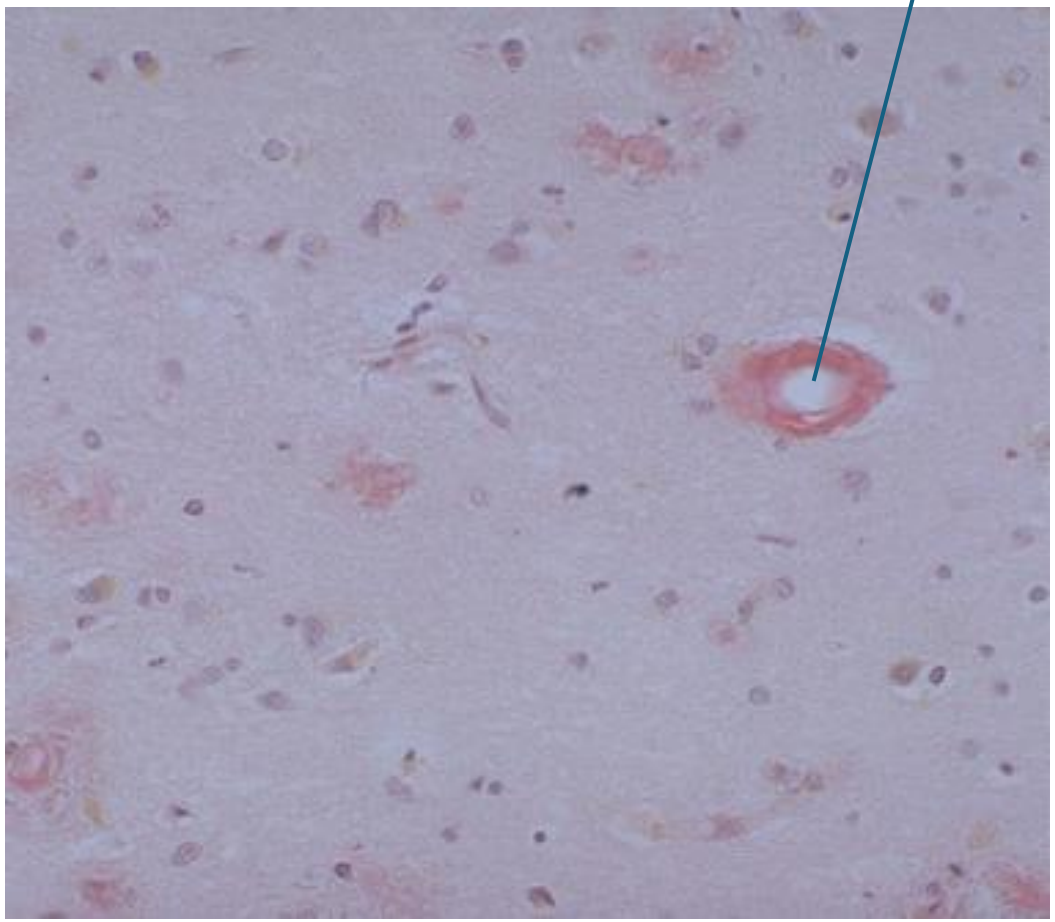
- Large nucleus , prominent nucleolus

# NEUROFIBRILLARY TANGLES

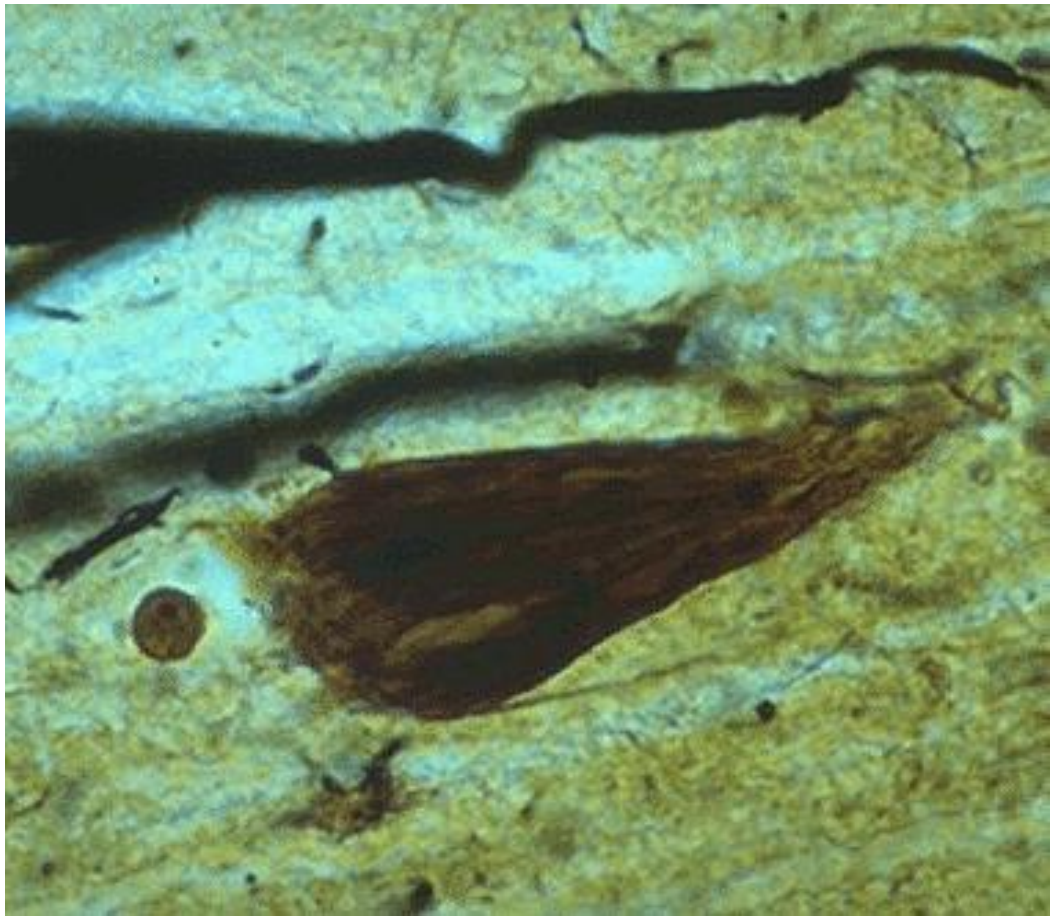


# Neurofibrillary tangles


NFT
Amyloid




Congo red stain for amyloid core of plaques.

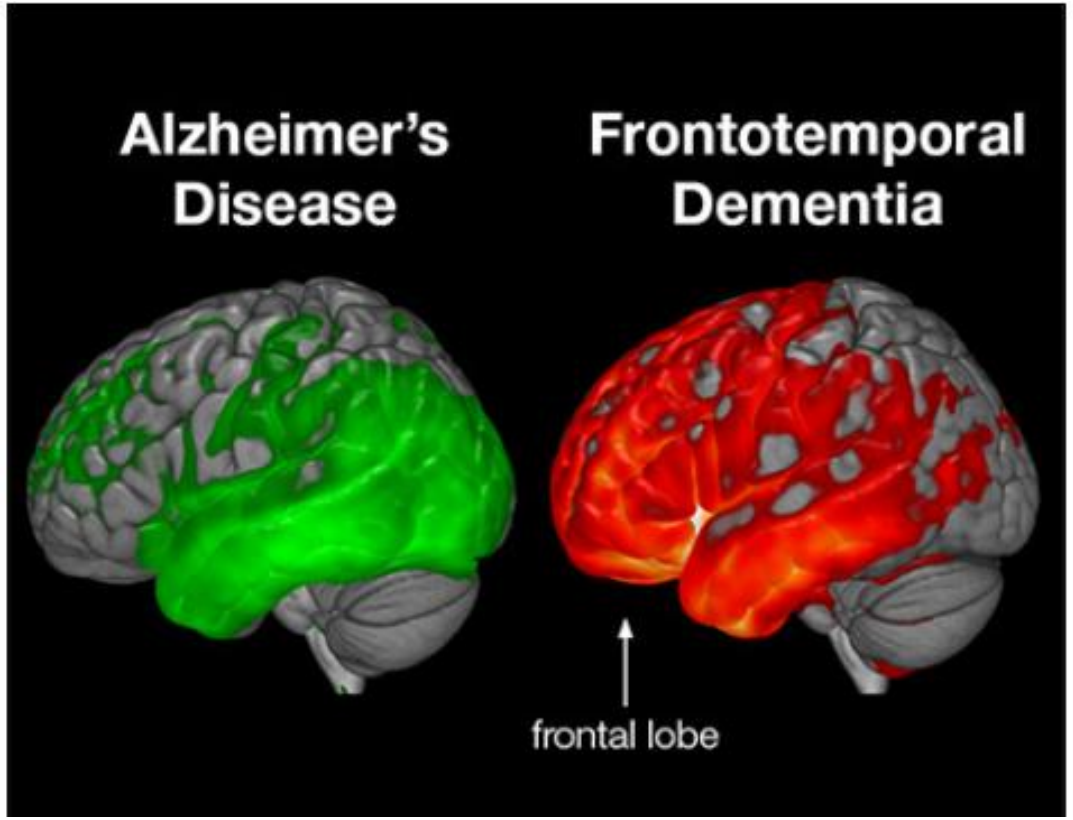


Silver stain
for NFT

# Frontotemporal Lobar Degeneration
# Frontotemporal dementias

- Several disorders, preferentially affect the frontal and/or temporal lobes ,**sparing the parietal lobe.**
- 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).

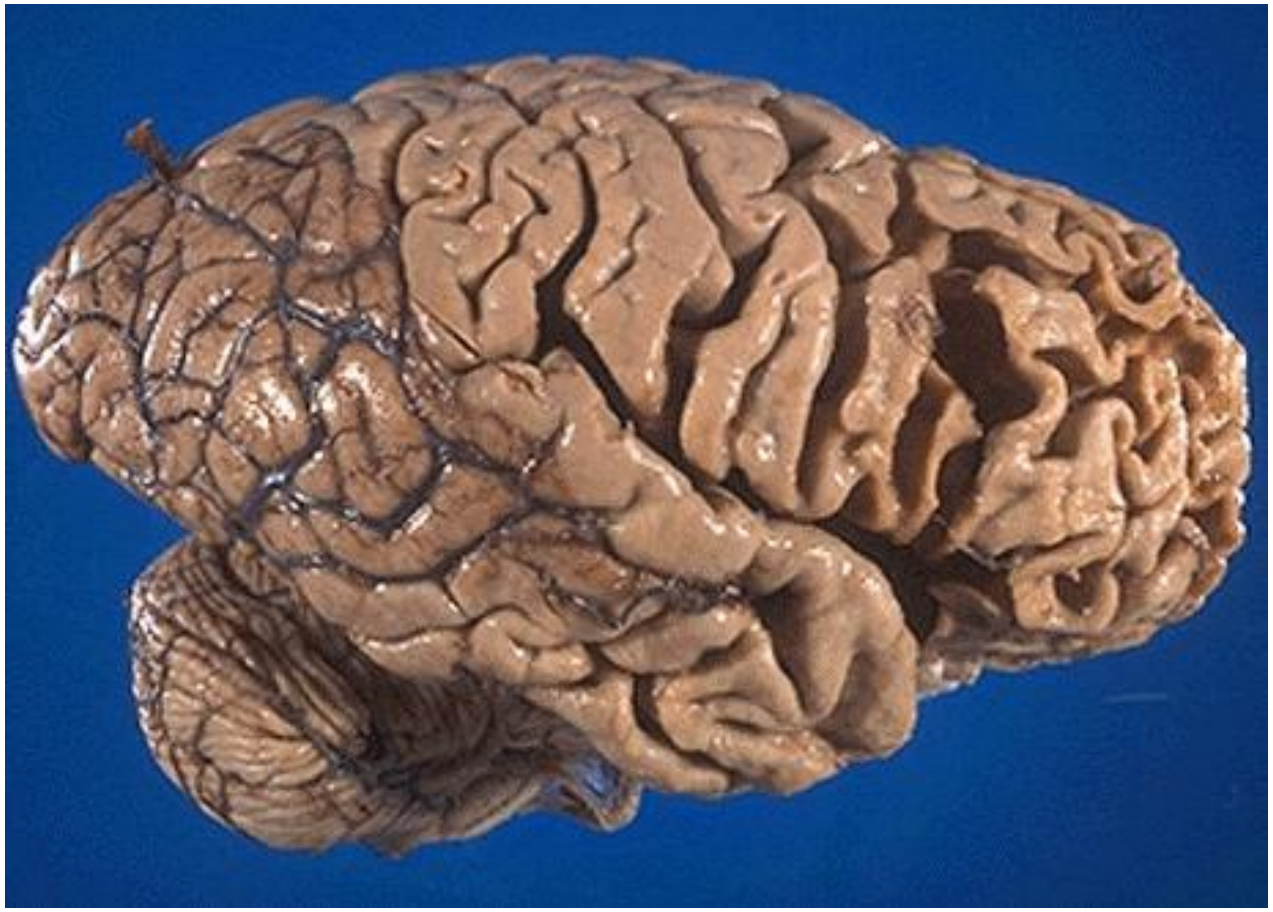
# In FTLD, frontal lobe is affected from the beginning, so patients present with behavioral problems first.



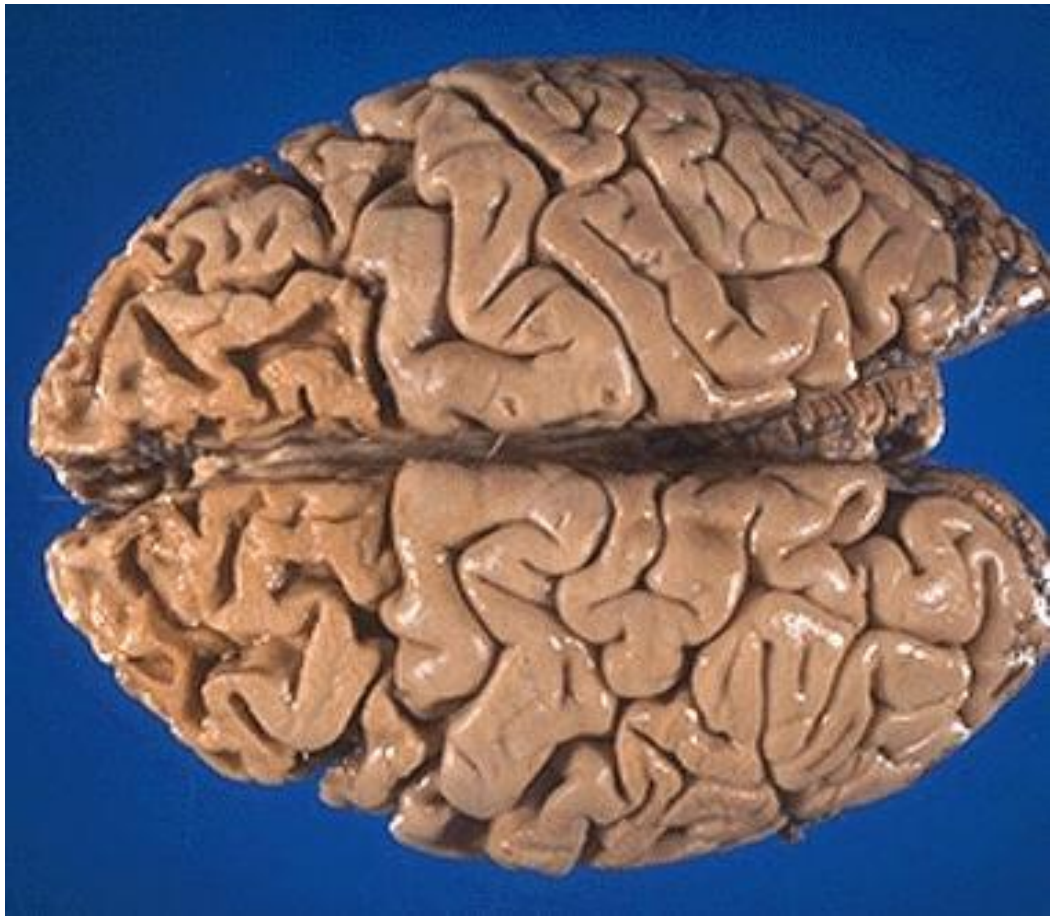

- In AD there is sparing of the frontal lobe, at least at the beginning so behavioral changes are a late manifestation.

# MORPHOLOGY

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

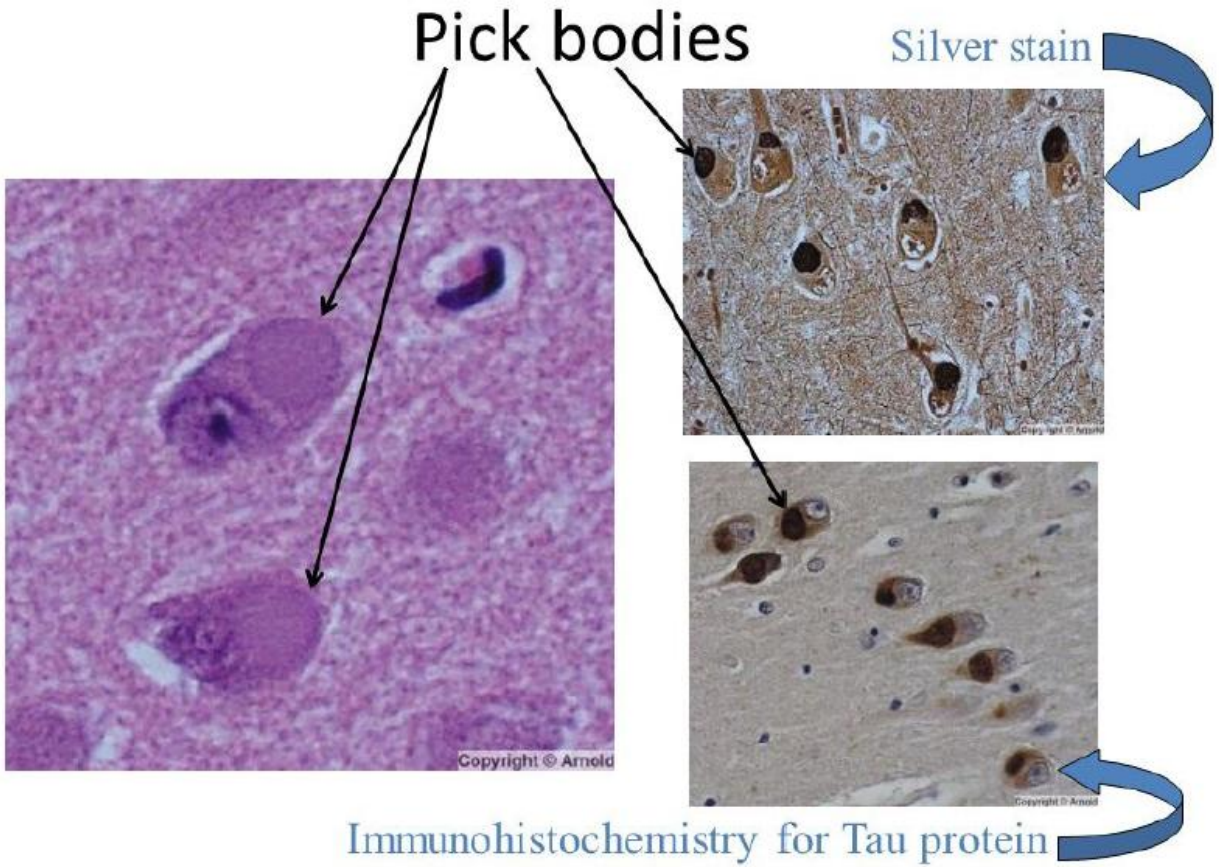


- Very marked **frontal lobe atrophy** and **temporal lobe atrophy.**



Frontal lobes are markedly thinned

**Rounded inclusions within the neurons**



Additional sources

1. **Robbins pathology**
2. Youtube videos
3. Webpages…etc

وَمَن يَتَوَكَّلْ عَلَى اللَّهِ فَهُوَ حَسْبُهُ


| VERSIONS | SLIDE # | BEFORE CORRECTION | AFTER CORRECTION |
|---|---|---|---|
| V1→ V2 | | | |
| V2→V3 | | | |

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!