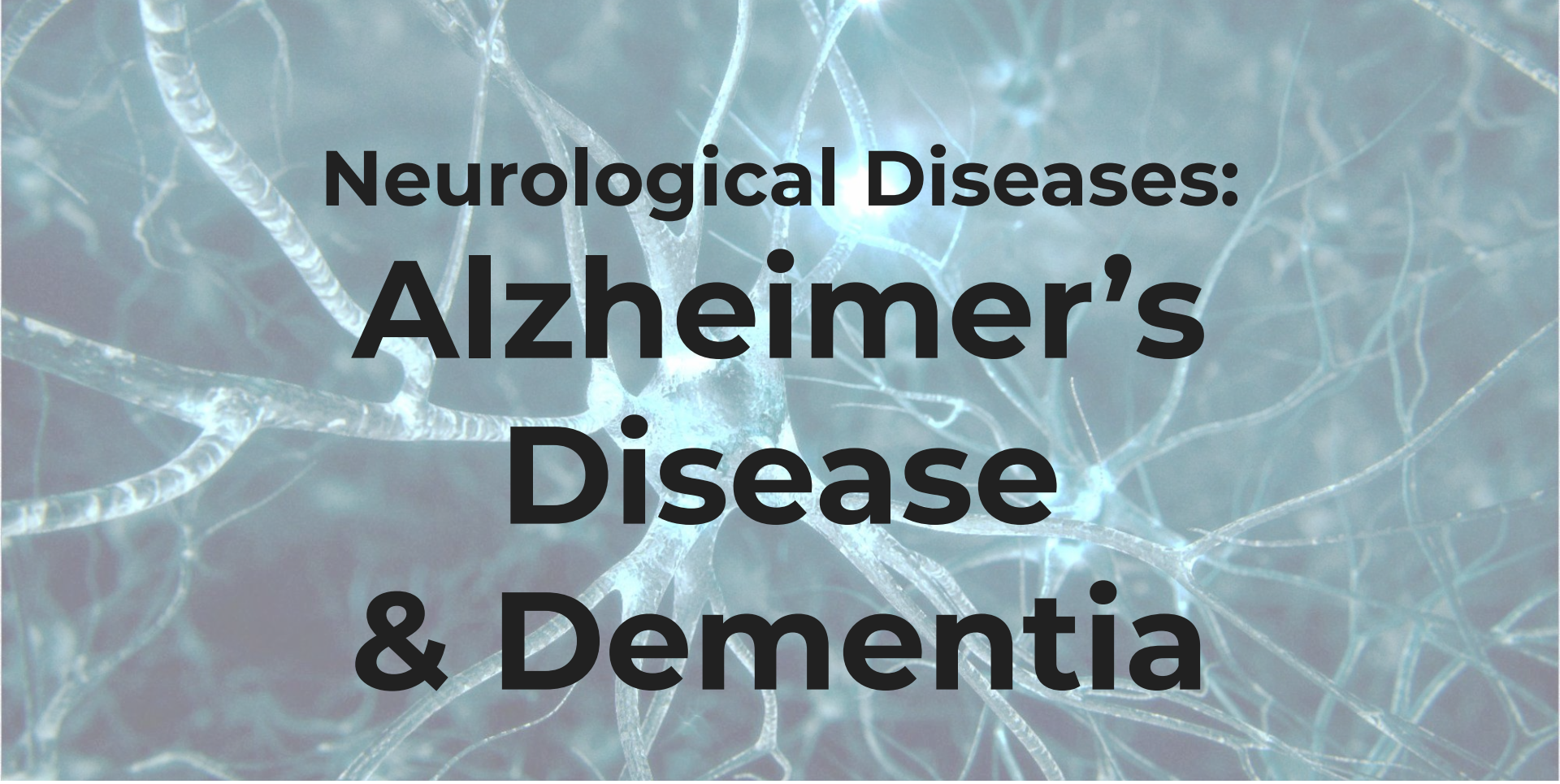


Neurological Diseases: Alzheimer's Disease & Dementia

07.18.2020

Andrés, Audrey, Daniel, and Joyce

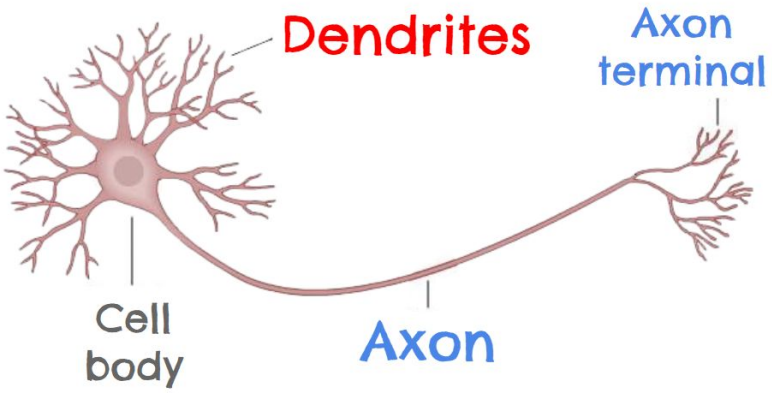
Recap of last week

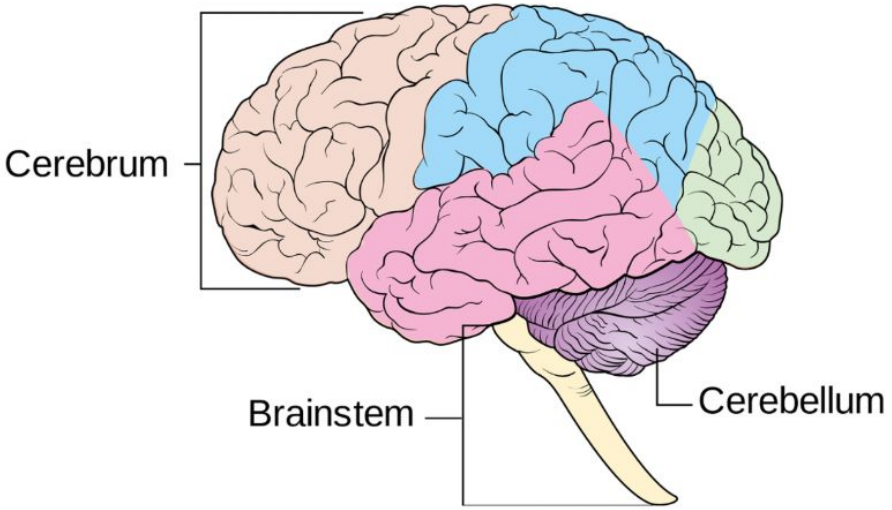
Join at **www.kahoot.it**
(phone, tablet, or computer are OK)

With Game PIN **8993465**

We will start the game when everyone has joined

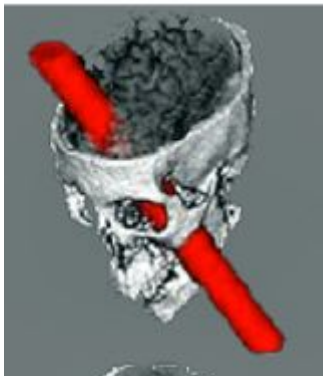
Recap answers





86 BILLION neurons, over 100 trillion synapses

Electrical signals flow one direction. This is called an action potential



Outline for today

What is Alzheimer's Disease?

- Stages, symptoms, and risk factors
- Changes in the brain

Biology of AD

- Amyloid beta and tau hypothesis
- Laboratory models of AD
- Clinical trials

New possible treatment from MIT

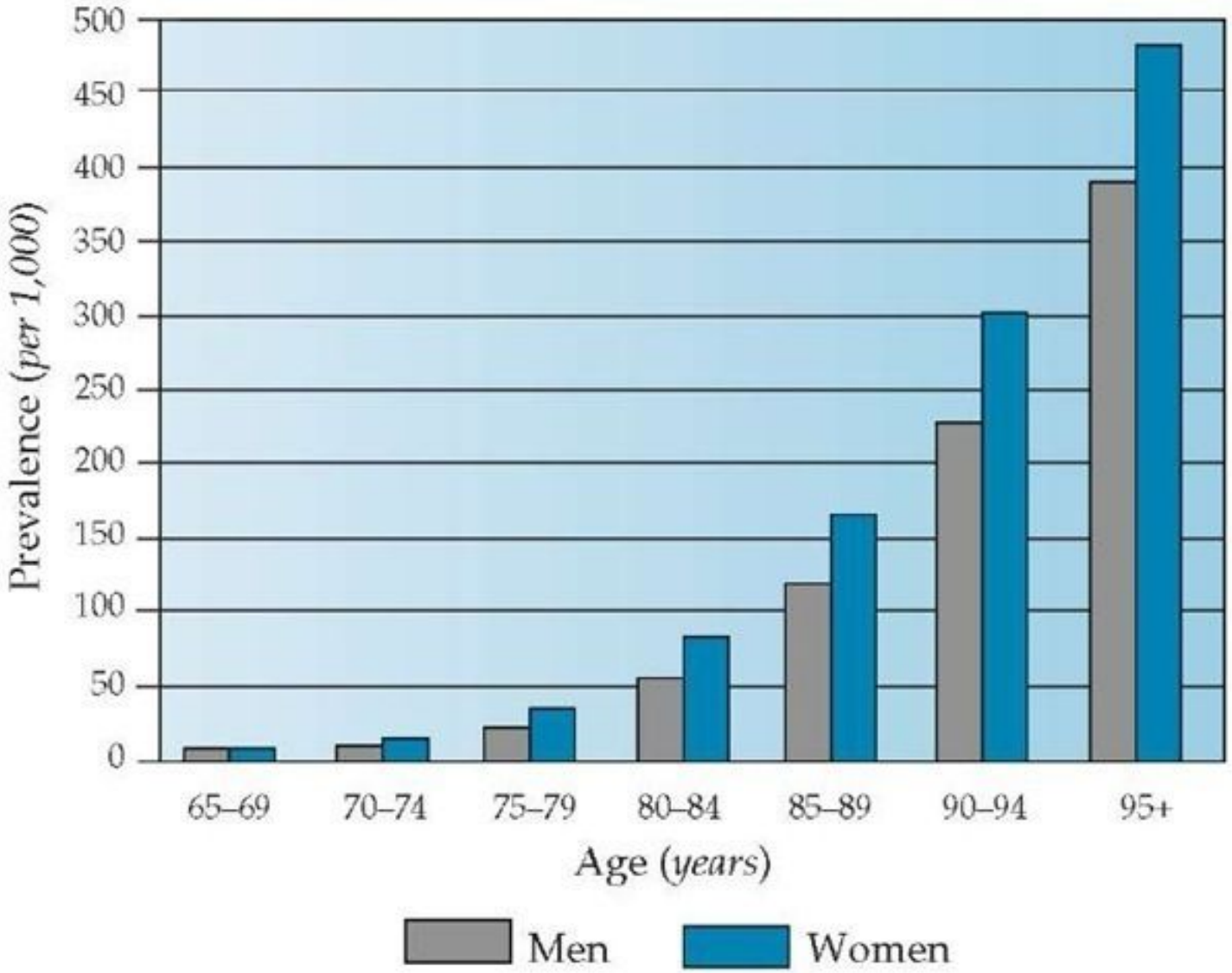
Alzheimer’s disease (AD)

Most common cause of **dementia**

Associated with age

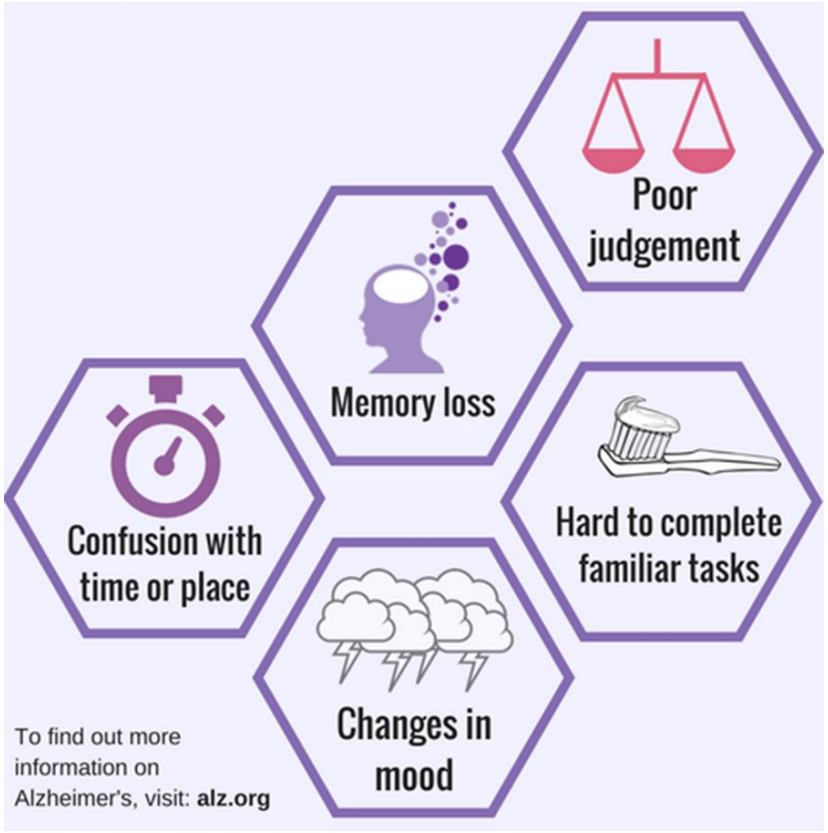
Life expectancy after diagnosis: 3-9 years

Age is the biggest AD risk factor



Early stages of AD

- General forgetfulness
- Impaired short-term memory
- Confusion in unfamiliar places or situations

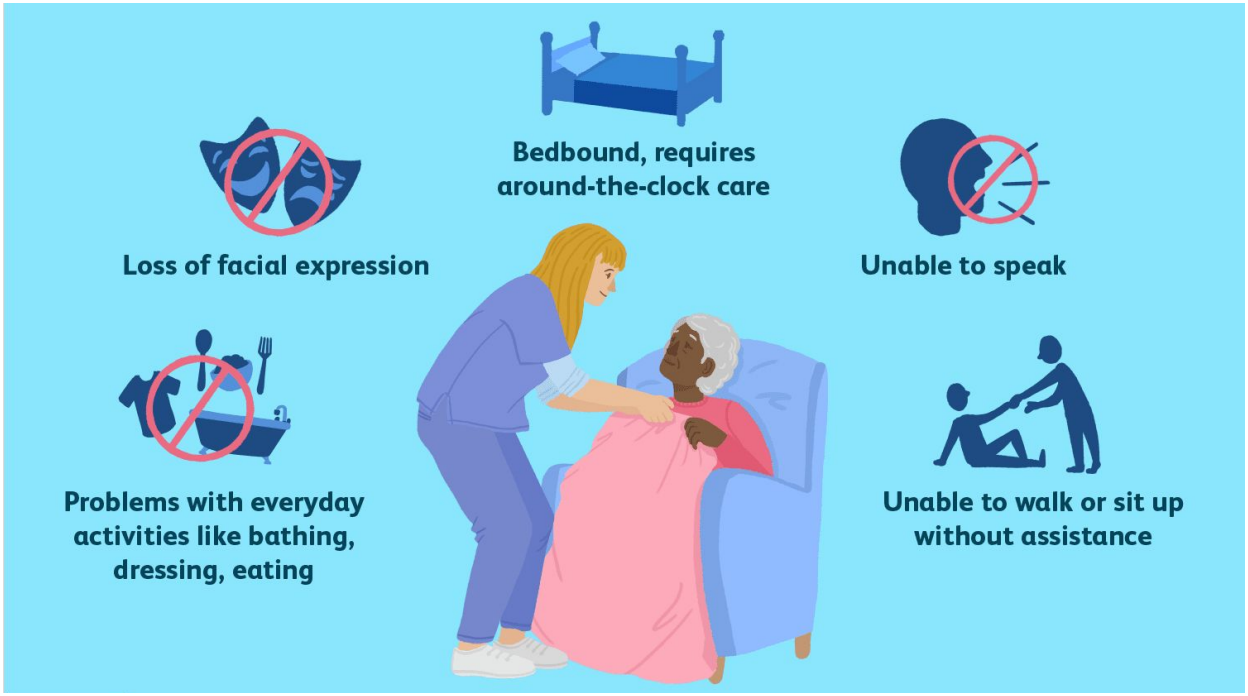


Middle stages of AD

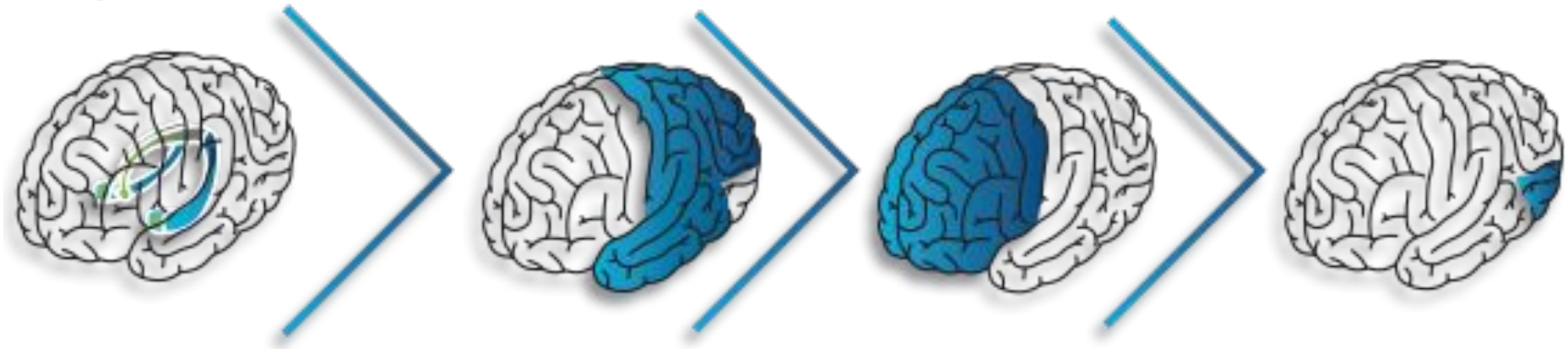
- Substantial memory impairments
- Difficulty performing everyday tasks
- Problems with speech, coordination, and attention
- Personality changes

Late stages of AD

- Complete dependence on caregivers
- Near total loss of speech
- Loss of mobility and muscle mass



Anatomy of AD progression



Duration: 7 years

Disease begins in Medial Temporal Lobe

Symptoms:
- Short-term memory loss

Duration: 2 years

Disease spreads to Lateral Temporal & Parietal Lobes

Symptoms include:
- Reading problems
- Poor object recognition
- Poor direction sense

Duration: 2 years

Disease spreads to Frontal Lobe

Symptoms include:
- Poor judgment
- Implusivity
- Short attention

Duration: 3 years

Disease spreads to Occipital Lobe

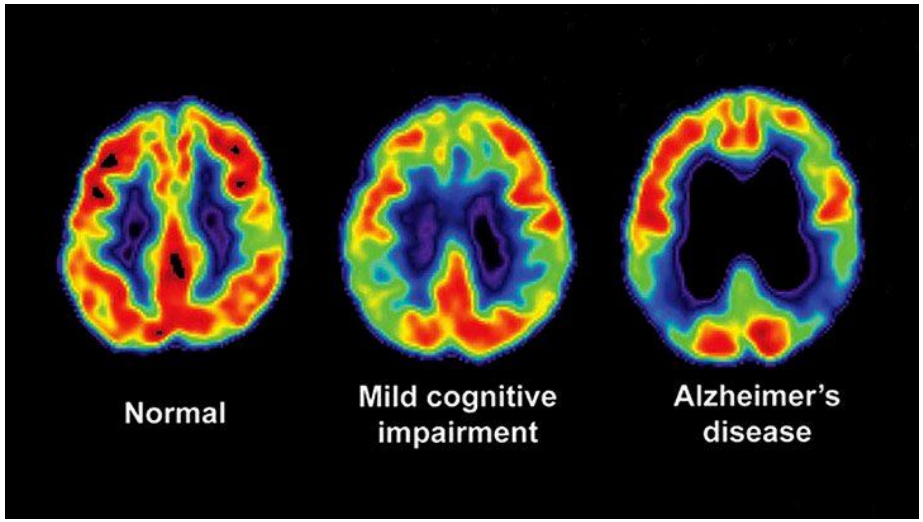
Symptoms include:
- Visual problems

How is AD diagnosed?

There is no conclusive test for AD. It can only be conclusively diagnosed after death.

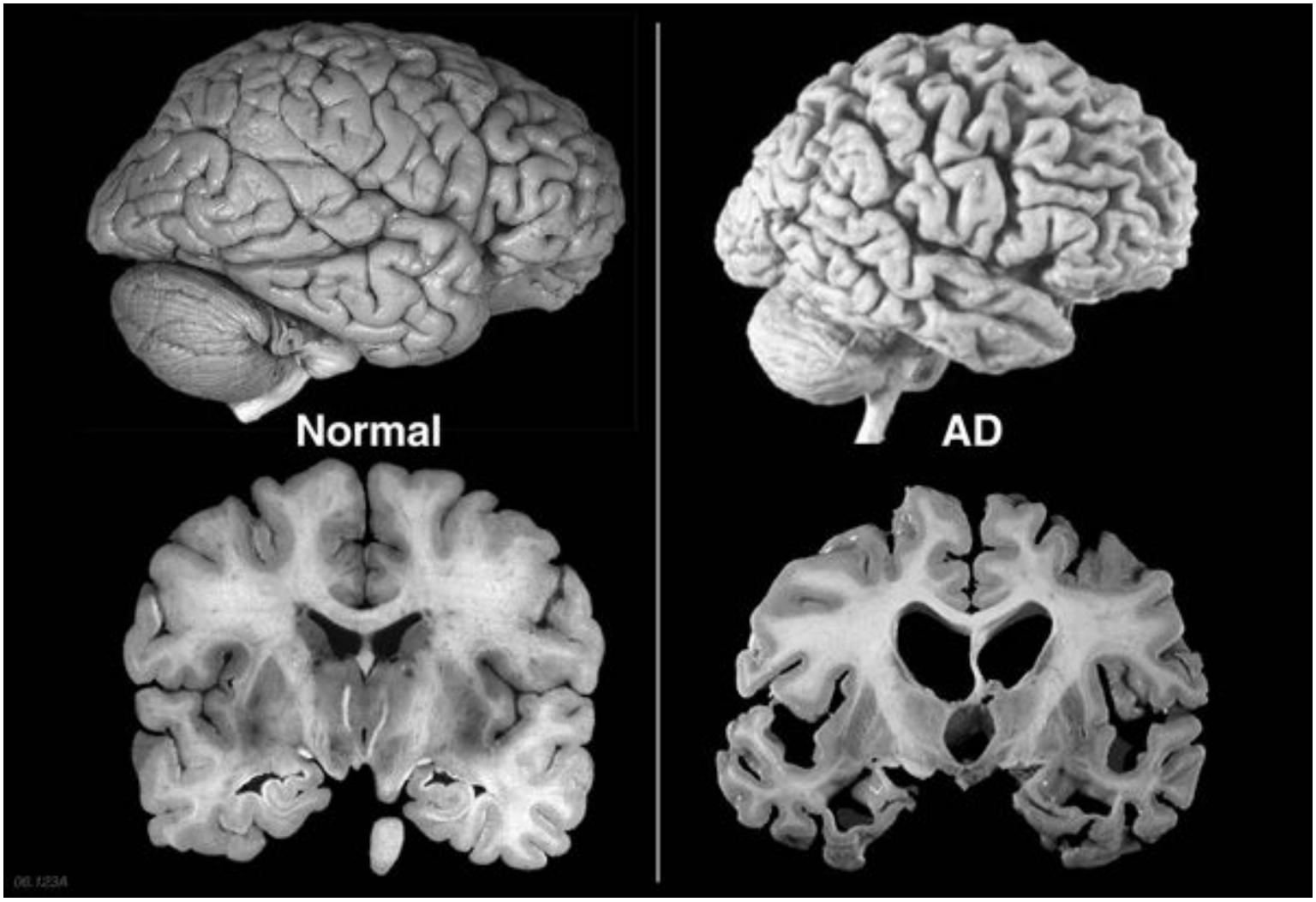
Potential methods to diagnose AD are being developed and tested:

- MRI and PET imaging
  - Structure
  - Brain activity
  - Metabolism
  - Amyloid/tau presence
- Cerebrospinal fluid (CSF) sampling



The biology of AD

Large-scale changes in AD

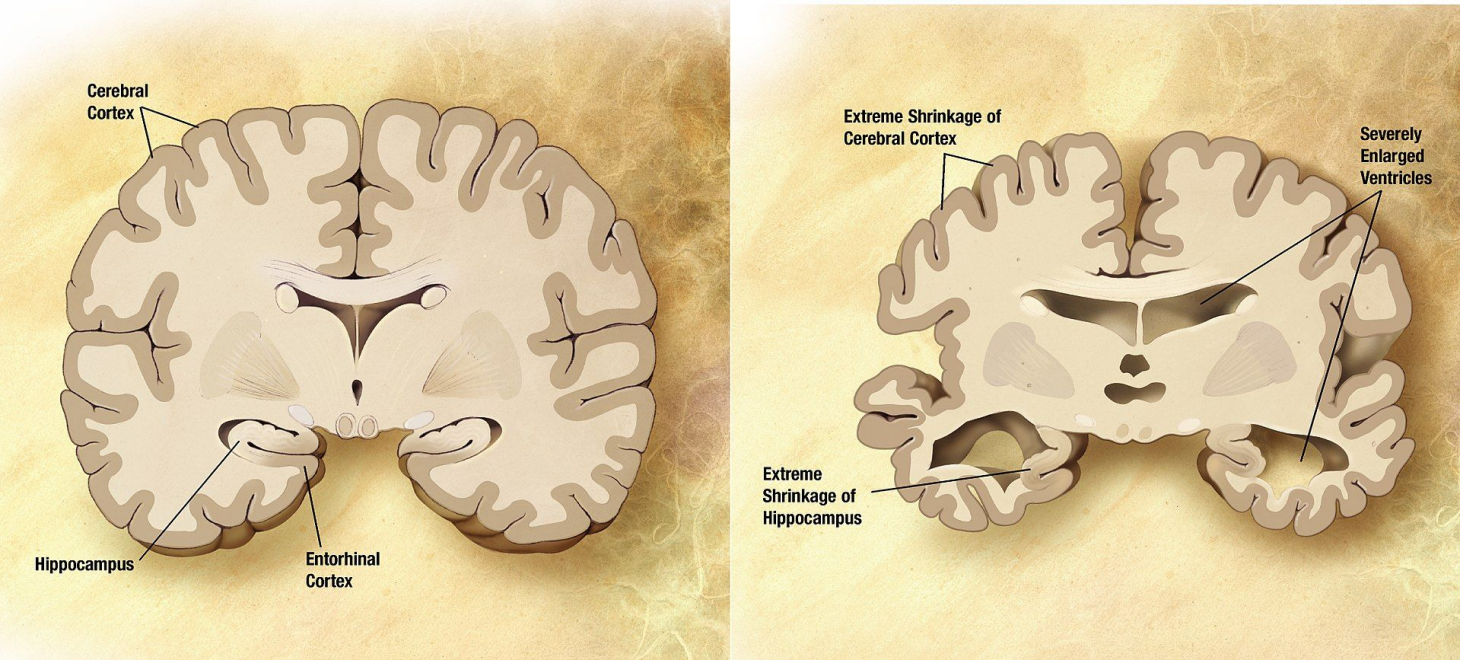


Neurodegeneration

The progressive loss of structure or function of neurons

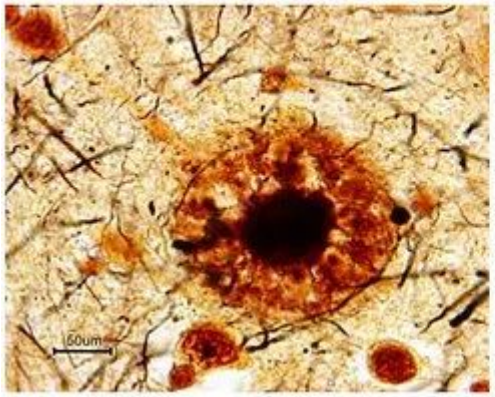
- Reduced cell number (**cell death**)
- Reduced brain volume (**atrophy**)

Region-specific degeneration can cause specific cognitive deficits.



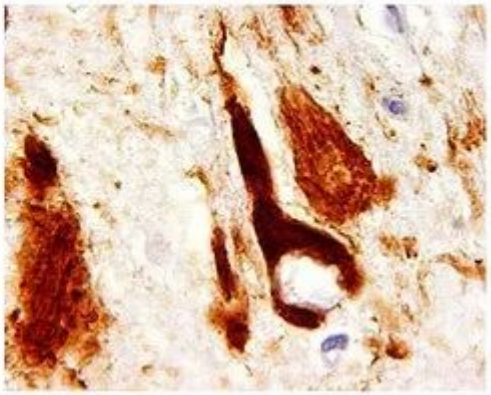
Molecular signature of AD

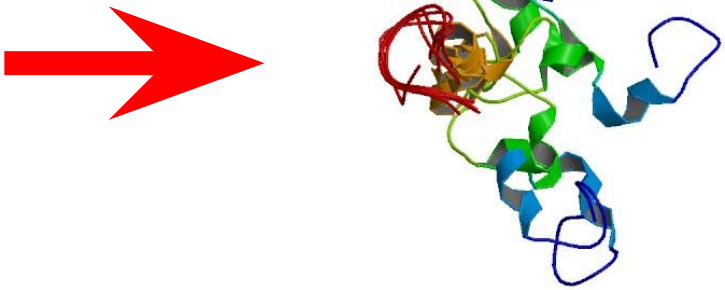
Plaques



Amyloid beta

Neurofibrillary Tangles

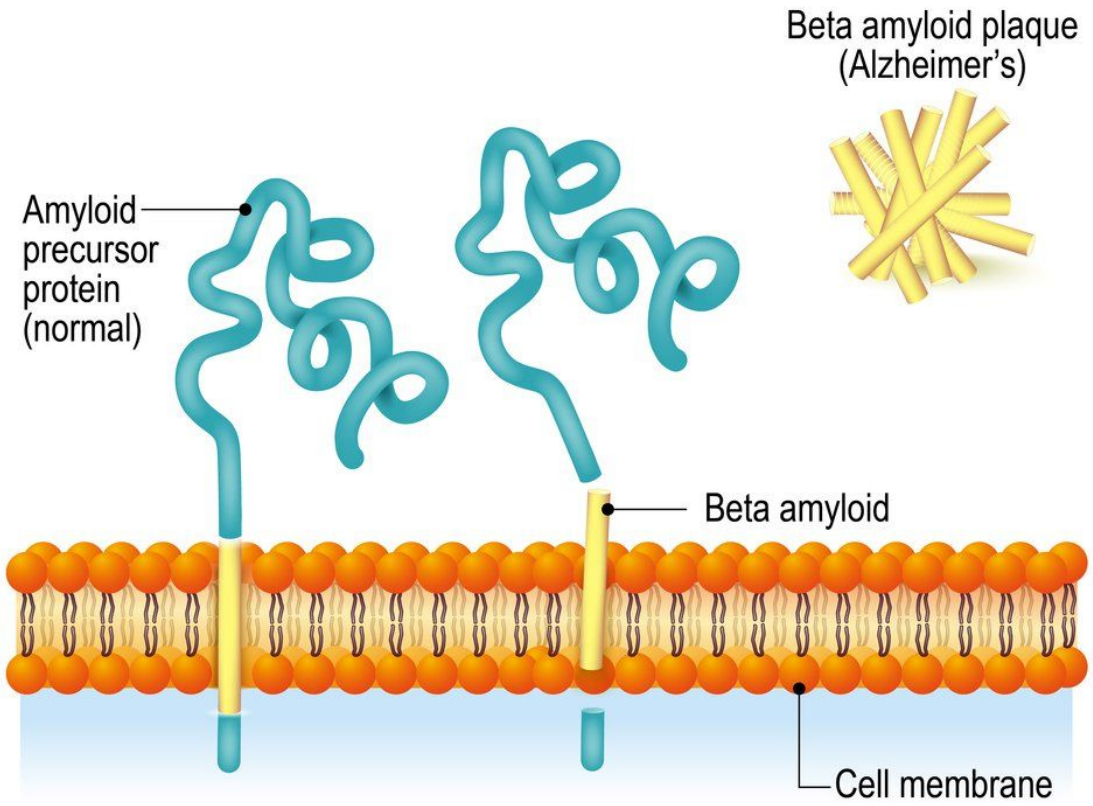


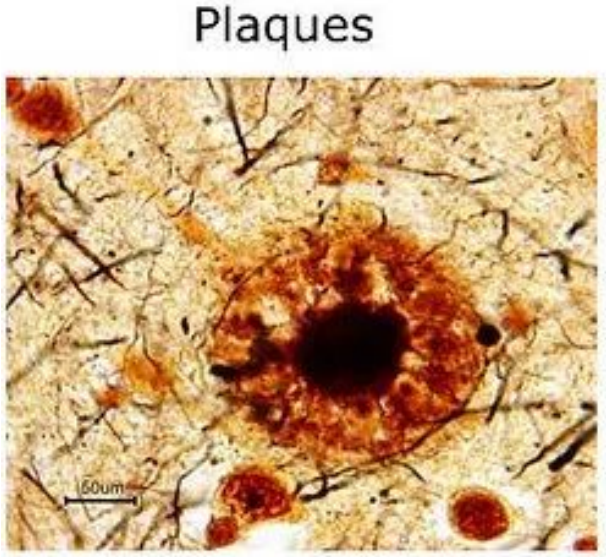


Tau

Role of amyloid in AD

Extracellular amyloid beta deposits contribute to neuronal damage in AD.

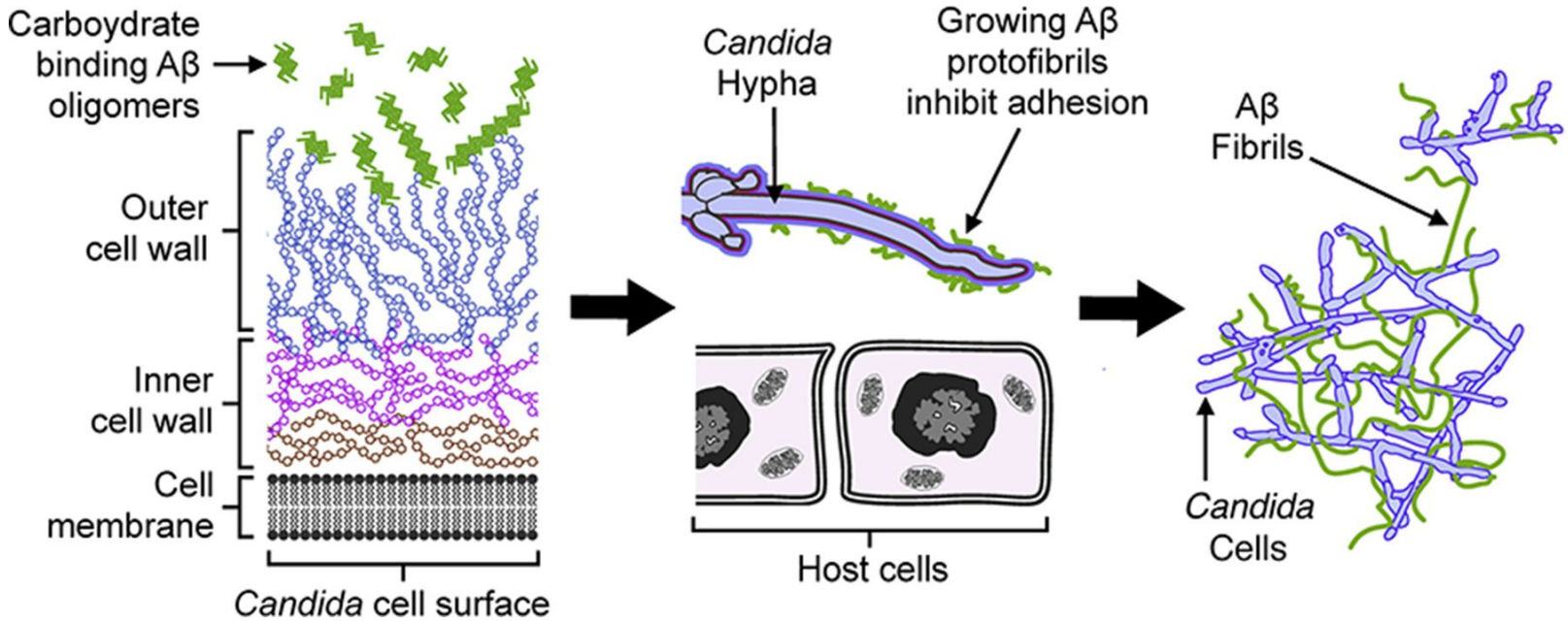




Why do we have amyloid?

Amyloid beta could have a protective anti-microbial function:

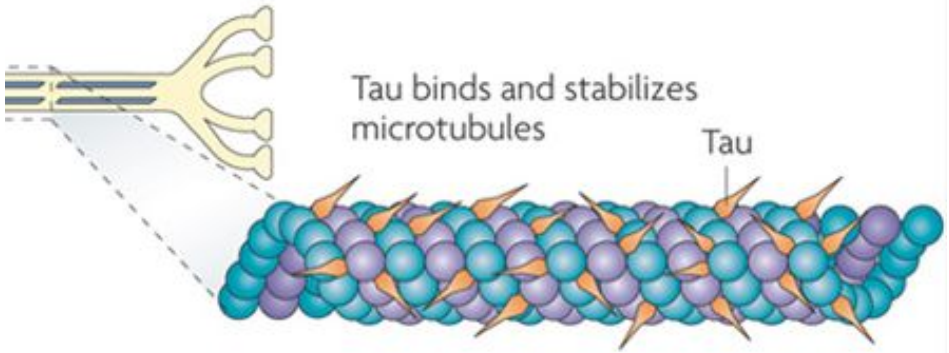
- Binds to cell wall of microbes
- Blocks microbes from sticking to healthy host cells
- Traps bacteria within a resistant matrix



Role of tau in AD

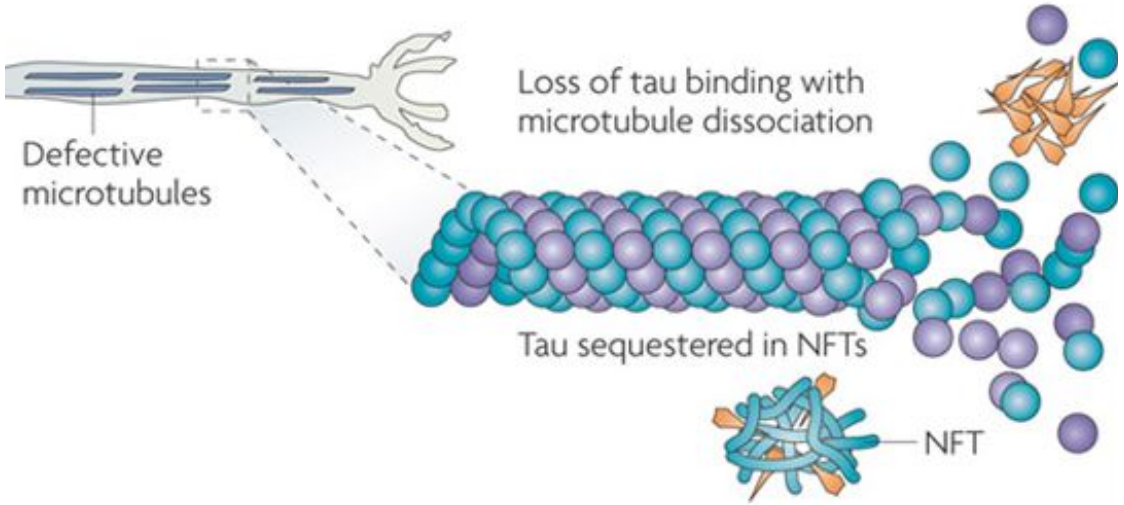
Healthy tau:

- Normally found in axons
- Stabilizes cytoskeleton

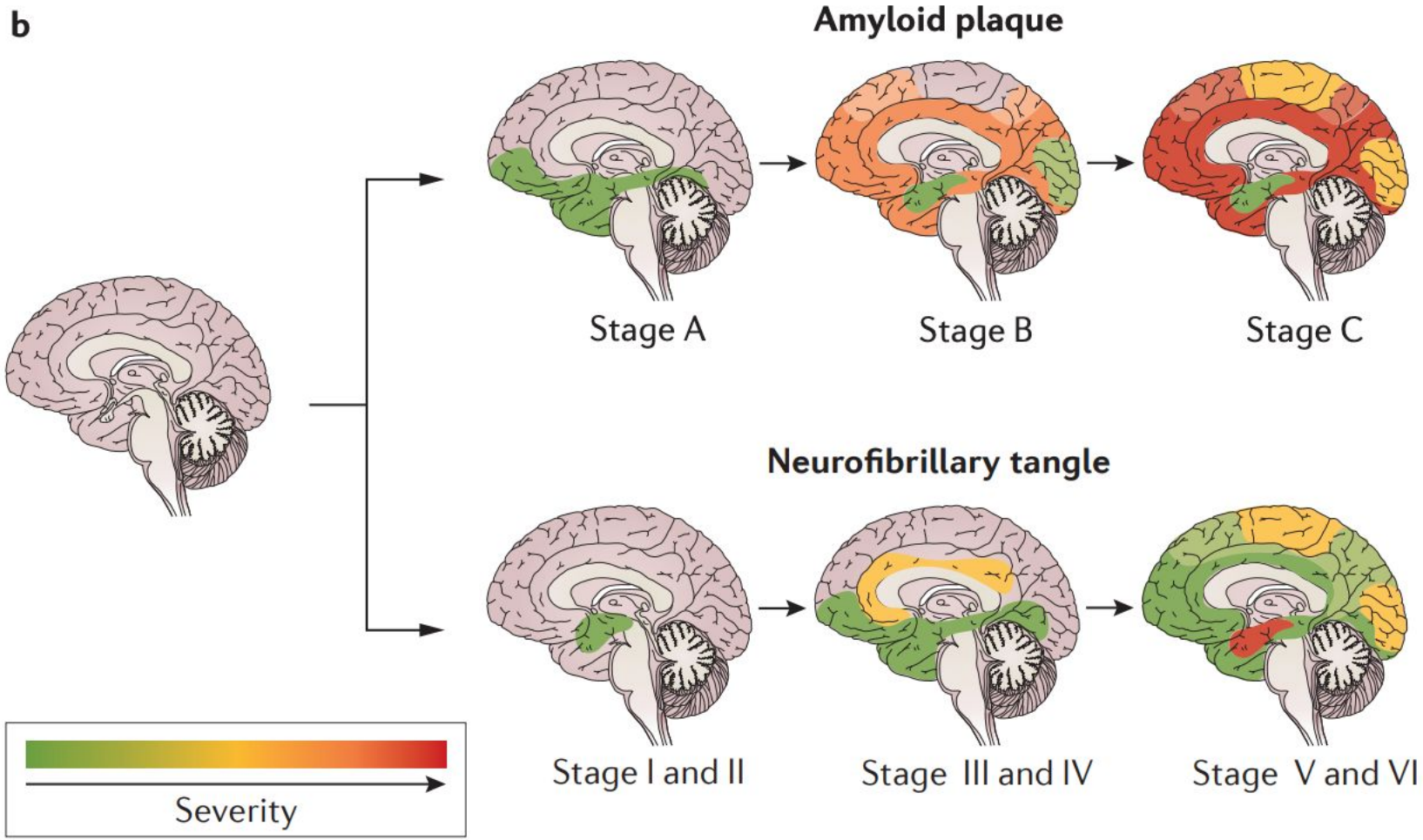


Neurofibrillary tangles:

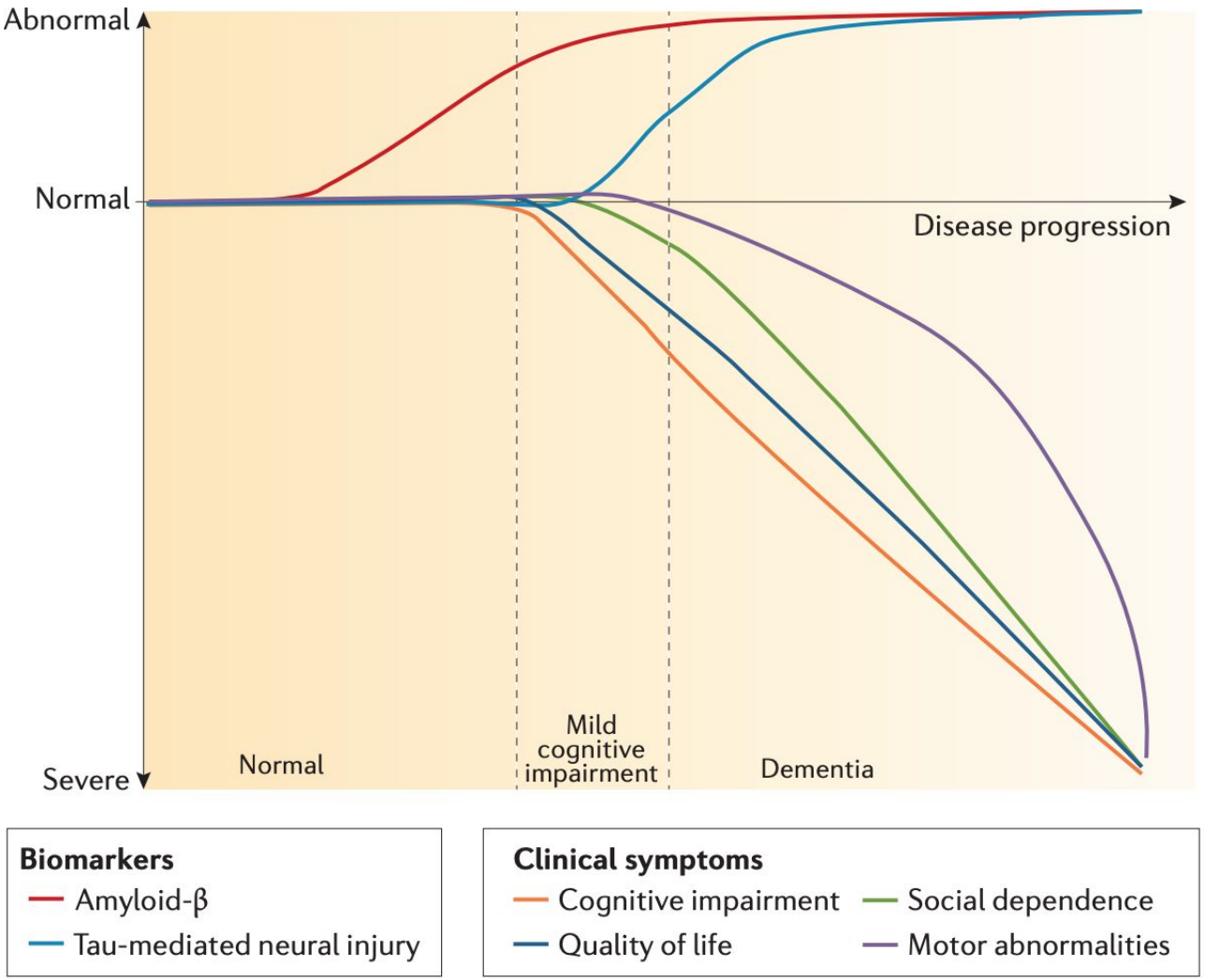
- Tau separates from cytoskeleton
- Tau aggregates within NFTs
- Cytoskeleton becomes unstable



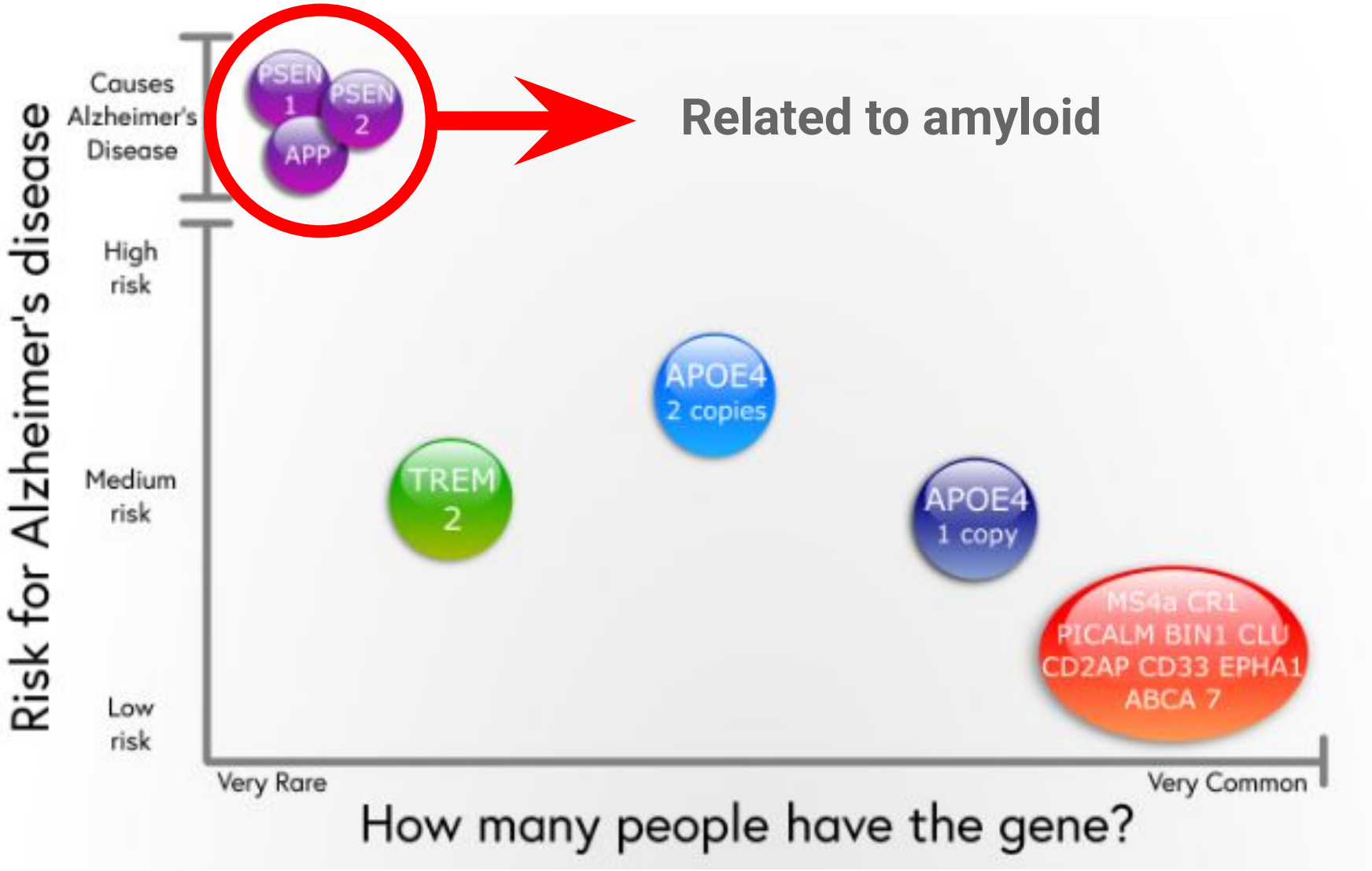
Spread of amyloid, tau, and neurodegeneration



Spread of amyloid, tau, and neurodegeneration



Genetic risk factors for AD



AD is mostly NOT inherited

Familial AD (fAD)

- Inherited (genetic) cause

Sporadic AD (sAD)

- No family link
- Likely caused by genetics and lifestyle

Early onset

(<10% of cases)

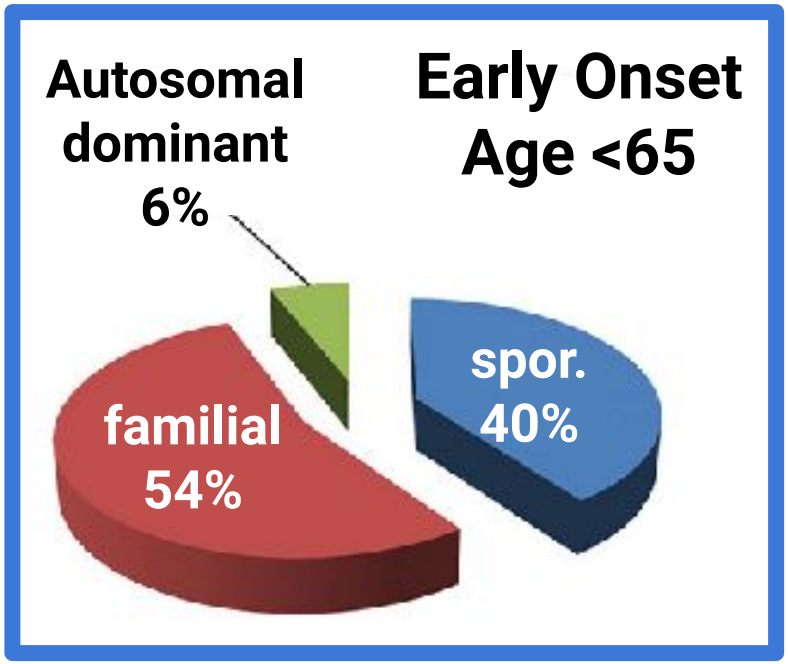
- Before age 65
- Genetic causes
- **More likely to be fAD**

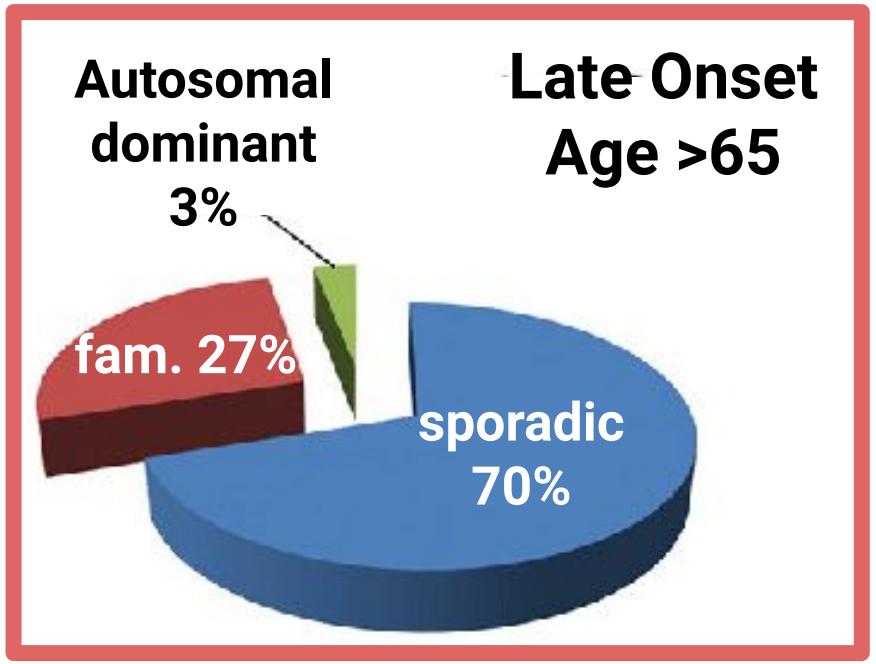
Late onset

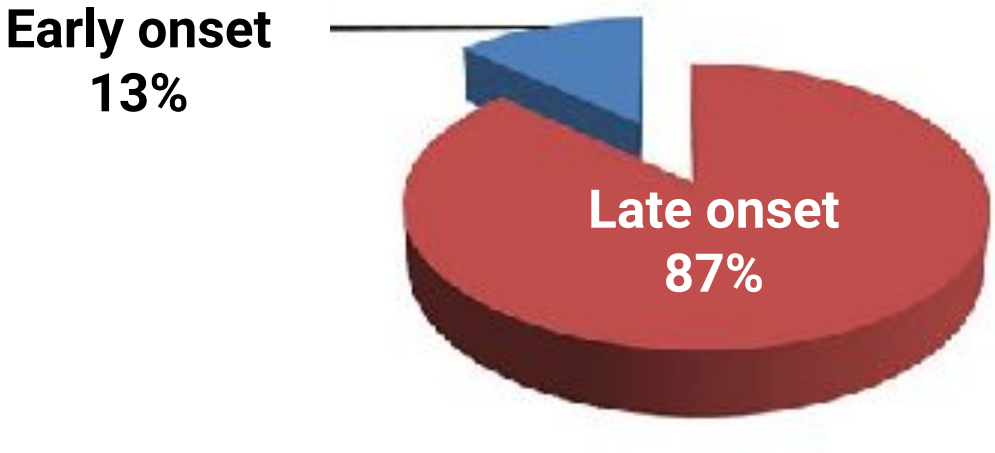
(>90% of cases)

- After age 65
- **More likely to be sAD**

Breakdown of AD cases



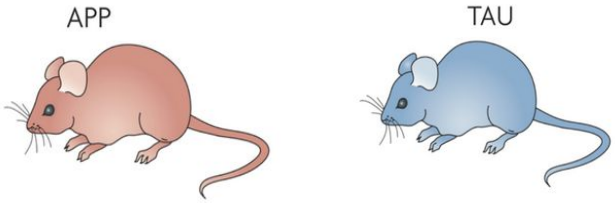




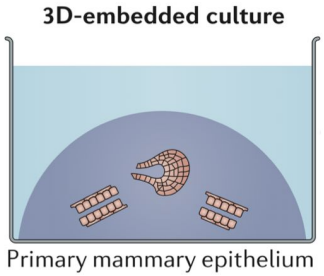
Modeling AD in the lab

Knowledge of amyloid and tau has allowed scientists to create models of AD to study potential mechanisms and treatments for AD.

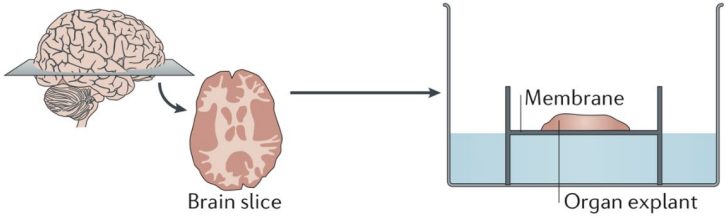
Mouse models



Cell culture



Human tissue



Treatments for AD

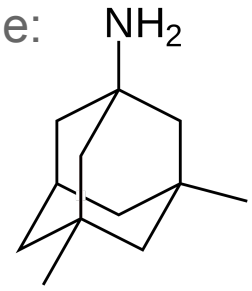
Exercise, memory training, and social engagement can lower risk and improve quality of life.

Two classes of approved drugs:

- Acetylcholinesterase (AChE) inhibitors
- NMDA receptor (NMDAR) antagonists

These treat disease symptoms, but don’t slow/stop AD.

Memantine:



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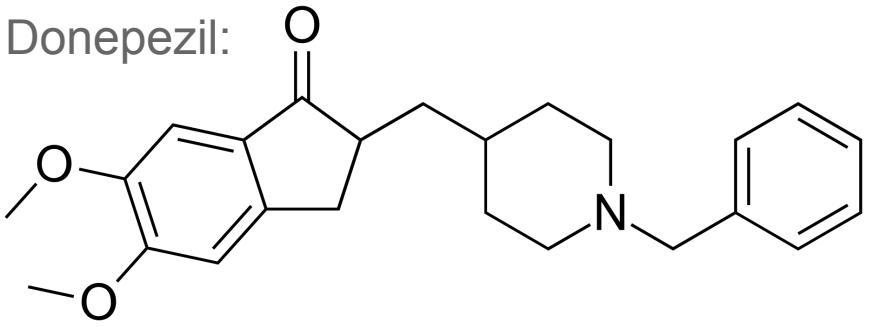
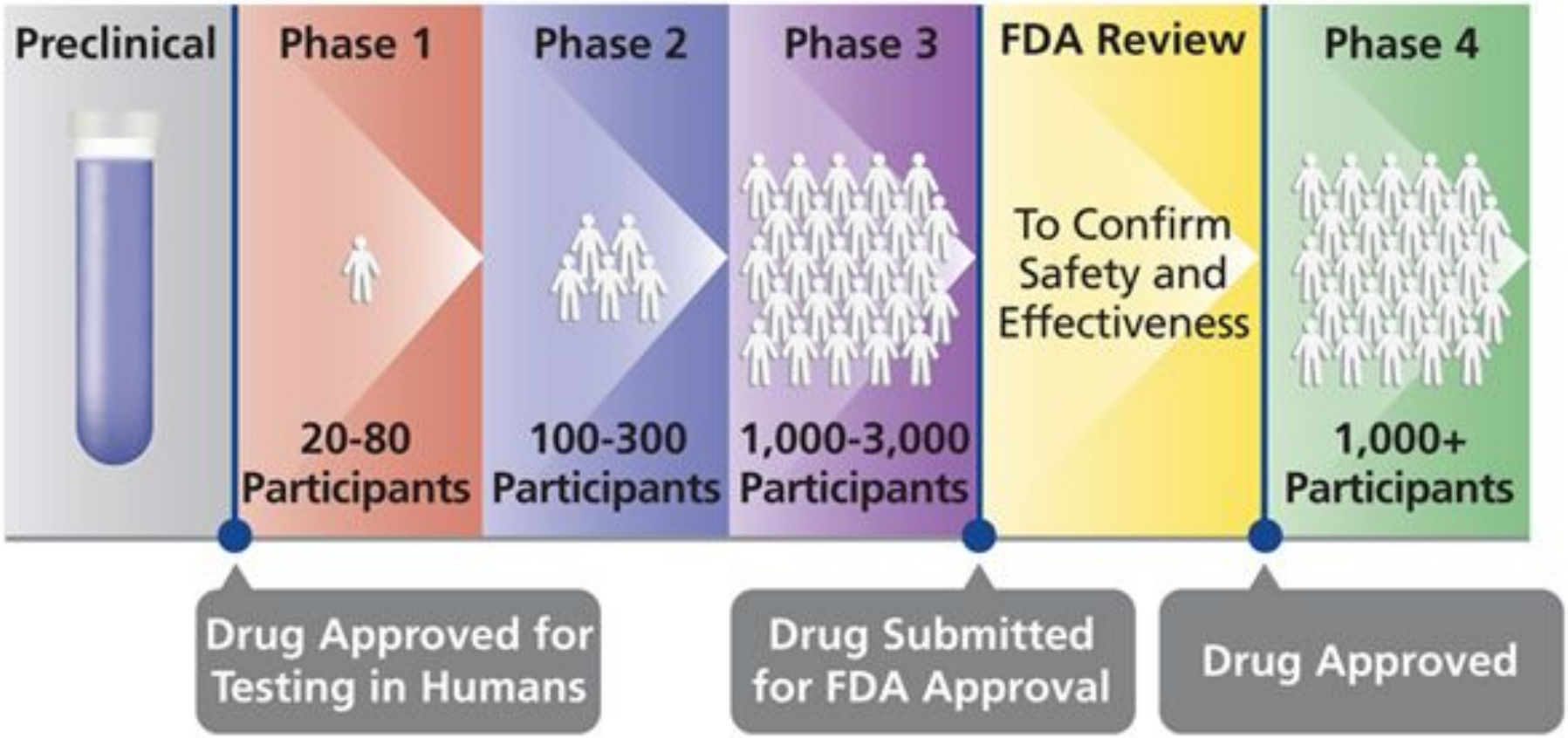


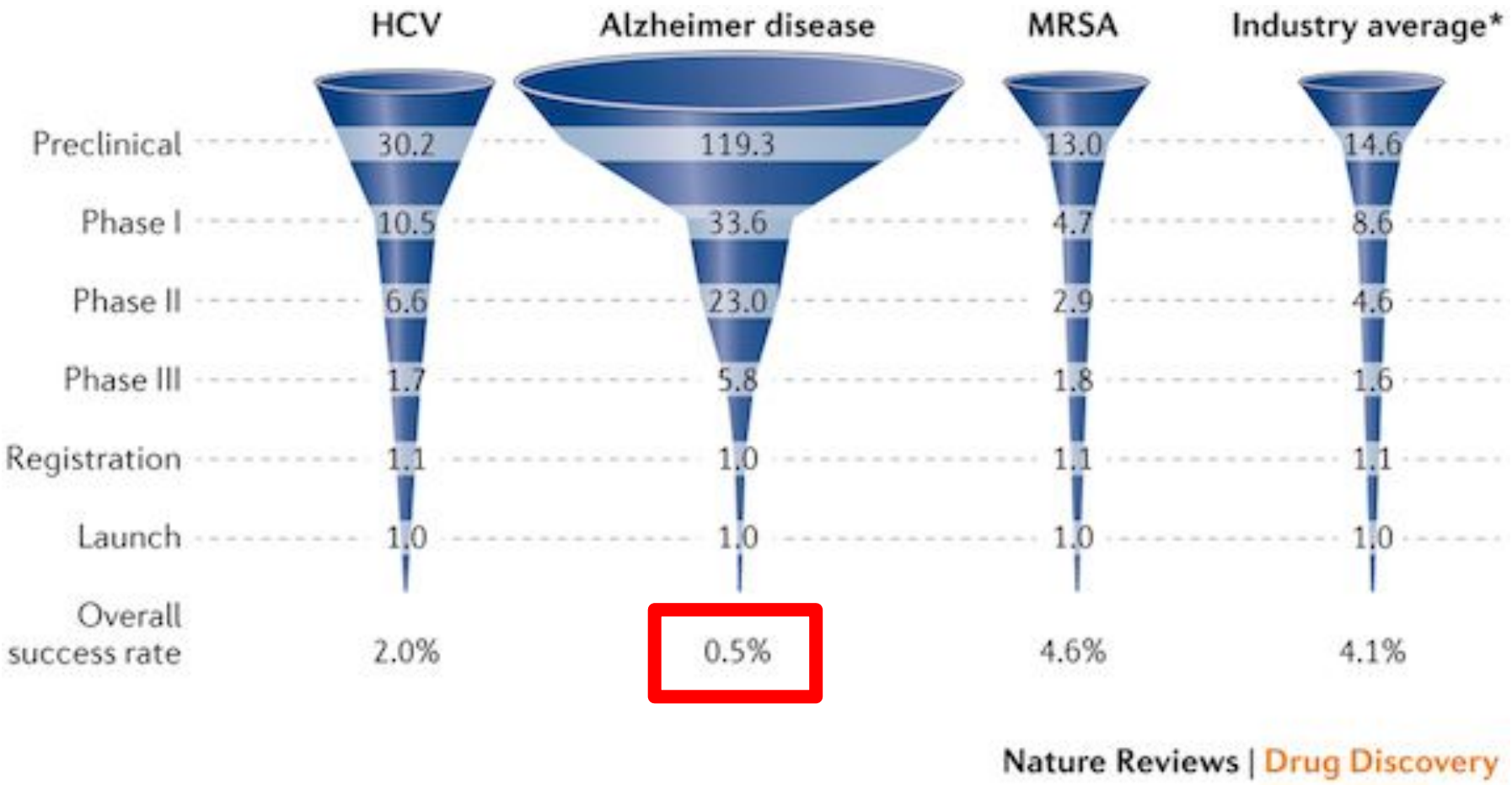
Clinical trials in the US



A typical drug costs **$1B** to get approved.

An AD drug costs **$5.7B**.

Many try, but few succeed



Potential new treatments

Questions?