WEEK 9

ALZHEIMER'S DISEASE

Learning objectives

- Know about
  - Pathophysiological stages of AD – spreading
  - Tau pathophysiology
  - Amyloid cascade
  - Diagnostic tools
  - Treatment options
- Be able to explain
  - Amyloid cascade hypothesis
  - Multiple hit hypothesis
  - Difficulties for finding AD treatments
  - Familial vs sporadic AD
  - Difficulties with animal models of the disease

Wordle

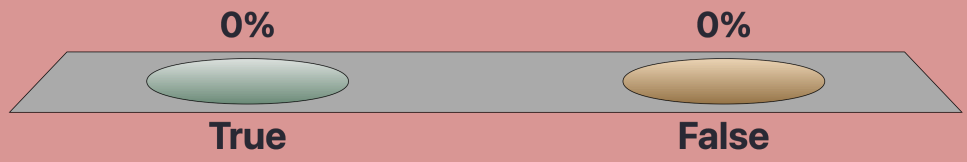

Familial
Aricept
Anomia
Apraxia
Multiple-Hit
Degeneration
Sporadic
Plaques
Tau
Agnosia
Fibrils
Acetylcholine
Glutamate
Dementia
ApoE4
Amyloid
Memantine
Aphasia
Braak
Amnesia
MMSE
BACE
Reserve
Ab42

Alzheimer's Disease – Overview

1) Check your knowledge about AD
2) Prevalence and history
3) Symptomatology
4) Pathophysiological hallmarks
   - Tau tangles
   - Amyloid plaques
5) Risk factors
   - Genes
   - Environment
6) Treatment approaches
7) Diagnostics and biomarkers

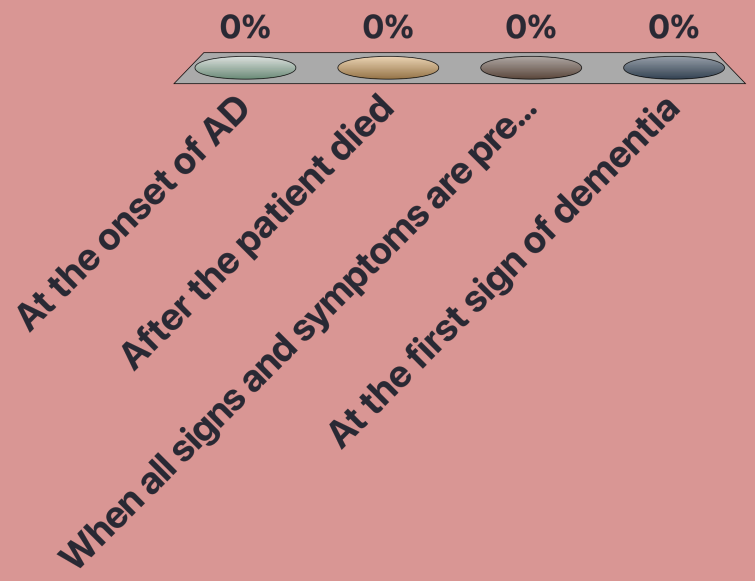
Alzheimer’s disease can be cured if detected early

A. True
B. False



At what time can a definite diagnosis of AD be made?

A. At the onset of AD
B. After the patient died
C. When all signs and symptoms are present
D. At the first sign of dementia

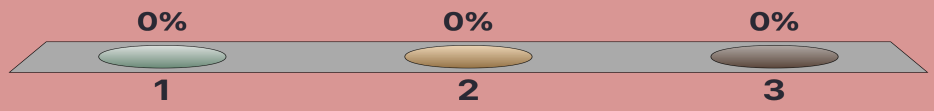


By 2080, how many of these students will have AD?

A. 1

B. 2

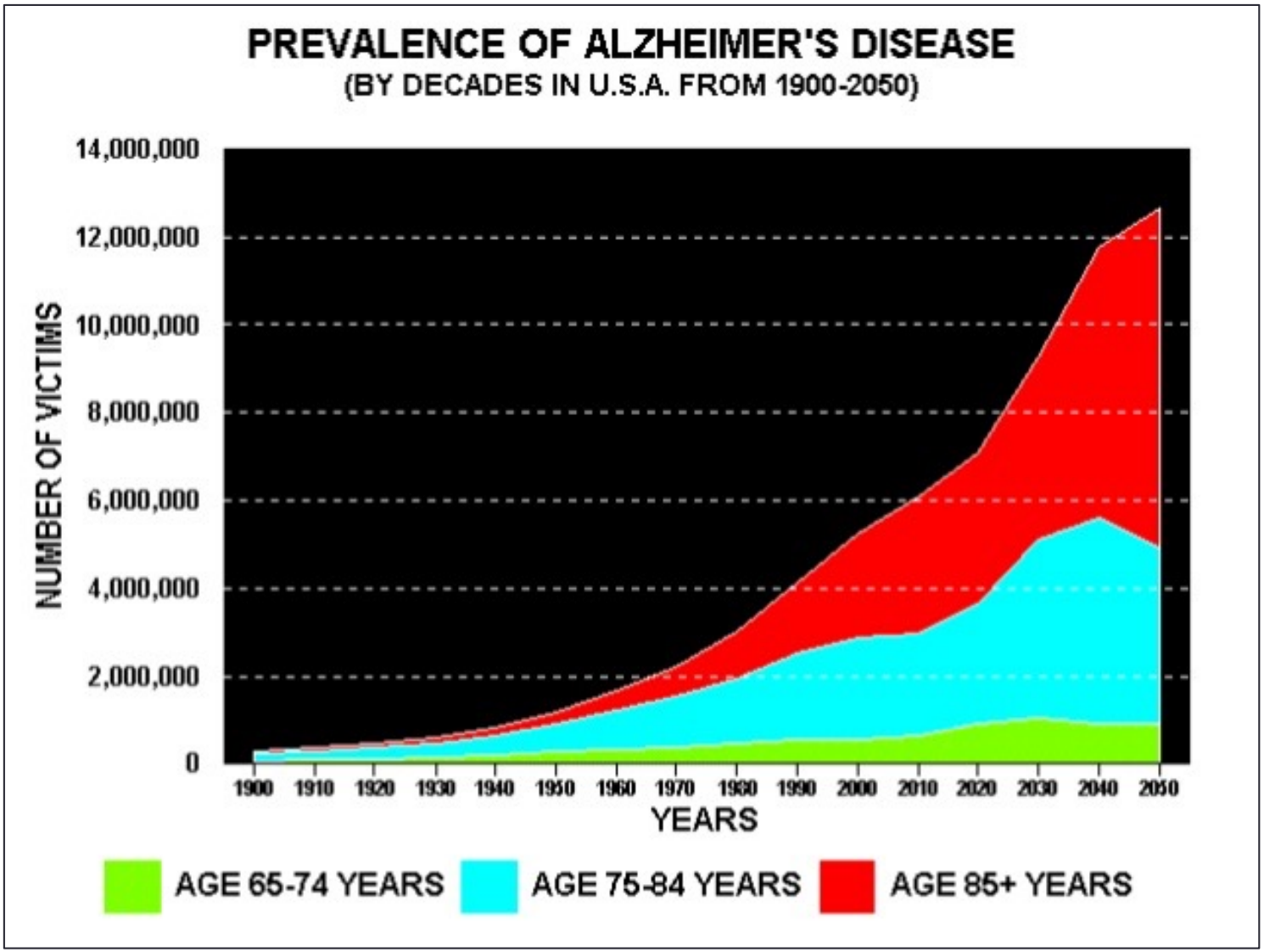
C. 3



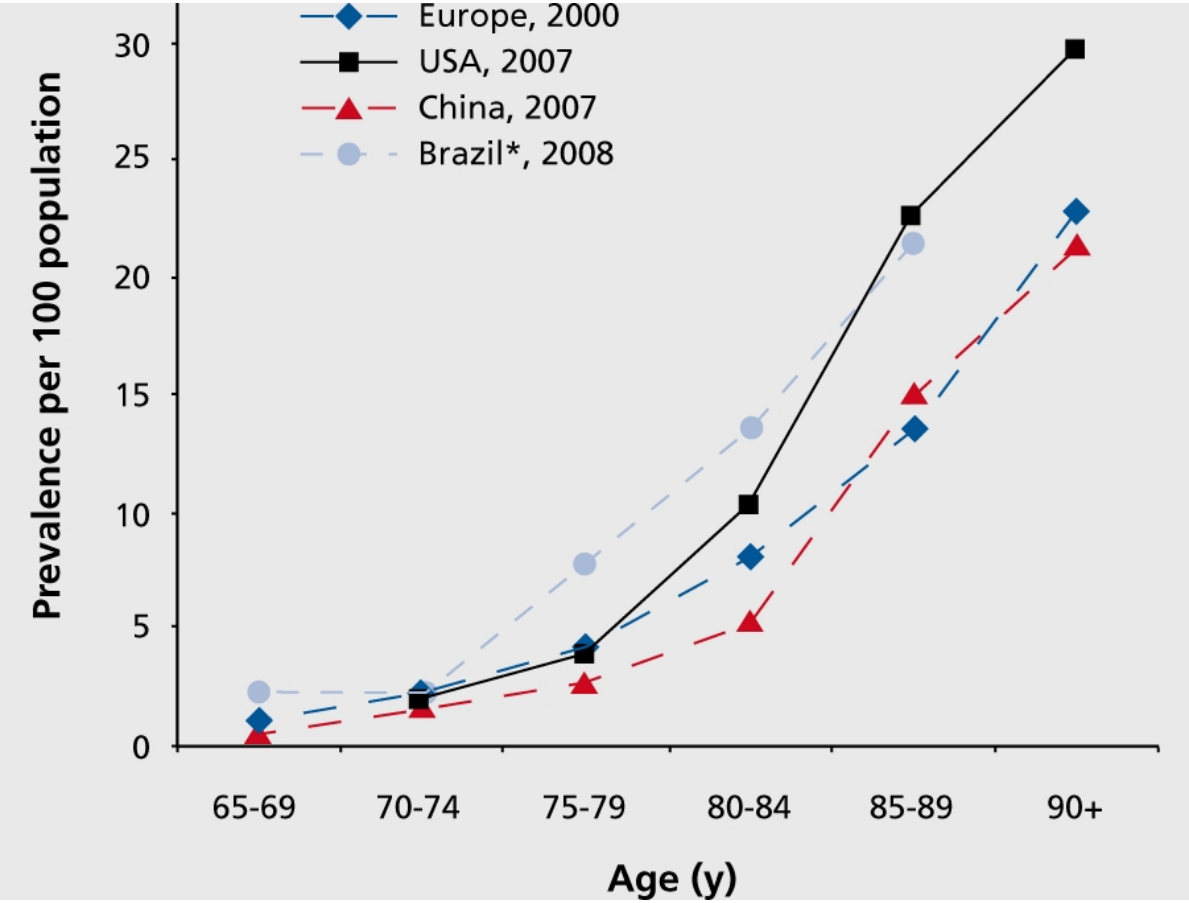
Alzheimer's Disease – Overview

1) Check your knowledge about AD
2) **Prevalence and history**
3) Symptomatology
4) Pathophysiological hallmarks
   - Tau tangles
   - Amyloid plaques
5) Risk factors
   - Genes
   - Environment
6) Treatment approaches
7) Diagnostics and biomarkers

Prevalence



Prevalence



Estimated cases in U.S.

Year	Patients (millions)
2010	5.8
2020	6.8
2030	8.7
2040	11.8
2050	14.3

Impact of AD

- AD is the 6th leading cause of death in the U.S. (Heart Disease is #1)
- Length of the disease is 3 – 20 years (average 9y)
- By 2029 all Baby Boomers (1946-1964) will be at least 65 – 10 million of the 78 million are predicted to develop AD.
- 2010 Cost of Care is estimated at $172 billion (Healthcare and Long Term Care)
- Other economic costs:
  - Cost to businesses – lost work time, absenteeism, leaves of absence, quitting work.

Impact of AD

It's the only cause of death in the top 10 in America that CANNOT BE PREVENTED, CURED OR SLOWED.

ALMOST TWO THIRDS of Americans with Alzheimer's disease are women.

SENIORS dies with Alzheimer's or another dementia.

Only **45%** of people with **ALZHEIMER'S** disease or their caregivers report **BEING TOLD OF THEIR DIAGNOSIS.**

More than **90%** of people with the four most common types of **CANCER** have been **TOLD OF THEIR DIAGNOSIS.**

By 2050, these costs could rise as high as **$1.1 TRILLION.**

In 2015, Alzheimer's and other dementias will cost the nation **$226 BILLION.**

Impact of AD in CH

- 3rd leading cause of death
- 160’000 people in CH live with dementia
- 35’000 new cases/y
- Cost of Care is estimated at CHF 12 billion/y

Impact of AD

- AD is by far the most common neurodegenerative disease!

Neurodegenerative Disease	Identifier	Frequency in US	Genetic?
Parkinson's	James Parkinson 1817	500 K	low
Alzheimer's	Alois Alzheimer 1906	5.4 million	moderate
Huntington's	George Huntington 1872	30 K	high
ALS	Jean Martin Charcot	25 K	low

History of AD:

- Alois Alzheimer
  - German psychiatrist
  - Described symptoms + pathology
    - Neuronal loss
    - Plaques
    - Tangles
  - Patient Mrs. Auguste Deter

1864-1913

Prevalence and history

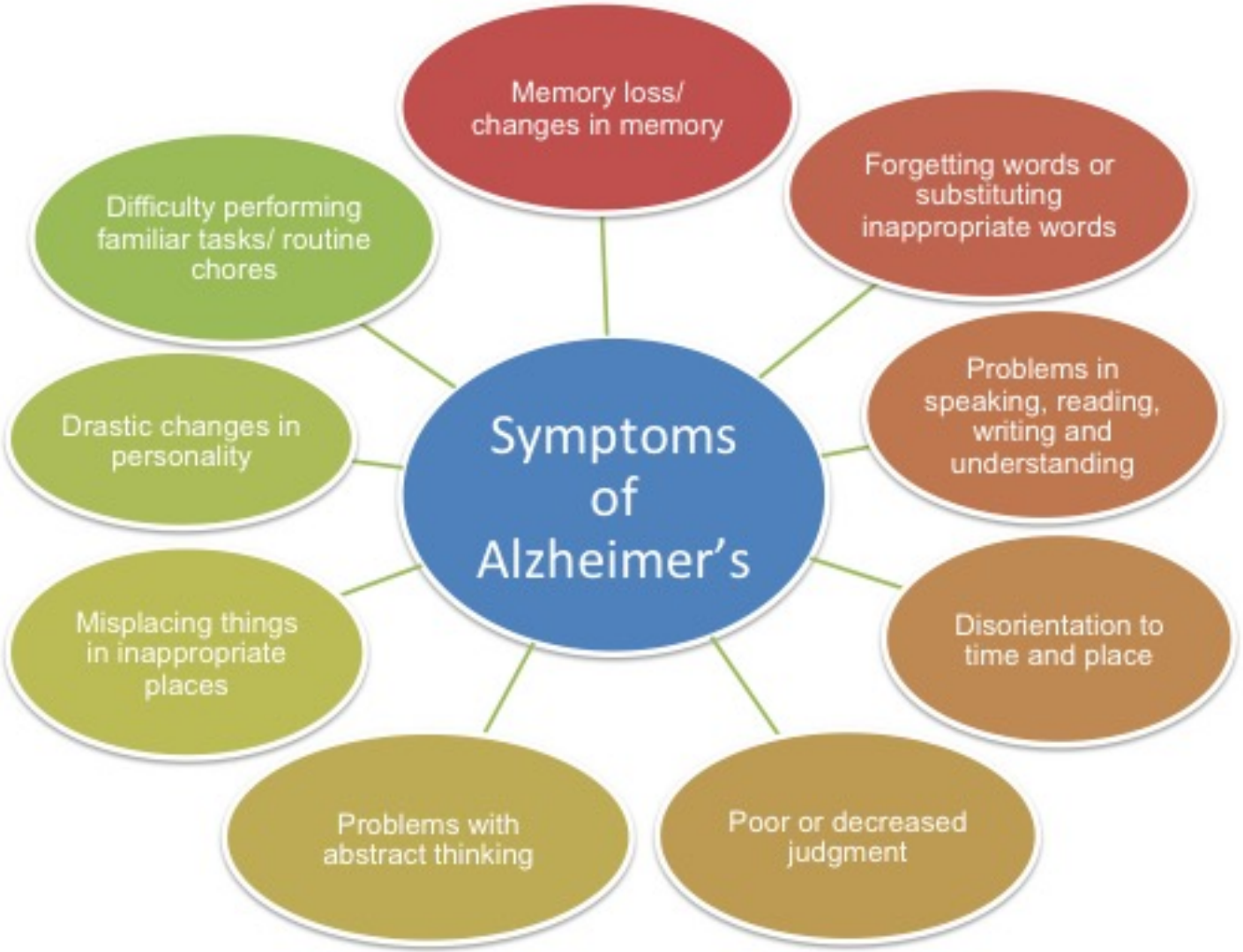
Alzheimer first met his now famous patient, Mrs Deter, on November 26, 1901. She had been admitted the day before to municipal mental asylum in Frankfurt. She was sitting on the bed with a helpless expression. According to the husband, the couple had been harmoniously married since 1873, but he had recently noticed a gradual decline in his wife. Her symptoms began at age 51 years. For 8 months she had been developing progressive changes in her personality. She presented with ideas of jealousy toward her husband, a rapidly worsening memory weakness and pronounced psychosocial impairment; sometimes she felt that someone wanted to kill her and began to shout wildly. At the clinic, she was disorientated to time and place and confused. Over time, her state generally worsened. Her speech became completely unintelligible. In her final year, she was totally apathetic and spent most of her time in bed with legs pulled up.

1851-1906

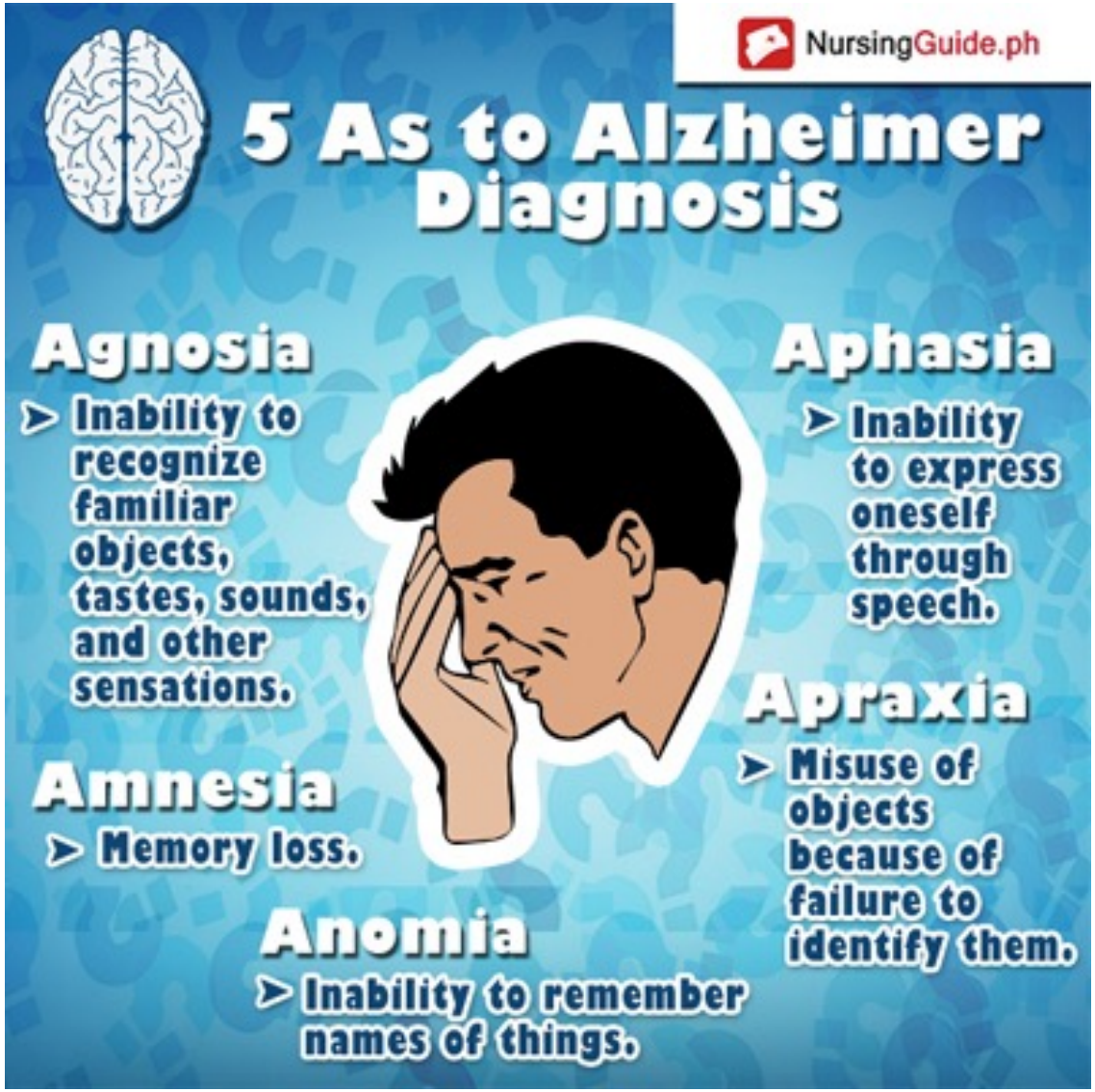
Alzheimer's Disease – Overview

1) Check your knowledge about AD
2) Prevalence and history
3) **Symptomatology**
4) Pathophysiological hallmarks
   - Tau tangles
   - Amyloid plaques
5) Risk factors
   - Genes
   - Environment
6) Treatment approaches
7) Diagnostics and biomarkers

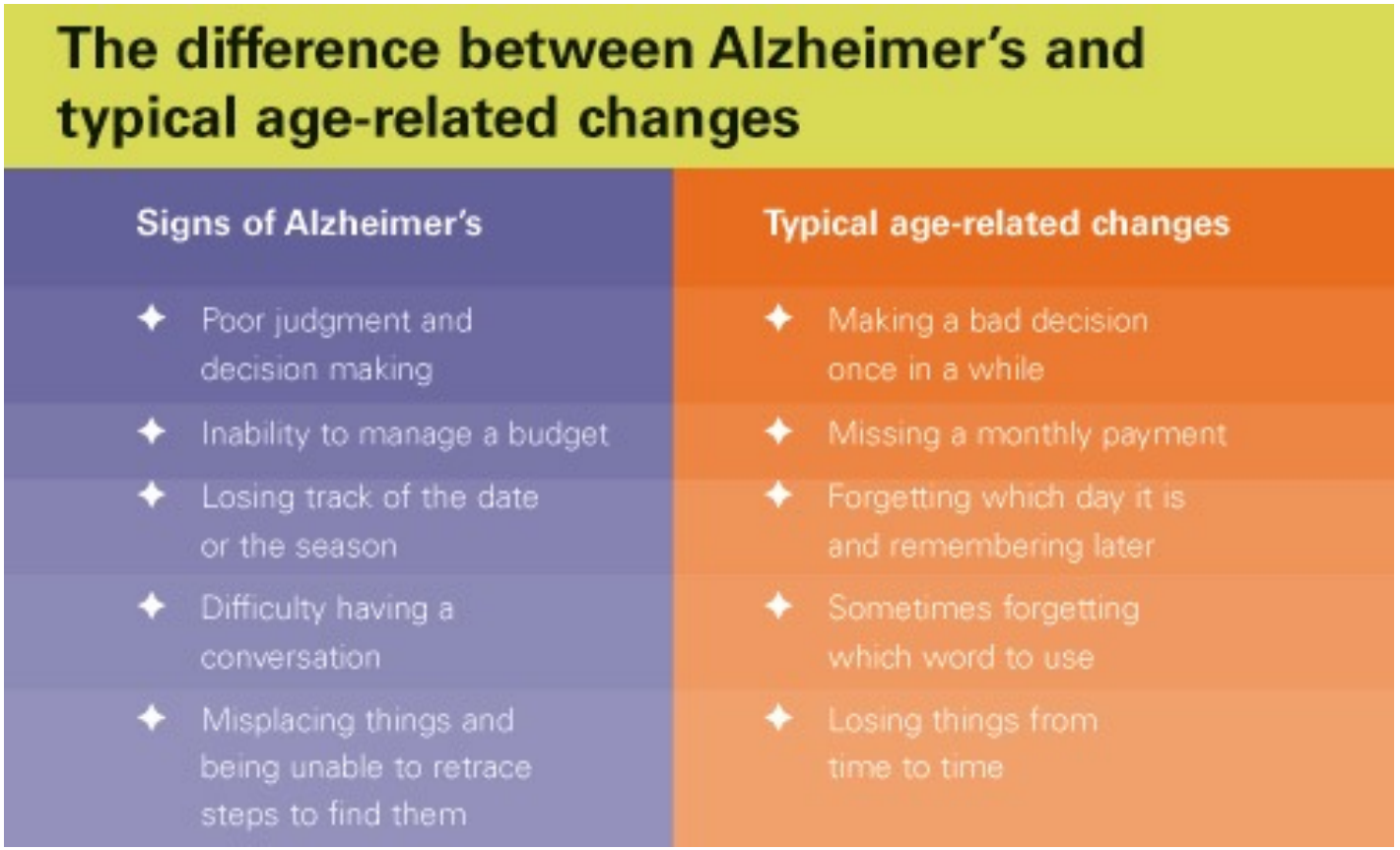
Symptoms of AD



Symptoms of AD



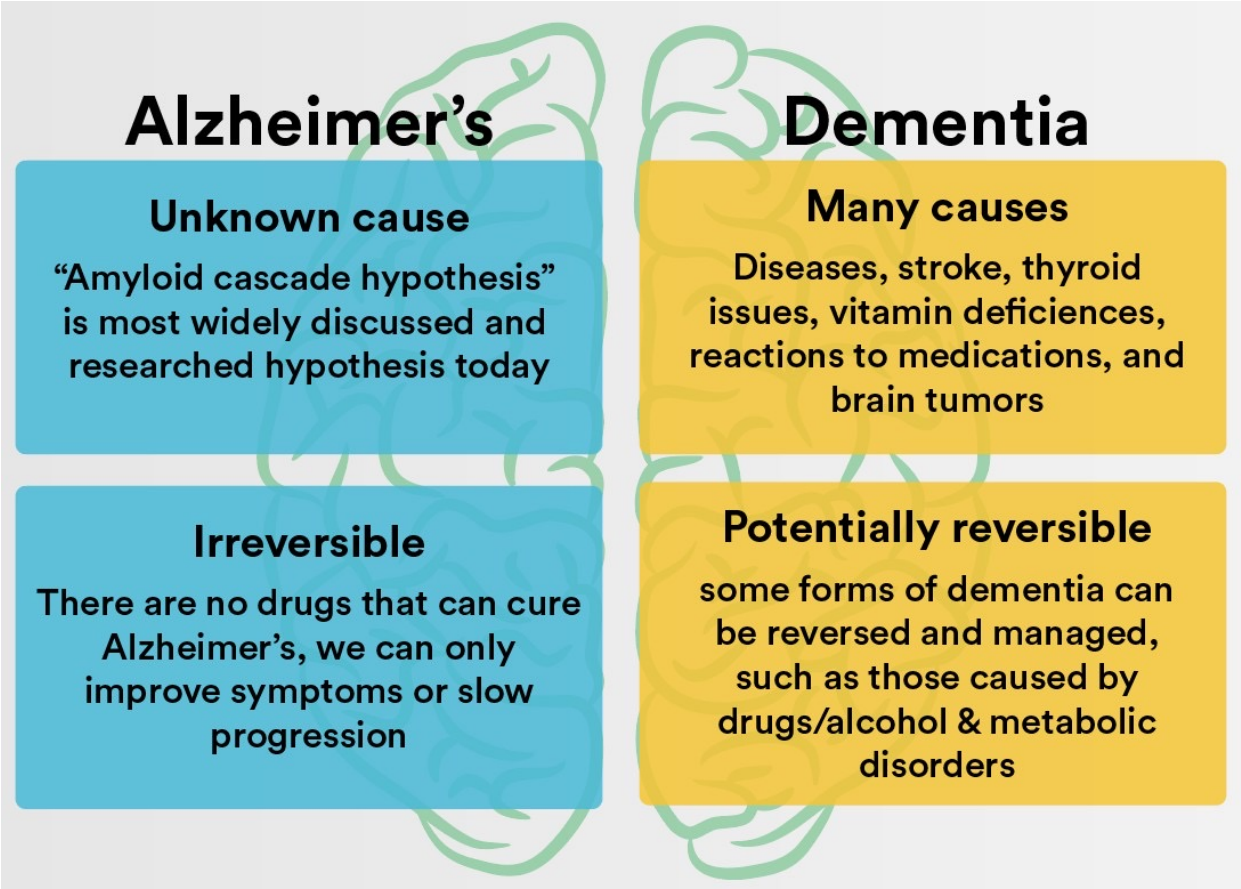
Difference between AD and non-AD, age-related dementia



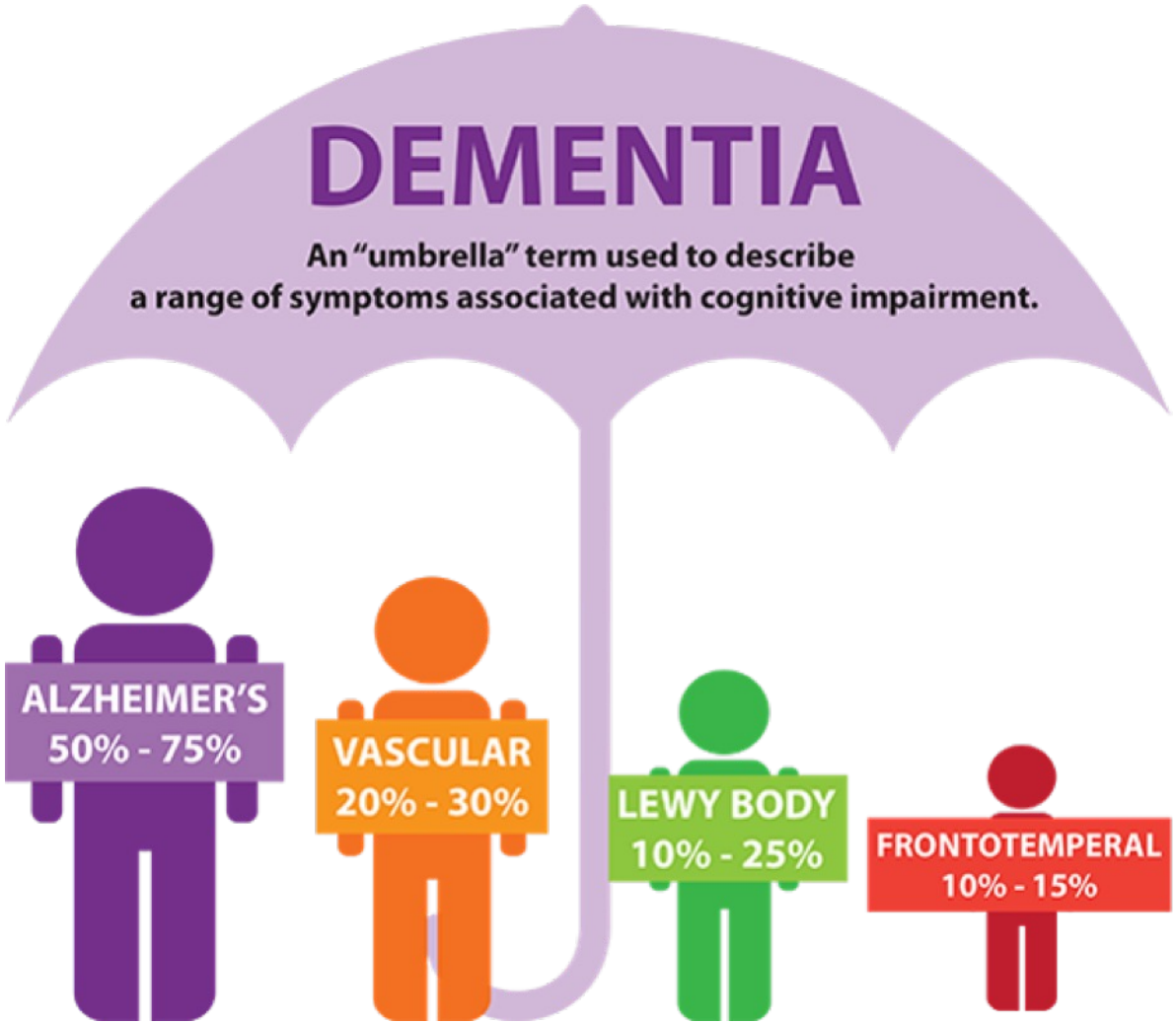
The difference between Alzheimer's and typical age-related changes

Signs of Alzheimer's	Typical age-related changes
✦ Poor judgment and decision making	✦ Making a bad decision once in a while
✦ Inability to manage a budget	✦ Missing a monthly payment
✦ Losing track of the date or the season	✦ Forgetting which day it is and remembering later
✦ Difficulty having a conversation	✦ Sometimes forgetting which word to use
✦ Misplacing things and being unable to retrace steps to find them	✦ Losing things from time to time

Difference between AD and non-AD, age-related dementia



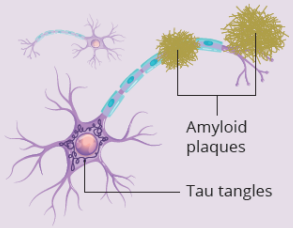
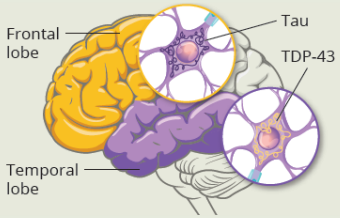
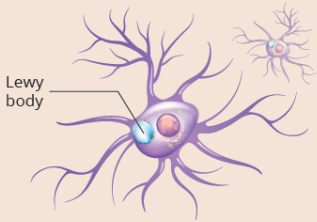
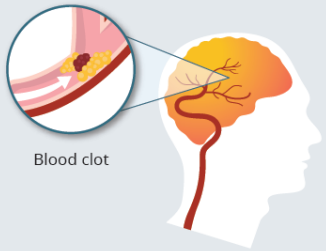
Of note: Other types of dementia



Of note: Other types of dementia

- **Alzheimer's disease**
  - most common
- **Vascular dementia**
  - stroke related, 2nd most common type of dementia
- **Dementia with Lewy Body**
  - Lewy bodies are deposits of a protein called alpha-synuclein that form inside the brain's nerve cells. Affects memory, concentration, speech.
- **Frontotemporal dementia**
  - a rare disorder that affects the frontal lobes and the temporal lobes of the brain. Affects behavior, personality and memory late in life.

TYPES OF DEMENTIA

Alzheimer's Disease	Frontotemporal Dementia	Lewy Body Dementia	Vascular Dementia
What Is Happening in the Brain?*			
Abnormal deposits of proteins form amyloid plaques and tau tangles throughout the brain. 	Abnormal amounts or forms of tau and TDP-43 proteins accumulate inside neurons in the frontal and temporal lobes. 	Abnormal deposits of the alpha-synuclein protein, called "Lewy bodies," affect the brain's chemical messengers. 	Conditions, such as blood clots, disrupt blood flow in the brain. 
*These changes are just one piece of a complex puzzle that scientists are studying to understand the underlying causes of these forms of dementia and others.			
Symptoms			
Mild • Wandering and getting lost • Repeating questions **Moderate** • Problems recognizing friends and family • Impulsive behavior **Severe** • Cannot communicate	**Behavioral and Emotional** • Difficulty planning and organizing • Impulsive behaviors • Emotional flatness or excessive emotions **Movement Problems** • Shaky hands • Problems with balance and walking **Language Problems** • Difficulty making or understanding speech *There are several types of frontotemporal disorders, and symptoms can vary by type.*	**Cognitive Decline** • Inability to concentrate, pay attention, or stay alert • Disorganized or illogical ideas **Movement Problems** • Muscle rigidity • Loss of coordination • Reduced facial expression **Sleep Disorders** • Insomnia • Excessive daytime sleepiness **Visual Hallucinations**	• Forgetting current or past events • Misplacing items • Trouble following instructions or learning new information • Hallucinations or delusions • Poor judgment
Typical Age of Diagnosis			
Mid 60s and above, with some cases in mid-30s to 60s	Between 45 and 64	50 or older	Over 65

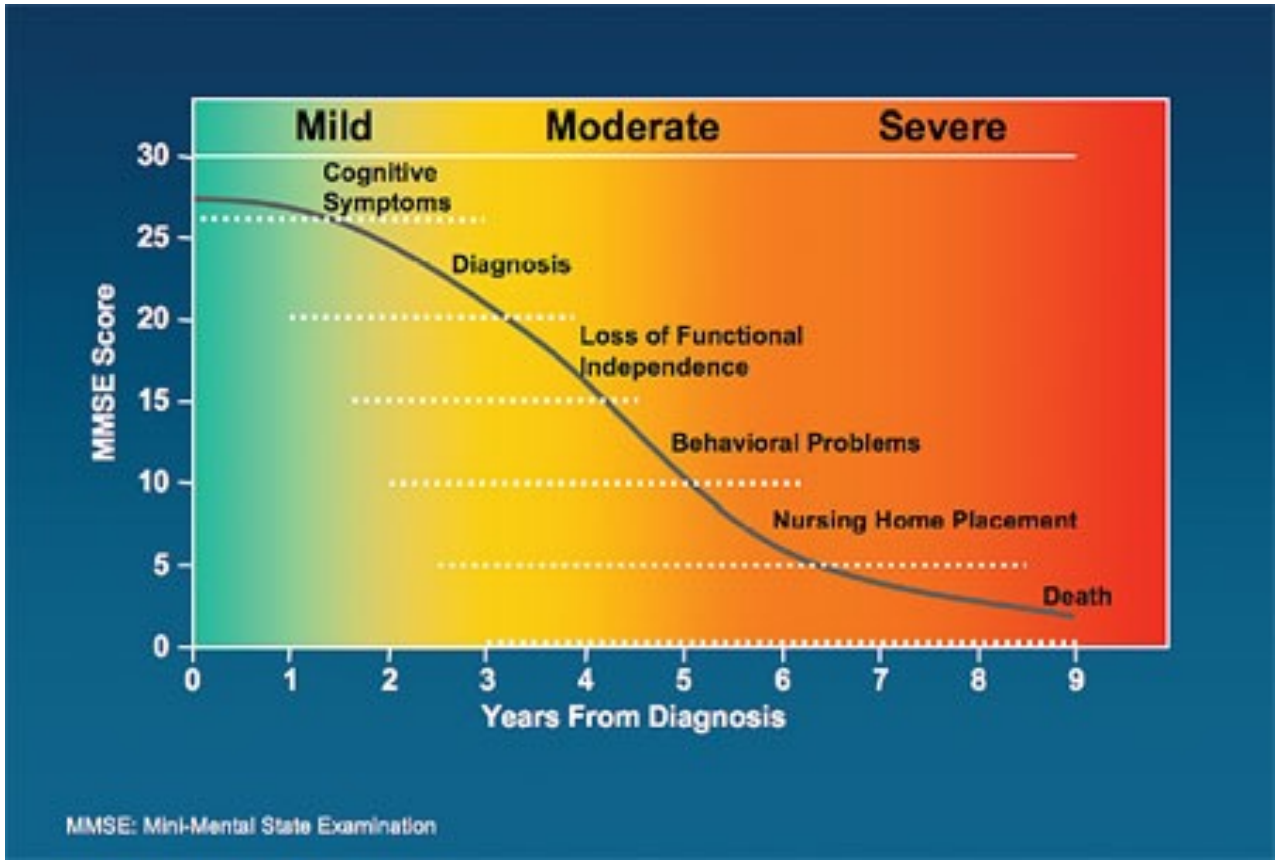
Diagnosis

Symptoms can be similar among different types of dementia, and some people have more than one form of dementia, which can make an accurate diagnosis difficult. Symptoms can also vary from person to person. Doctors may ask for a medical history, complete a physical exam, and order neurological and laboratory tests to help diagnose dementia.

Treatment

There is currently no cure for these types of dementia, but some treatments are available. Speak with your doctor to find out what might work best for you.

Main symptom: Cognitive decline



How to test cognitive decline: Mini mental state examination test

The mini mental state examination

Orientation

Year, month, day, date. season _____/5
Country, county, town, hospital, ward (clinic) _____/5

Registration

Examiner names three objects (for example, apple, pen, and table)
Patient asked to repeat objects, one point for each. _____/3

Attention

Subtract 7 from 100 then repeat from result, stop after five subtractions. (Answers: 93, 86, 79, 72, 65)
Alternatively if patient errs on subtraction get them to spell world backwards: D L R O W
Score best performance on either task. _____/5

Recall

Ask for the names of the objects learned earlier. _____/3

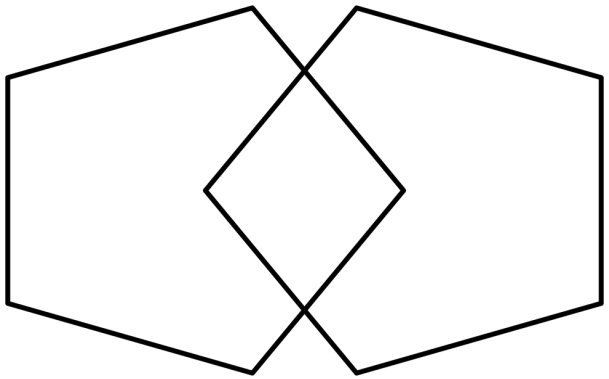
Language

Name a pencil and a watch. _____/2
Repeat: 'No ifs, and or buts.' _____/1
Give a three stage command. Score one for each stage (for example, 'Take this piece of paper in your right hand, fold it in half and place it on the table.' _____/3
Ask patient to read and obey a written command on a piece of paper stating: 'Close your eyes.' _____/1
Ask patient to write a sentence. Score correct if it has a subject and a verb. _____/1

Copying

Ask patient to copy intersecting pentagons.
Score as correct if they overlap and each has five sides. _____/1

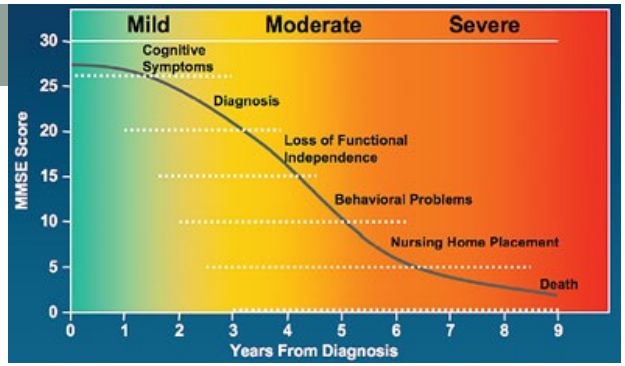
Total score: _____/30



Mini mental state examination test

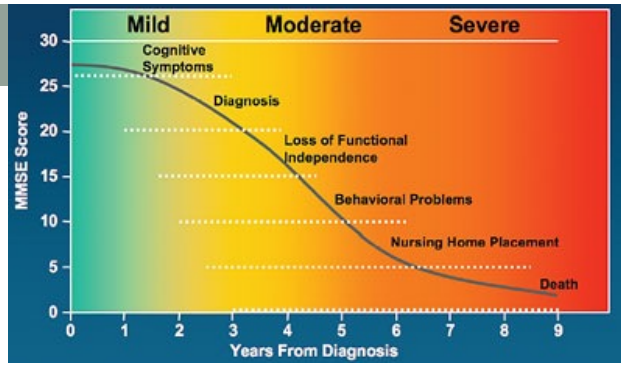
MMSE Score	Cognitive Function
27-30	normal cognitive function
21-26	mild cognitive impairment
11-20	moderate cognitive impairment
0-10	severe cognitive impairment

Stages of cognitive decline



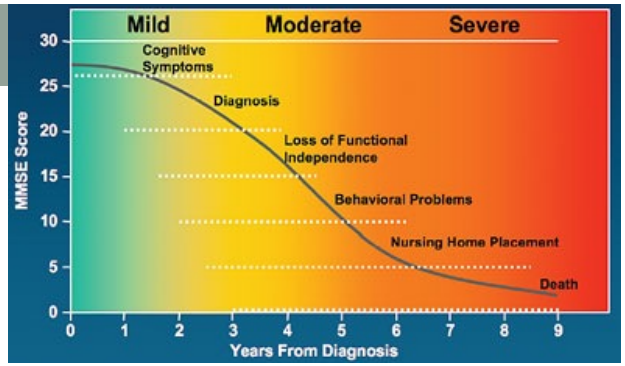
- **Mild or Early Stage (Mild cognitive impairment, MCI)**
  - Friends, family or co-workers begin to notice deficiencies:
    - Word finding problems
    - Decreased ability to remember names
    - Performance issues in social or work settings
    - Reading a passage and retaining little material
    - Losing or misplacing a valuable object
    - Decline in ability to plan or organize

Stages of cognitive decline



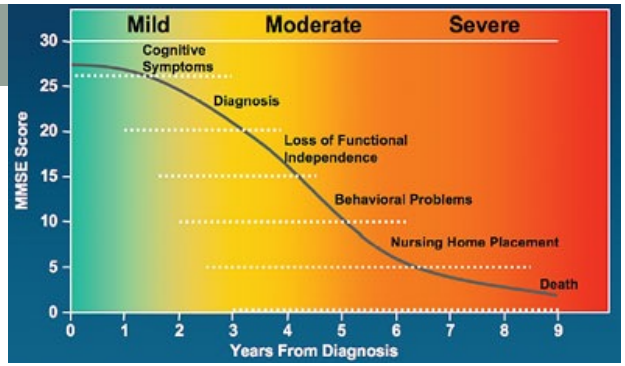
- **Moderate or Middle Stage**
  - Major gaps in memory and deficits in cognitive function emerge.
  - Assistance with day-to-day activities becomes essential.
  - Deficits include:
    - Inability to recall important details such as their current address, their telephone number.
    - Confused about where they are or about the date, day of the week or season.
    - Need help choosing proper clothing for the season or the occasion.
    - May have increasing episodes of urinary or fecal incontinence and need assistance with toileting and personal care.

Stages of cognitive decline



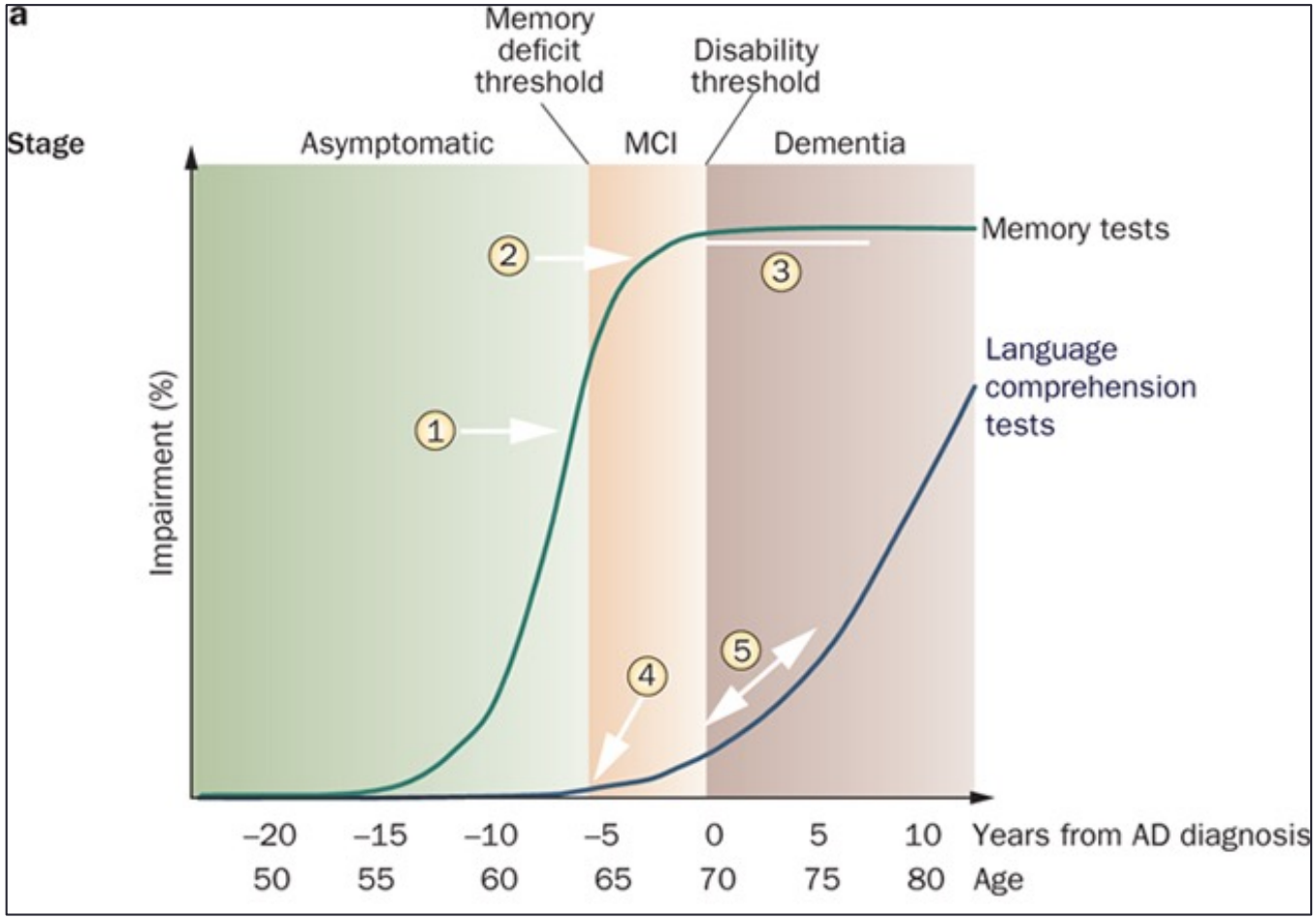
- **Moderate or Middle Stage**
  - Deficits c'd:
    - Lose most awareness of recent experiences and events as well as of their surroundings.
    - Tend to wander and become lost.
    - Experience significant personality changes and behavioral symptoms.
    - Including suspiciousness and delusions (for example, believing that their caregiver is an impostor)
    - Hallucinations (seeing or hearing things that are not really there)
    - Compulsive, repetitive behaviors such as hand-wringing or tissue shredding

Stages of cognitive decline

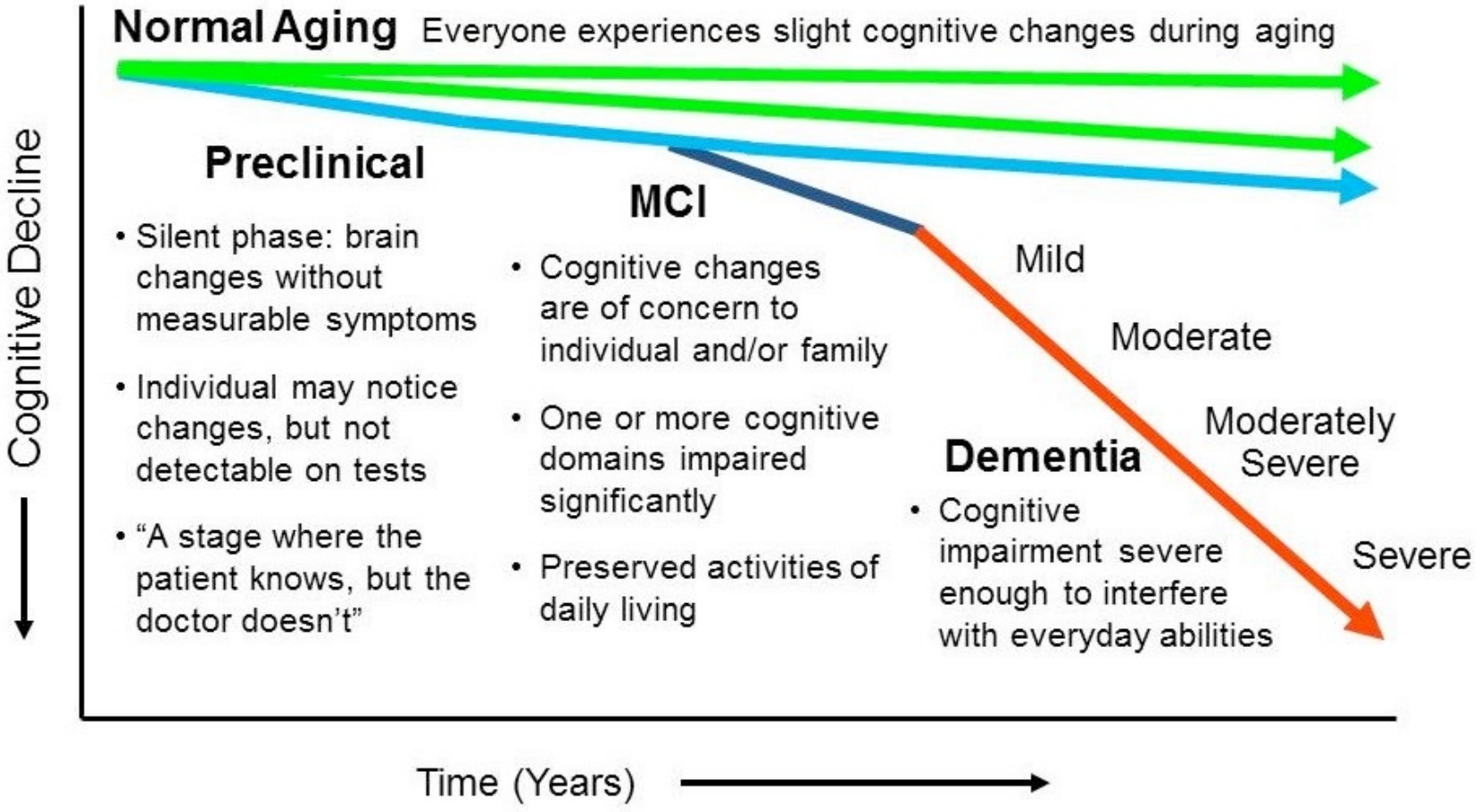


- **Severe or late stage**
  - Need full assistance with eating and toileting; general incontinence.
  - Frequent loss of recognizable speech, although words or phrases may occasionally be uttered.
  - Reflexes become abnormal and muscles grow rigid
  - Individuals lose the ability to:
    - walk without assistance
    - sit without support
    - hold their head up
    - swallowing

Stages of cognitive decline



Stages of cognitive decline



https://www.mind.uci.edu/dementia/mild-cognitive-impairment/

What are the main characteristics of Alzheimer's Disease?

Alzheimer's Disease – Overview

1) Check your knowledge about AD
2) Prevalence and history
3) Symptomatology
4) **Pathophysiological hallmarks**
   - Tau tangles
   - Amyloid plaques
5) Risk factors
   - Genes
   - Environment
6) Treatment approaches
7) Diagnostics and biomarkers

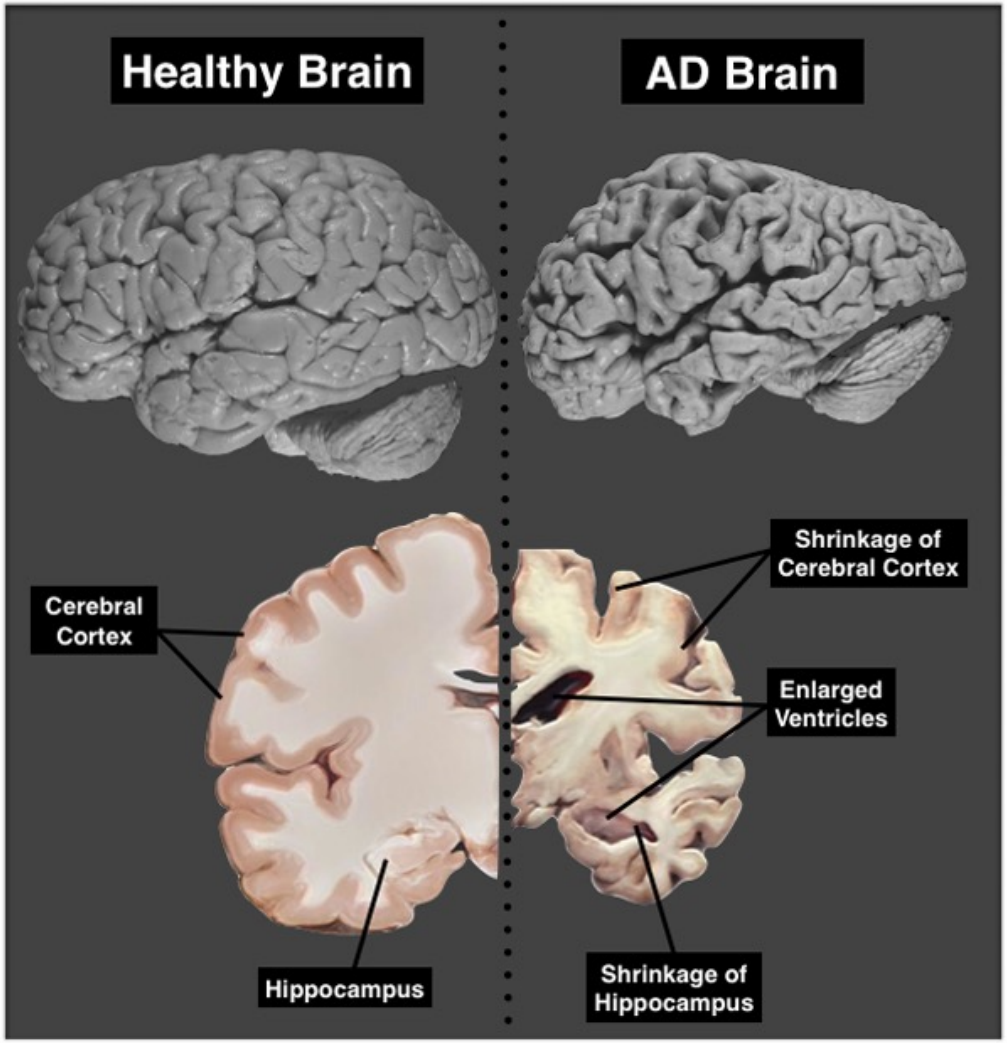
Alzheimer's Disease – Definition

- Alzheimer's Disease (AD) is a progressive, degenerative and incurable neurological brain disease that causes deterioration of brain nerve cells and ultimately death.

- The deterioration is caused by:
  - Build up of abnormal substances called **amyloid plaques.**
  - Build up of abnormal substances called **neurofibrillary tangles**.
  - Severe neurodegeneration (i.e., **neuronal loss**).

Pathophysiological hallmarks

1) **Neuronal loss:**
   - Retraction (shriveling) of the **cortex**: Damaging areas involved in thinking, planning and remembering.
   - Shrinkage is also especially severe in the **hippocampus**, a brain area that plays a key role in formation of new memories.
   - **Ventricles** (cerebrospinal fluid-filled spaces within the brain) grow large



Brain shrinkage:

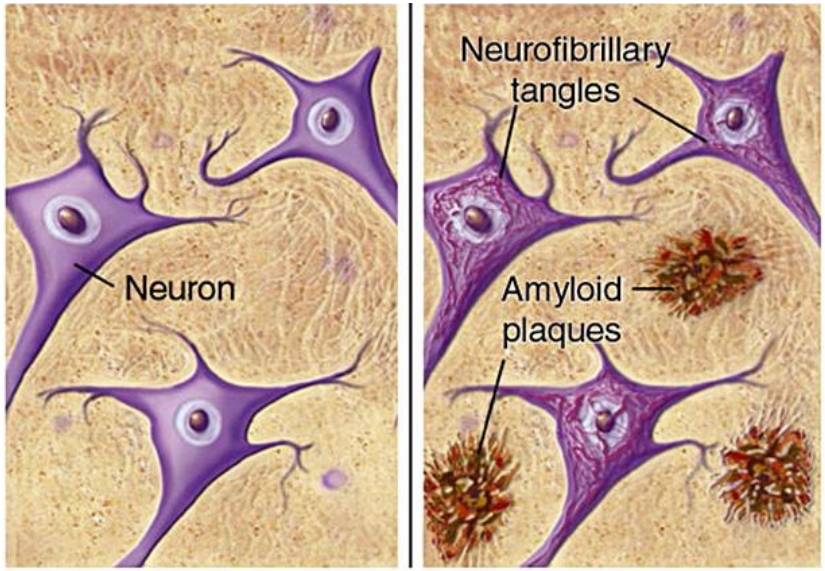
Pathophysiological hallmarks

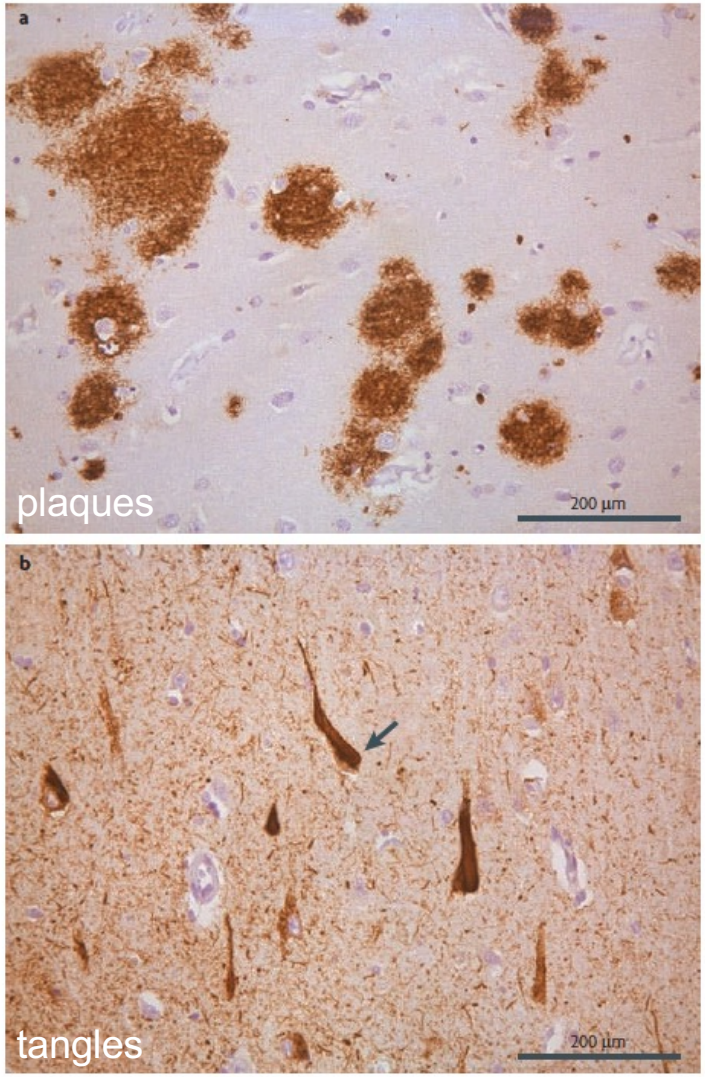
2) **Neurofibrillary tangles**

= intracellular accumulation of Tau protein

3) **Amyloid plaques**

= extracellular aggregates of β-amyloid



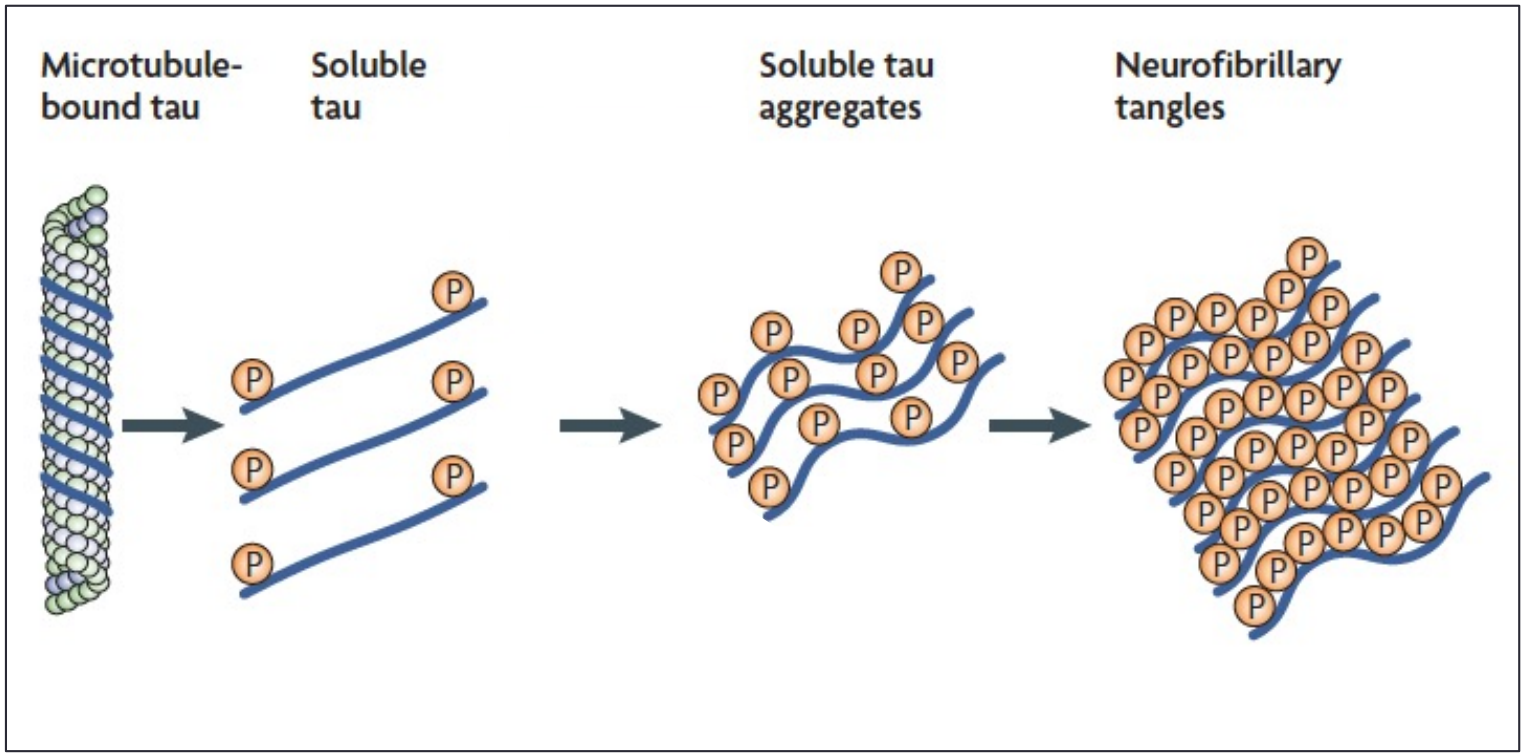


Alzheimer's Disease – Overview

1) Check your knowledge about AD
2) Prevalence and history
3) Symptomatology
4) **Pathophysiological hallmarks**
   - **Tau tangles**
   - Amyloid plaques
5) Risk factors
   - Genes
   - Environment
6) Treatment approaches
7) Diagnostics and biomarkers

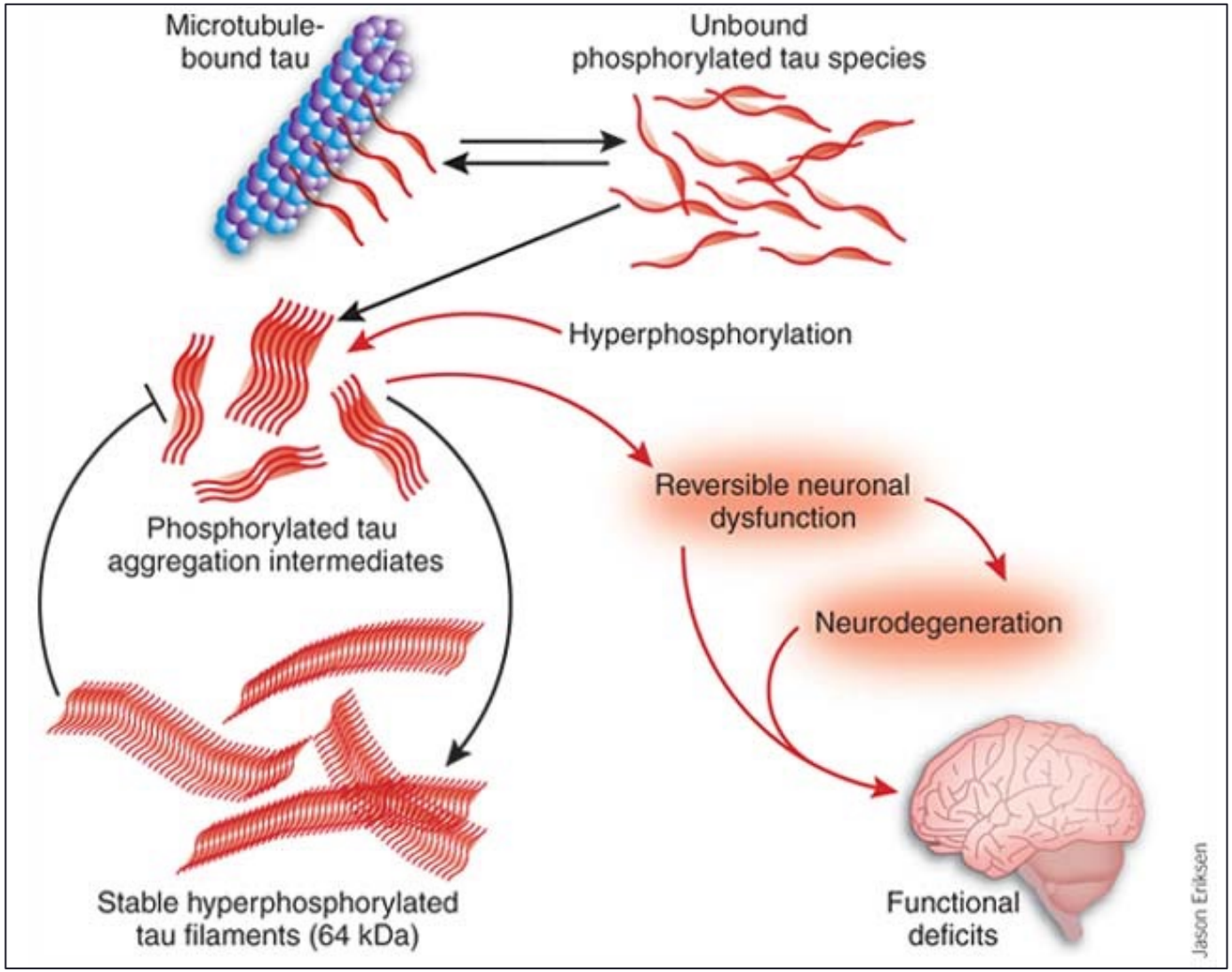
Pathophysiology: Tau Tangles

- Hyperphosphorylation of tau protein leads to aggregation



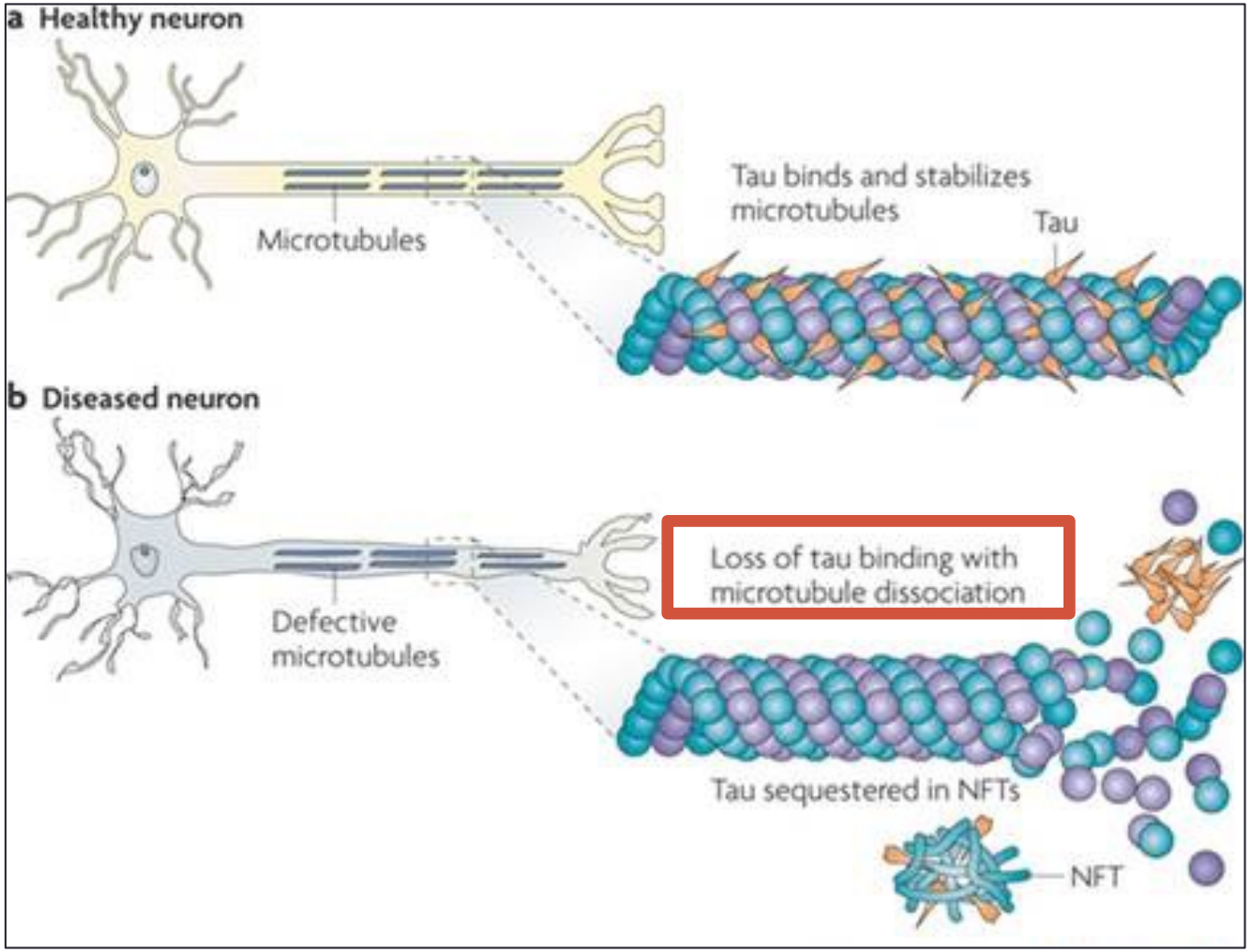
potential treatment strategies

Pathophysiology: Tau Tangles

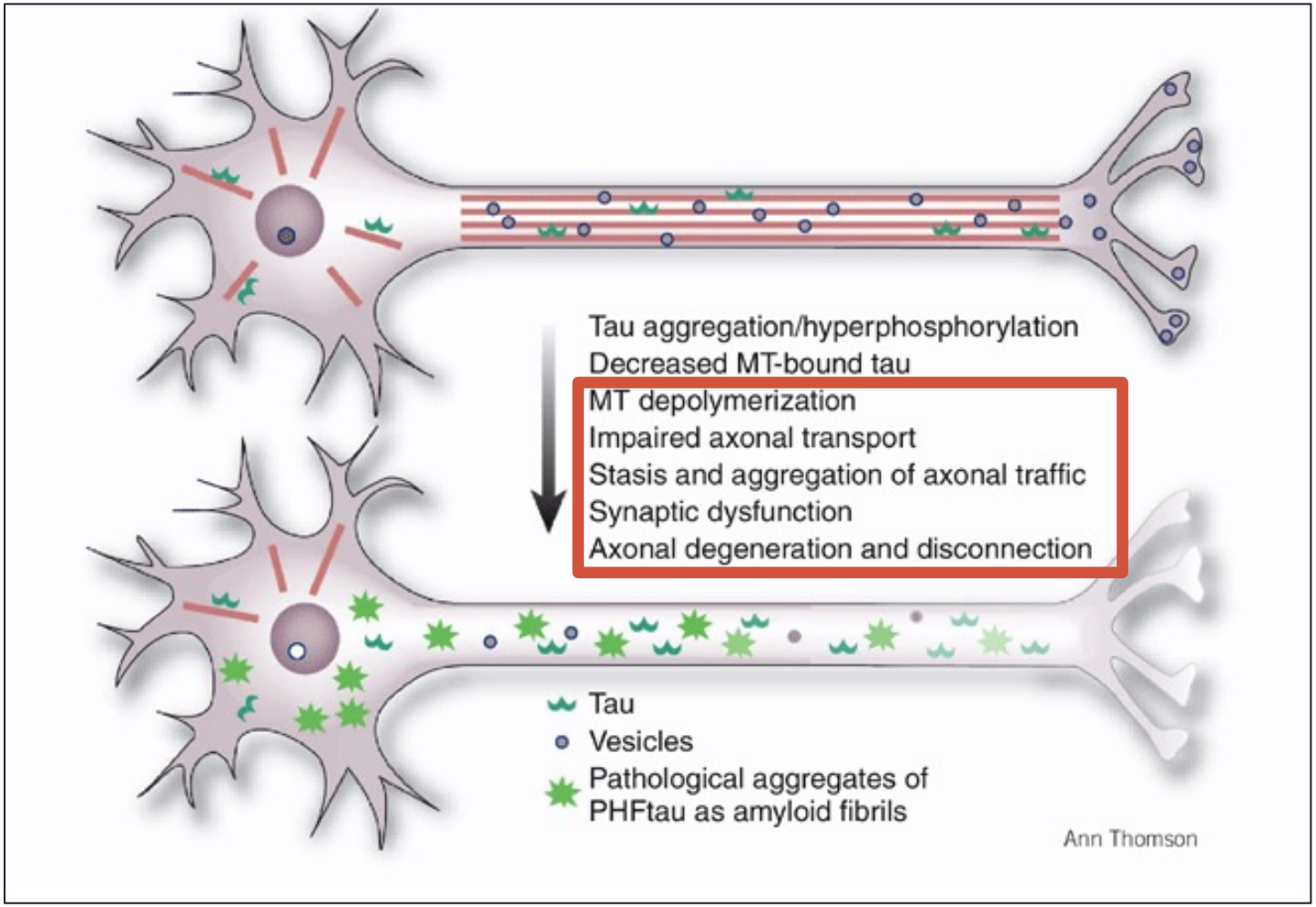


Paired helical filaments

Pathophysiology: Effect of Tau Tangles

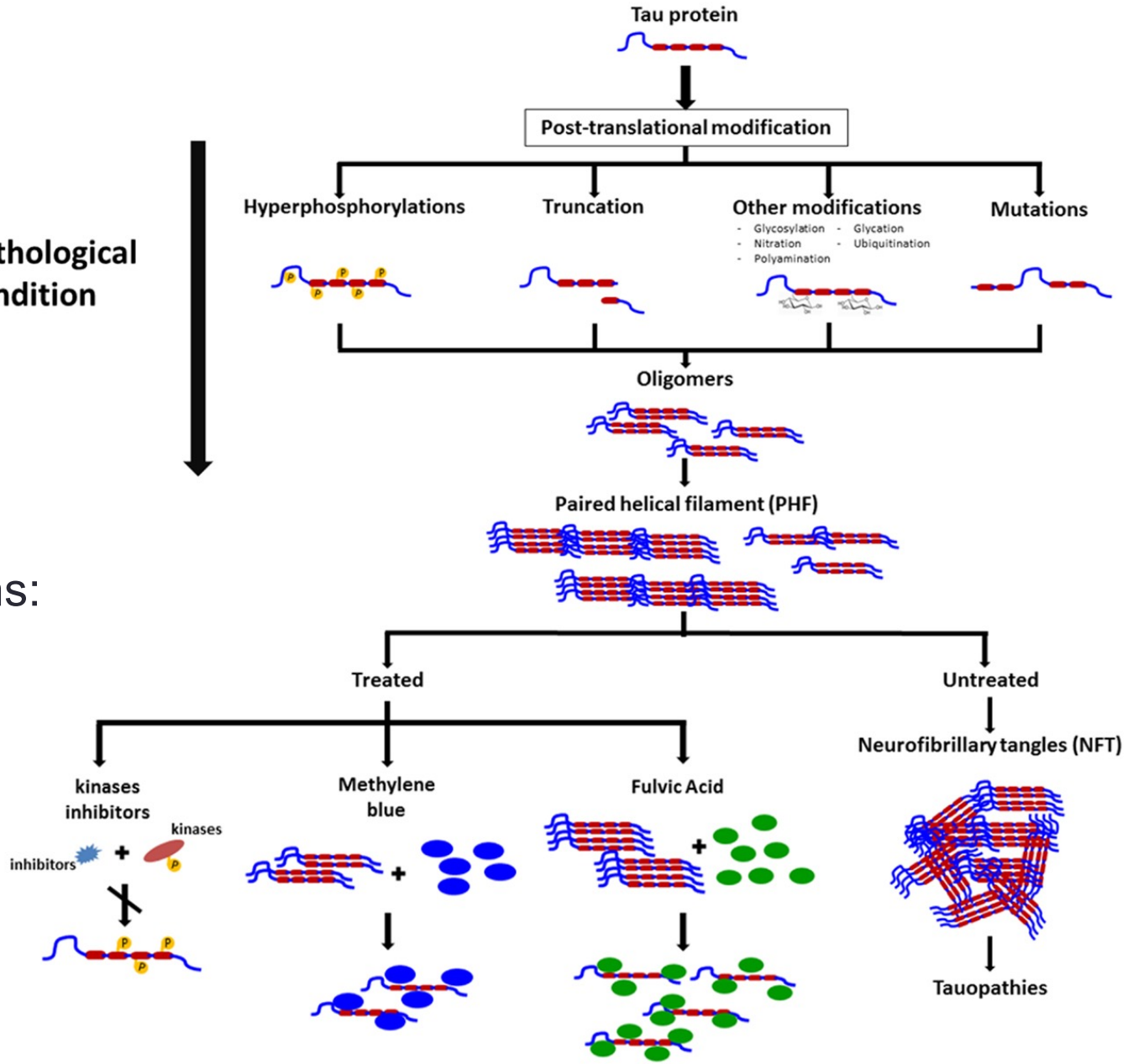


Pathophysiology: Effect of Tau Tangles



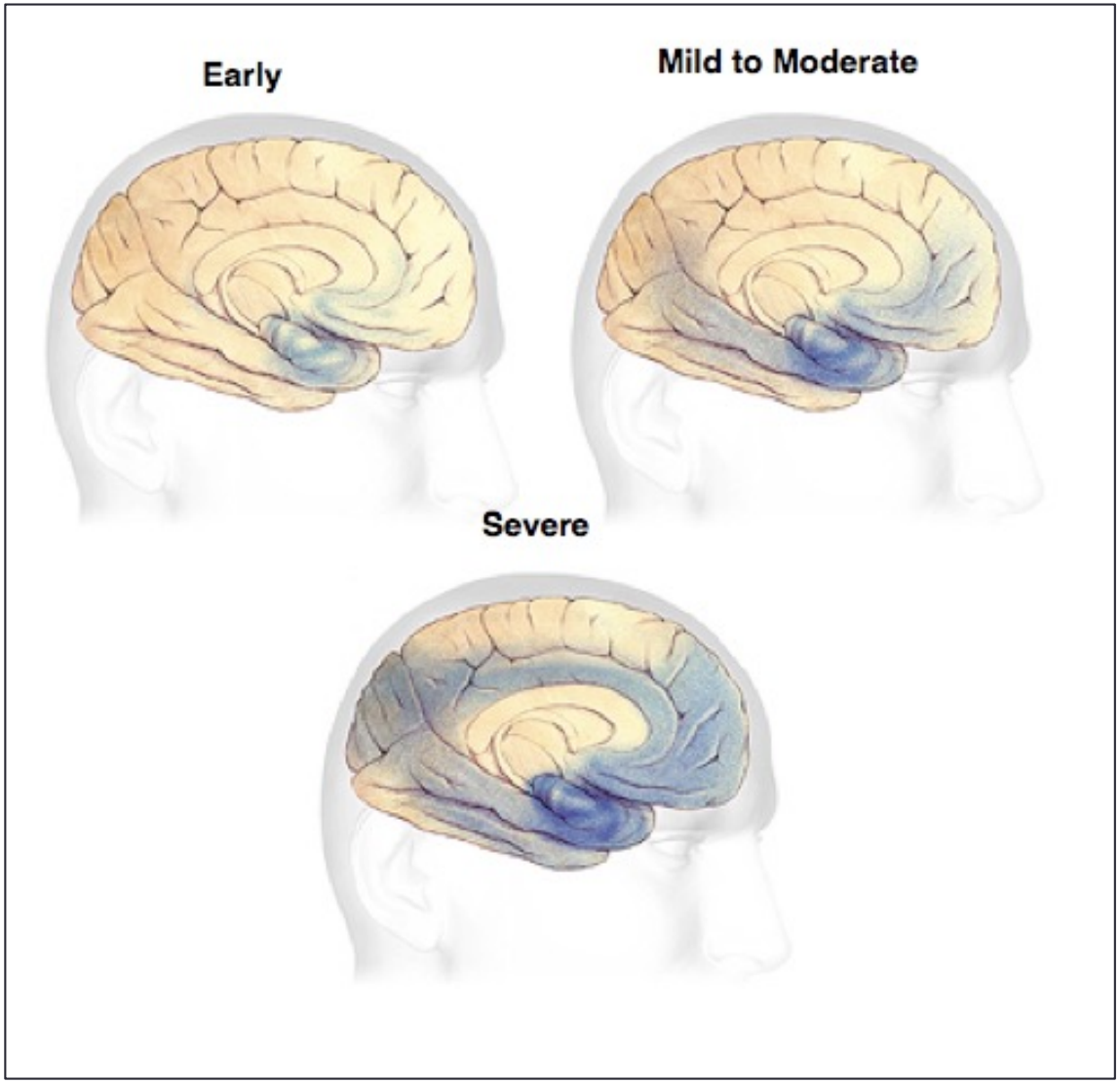
Tau: Other pathological modifications

- Other tau modifications:
  - Truncation
  - Mutations
  - Other modifications:
    - Glycosylation
    - Nitration
    - Ubiquitination
    - Polyamination

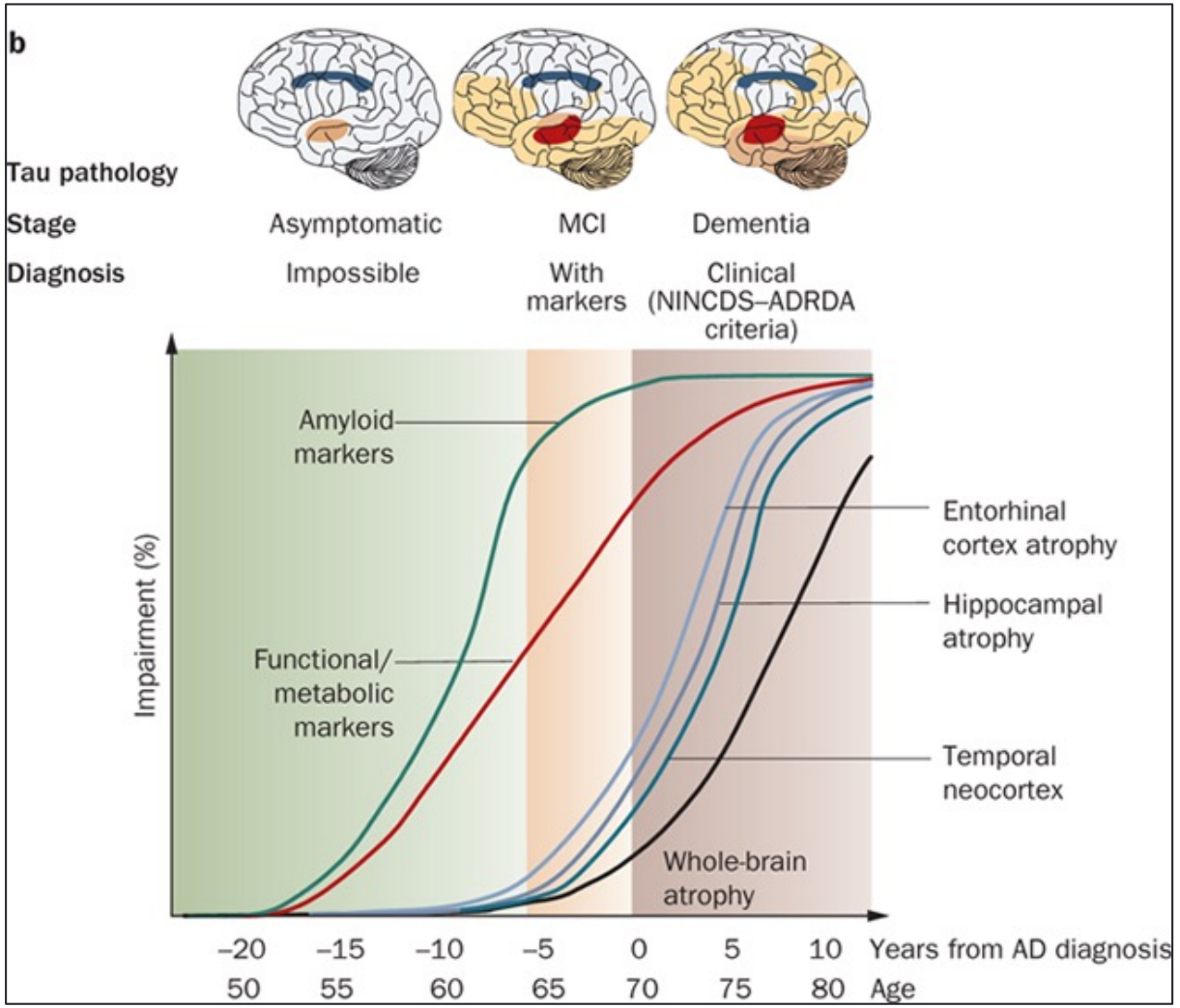


Why does AD get worse with time?

Spreading!

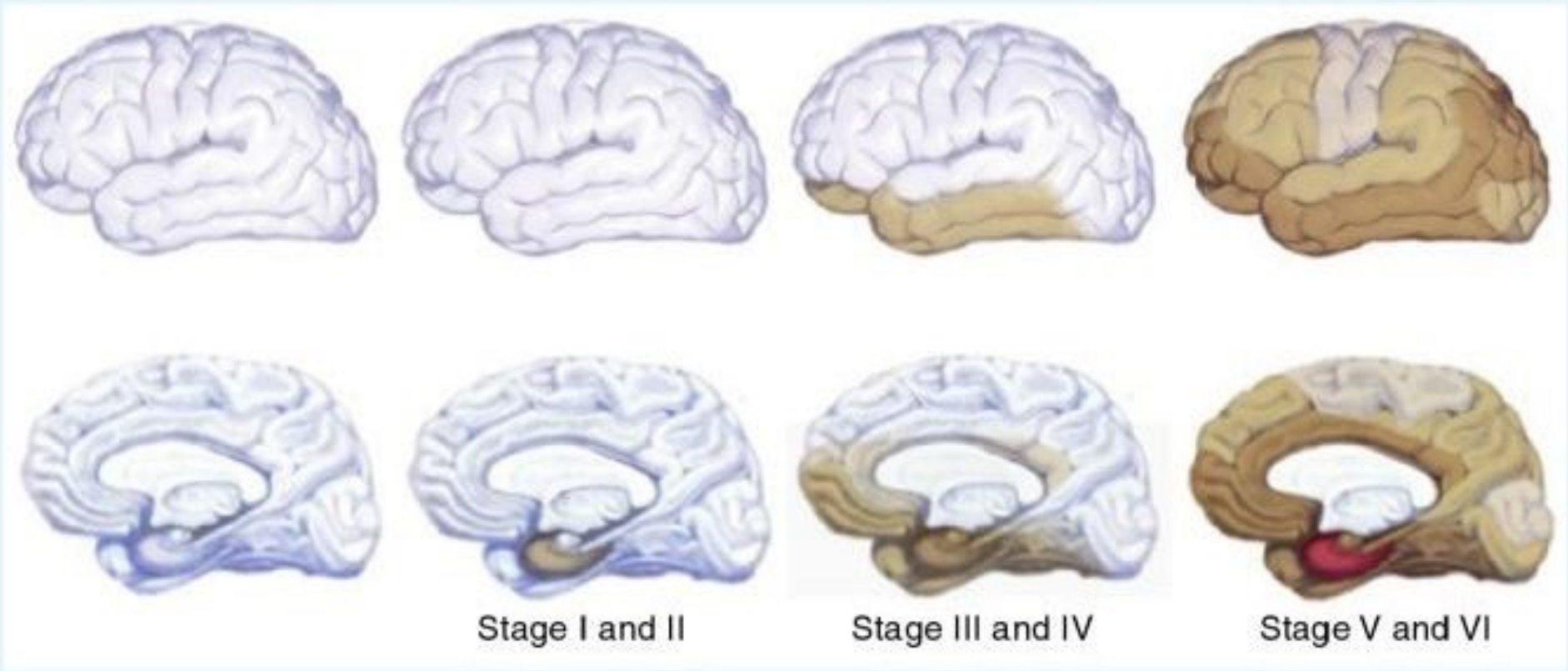


Spreading of brain pathologies



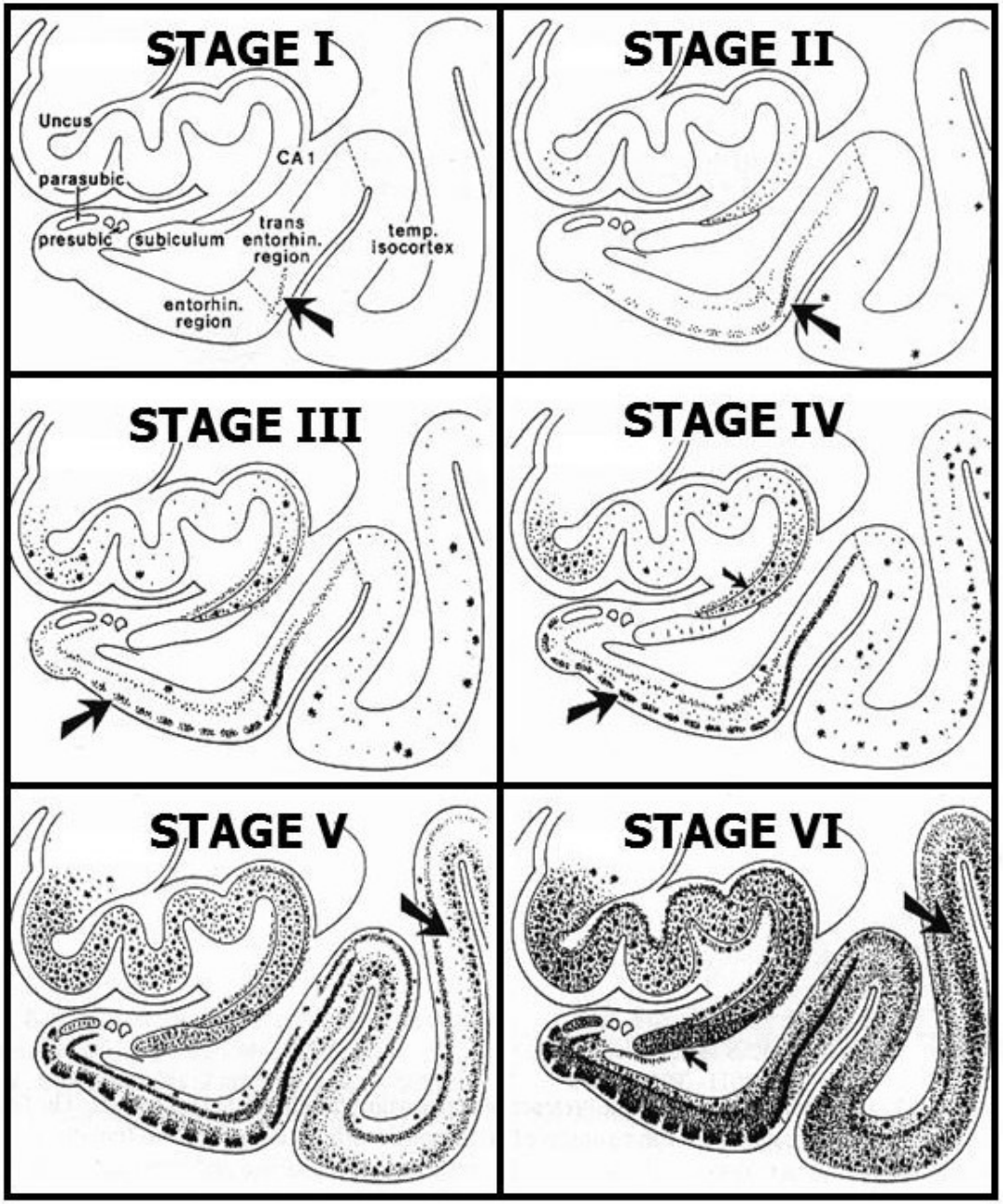
Spreading of brain pathologies

- **Braak and Braak Stages**: I-VI
  - Based on spreading of neurofibrillary tangles

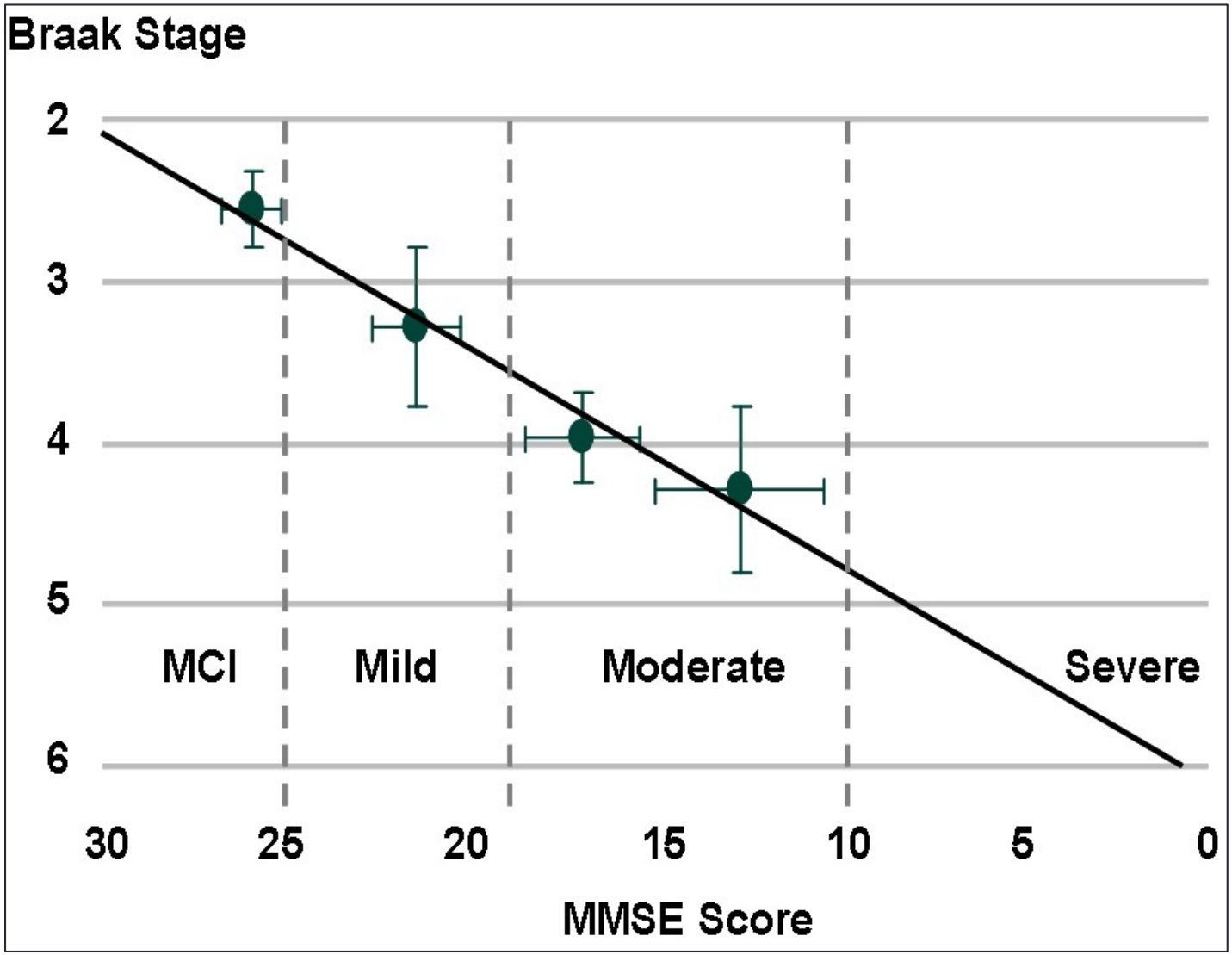


Braak Stages:

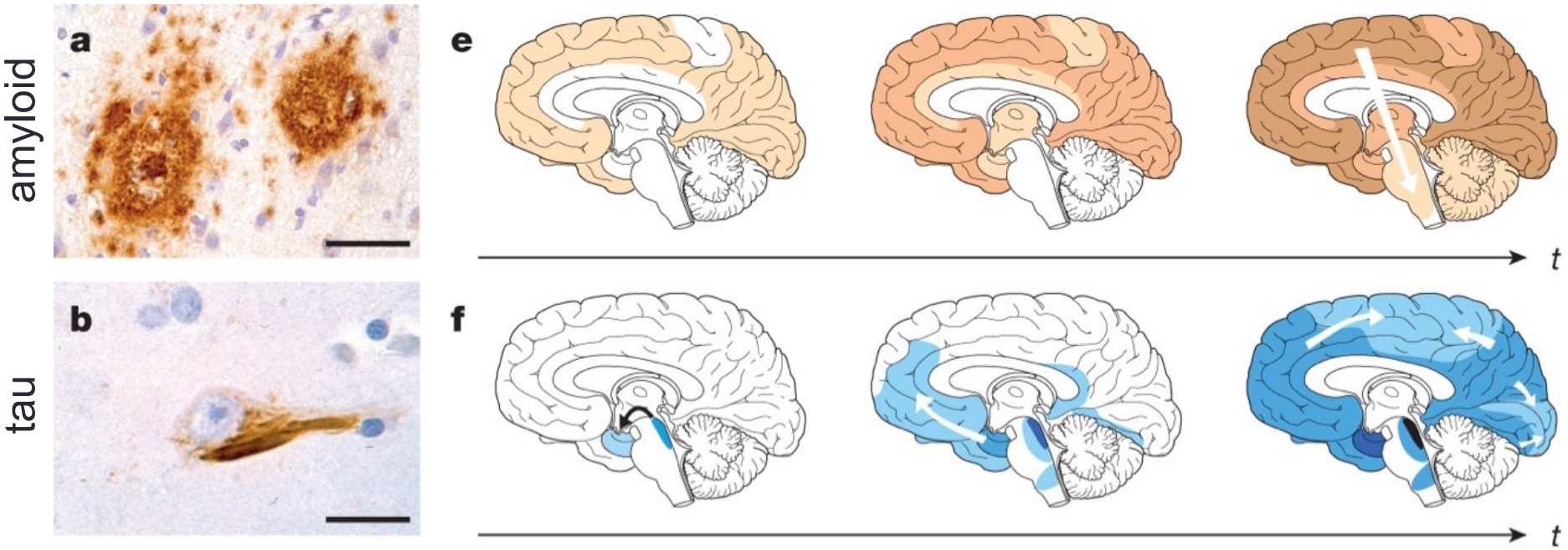
- I/II:
  - Entorhinal cortex
- III/IV:
  - Lymbic regions, including subiculum, hippocampus
- V/VI:
  - Cortical areas
  - Rest of the brain



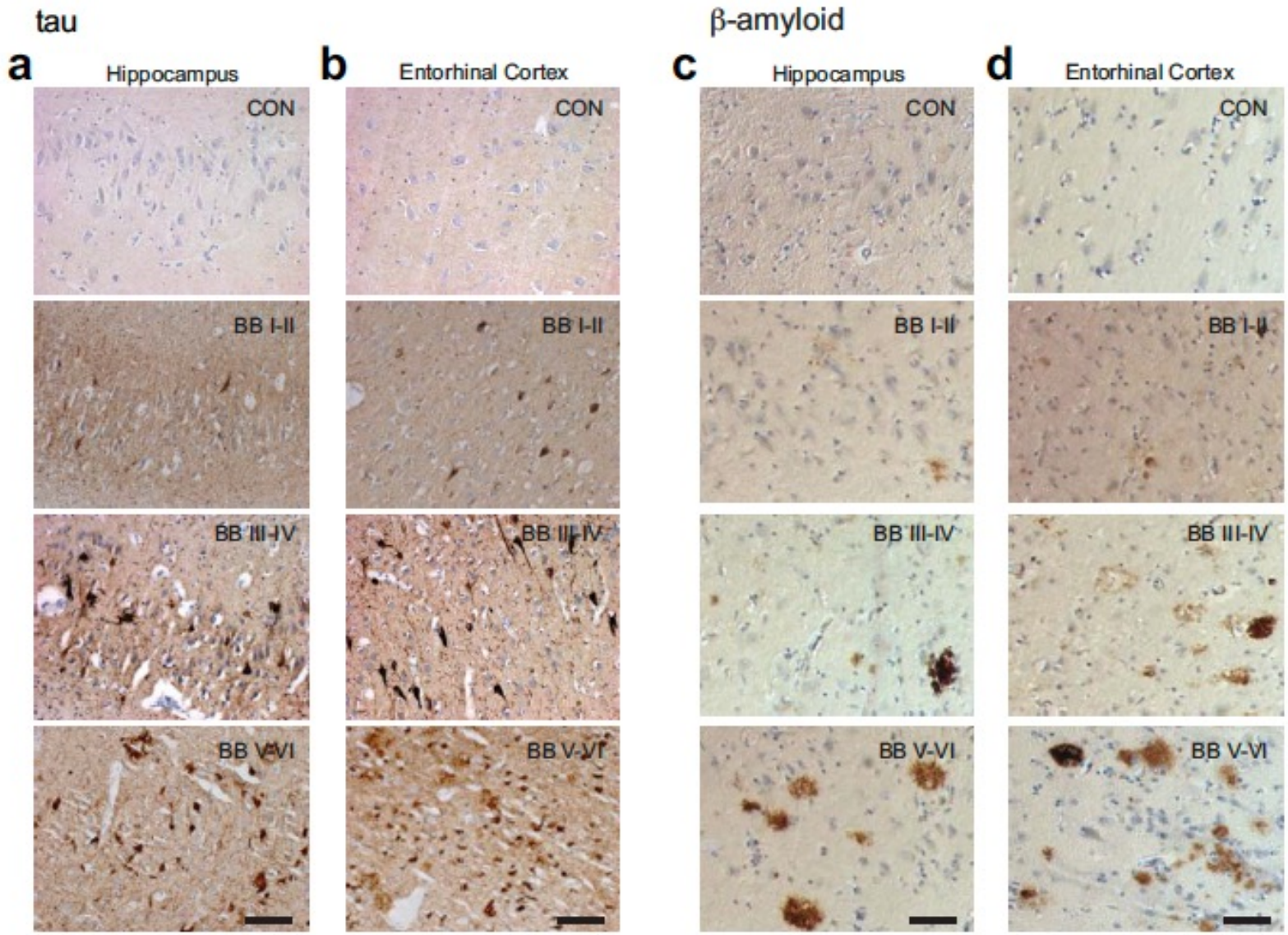
Braak Stages and Cognitive Decline



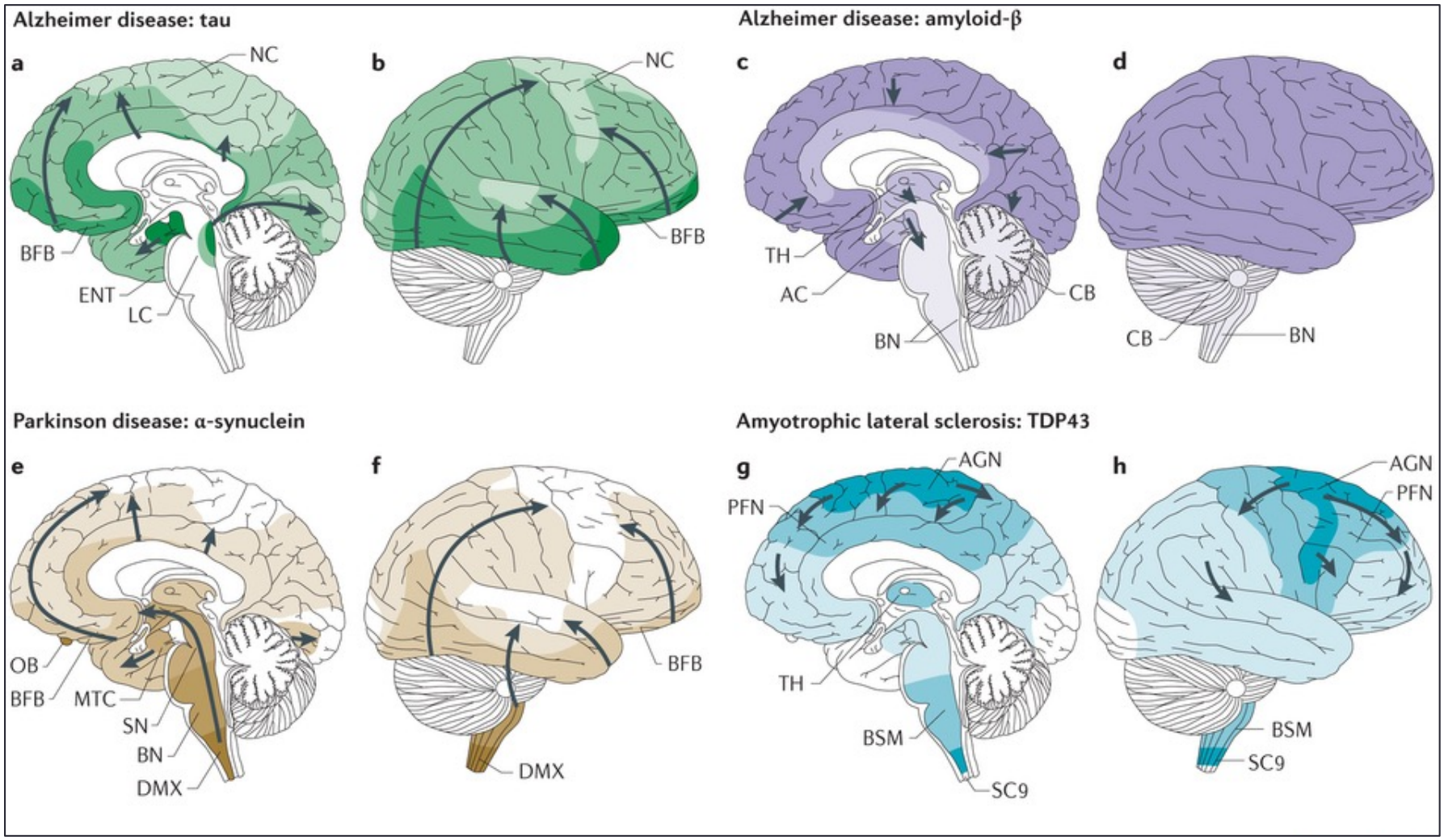
Spreading of both tau and amyloid in AD!



Spreading of both tau and amyloid in AD!

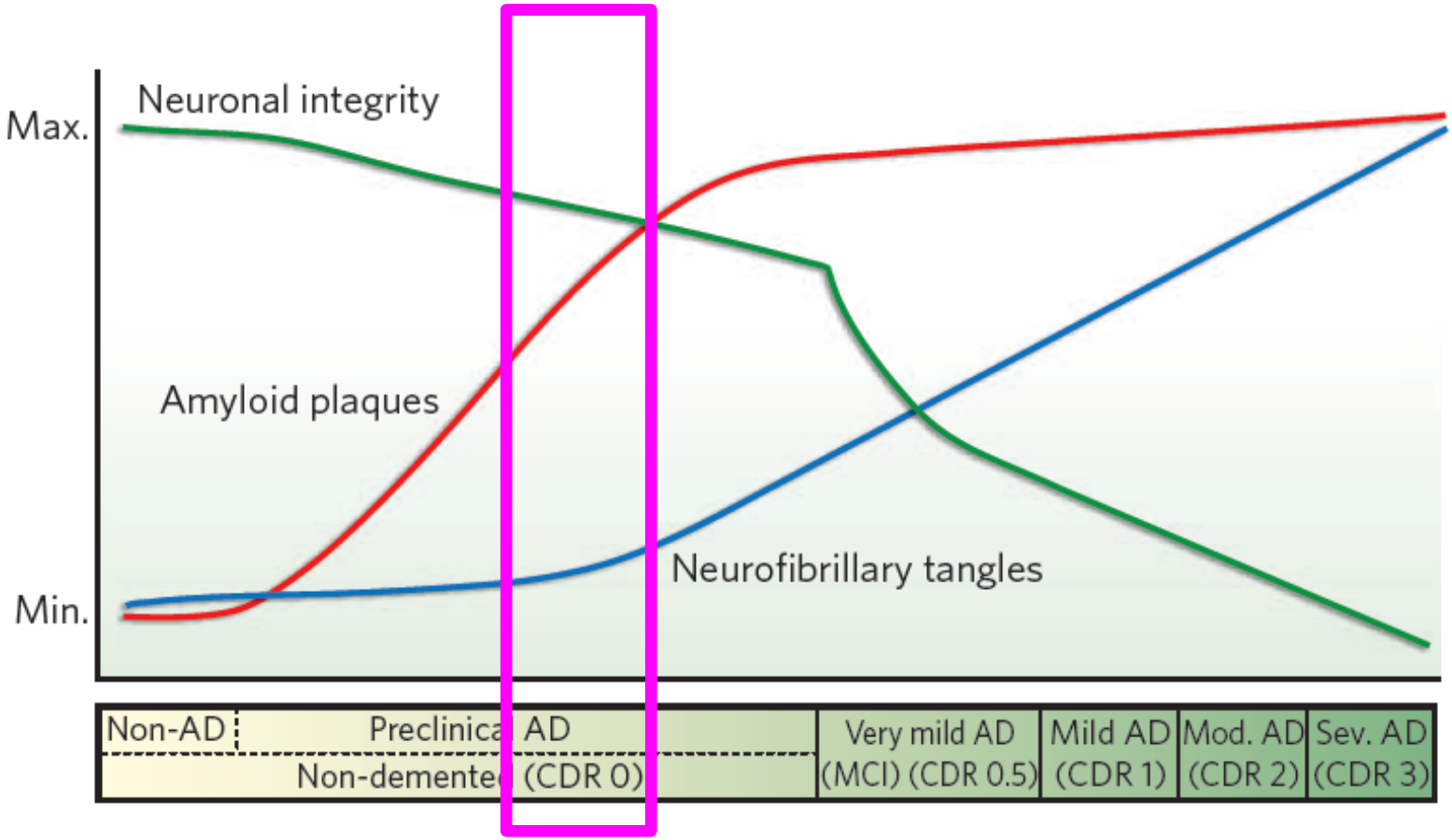


Spreading also in other neurodegen. diseases



- A commonality between different neurodegenerative diseases!

Timing of pathophysiological hallmarks



Major issues with NFTs in AD:

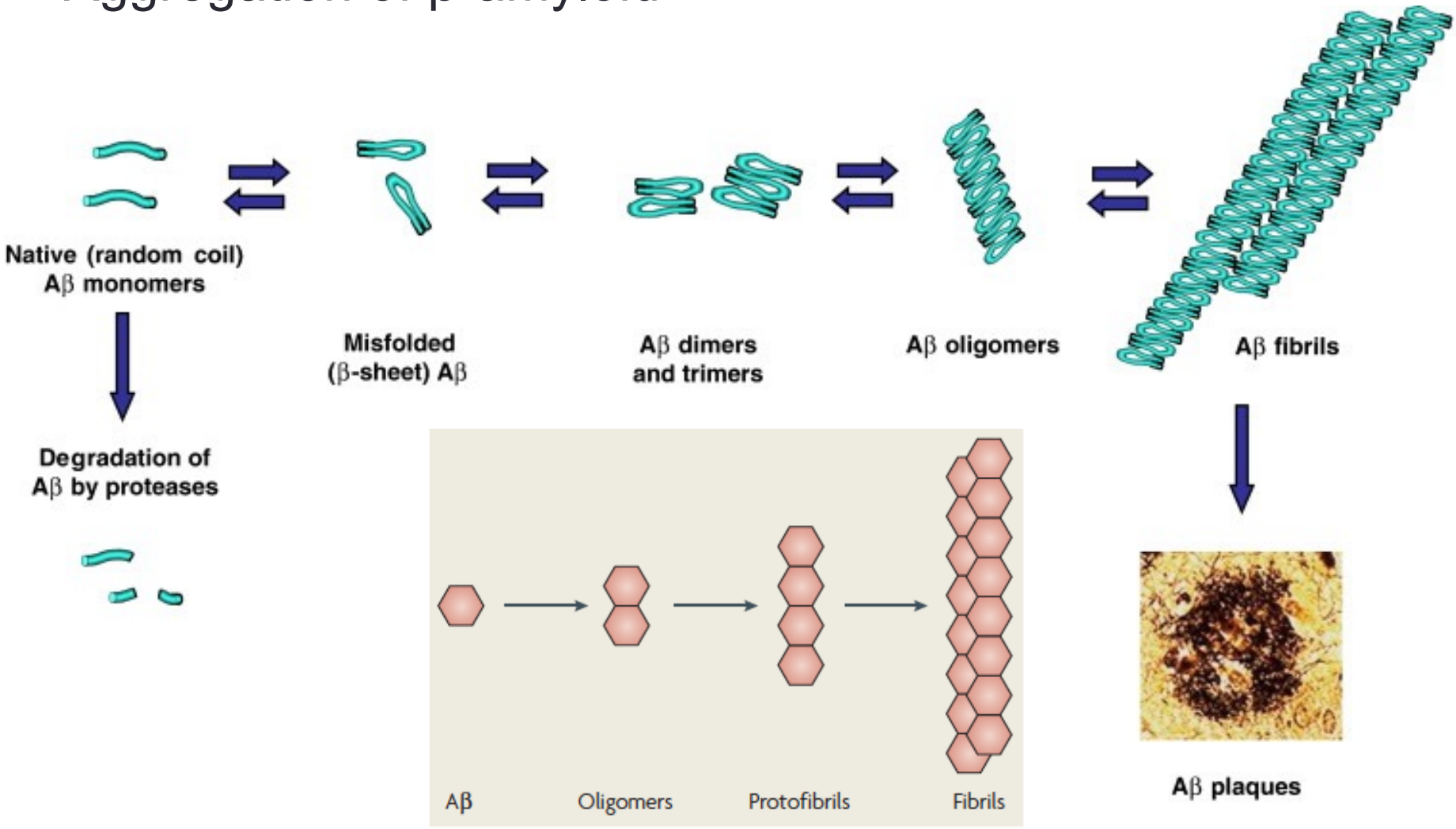
1) They appear rather late for AD diagnosis (see also diagnostics part)!
2) They don't correlate with loss of neuronal integrity

Alzheimer's Disease – Overview

1) Check your knowledge about AD
2) Prevalence and history
3) Symptomatology
4) **Pathophysiological hallmarks**
   - Tau tangles
   - **Amyloid plaques**
5) Risk factors
   - Genes
   - Environment
6) Treatment approaches
7) Diagnostics and biomarkers

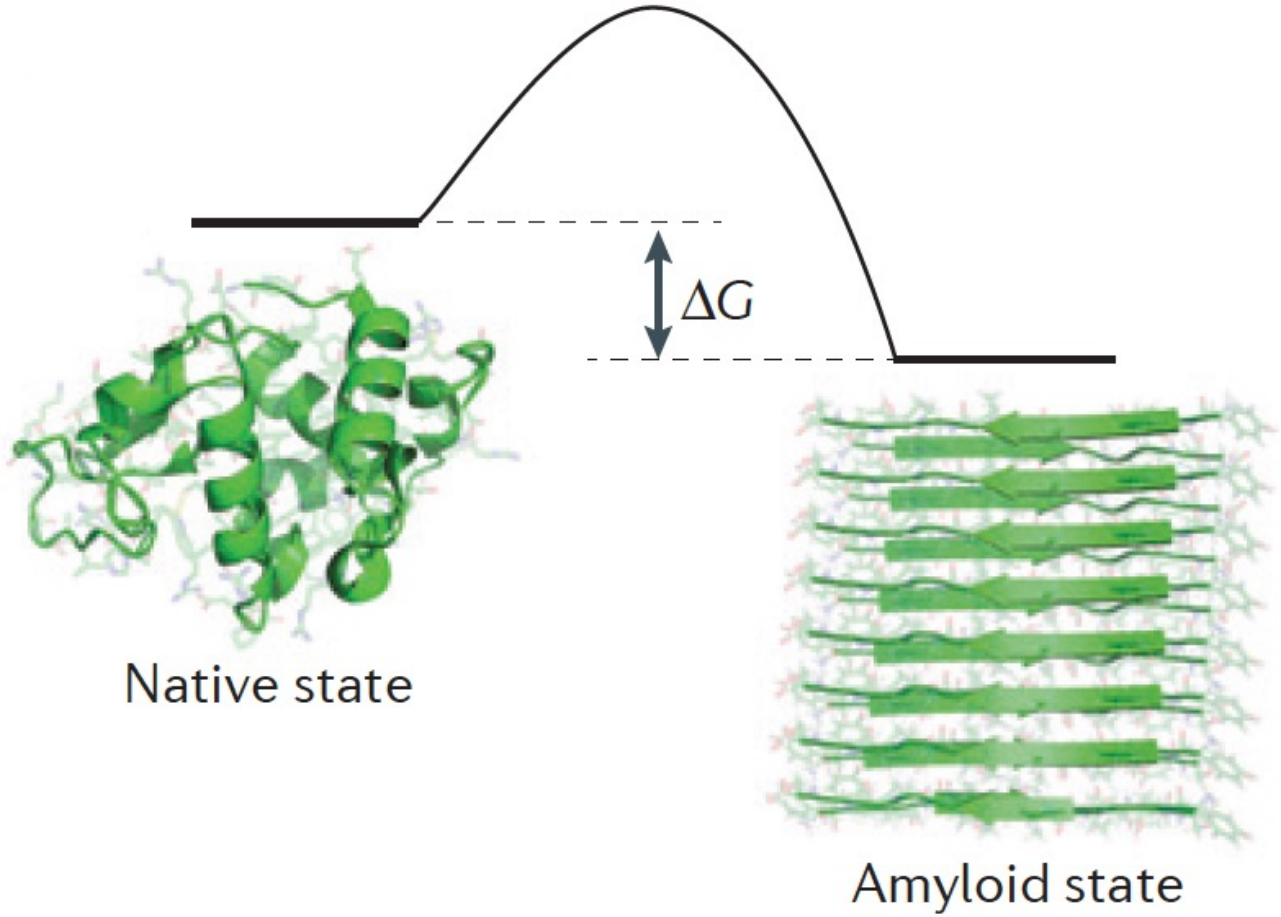
Pathophysiology: Amyloid plaques

= Aggregation of β-amyloid



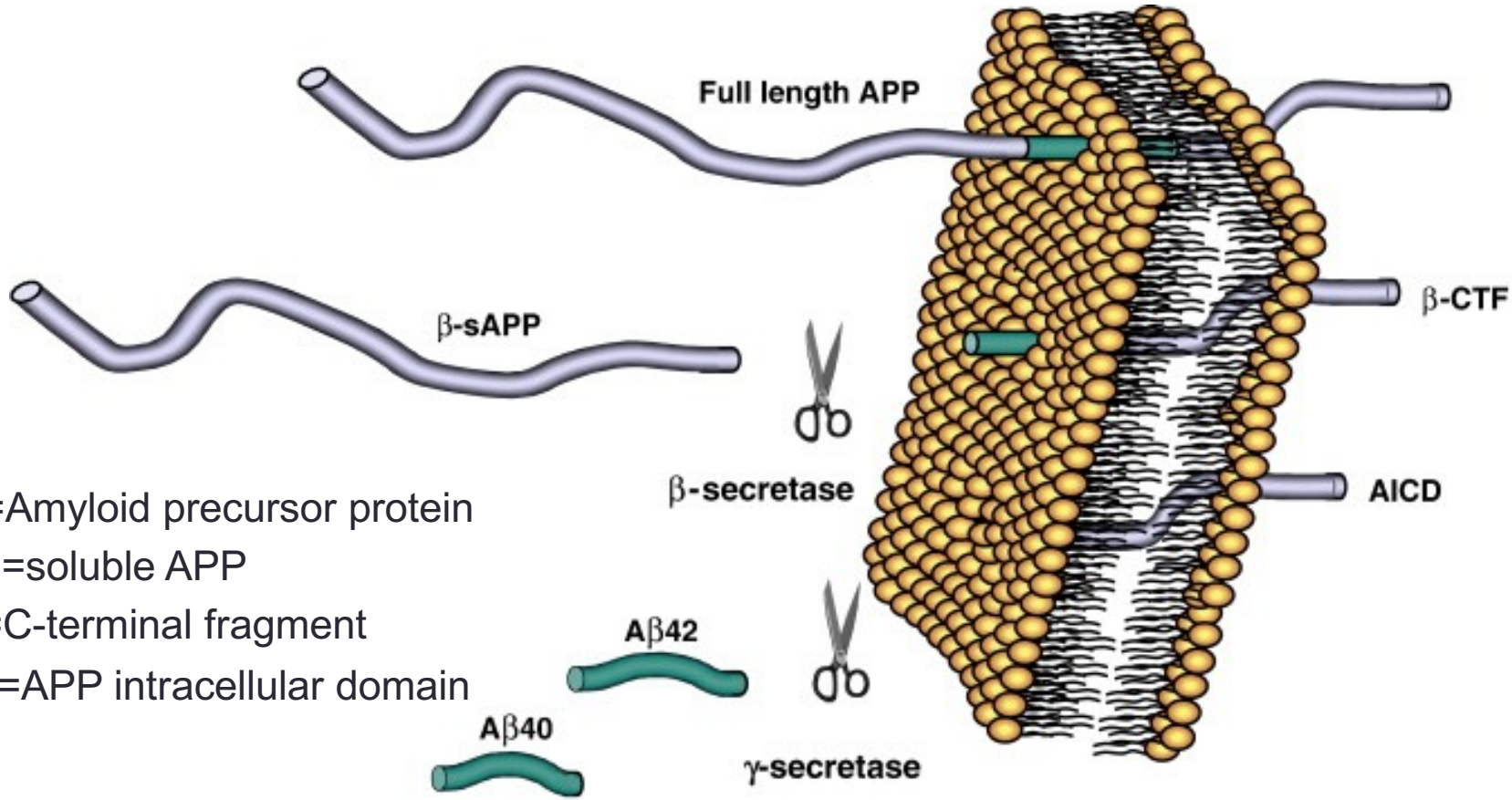
Pathophysiology: Amyloid plaques

- β-amyloid aggregates are thermodynamically favoured
  - Lower free energy



Pathophysiology: Amyloid plaques

- Generation of β-amyloid protein:

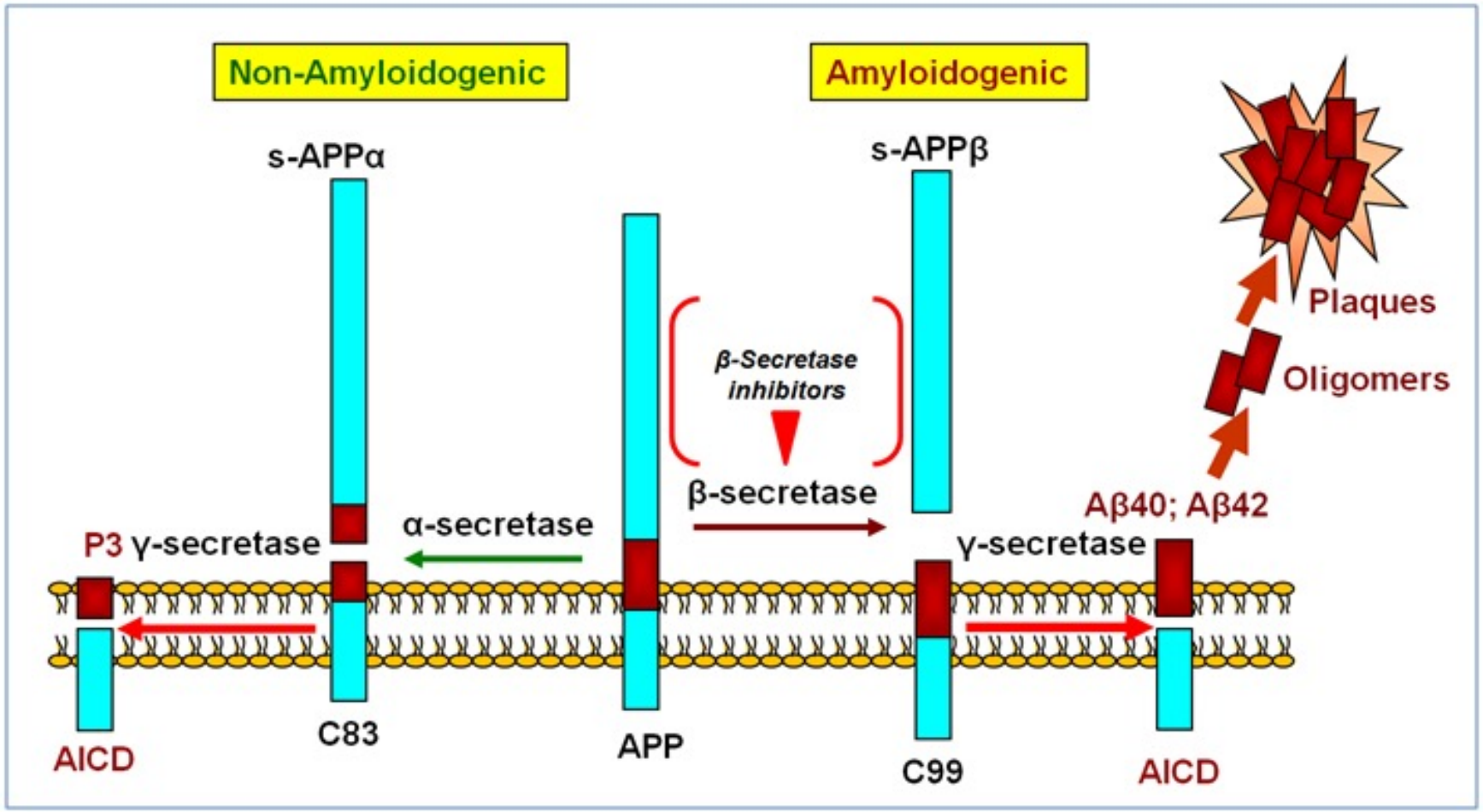


APP=Amyloid precursor protein
sAPP=soluble APP
CTF=C-terminal fragment
AICD=APP intracellular domain

Pathophysiology: Amyloid plaques

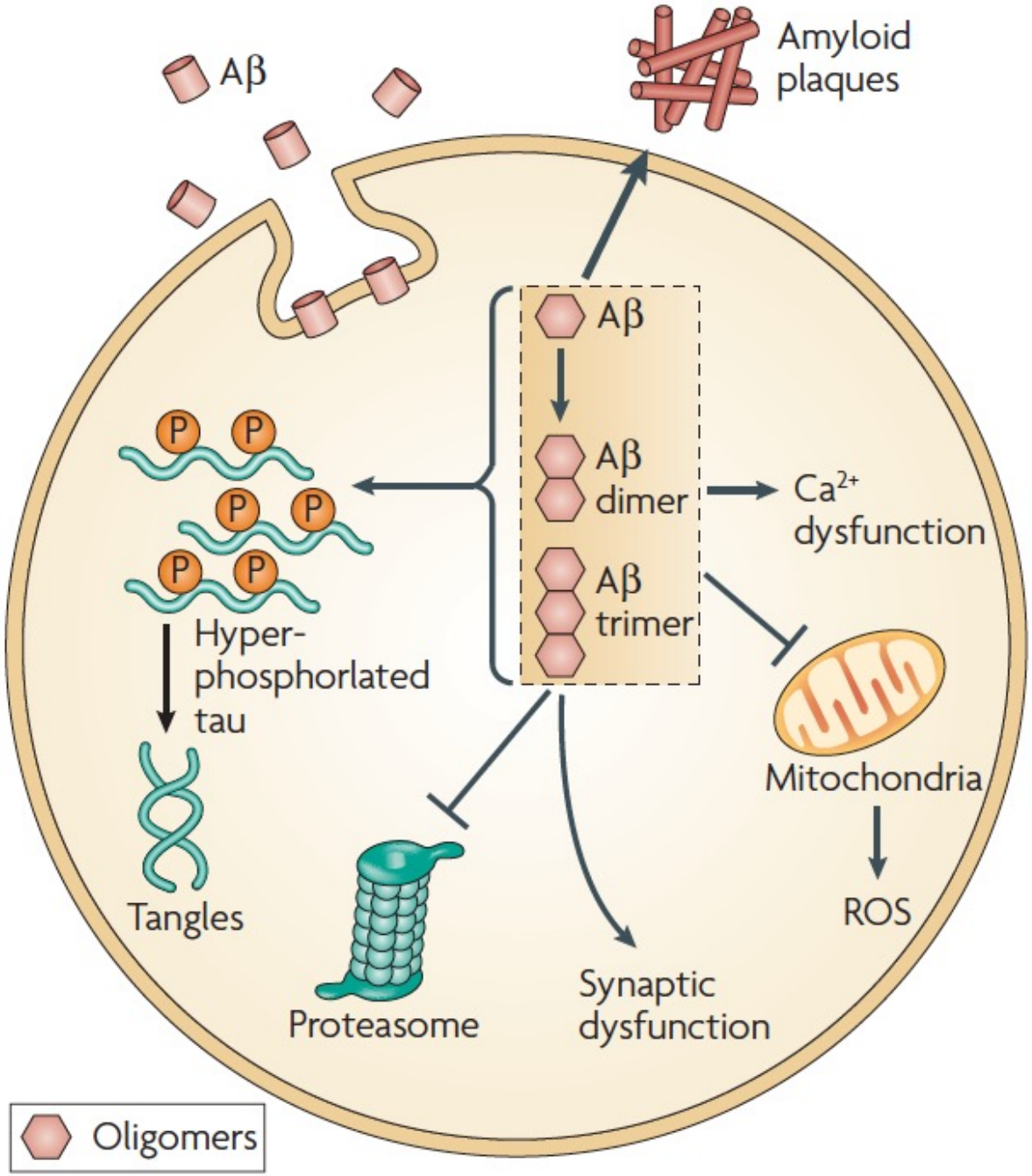
- Generation of β-amyloid protein:
  - An amyloidogenic and a non-amyloidogenic pathway

APP=Amyloid precursor protein sAPP=soluble APP CTF=C-terminal fragment AICD=APP intracellular domain

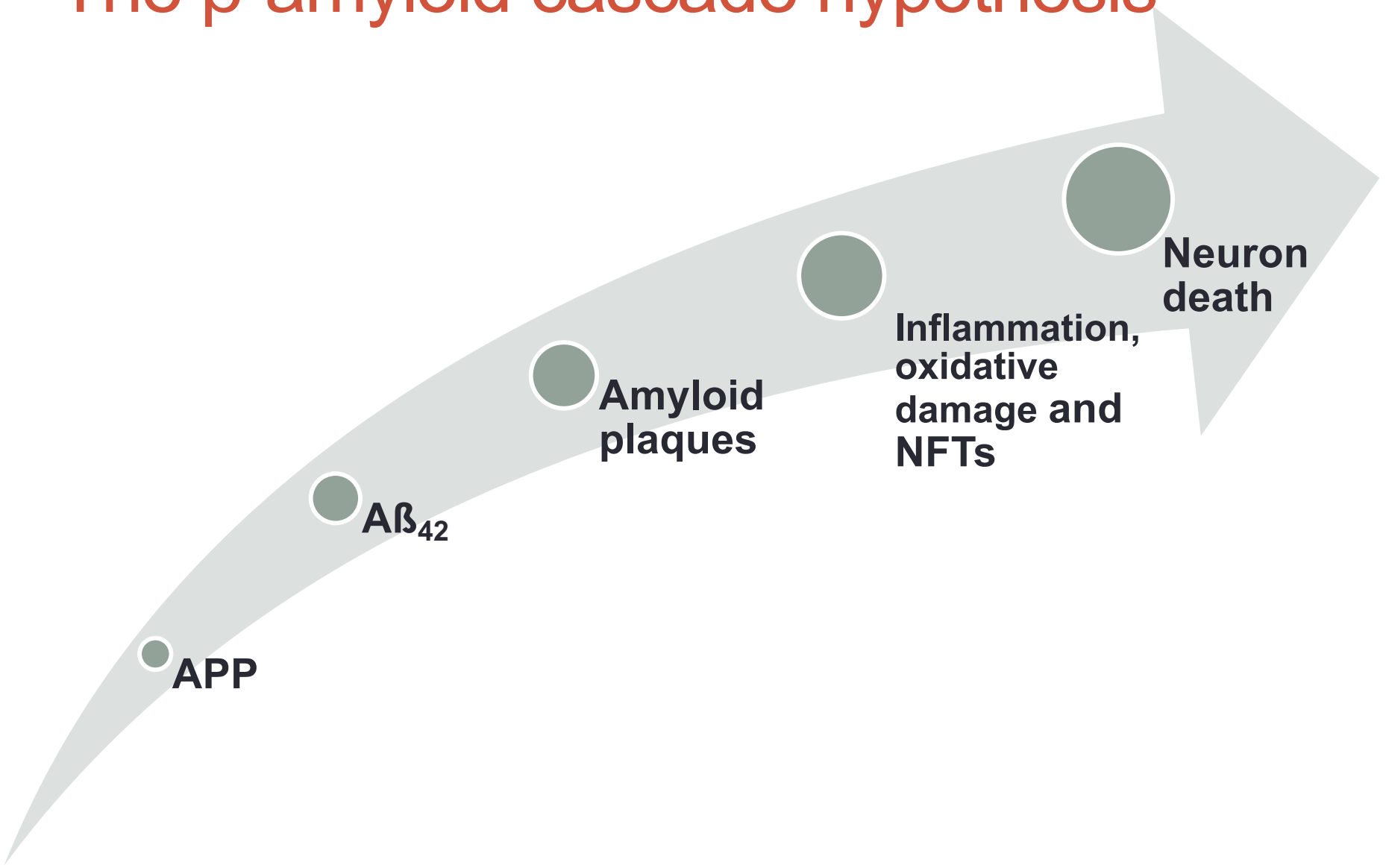


B-amyloid:

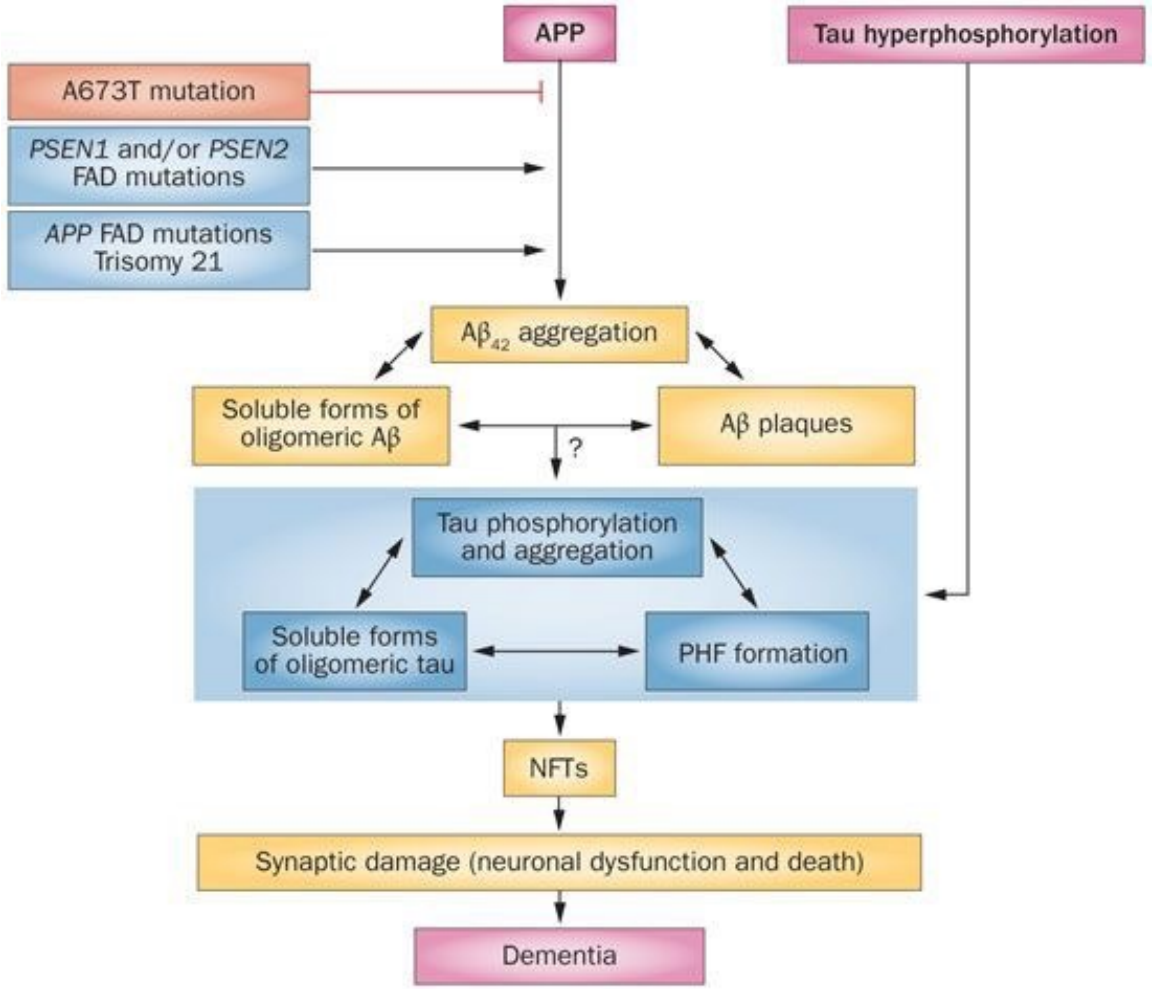
- The majority of β-amyloid is **extracellular**
- But **intracellular** β-amyloid also exists



The β-amyloid cascade hypothesis

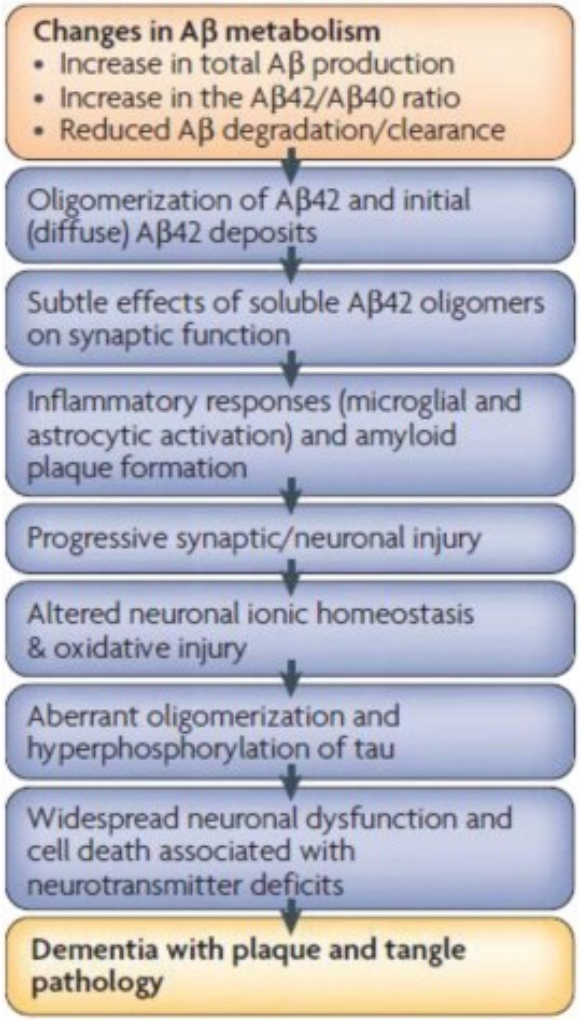


The β-amyloid cascade hypothesis



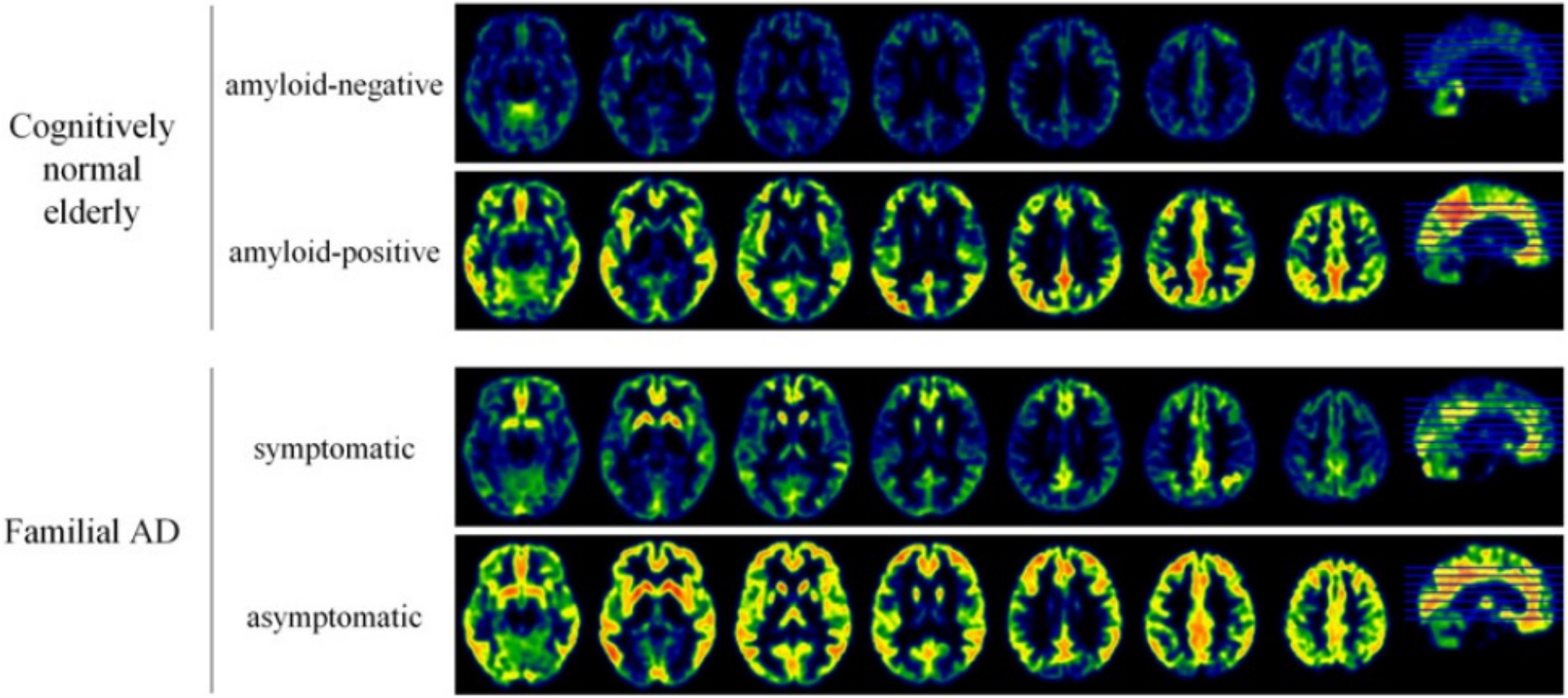
Consequences of amyloid aggregation:

Induced toxicity and neurodegeneration



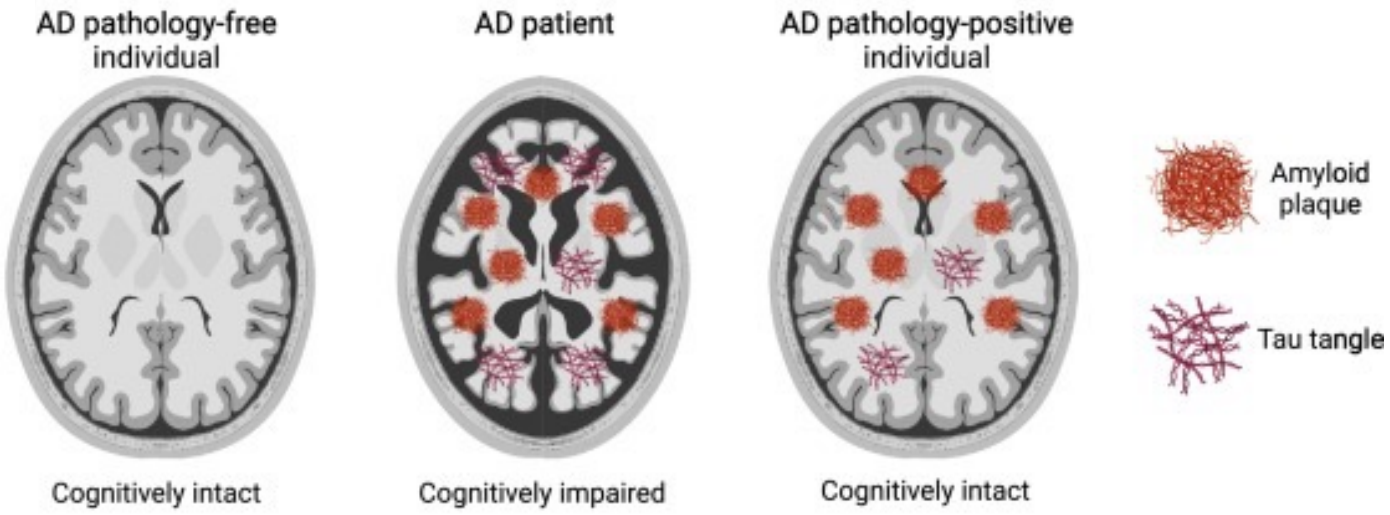
But: Validity of β-amyloid cascade hypothesis?

- 20-30% of healthy elderly also have amyloid deposits
- Not all (familial) AD cases show amyloid deposits



Resilient individuals

- 20-30% of healthy elderly also have amyloid deposits



Non pathological roles for amyloid etc

Not just amyloid: physiological functions of the amyloid precursor protein family

Ulrike C. Müller[1], Thomas Deller[2] and Martin Korte[3,4]**

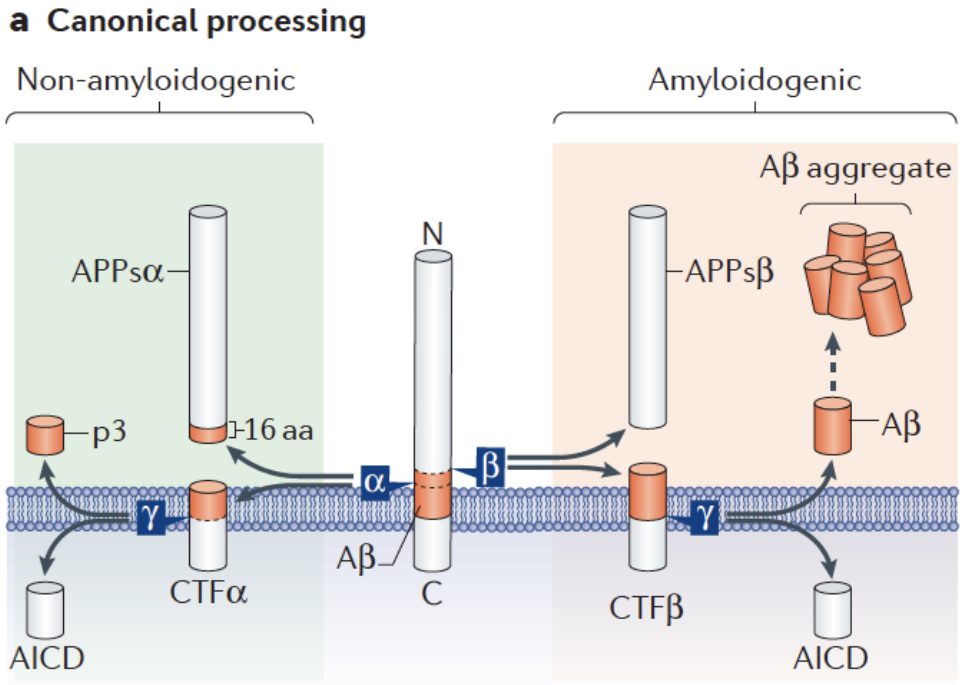
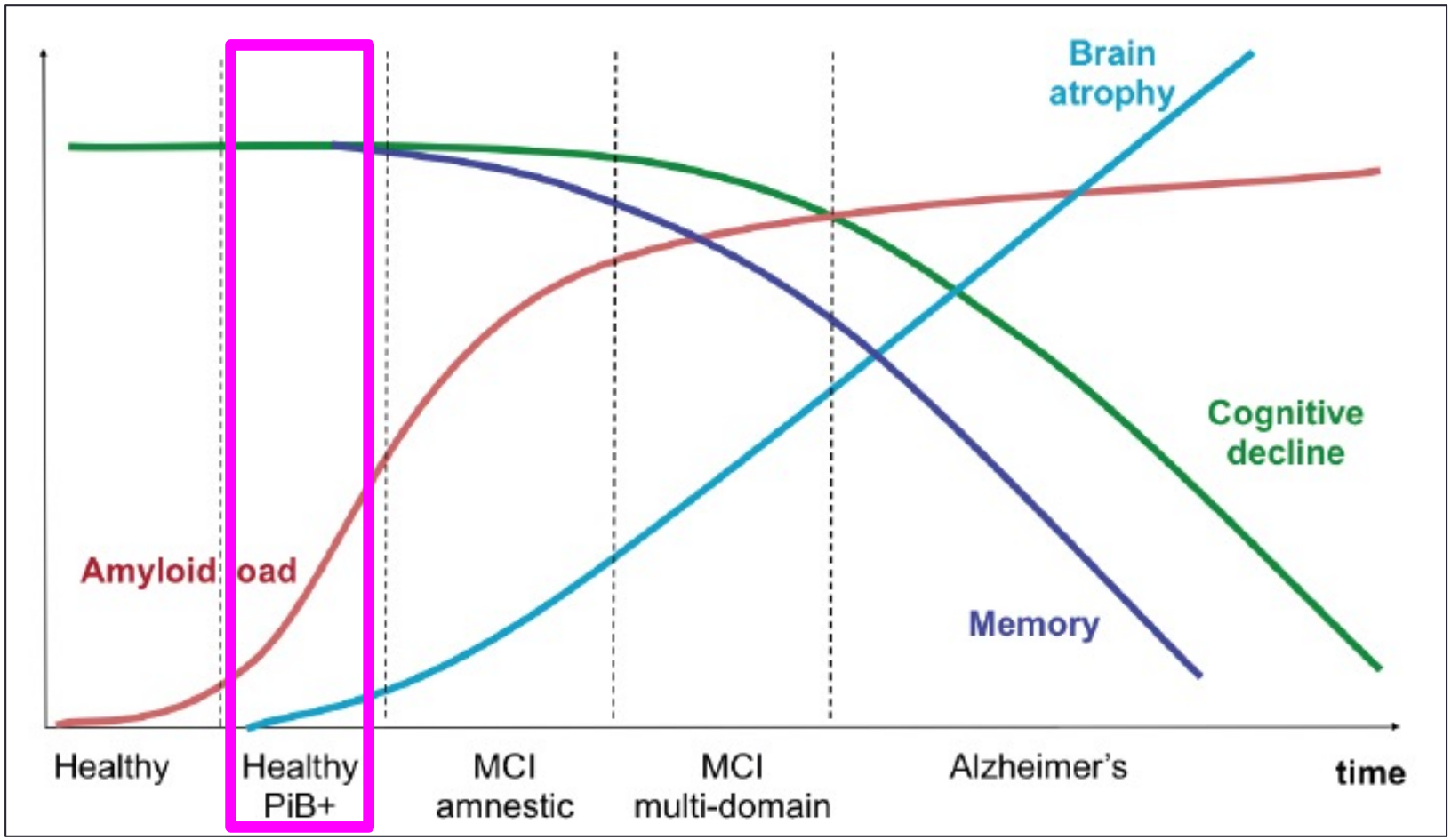


Table 2 | ***In vivo* functions of APP fragments in the mammalian CNS**

APP fragment	Functions and effects
APPsα	• ↑ Memory[142] • ↑ LTP and NMDAR currents in DG of anaesthetized rats[151] • Rescues memory[154] and LTP in aged rats[153] • Rescues spine density of *App*$^{-/-}$ organotypic hippocampal cultures[127]; rescues LTP and spatial learning in aged *App*$^{-/-}$ mice[91]; rescues LTP in NexCre-cDKO mice[22] • Tg OE in APP/PS1 mice inhibits the amyloidogenic pathway, reduces plaque deposition[5] and reduces GSK3β-dependent tau phosphorylation[199] • Viral OE in APP/PS1 mice rescues spine density, LTP and memory[132] • Protects against: TBI[166]; neuronal death during transient ischaemia[200]; and hypoxia in acute hippocampal slices[93] • Stimulates adult neurogenesis at the subventricular zone[196] • Tg OE associated with impaired social interaction in male mice[201]
APPsβ	Stable metabolite *in vivo*, not associated with increased cell death, induces transcription of transthyretin and klotho[126]
Aβ	• Regulates neuronal homeostasis: picomolar (but not higher) amounts stimulate PTP, LTP and memory; suggested to stimulate presynaptic transmitter release, via effects blocked by nAChR inhibitors[202–204] • Major APP fragment associated with AD pathogenesis; gives rise to Aβ oligomers and plaques, inhibits synaptic plasticity and memory (for reviews see REFS 88,138)
$Aβ^*_{2-x}$	• Generated by meprin cleavage • High aggregation propensity; potential seed for Aβ deposition[205]
p3	Physiological or trophic function unknown; no pathological effects reported
Aη-α	• Upregulated upon β-secretase inhibition[48] • ↓ Neuronal activity and LTP in wild-type hippocampal slices[48]
Aη-β	None of the pathological properties reported for Aη-α[48]
APPsη ($APP_{1–585}$, $APP_{1–373}$ or $APP_{374–585}$)	• η-secretase-derived • Physiological function unknown
APPsδ ($APP_{1–448}$, $APP_{1–660}$ or $APP_{449–660}$)	• δ-secretase-derived • Physiological function unknown (only detectable in low amounts in aged mice) • Tg AD model mice that also lack δ-secretase show reduced Aβ load and ameliorated functional deficits[52]
Meprin-derived APPs ($APP_{1–124}$, $APP_{1–305}$ or APPsβ*)	• Generated by meprin cleavage • Physiological function unknown
CTFα	Physiological function unknown
CTFβ	• Injection of CTFβ impairs working memory and induces neurodegeneration and gliosis[206] • Tg CTFβ OE induces neurodegeneration, reduces LTP and impairs cognition[207,208] • Viral or Tg CTFβ OE impairs lysosomal autophagic function[209] • CTFβ accumulation impairs LTP[67]
CTFη	Associated with plaques, upregulated upon β-secretase inhibition[48]
AICD	• Transcriptional regulation (physiological or pathological relevance controversial)[49,60,73] • Tg AICD OE may lead to hippocampal degeneration, tau phosphorylation and deficits in working memory[210], but see also REF. 211

Appearance of amyloid pathologies:



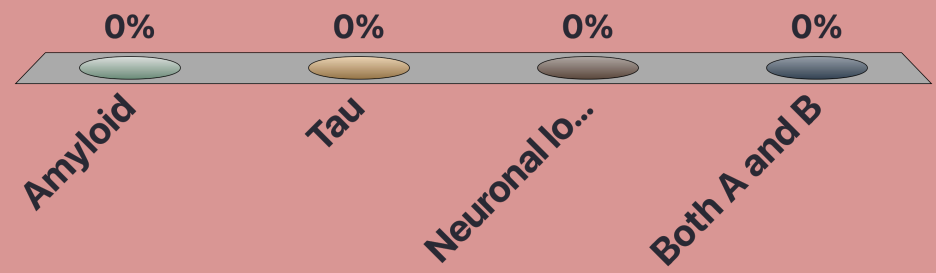
Major issues with plaques in AD:

1) They appear (too) early for AD diagnosis, at non-symptomatic stages
2) They don't always correlate with AD

PiB+: Pittsburgh Compound B (amyloid-based diagnostic tool)

What is the primary trigger for AD?

A. Amyloid
B. Tau
C. Neuronal loss
D. Both A and B



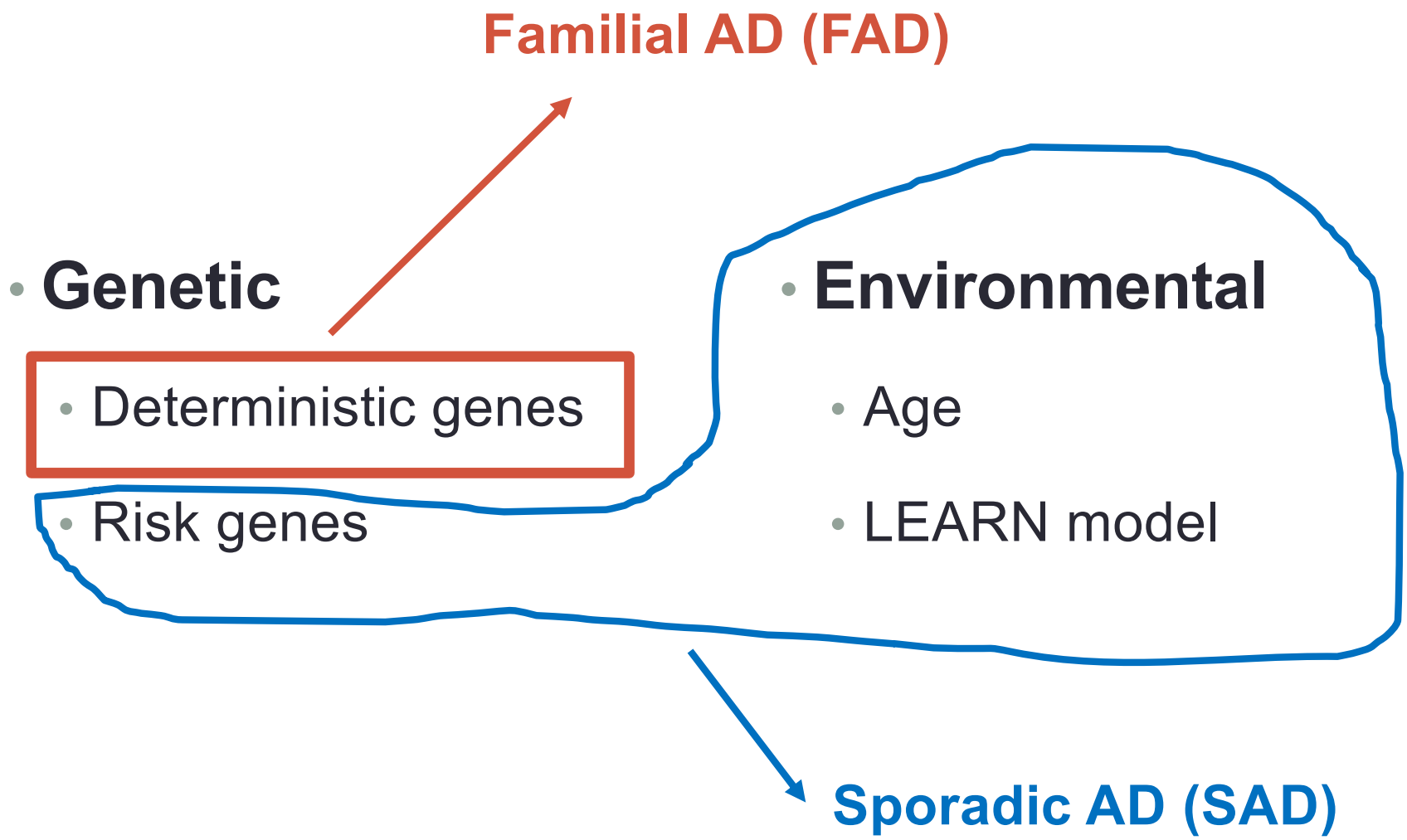
What is the first pathological **proteinaceous** sign of Alzheimer's disease?

ttpoll.eu → bio480jg

Alzheimer's Disease – Overview

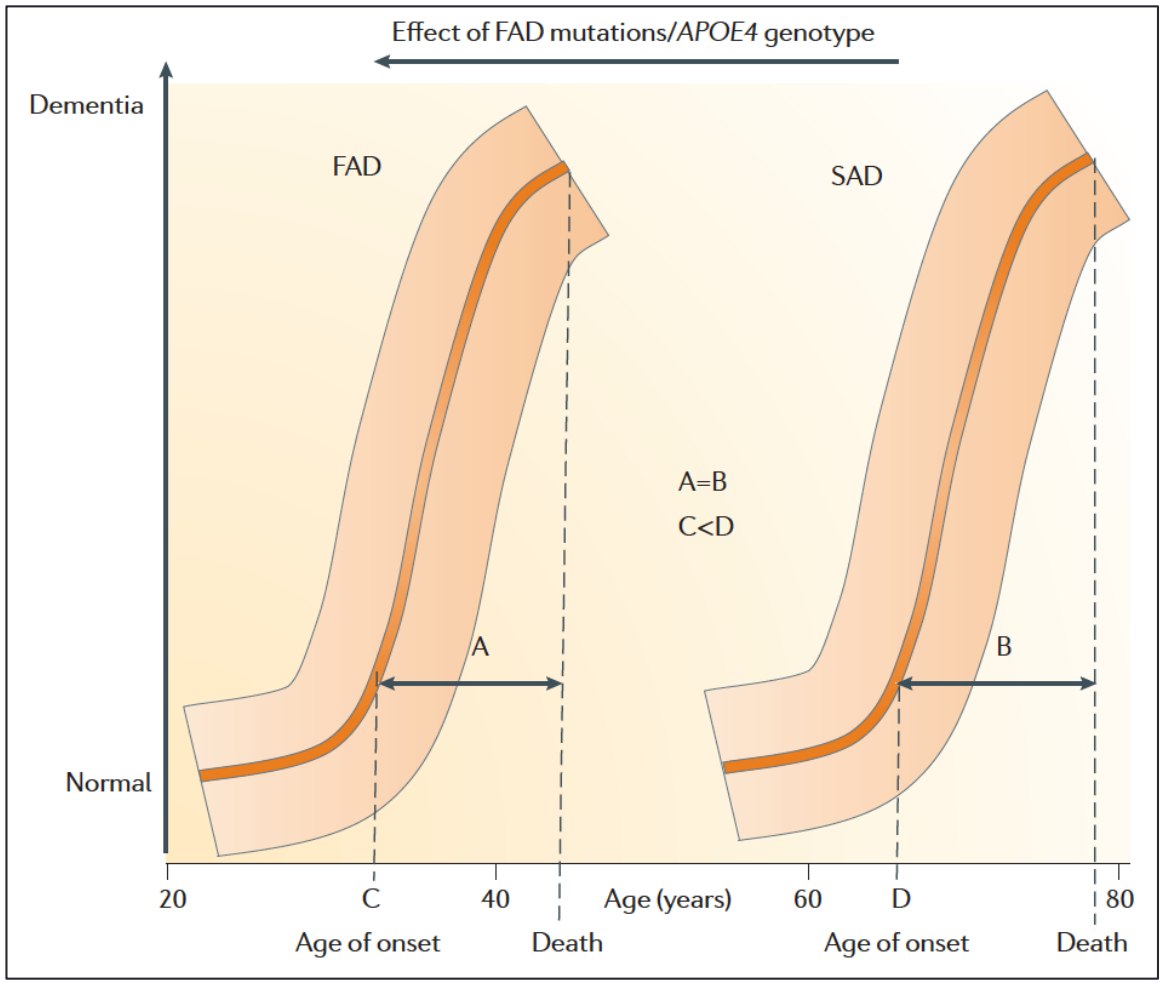
1) Check your knowledge about AD
2) Prevalence and history
3) Symptomatology
4) Pathophysiological hallmarks
   - Tau tangles
   - Amyloid plaques
5) **Risk factors**
   - Genes
   - Environment
6) Treatment approaches
7) Diagnostics and biomarkers

Risk factors for AD



Familial vs sporadic AD:

Familial AD (FAD)



Sporadic AD (LOAD)

LOAD=Late-onset Alzheimer's disease

Genetic risk factors for AD

- **Deterministic vs risk genes**:

1. **Deterministic genes**

= Directly cause a disease, everyone inheriting them will develop the disorder.

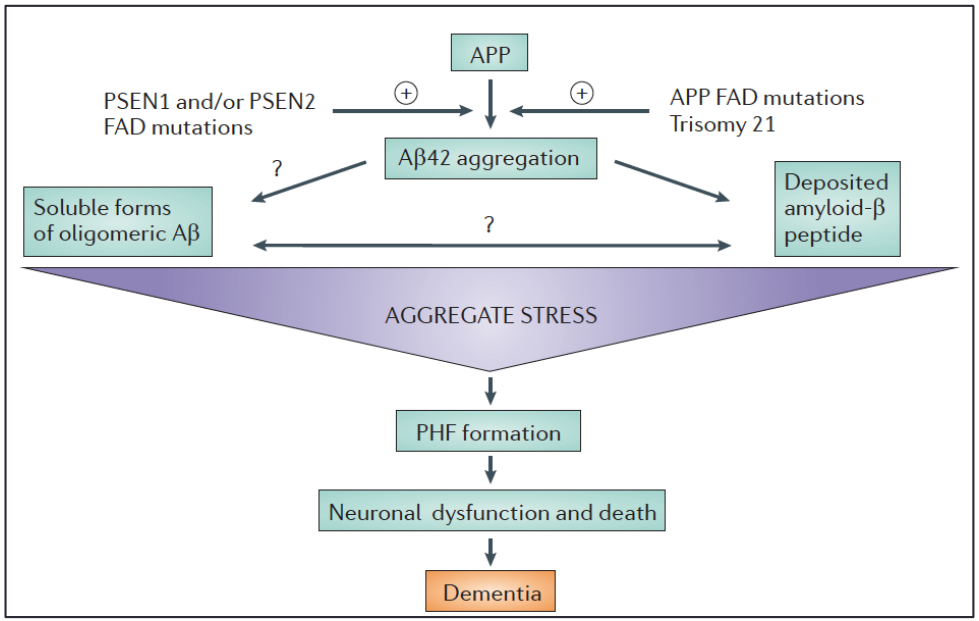
- Rare genes that directly cause Alzheimer's in only a few hundred extended families worldwide.
- These genes cause an early-onset of the disease
- This type is known as **"Familial Alzheimer's disease" (FAD)**
- **BUT**: True familial AD accounts for **less than 5%** of the cases.
  - The majority of cases do not have a genetic underpinning with high penetrance
  - This type of the disease is known as **"Sporadic Alzheimer's disease"**

Genetic risk factors for AD

- **Deterministic, early-onset genes**:
  - APP mutations
  - Mutations in PSEN1 and/or PSEN2:
    - Code for γ-secretase complex

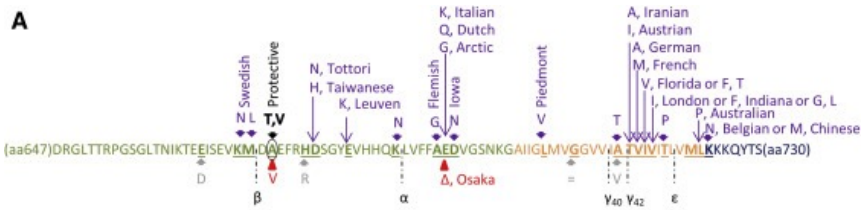
AD-Mutations

Chromosome 21	Chromosome 14	Chromosome 1
Abnormal **amyloid precursor protein (APP).**	Abnormal **presenilin 1**	Abnormal **presenilin 2**

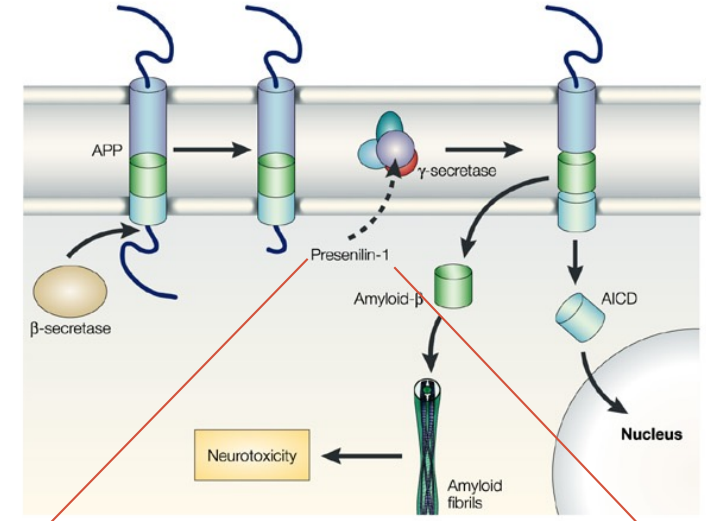


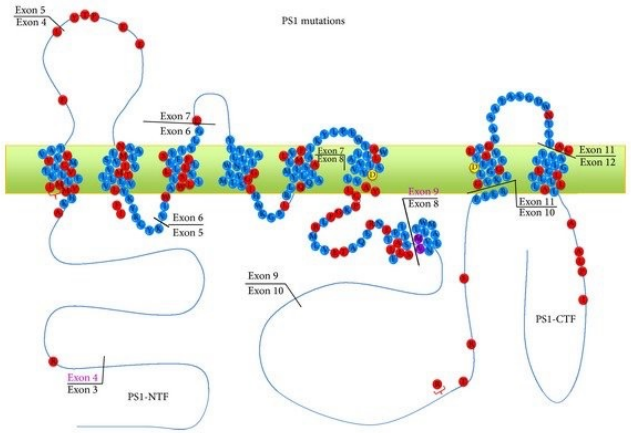
Genetic risk factors for AD

- APP mutations:



- PSEN mutations





Familial AD

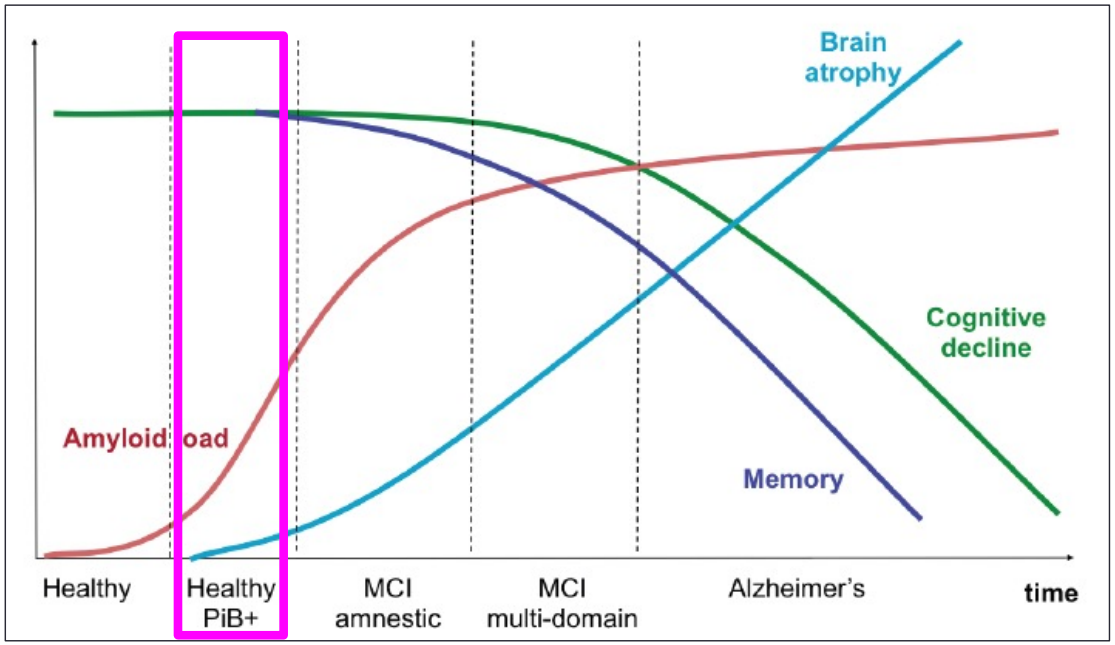
- The case of a Columbian village – The advantage:

Familial AD

- The case of a Columbian village:
  - Yarumal, Columbia and its surroundings are home to the world's largest group of individuals with a hereditary form of AD
  - Members of 25 extended families, with 5,000 members, developed early onset Alzheimer's, if they have the mutated E280A in *PSEN1*
  - This population is the basis for an approach that will test drugs in patients **before the first signs of dementia appear**.

Familial AD

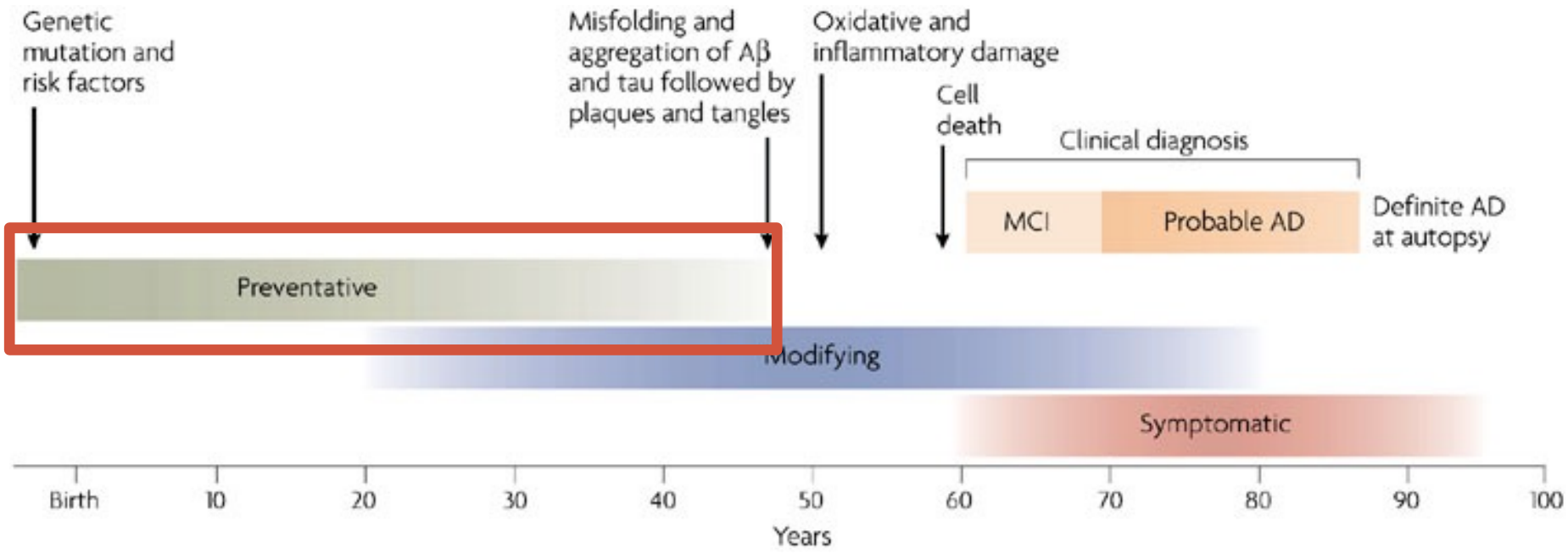
- The case of a Columbian village – The advantage of a clear trajectory:



Major issues with plaques in AD:
1) They appear (too) early for AD diagnosis, at non-symptomatic stages
2) They don't always correlate AD

Familial AD

- The case of a Columbian village – The advantage of an early treatment:



- Testing the amyloid cascade hypothesis

Genetic risk factors for AD

2. **Risk Genes**

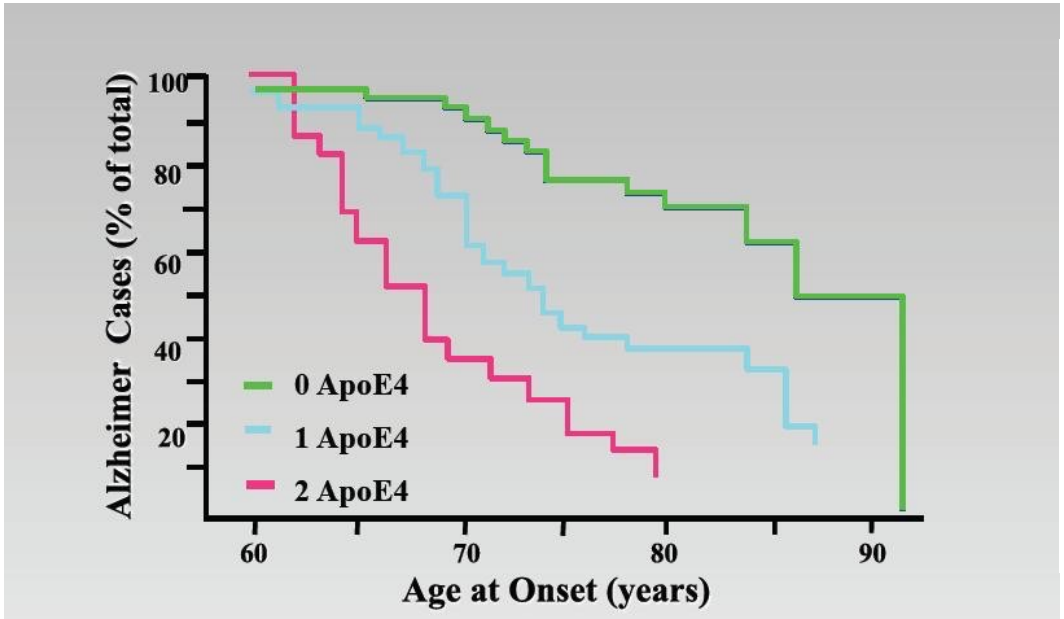
- Risk genes increase the likelihood of developing a disease but do not guarantee it will happen.
- **APOE-e4**

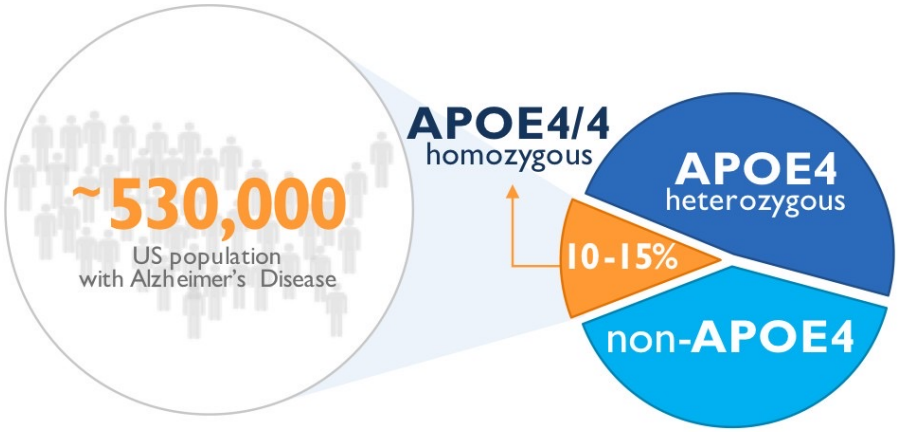
= one of three common forms of the APOE (apolipoprotein) gene.

- Those who inherit one copy of APOE-e4 have an increased risk of developing Alzheimer's.
- Those who inherit two copies have an even higher risk.
- In addition to raising risk, APOE-e4 may tend to make symptoms appear at a younger age than usual.

APOE4 is the strongest genetic risk factor for patients with late-onset (sporadic) Alzheimer's disease

Survival Curve





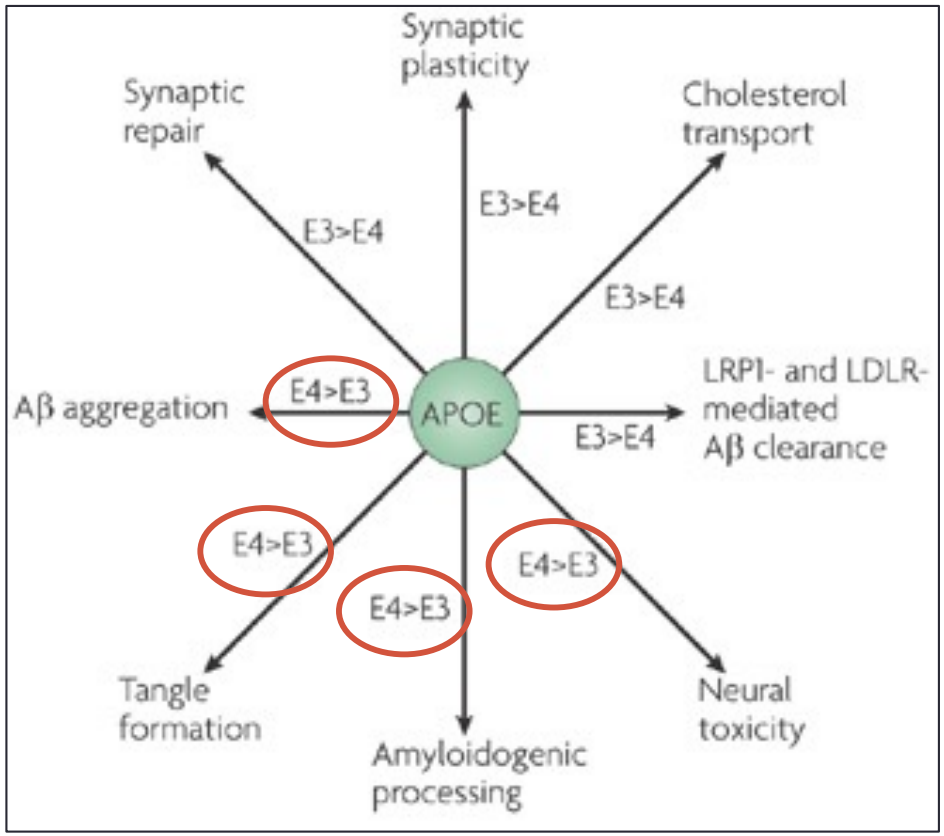
There are three major isoforms (ApoE2, ApoE3, and ApoE4) in humans.

- ApoE is produced predominantly by astrocytes and to some extent microglia
- ApoE is also expressed in neurons in response to excitotoxic injury
- ApoE plays important role in the transport of HDL-like particles cholesterol and phospholipid between cells.

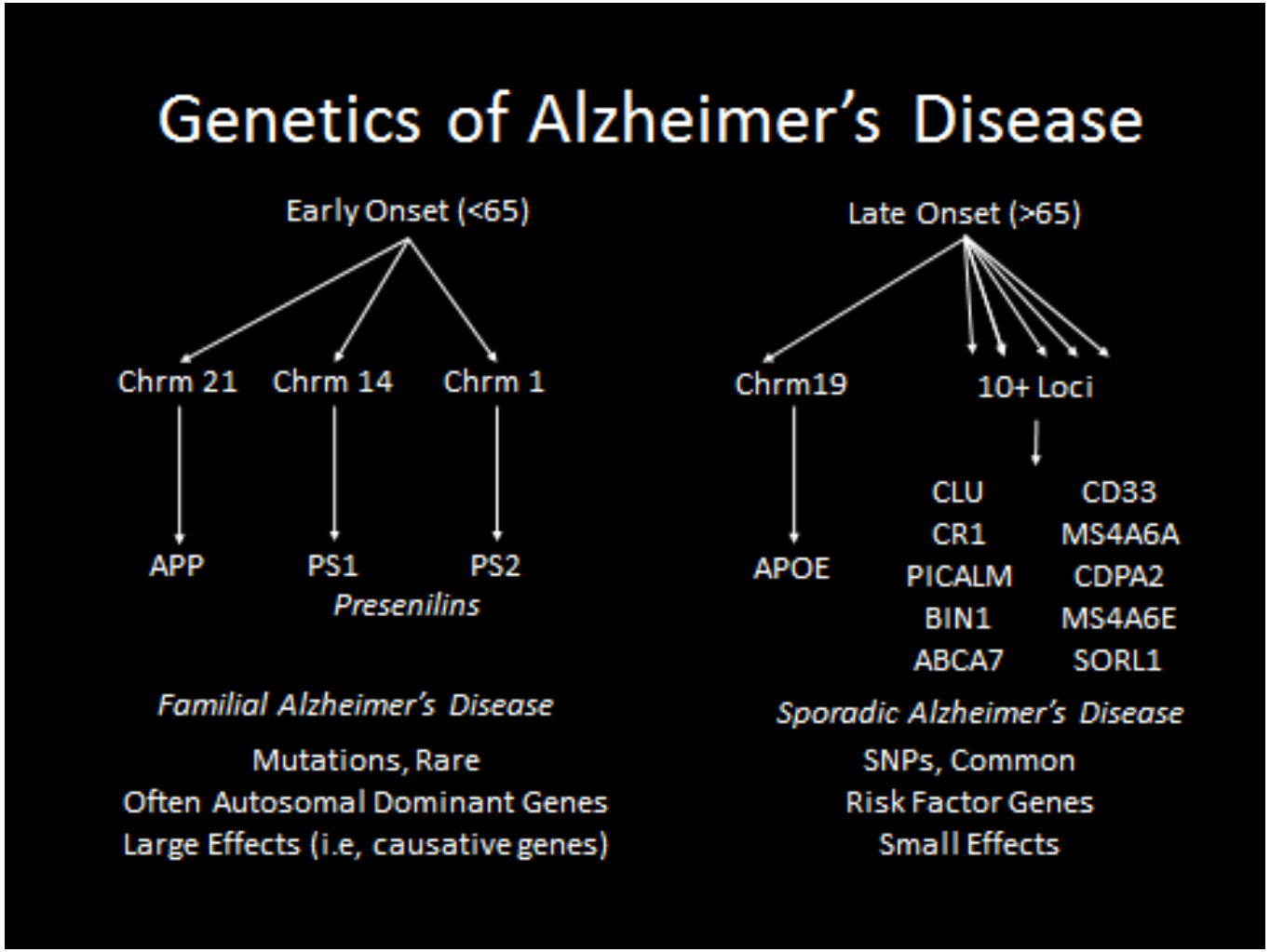
Genetic risk factors for AD: APOE4

- Mechanism of Action:

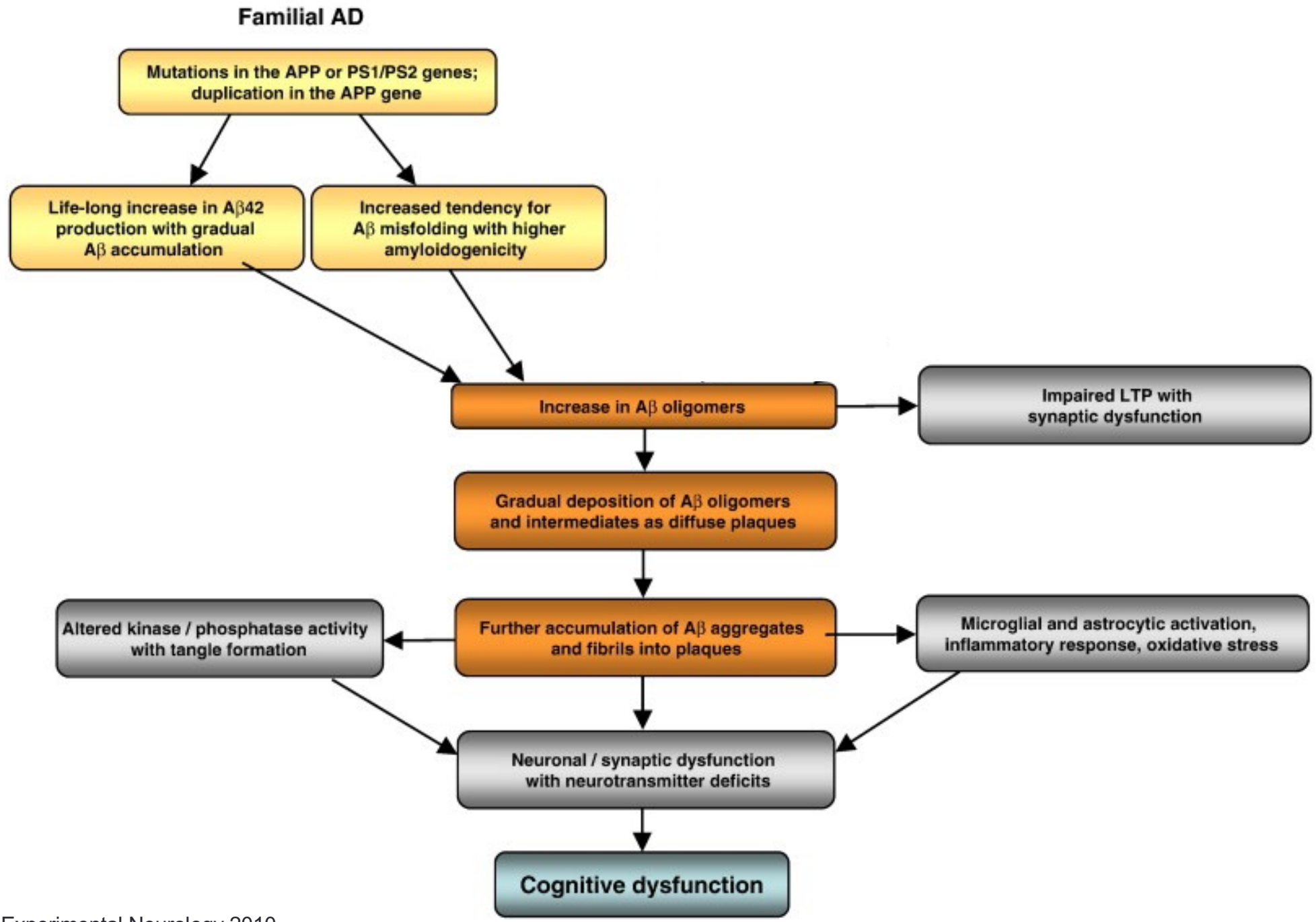
ApoE4



Summary genetic risk factors:

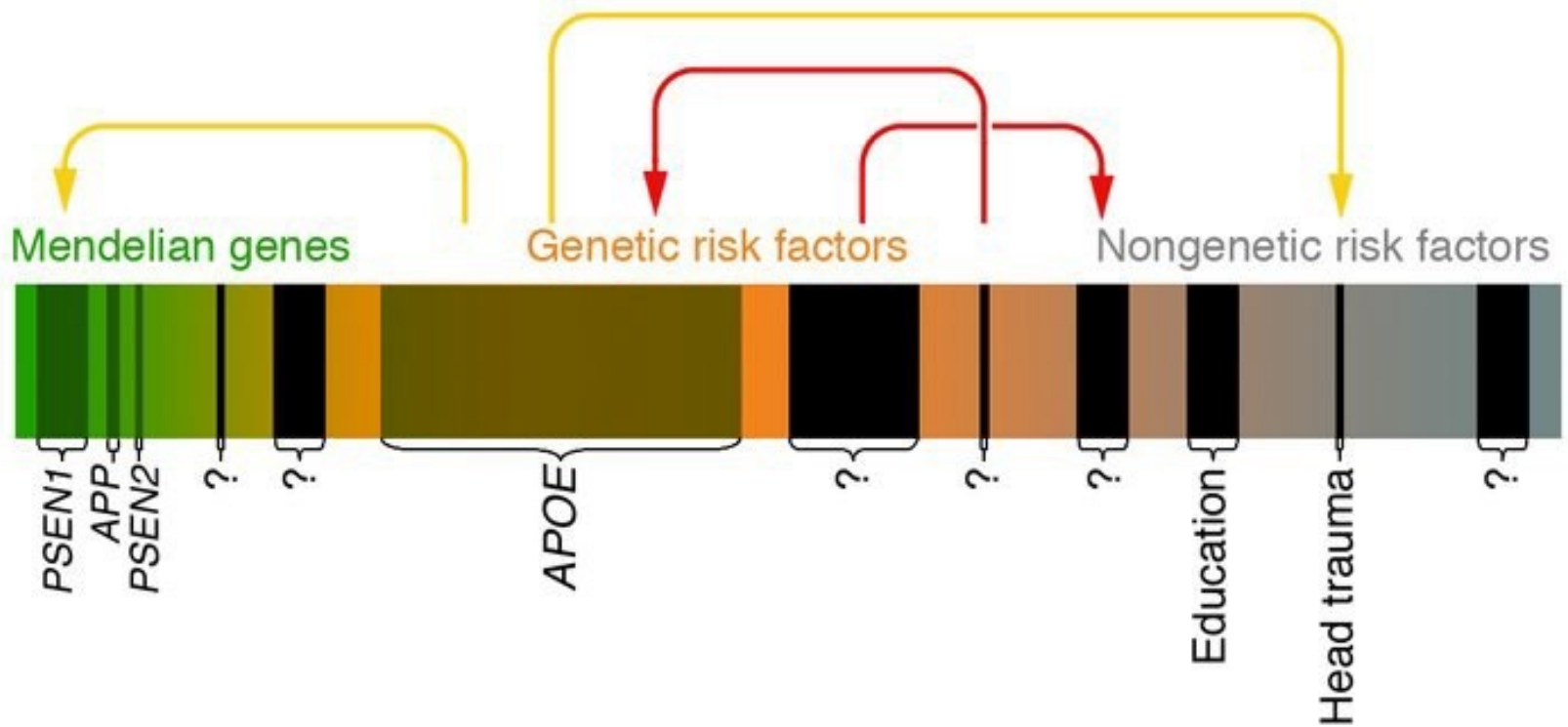


Alzheimer's Disease: FAD vs SAD



The (genetic) etiology of AD

The **risk spectrum** predisposing to AD as one continuum



- The width of these boxes approximately represents the relative contribution to the overall risk
- Colored arrows indicate possible gene-gene and gene-environment interaction patterns