

Diagnosing Alzheimer's disease: From genetics, neuropathology, to common and rare clinical manifestations of the disease.

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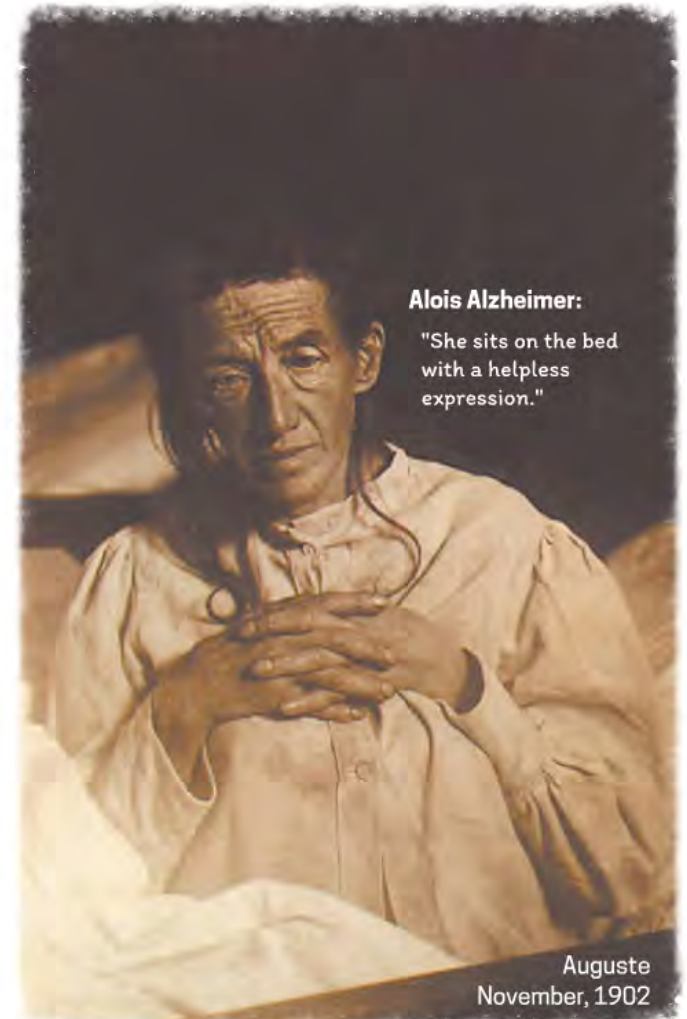
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A tale to remember....

On November 25th, 1901, Karl, a German office clerk, brought his wife, Auguste, of 51 years of age, to a mental institution in Frankfurt, Germany. Karl was having a difficult time caring for his wife, who started having memory loss a few years before, as well as paranoia, feelings of jealousy, a conviction that someone wanted to kill her, difficulty speaking, auditory hallucinations and unpredictable behavior. The physician on call who examined her was named Alois Alzheimer, then 27 years old.



Alois Alzheimer:

"She sits on the bed with a helpless expression."

Auguste
November, 1902

Discovering the signs and symptoms of advanced Alzheimer's disease...

What is your name?

- *Auguste*

Last name?

- *Auguste*

What is your husband's name?

- *Auguste, I think.*

Your husband?

- *Ah, my husband.*

(she looks as if she didn't understand the question)

Are you married?

- *To Auguste.*

Mrs. D?

- *Yes, yes, Auguste D.*

How long have you been here?

(she seems to be trying to remember)

- *Three weeks.*

What is this?

(I show her a pencil)

- *A pen.*

What did I show you?

- *I don't know, I don't know.*

It's difficult isn't it?

- *So anxious, so anxious...*

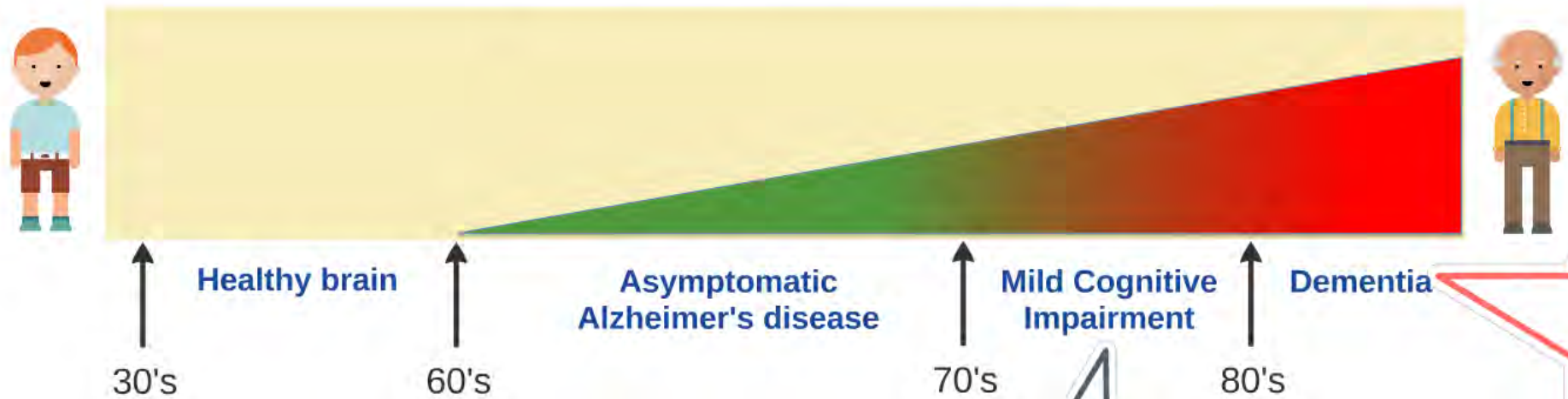
"A characteristic serious disease of the cerebral cortex"

- Auguste passed away April 8, 1906.
- Alois Alzheimer asked for her brain and described his findings in 1907.
- He described what we now know as neurofibrillary tangles and amyloid plaques, the pathological hallmarks of the disease.
- The term "Alzheimer's disease" was coined in 1910 by Kraepelin in the Handbook of Psychiatry.

Outline:

- 1) Principal clinical syndromes of Alzheimer's disease:
 - Memory syndrome
 - Visual syndrome
 - Language syndrome
 - Frontal syndrome
- 2) Neuropathology
- 3) Genetic factors
- 4) Modern biomarkers

Stages of Alzheimer's disease



The term MCI describes a clinical state of cognitive and/or behavioral decline of any cause that does NOT significantly interfere with independent living.

The des state or be any c sign with comp

**Asymptomatic
Alzheimer's disease**

↑
70's

**Mild Cognitive
Impairment**

↑
80's

Dementia

*The term MCI describes
a clinical state of
cognitive and/or
behavioral decline of
any cause that does
NOT significantly
interfere with
independent living.*



30's

Dementia



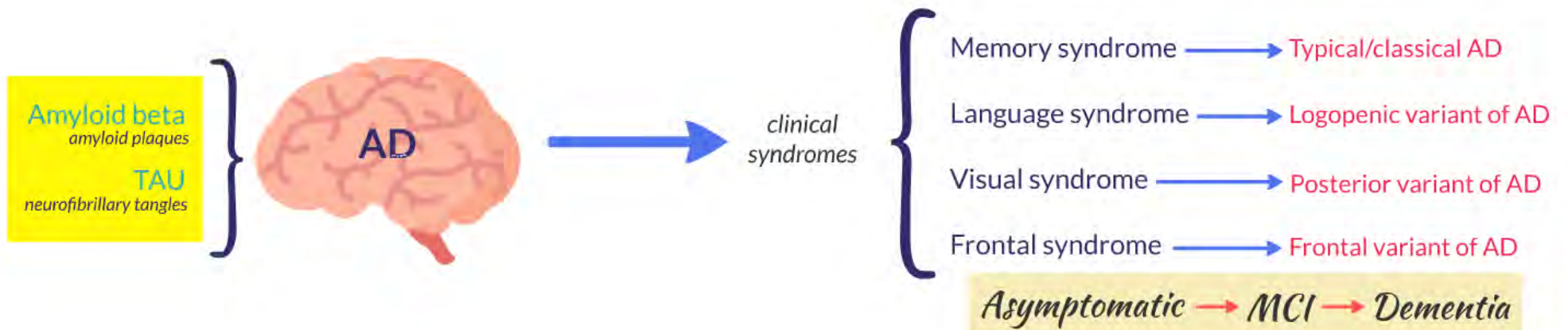
The term dementia describes a clinical state of cognitive and/or behavioral decline of any cause that DOES significantly interfere with independence in completing daily tasks.

Key points:

Not every person who has dementia or MCI has Alzheimer's disease.

Not every person who has MCI goes on to develop dementia.

Alzheimer's disease (AD): from neuropathology to clinical syndromes



Emily Dickinson

A Thought went up my mind today –
That I have had before –
But did not finish – some way back –
I could not fix the Year –

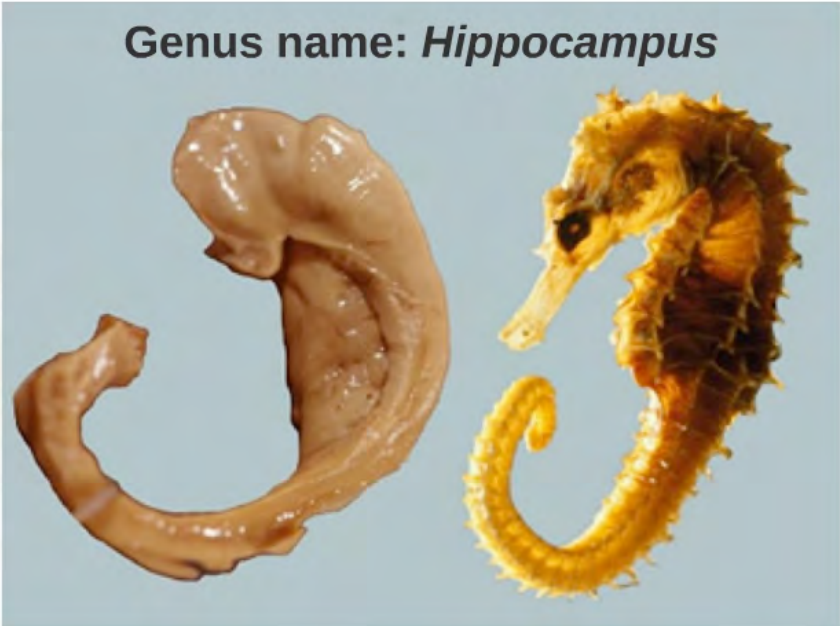
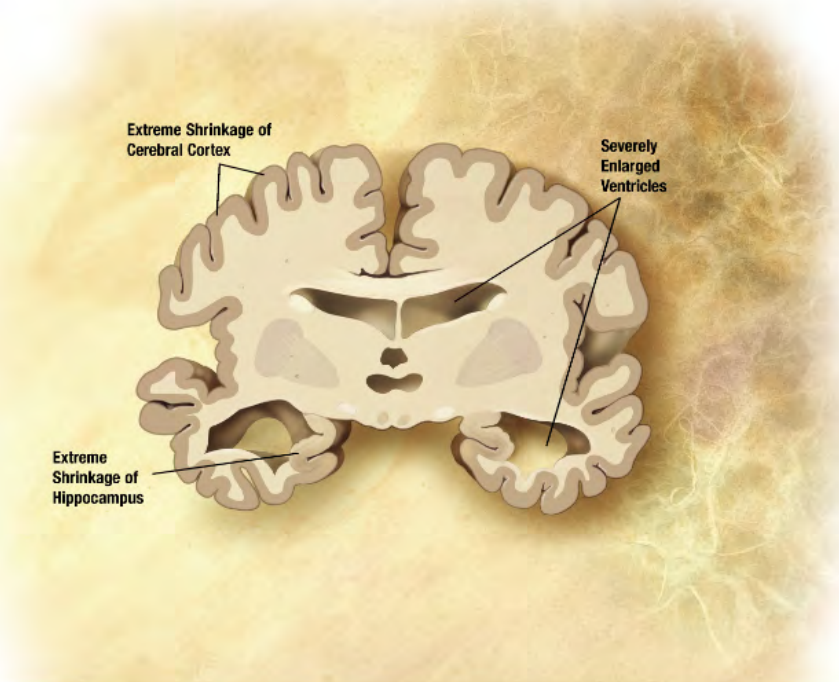
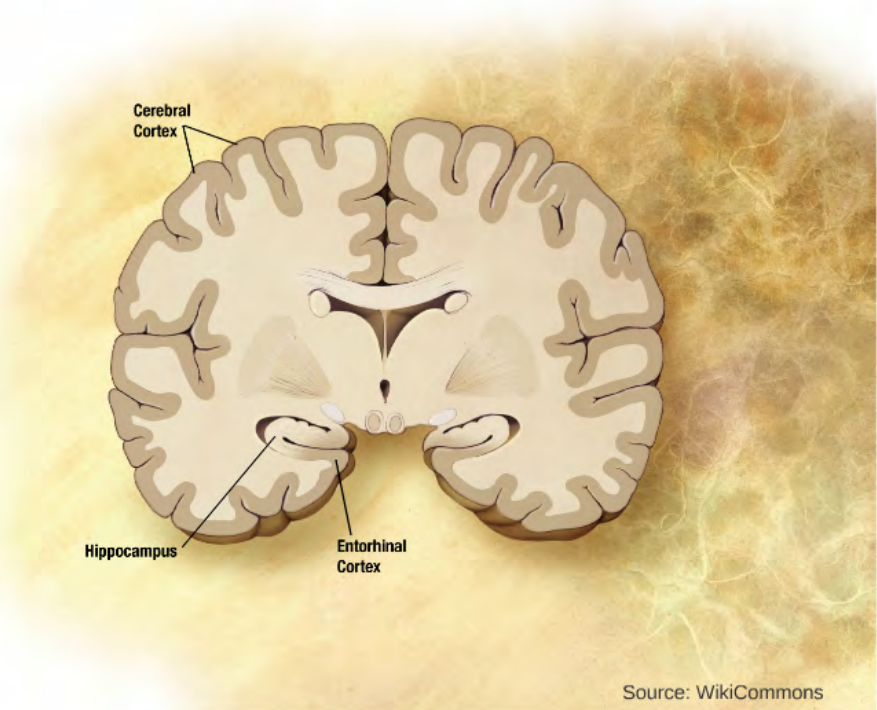
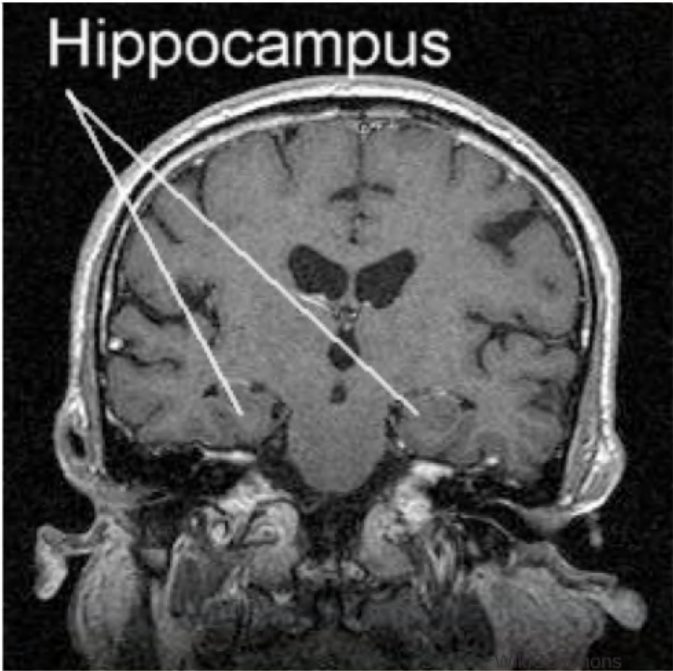
Nor where it went – nor why it came
The second time to me –
Nor definitely, what it was –
Have I the Art to say –

But somewhere – in my Soul – I know –
I've met the Thing before –
It just reminded me – 'twas all –
And came my way no more

Memory syndrome: **Typical/Classical AD**

- First sign/symptom is short-term memory loss.
- Long term, distant memories are often preserved.
- May forget events, conversations, repeat stories, misplace belongings.
- Over time, progresses to affect navigation and people may start getting lost.
- Language, behavior, or other cognitive domains may be affected later in the disease.

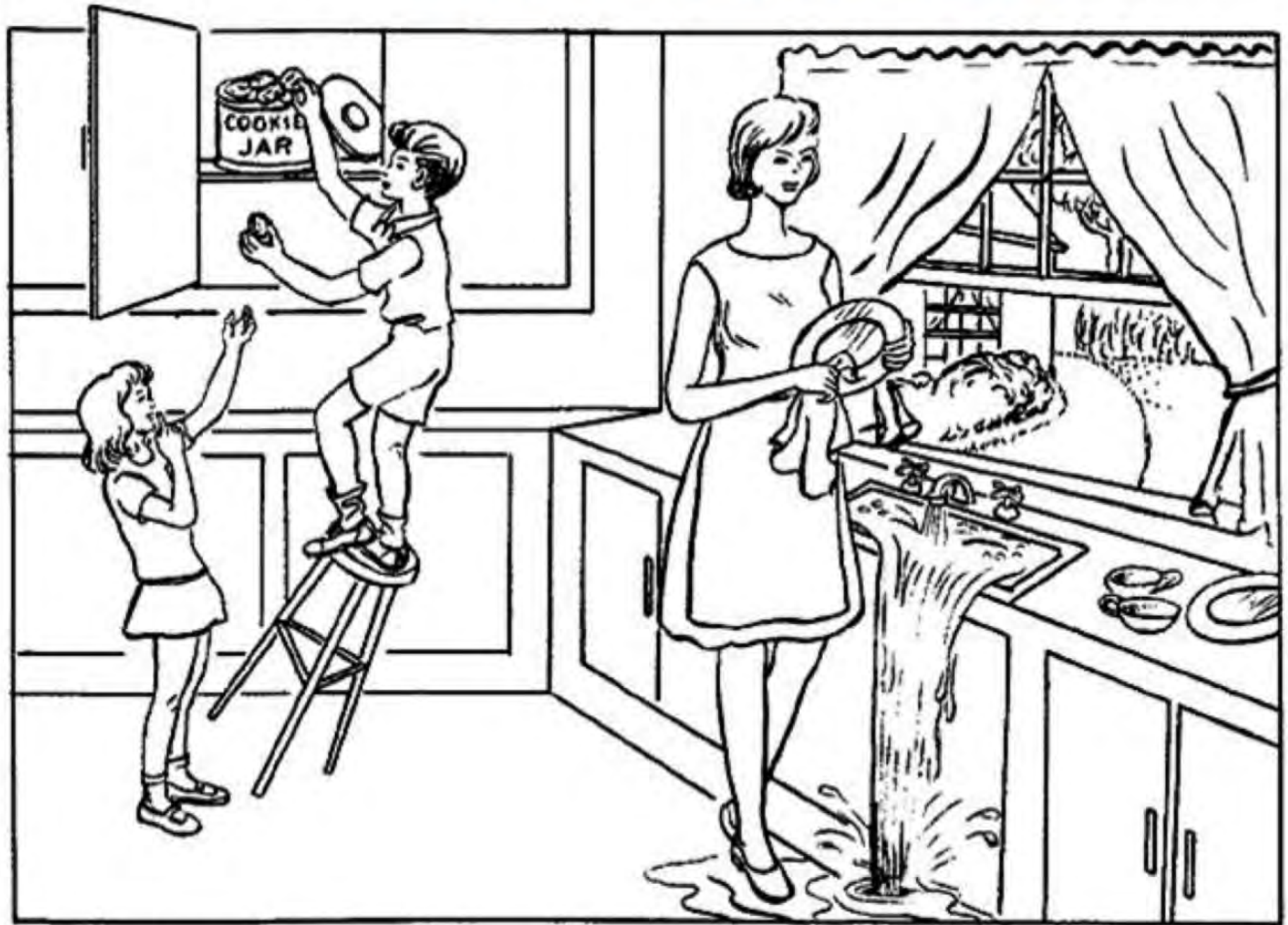
Memory syndrome: Typical/Classical AD: Brain localization



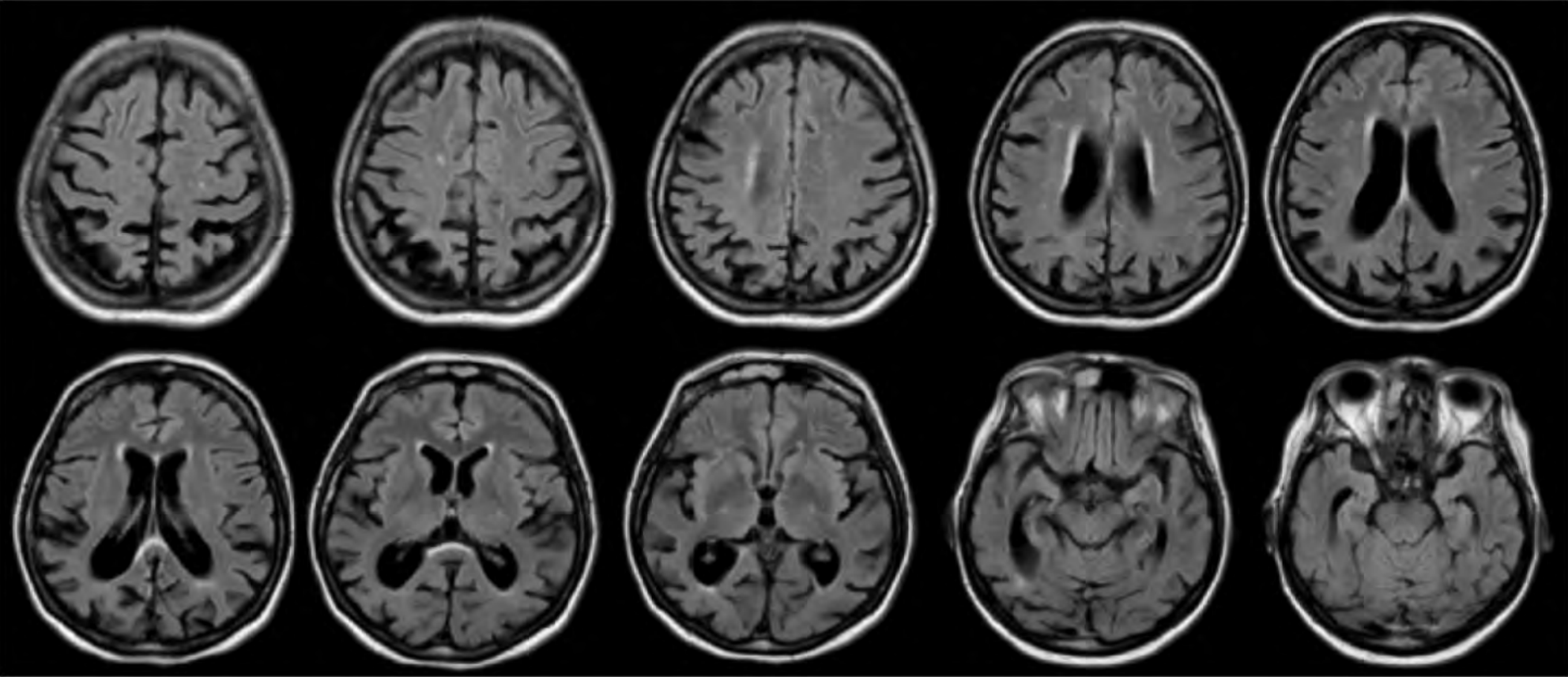
Visual syndrome: **Posterior variant of AD**, also known as **Posterior Cortical Atrophy (PCA)**

- First sign/symptom is impairment in visual processing.
- Difficulty navigating, locating objects in space, depth perception, tracking moving objects.
- Difficulty recognizing faces and objects.
- Over time, may progress to affect memory and language functions.
- Depression/anxiety might ensue.

Visual syndrome: **Posterior variant of AD/PCA**



Visual syndrome: **Posterior variant of AD/PCA: Brain Localization**



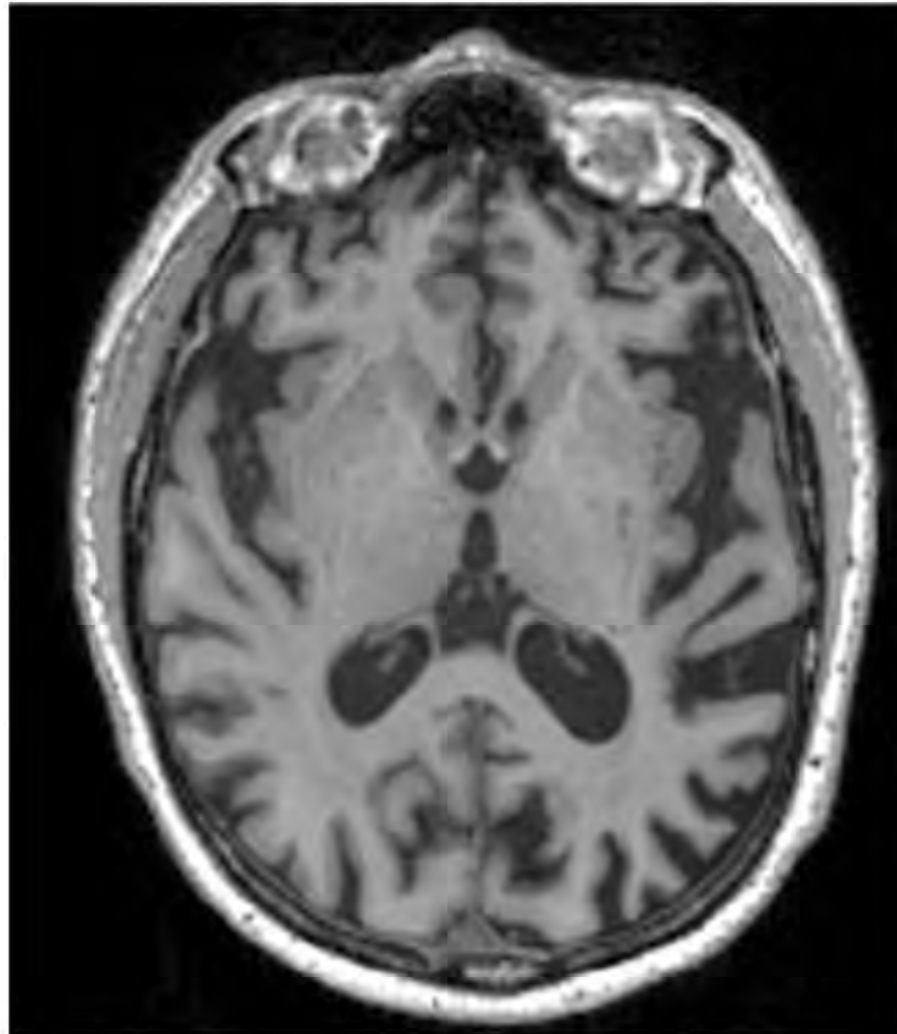
Language syndrome: **Logopenic variant of AD**

- First sign/symptom is language production difficulty.
- Word-finding difficulties in spontaneous speech.
- Impaired phonological processing affecting processing of sound of language, following long instructions, repetition, communication in crowded places or over the phone.
- Progressive impairment in communication, difficulty calculating, may involve visual function as the disease progresses.

Language syndrome: **Logopenic variant of AD**



Language syndrome: **Logopenic variant of AD:**
Brain localization



Frontal/executive syndrome: **Frontal variant of AD**

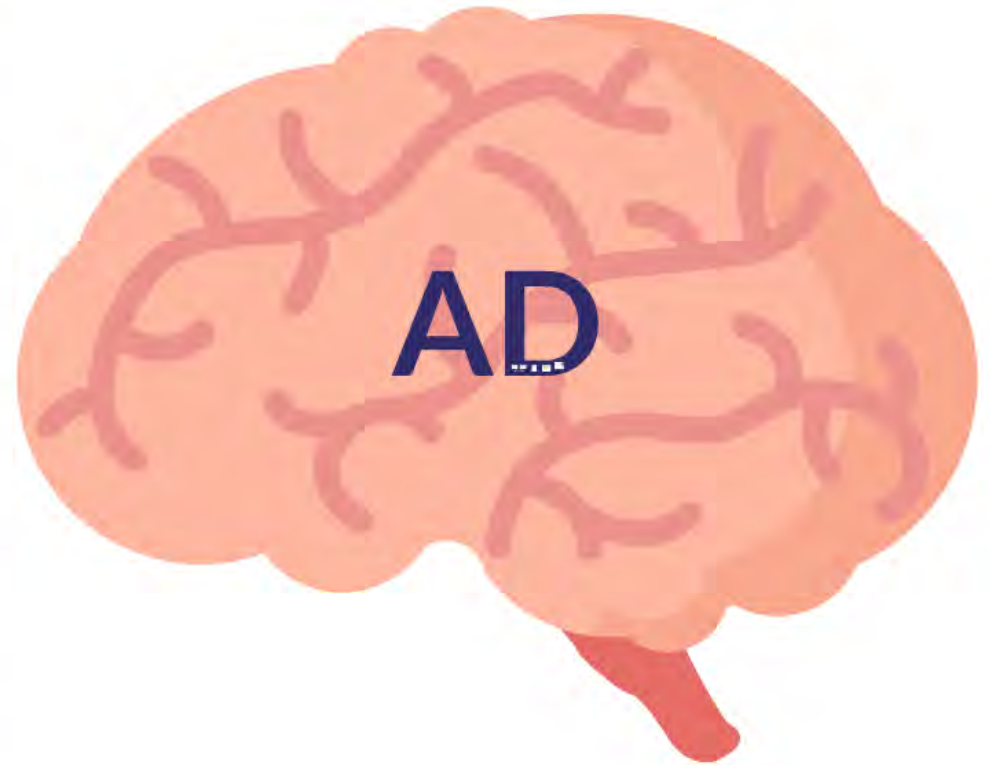
- Usually occurs at earlier age.
- First signs/symptoms involve executive functions, decision making, planning, organizing, multitasking, shifting between tasks.
- May involve changes in behavior: loss of motivation, disinhibition, social inappropriateness.
- Over time, may progress to involve other cognitive domains (memory, language, visual).

Outline:

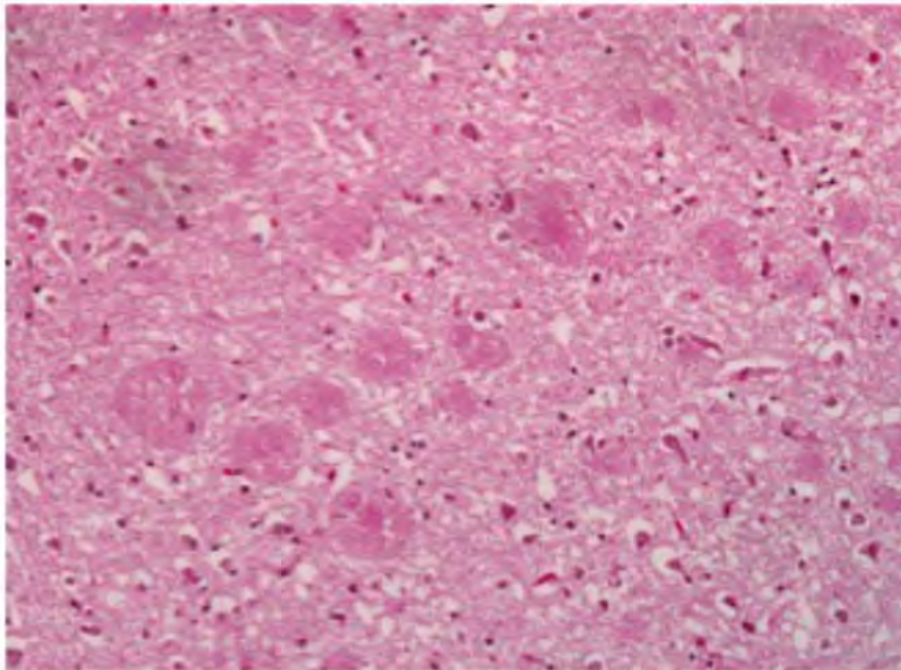
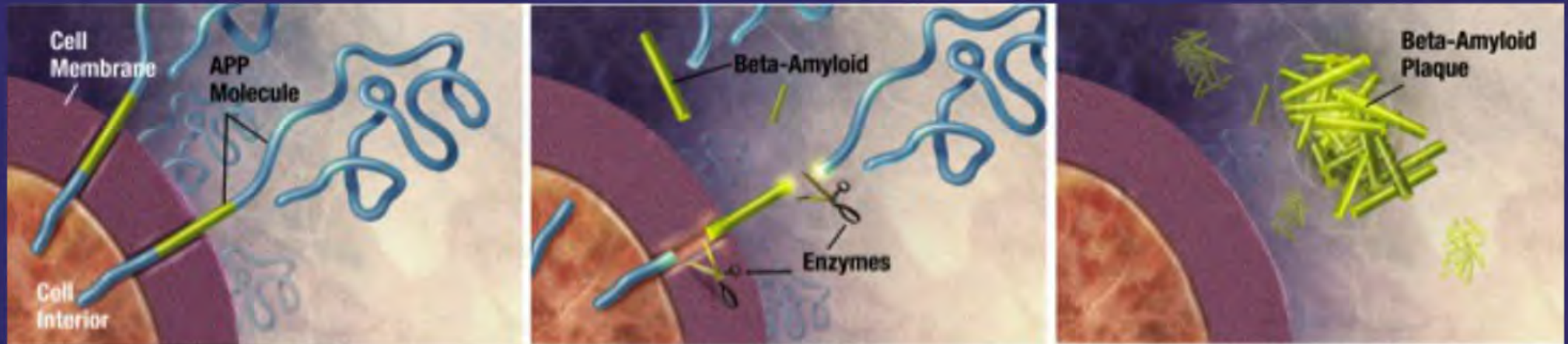
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Amyloid beta
amyloid plaques

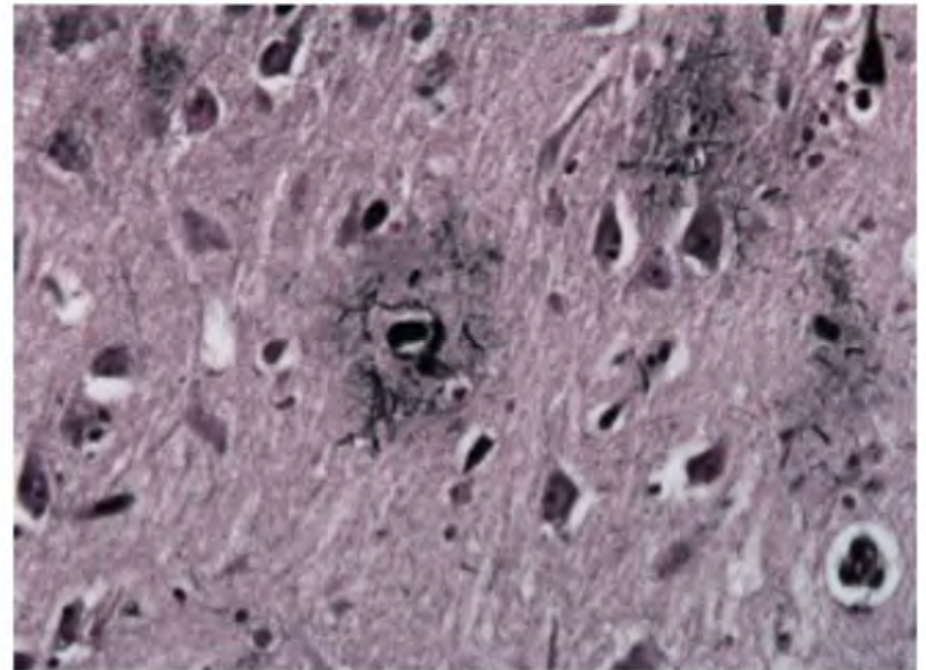
TAU
neurofibrillary tangles



Progressive accumulation of amyloid protein



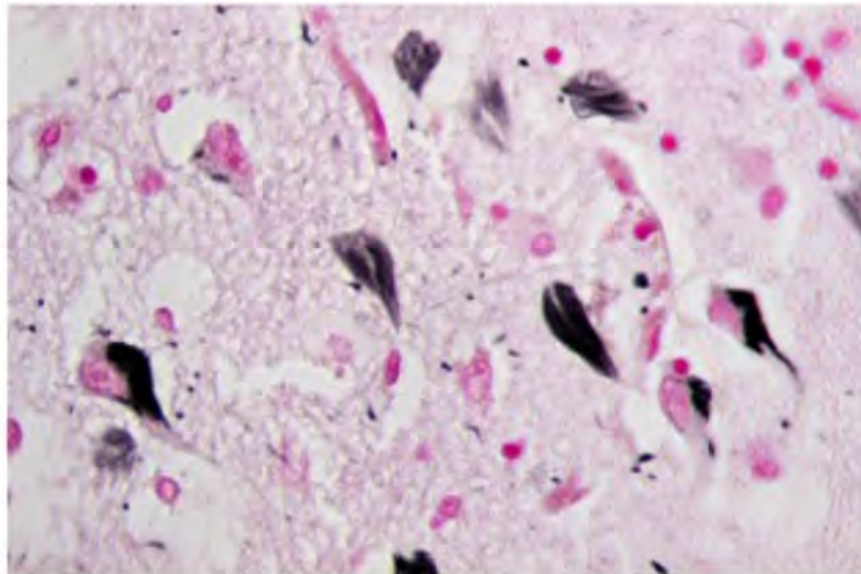
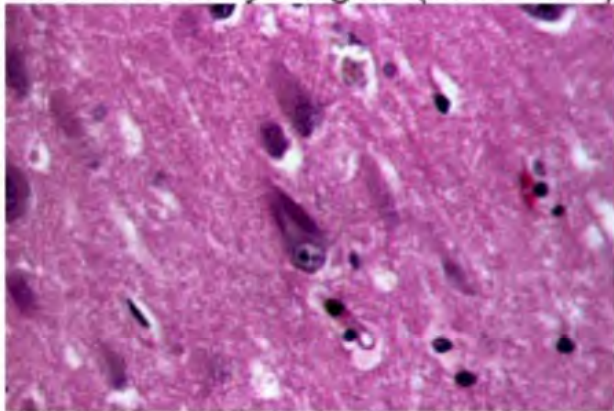
Diffuse plaques (H&E stain)



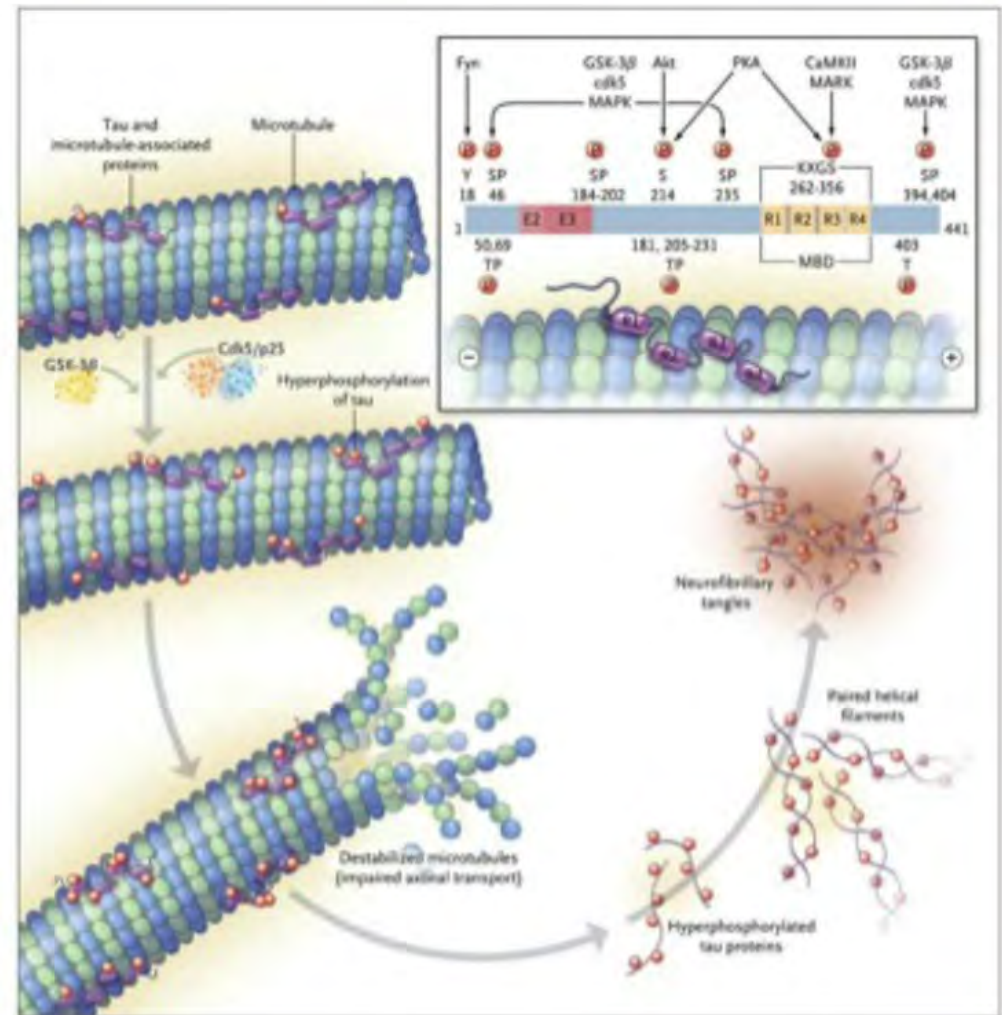
Neuritic plaques (silver stain)

Progressive accumulation of tau protein

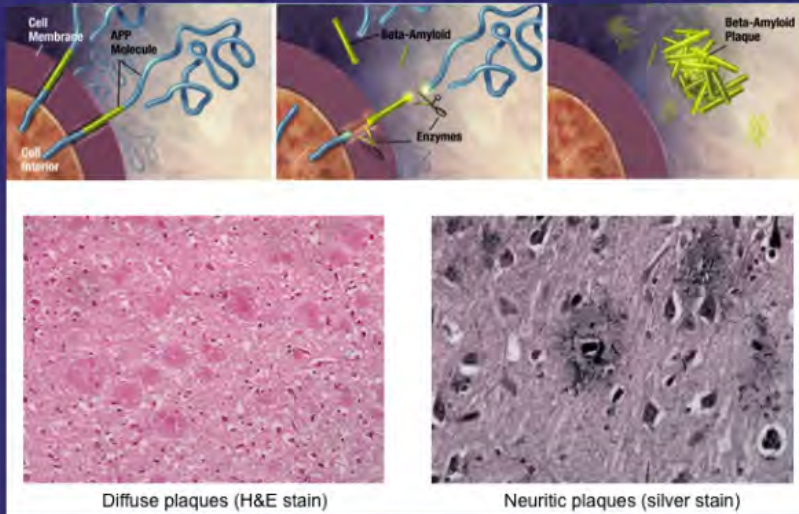
Neurofibrillary tangles (H&E stain)



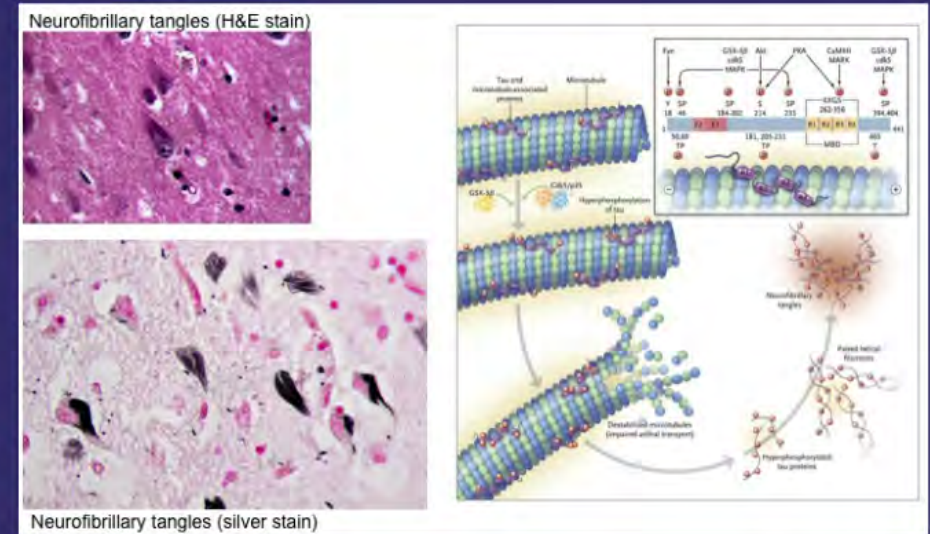
Neurofibrillary tangles (silver stain)



Progressive accumulation of amyloid protein

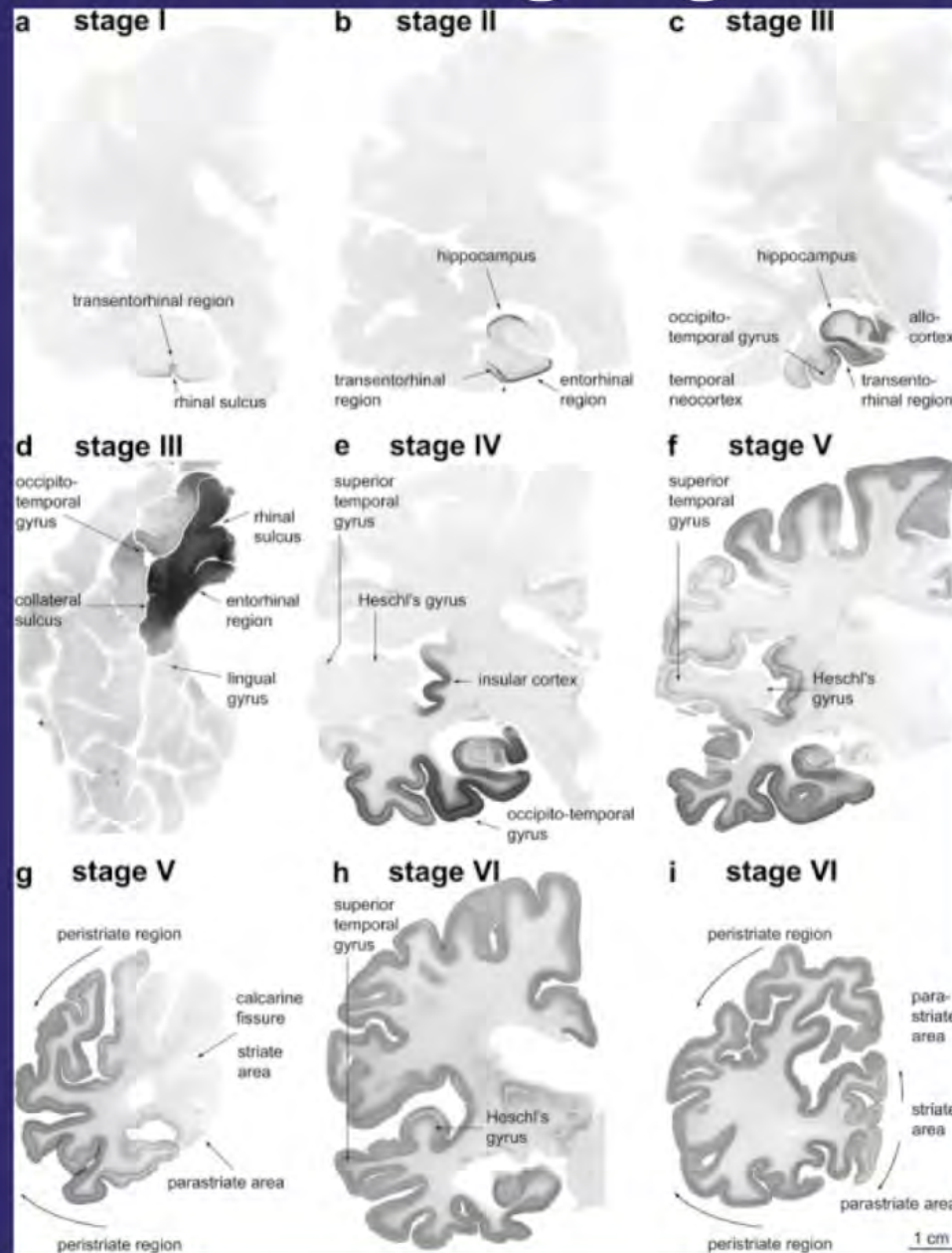


Progressive accumulation of tau protein



"Alzheimer's disease" is the term used to describe a specific neurodegenerative disease of the brain associated with the progressive accumulation of **amyloid plaques** and **tau tangles**, which over time lead to irreversible degeneration of neurons.

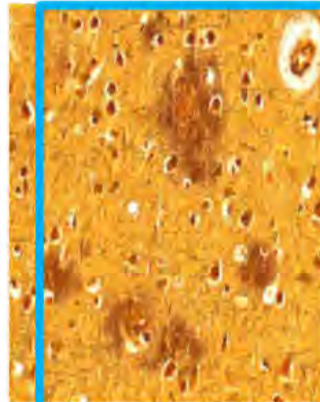
Braak staging



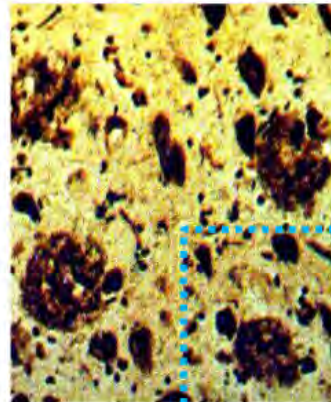
β -Amyloid deposits

amyloid- β ($A\beta$) 36-43 aa peptide derived from Amyloid Precursor Protein (APP)

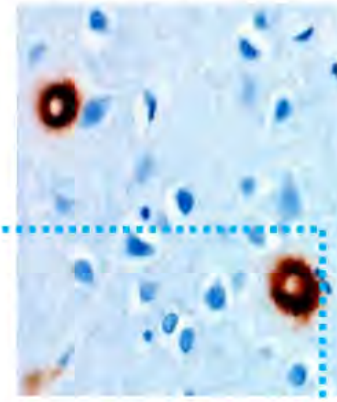
Different types of $A\beta$ deposits, including...



Diffuse deposits



Neuritic Plaques

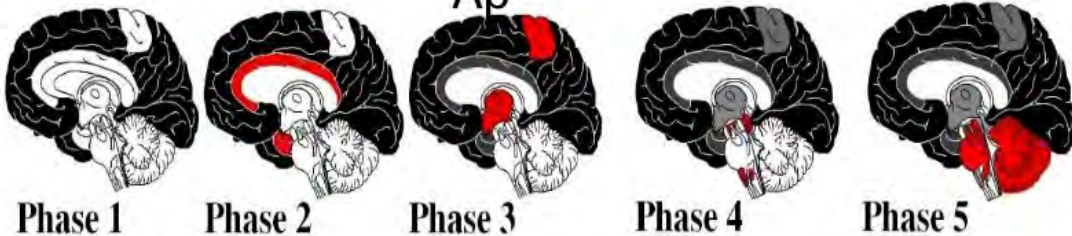


Cerebral Amyloid Angiopathy (CAA)

Thal phase

Distribution of diffuse + neuritic $A\beta$

$A\beta$



Phase 1

Phase 2

Phase 3

Phase 4

Phase 5

CERAD score

Neuritic Plaque Density (max score of all cortical areas)



None
0



Sparse
1-5 NP/mm²



Moderate
6-19 NP/mm²



Frequent
≥20 NP/mm²

Tau tangles in AD/aging

Hyperphosphorylated tau (3R+4R) aggregates in neurons

- neurofibrillary tangles (soma)
- neuropil threads (dendrites)
- in the crown of the neuritic plaque



Immunohistochemistry of P-tau with CP13

Courtesy of Salvo Spina

Stereotypical Braak stages

stage I

stage II

stage III

stage IV

stage V

stage VI

transentorhinal region

rhinal sulcus

hippocampus

transentorhinal region

entorhinal region

hippocampus

occipito-temporal gyrus

temporal neocortex

transentorhinal region

allo-cortex

superior temporal gyrus

Heschl's gyrus

insular cortex

occipito-temporal gyrus

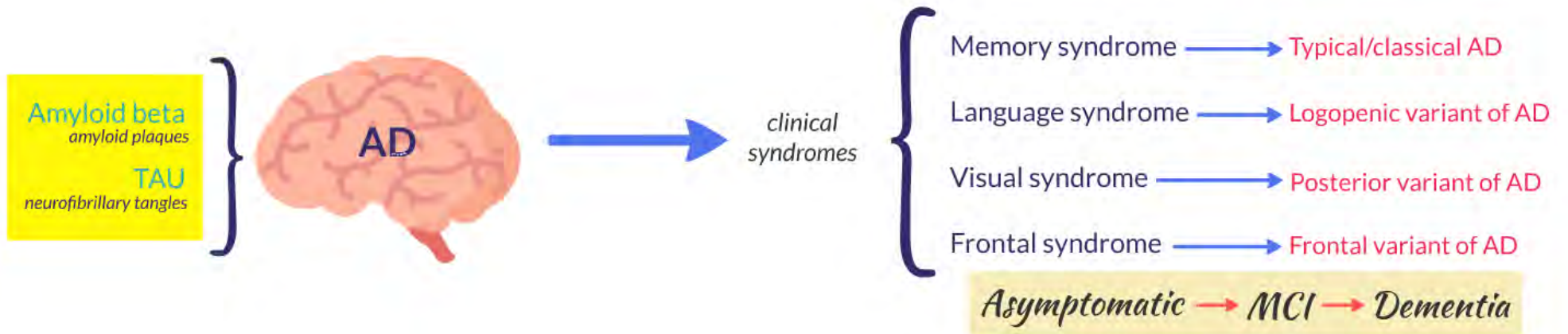
superior temporal gyrus

Heschl's gyrus

superior temporal gyrus

Heschl's gyrus

Alzheimer's disease (AD): from neuropathology to clinical syndromes

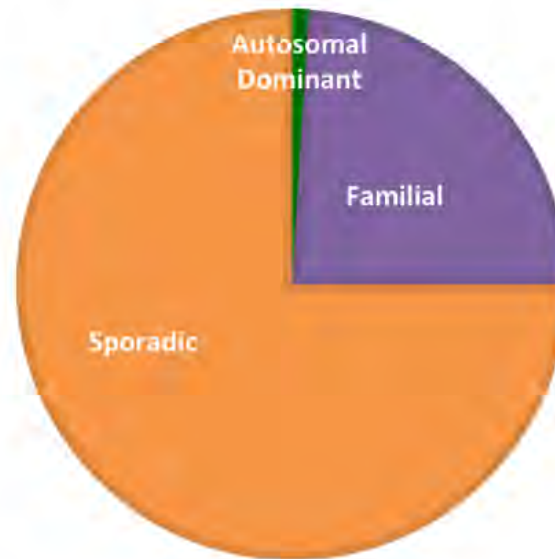


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Genetic factors: causative genes and risk-factor genes

Alzheimer's is rarely caused by single gene variant



Genetics of Alzheimer's

- **SPORADIC (75%)**
 - No family history
 - Recurrence risk for 1st deg relatives = 2x increase (20-25%)
 - Multifactorial
- **FAMILIAL (24%)**
 - 2 or more relatives (3rd deg or closer)
 - Recurrence risk increased, but difficult to quantify
 - Multifactorial
- **AUTOSOMAL DOMINANT (<1%)**
 - *PSEN1* (65%), *APP* (10-15%), *PSEN2* (rare)

Courtesy of our geneticist, Jamie Fong

Genetics of Alzheimer's

- SPORADIC (75%)
 - No family history
 - Recurrence risk for 1st deg relatives = 2x increase (20-25%)
 - Multifactorial
- FAMILIAL (24%)
 - 2 or more relatives (3rd deg or closer)
 - Recurrence risk increased, but difficult to quantify
 - Multifactorial
- AUTOSOMAL DOMINANT (<1%)
 - *PSEN1* (65%), *APP* (10-15%), *PSEN2* (rare)

Presenilin 1

- Chromosome 14
- Onset 25-60, mean 40
- Symptoms: Parkinsonism, ataxia, myoclonus, spastic paraparesis, behavioral changes
- Build up of amyloid beta
- Founder variants: Jalisco, Mexico; Caribbean Hispanics, Colombia, Finland

Presenilin 2

- Chromosome 1
- Onset 40-75, mean 50
- German, Italian, Spanish
- Build up of amyloid protein

Amyloid Precursor Protein

- Chromosome 21
- Onset 40-60 years old
- Symptoms: Dysautonomia, seizures, behavioral changes, cerebral amyloid angiopathy
- Build up of amyloid beta
- Increased risk in trisomy 21 (Down syndrome)

Apolipoprotein E

- Three major isoforms, three major alleles
- $\epsilon 2$ protective, $\epsilon 3$ neutral, $\epsilon 4$ risk-conferring
- $\epsilon 4$ decreases age of onset
- $\epsilon 4$ is neither necessary nor sufficient for disease
- Genotyping NOT recommended

Estimated Percentages of the U.S. Population with the Six Possible e2, e3 and e4 Pairs of the Apolipoprotein E (APOE) Gene

APOE Pair	Percentage
e2/e2	0.5
e2/e3	11
e2/e4	2
e3/e3	61
e3/e4	23
e4/e4	2

Created from data from Raber et al.⁴⁰

Percentages do not total 100 due to rounding.

ε4 confers significant Alzheimer's risk

ALZHEIMER'S RISK BY AGE 85

APOE	Men	Women
Without regard to genotype	10-11%	14-17%
ε2/ε2 or ε2/ε3	4-5%	6-8%
ε3/ε3	7-8%	10-12%
ε2/ε4	18-20%	27-31%
ε3/ε4	22-23%	30-35%
ε4/ε4	51-52%	60-68%

One ε4 copy is associated with 18-35% lifetime risk.

Two ε4 copies are associated with 31-40% lifetime risk.

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Modern biomarkers of AD: Proof of evidence

- Biomarkers may increase the certainty that the syndrome is caused by underlying AD neuropathology.

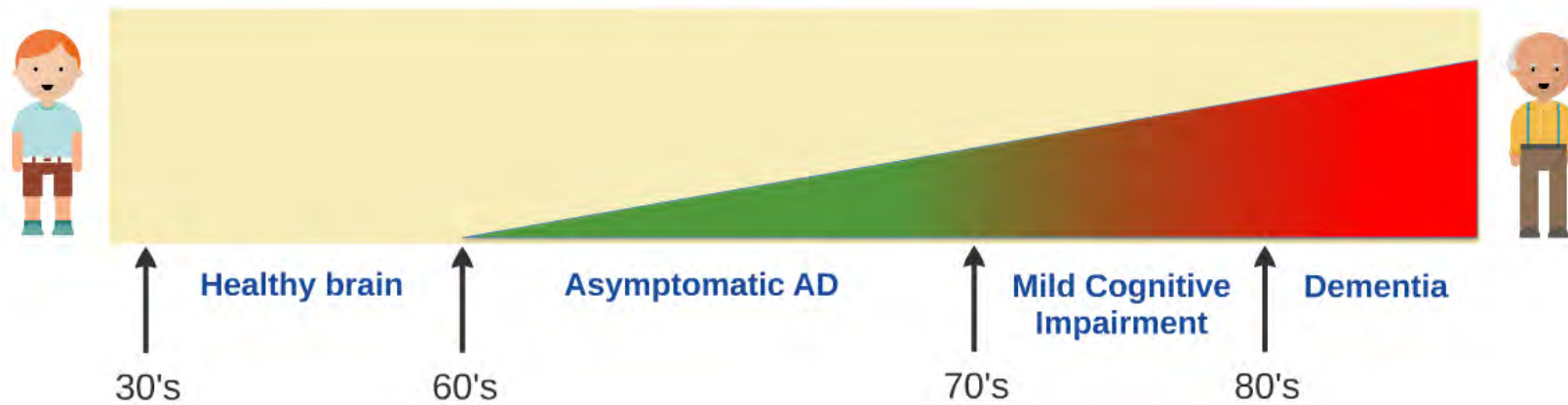
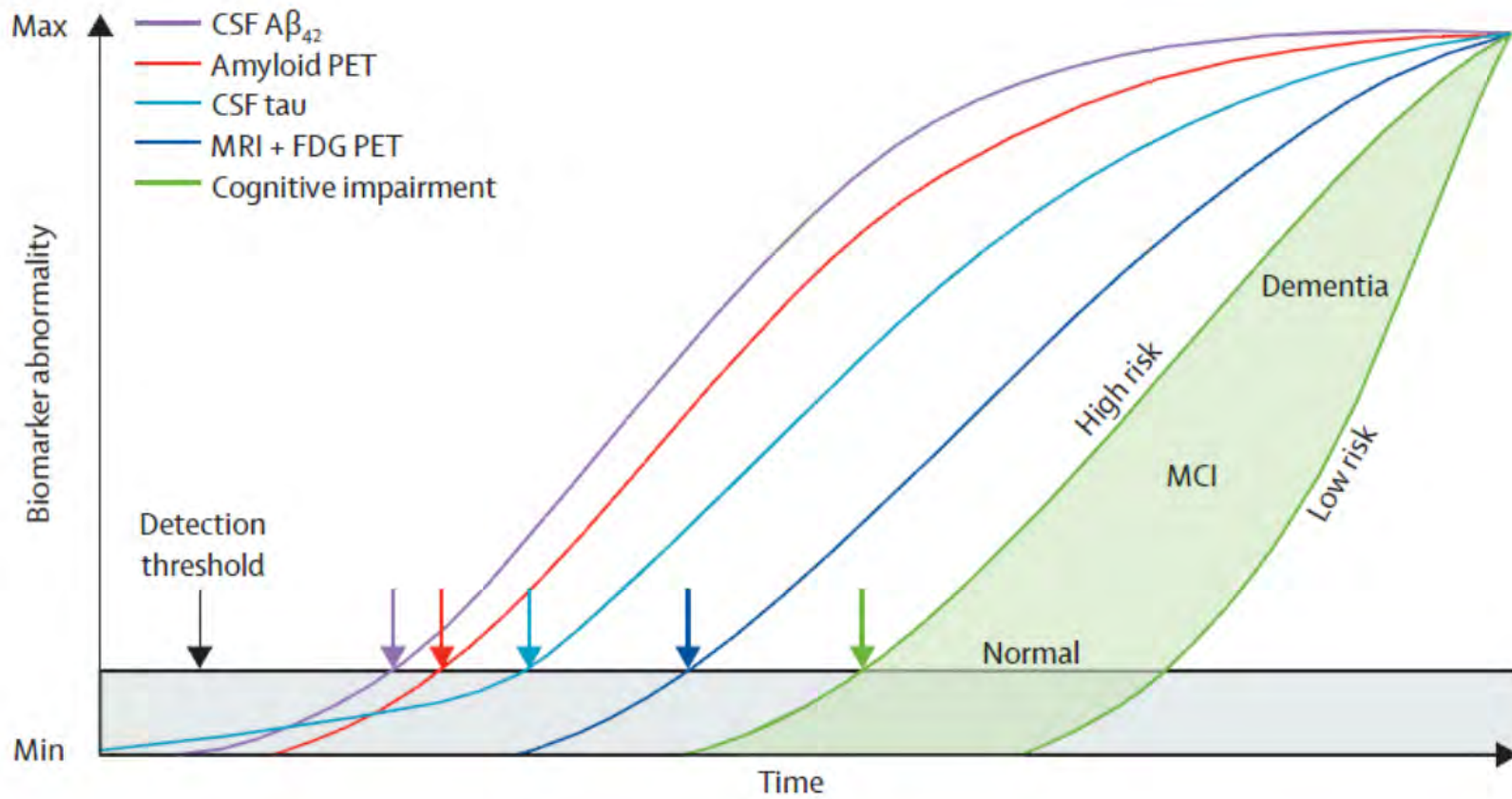
- AD biomarkers fall into two categories:

- 1) Biomarkers supporting amyloid deposition:

- Cerebrospinal fluid analysis: low CSF amyloid levels
- PET imaging: positive amyloid PET scan

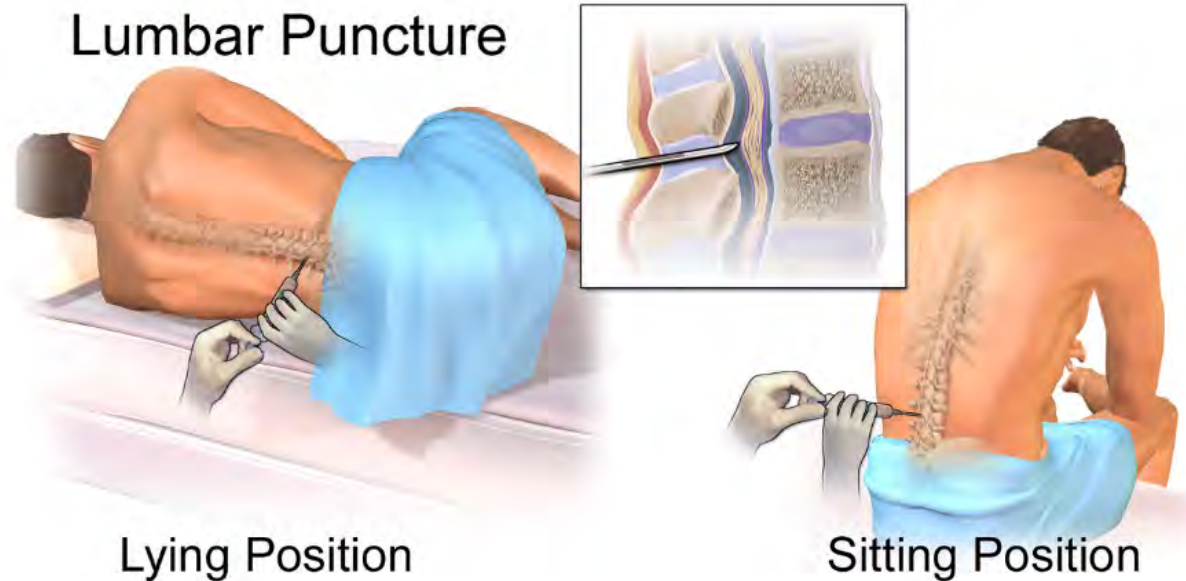
- 2) Biomarkers supporting "downstream" neuronal degeneration or injury:

- Cerebrospinal fluid analysis: elevated CSF tau, both total tau and phosphorylated tau (p-tau).
- PET imaging: decreased fluorodeoxyglucose (FDG) uptake on PET in temporoparietal cortex.
- MRI imaging: disproportionate, focal atrophy pattern.

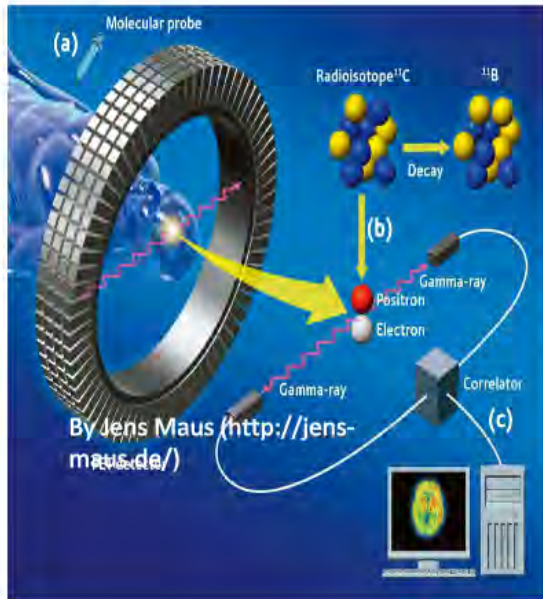


Cerebrospinal fluid of truth

- Lumbar puncture: cerebrospinal fluid.
- Levels of Amyloid and Tau.
- Low amyloid is a marker of amyloid pathology.
- High tau is a marker of neuronal loss.
- Allows testing for other causes: inflammation, autoimmune disease, cancer, etc.



Positron Emission Topography (PET)

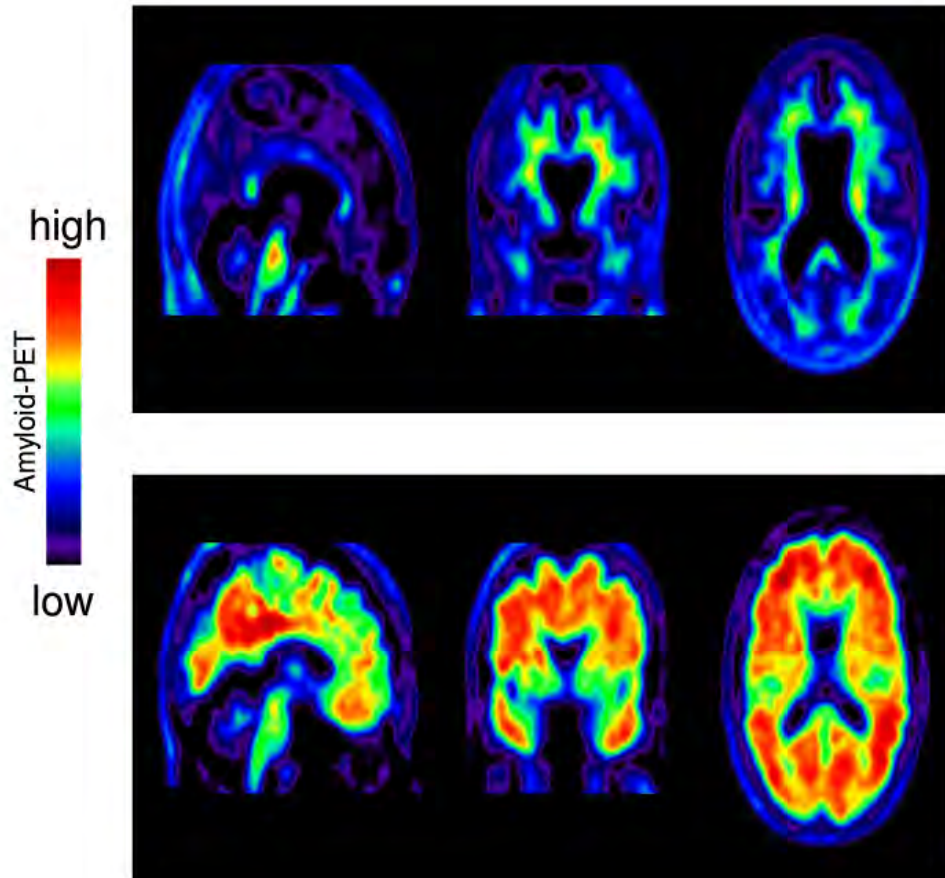


Nuclear medicine technique

(not just for brain imaging, widely used in oncology)

- IV injection of a small dose of a radioactive molecule (radiotracer).
- Tracer reaches the brain through blood flow
- Radioactive decay emits positron that creates 2 photons.
- PET scanner estimates where the photons are coming from.
- What you see depends on which tracer you injected!

β -Amyloid PET | binary visual read



Negative scan (no evidence for $A\beta$)

- Non specific binding in the white matter.
- Low signal in the gray matter/cortex.

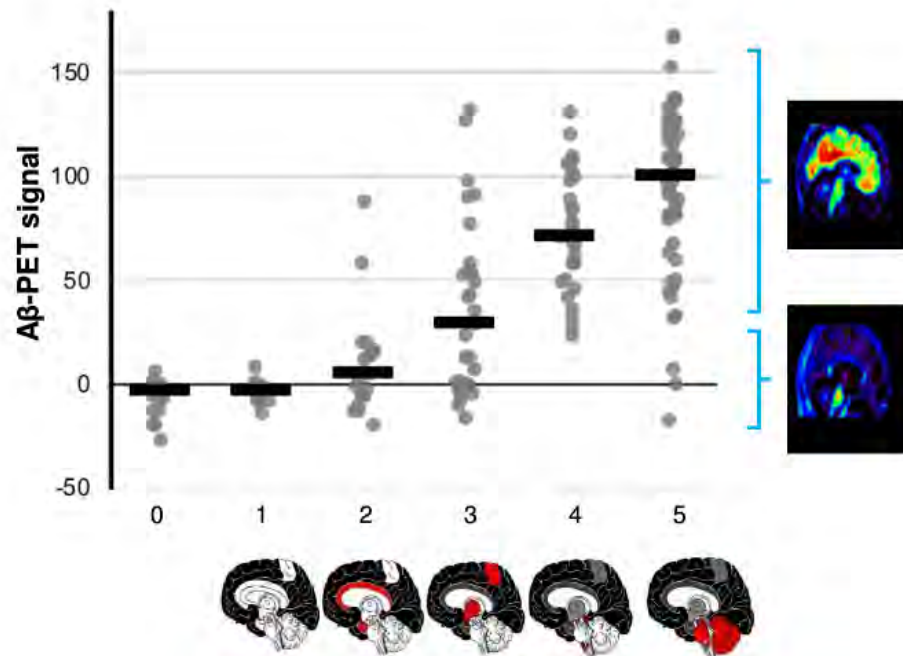
Positive scan (evidence for $A\beta$)

- Non specific binding in the white matter still here.
- High signal in most of the gray matter/cortex.

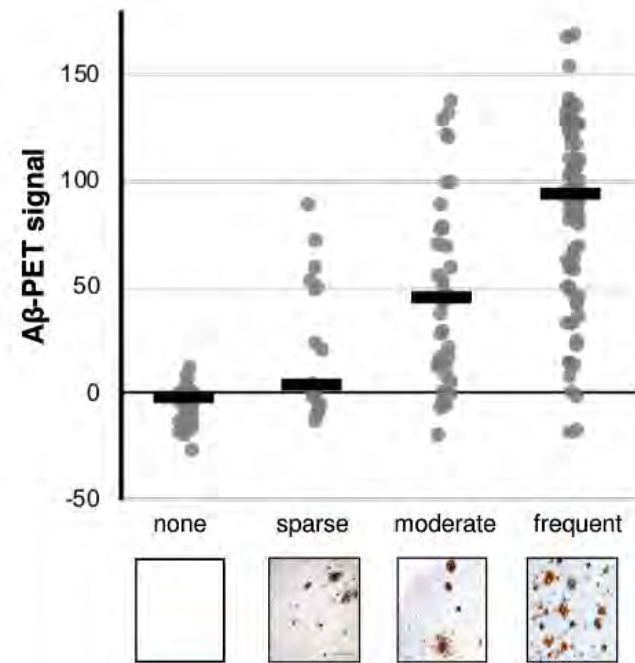
The intensity of the signal (how red it is) and the regional distribution (where the red is) usually does not correlate with symptoms.

β -Amyloid PET: validation against post mortem

Amyloid-PET signal increases with increasing amyloid pathology burden measured at autopsy (179 patients who died ~3 years after PET).

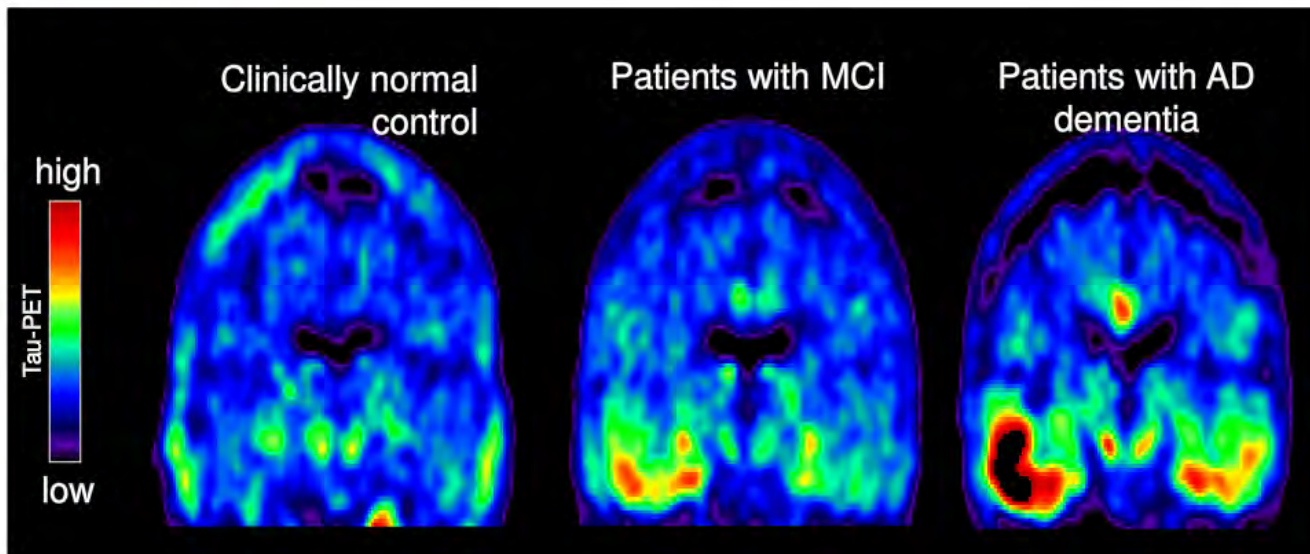


Thal phase



CERAD score

tau PET



Tau-PET signal goes up in AD

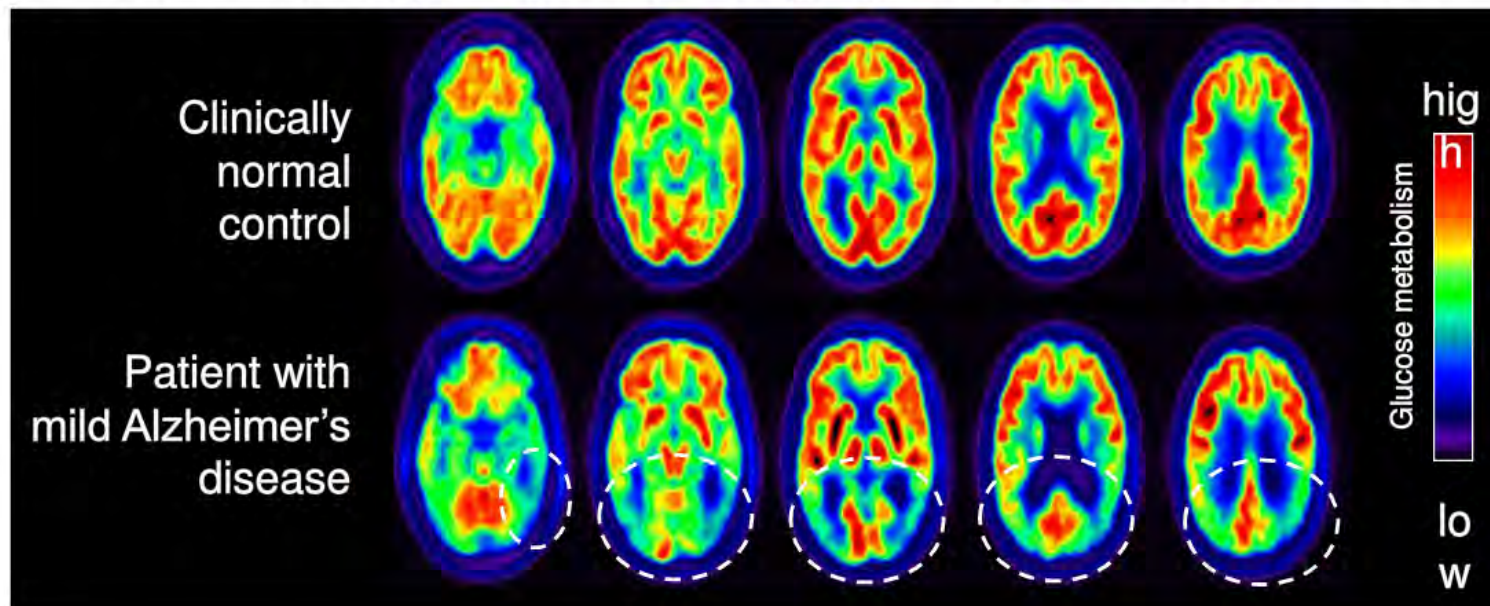
- Effect is focal in early disease stages.
- The severity and the regional distribution of the tau-PET parallel clinical progression.
- Highly elevated tau-PET signal is very specific to underlying AD pathology (versus other causes of cognitive deficits)

[¹⁸F]Fluorodeoxyglucose FDG-PET

Radio-labeled glucose that gets absorbed by highly metabolic cells

Glucose = main fuel for the brain (high energy demand to allow synaptic activity)

Normal scan: high signal in the grey matter, where neurons



Glucose metabolism goes down in AD (brain function ↓)

- Effect is pretty focal (posterior neocortex) in early disease stages
- The severity and the regional distribution of the hypometabolism parallel clinical progression
- Low FDG-PET signal reflects brain injury regardless of the underlying cause (not specific to AD)

Acknowledgements:

- Sergio Lanata
- Renaud La Joie
- Lea Grinberg
- Jamie Fong