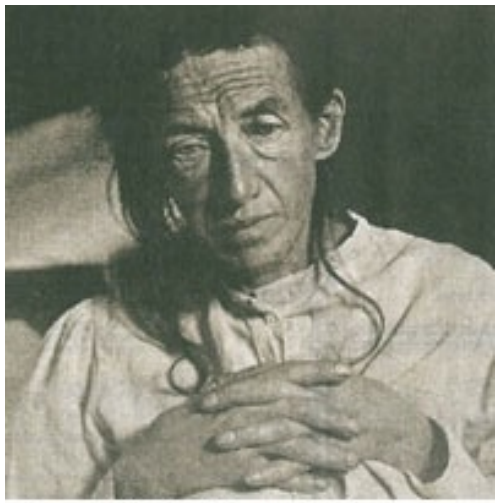
Alzheimer's Disease

- 1901 - Municipal Asylum of Frankfurt
- Auguste Deter, a 51 year old women
  - increasing short-term memory loss
  - strange behaviors:
    - could not find her way around her home
    - dragged objects to and fro
    - sometimes thought that people were out to kill her
    - did not understand when doctors tried to examine her

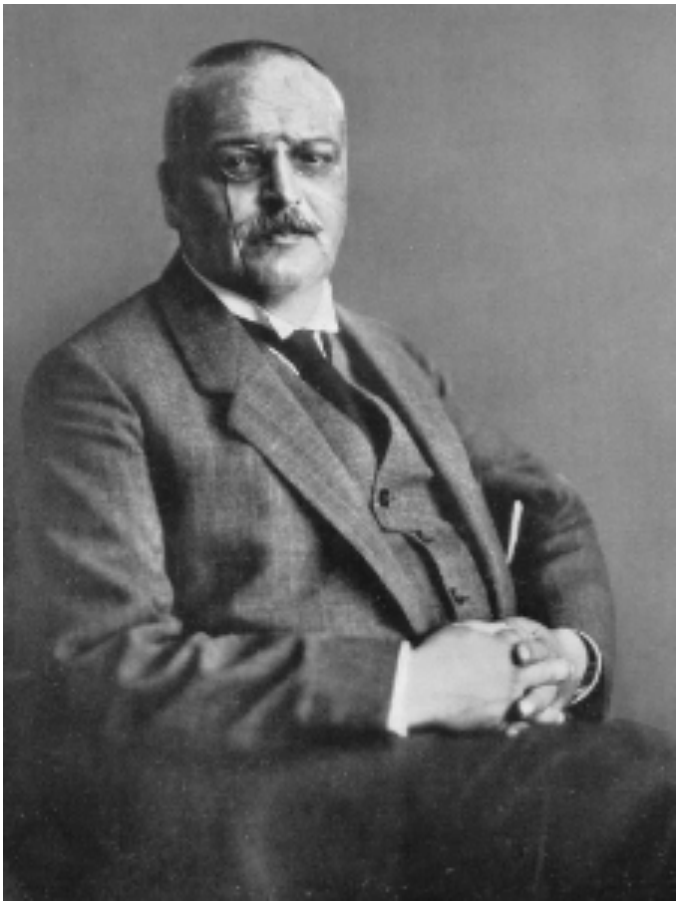


Auguste Deter - taken in 1906, shortly before her death, during her stay at Frankfurt's City Mental Institution.

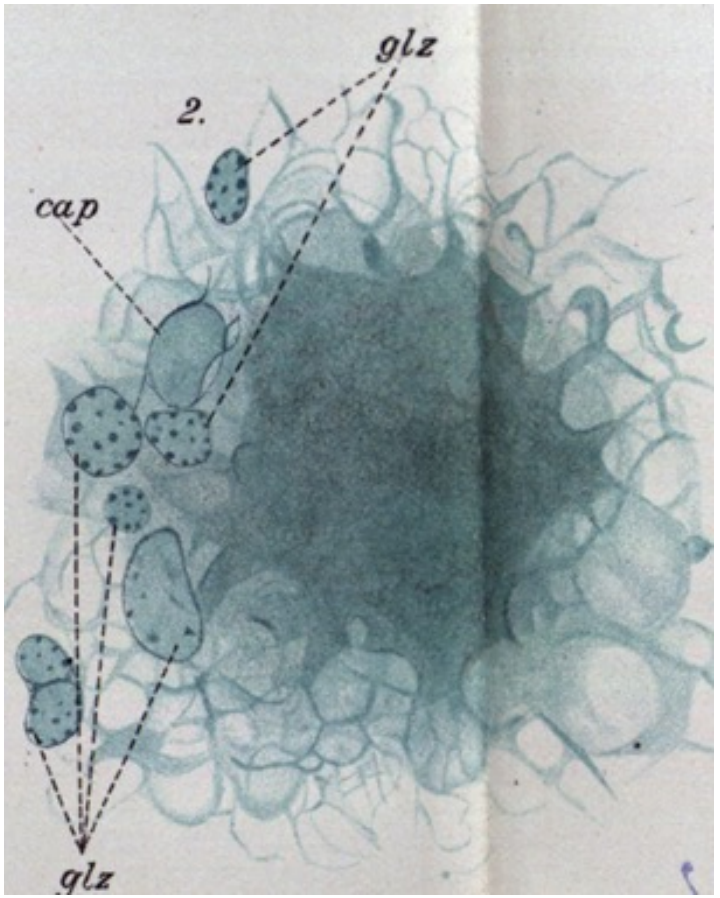
Alzheimer's Disease

Alois Alzheimer - 'the psychiatrist with the microscope'

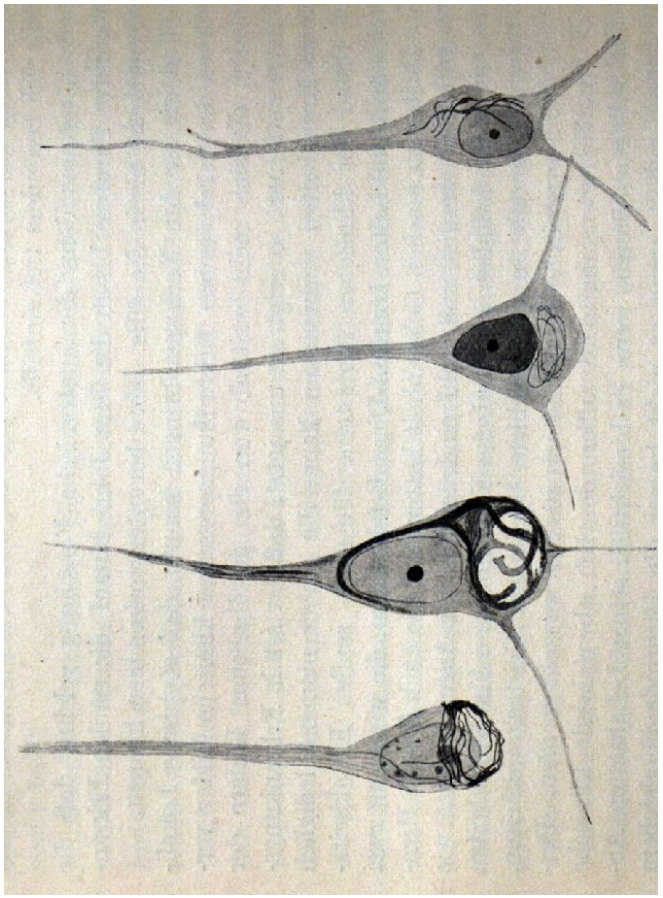
- believed in the "medical model" of psychiatry
  - mental illnesses were diseases of the brain



Extracellular
Plaque



Intracellular
Neurofibrillary Tangle

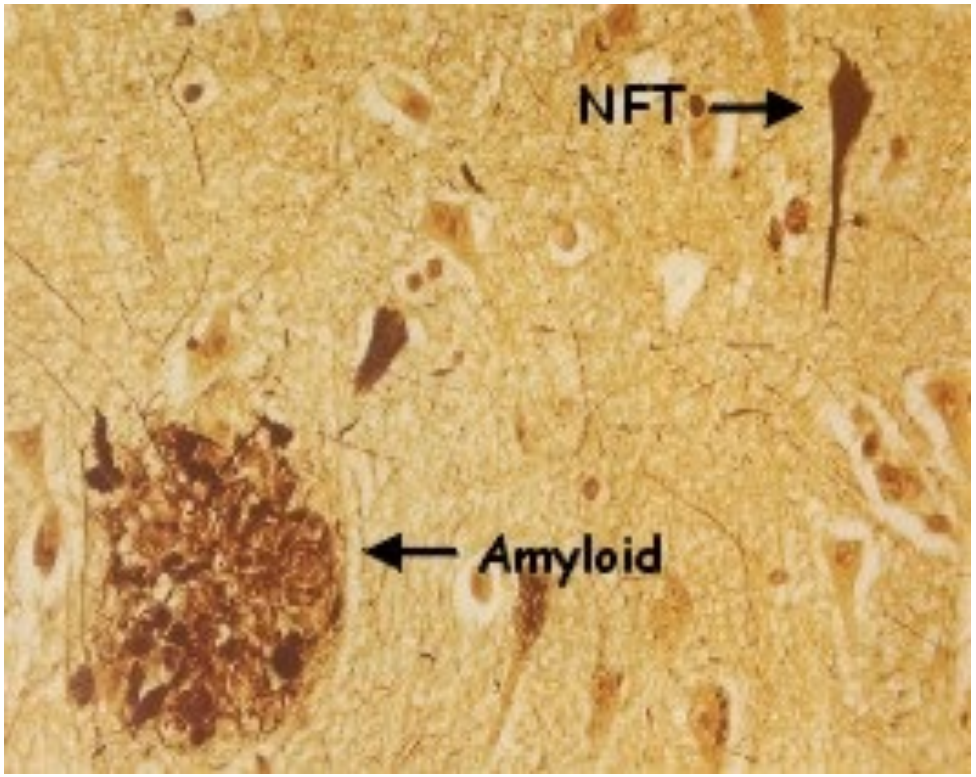


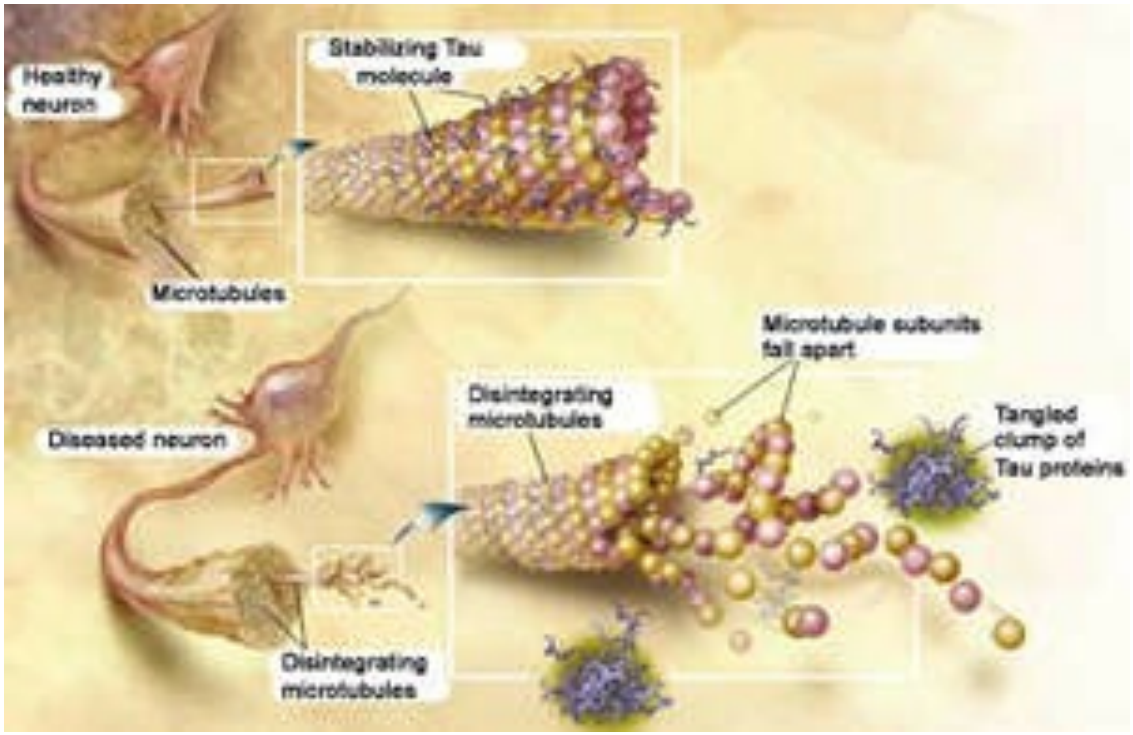
Alzheimer's Disease

- most common neurodegenerative disorder of aging
- most common cause of *dementia*
- ~1 in 10 individuals over the age of 65
  - incidence ~ doubles every 5 years
- **Symptoms:**
  - Memory loss for recent, but not distant, events
    - declarative / visuospatial / relational
  - progressive decline in cognitive and motor abilities

Alzheimer's Neuropathology

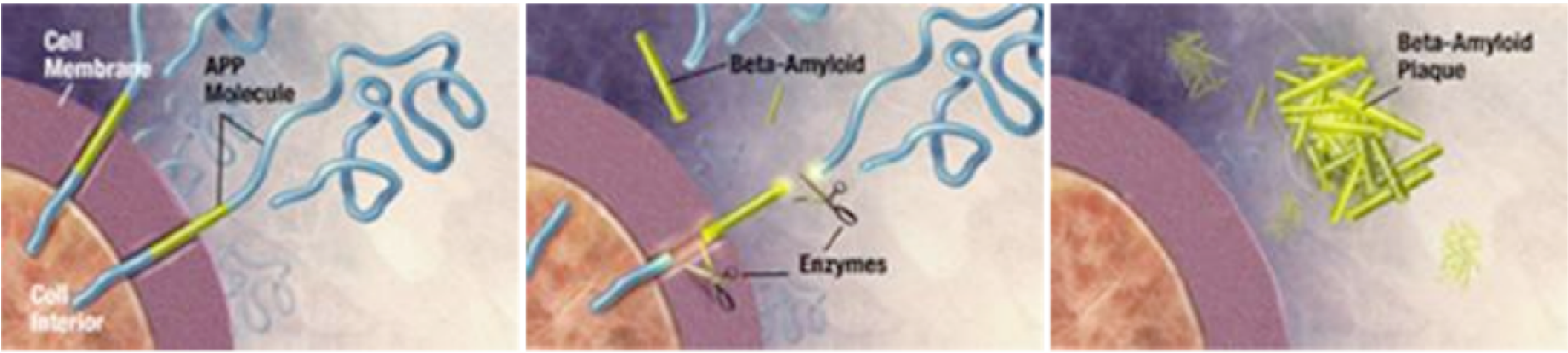
- **Neuropathological hallmarks:**
  - accumulation of protein deposits ("**plaques**") surrounding the brain's neurons (literally like cobwebs)
  - neurofibrillary **tangles** (NFTs) inside the neurons





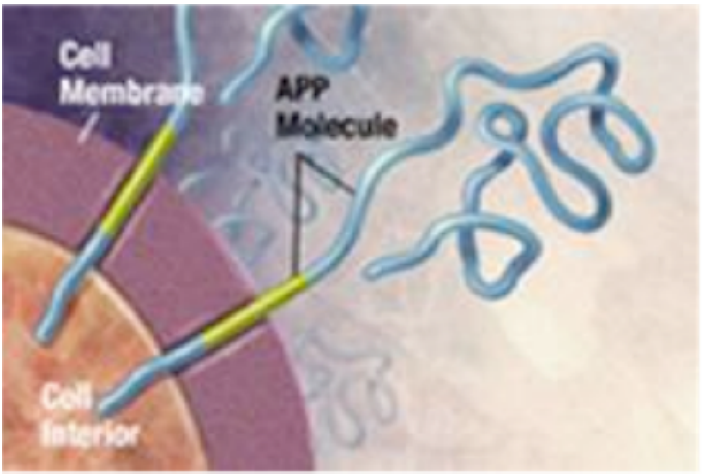
Plaque Development

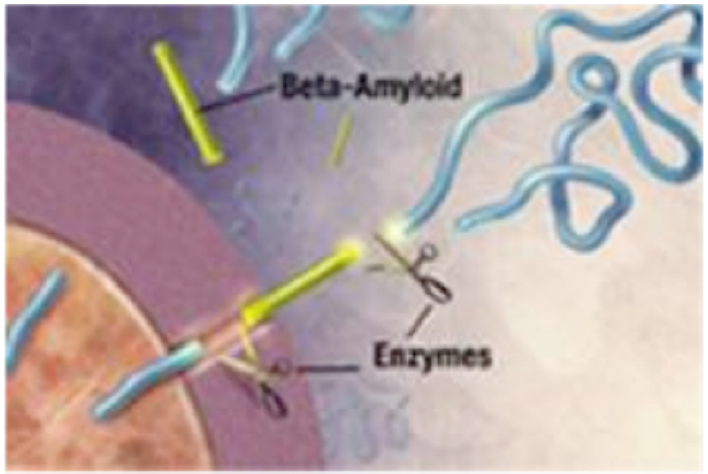
- The plaques that build up in the brain are composed predominantly of the <u>amyloid-β</u> (Aβ) peptide
  - 39-43 amino acid peptide enzymatically cleaved from *amyloid precursor protein* (APP)

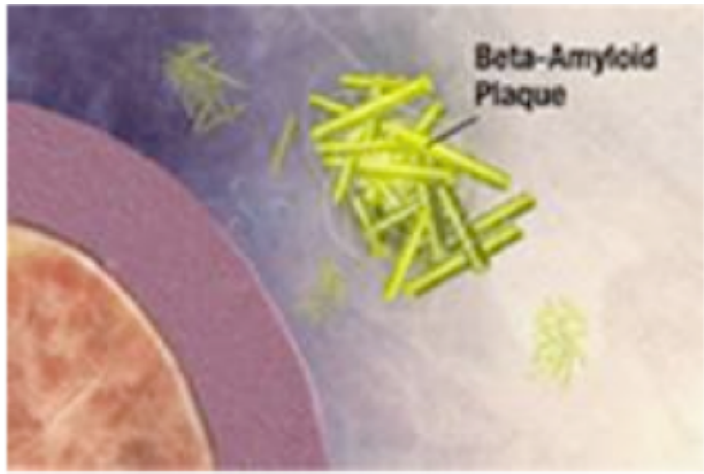


Plaque Formation

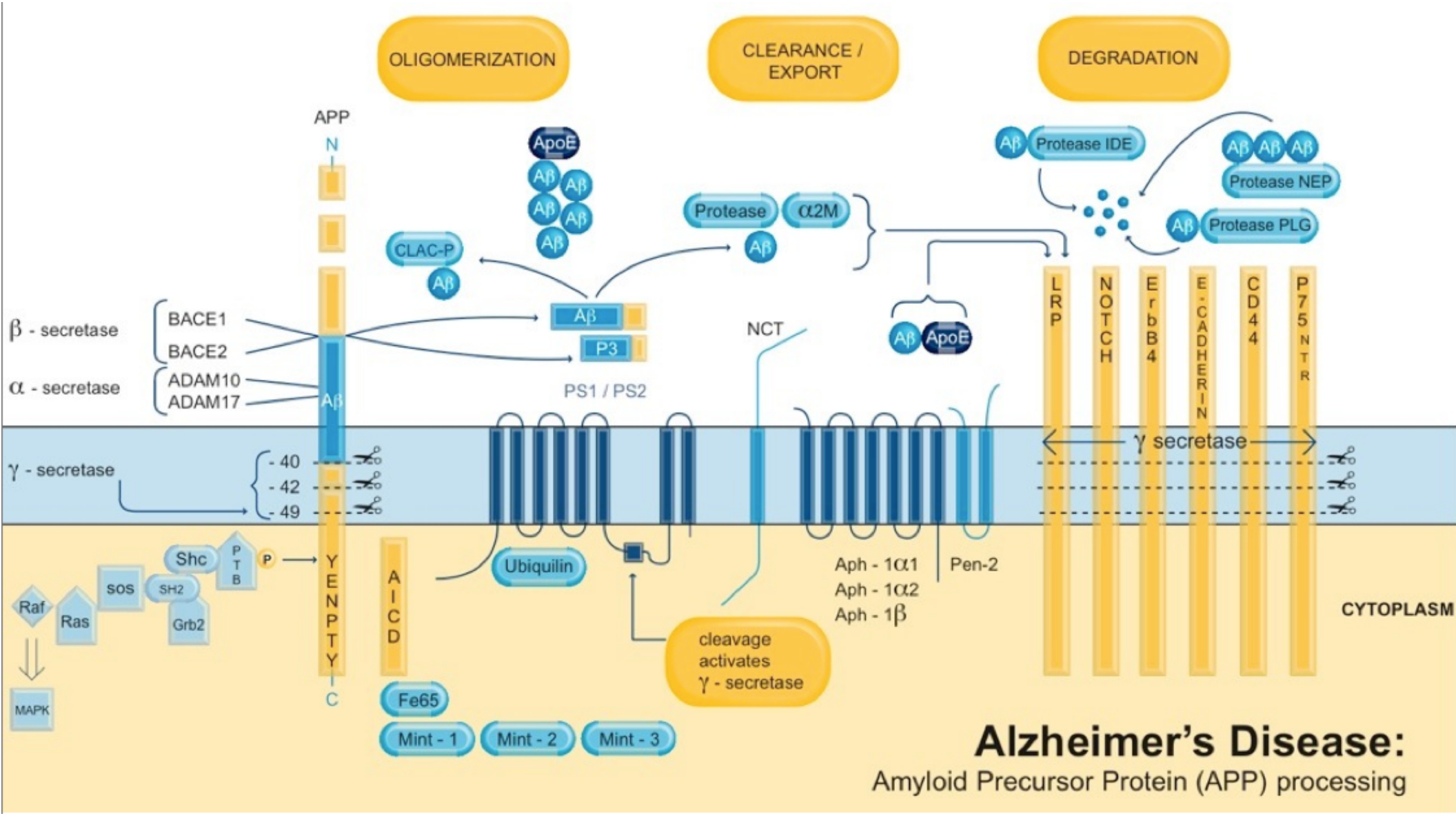
- α-, β-, and γ- secretases
  - one of two pathways
    - Aβ is produced by one, prevented by the other



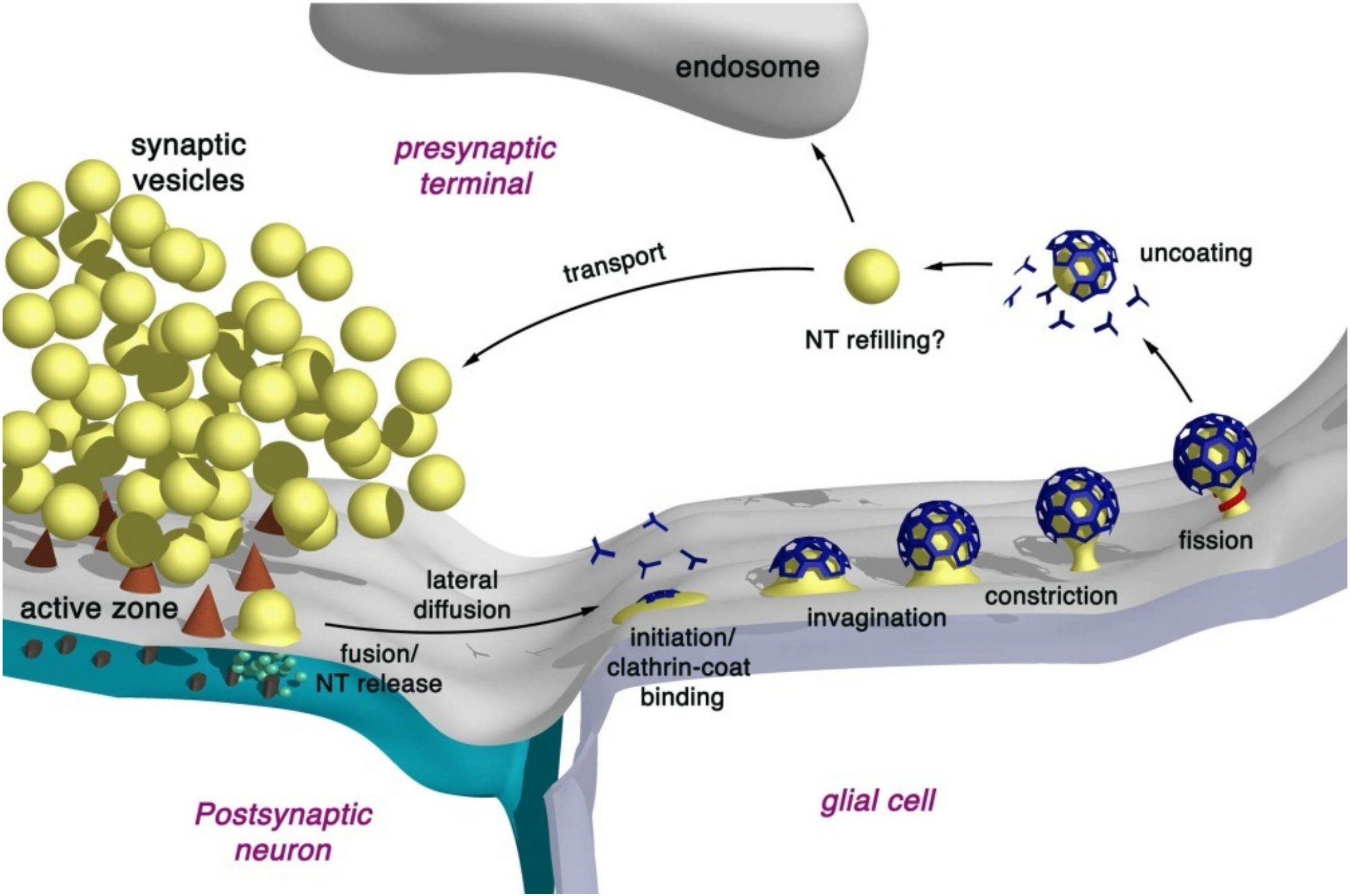




The "Amyloidogenic" Pathway

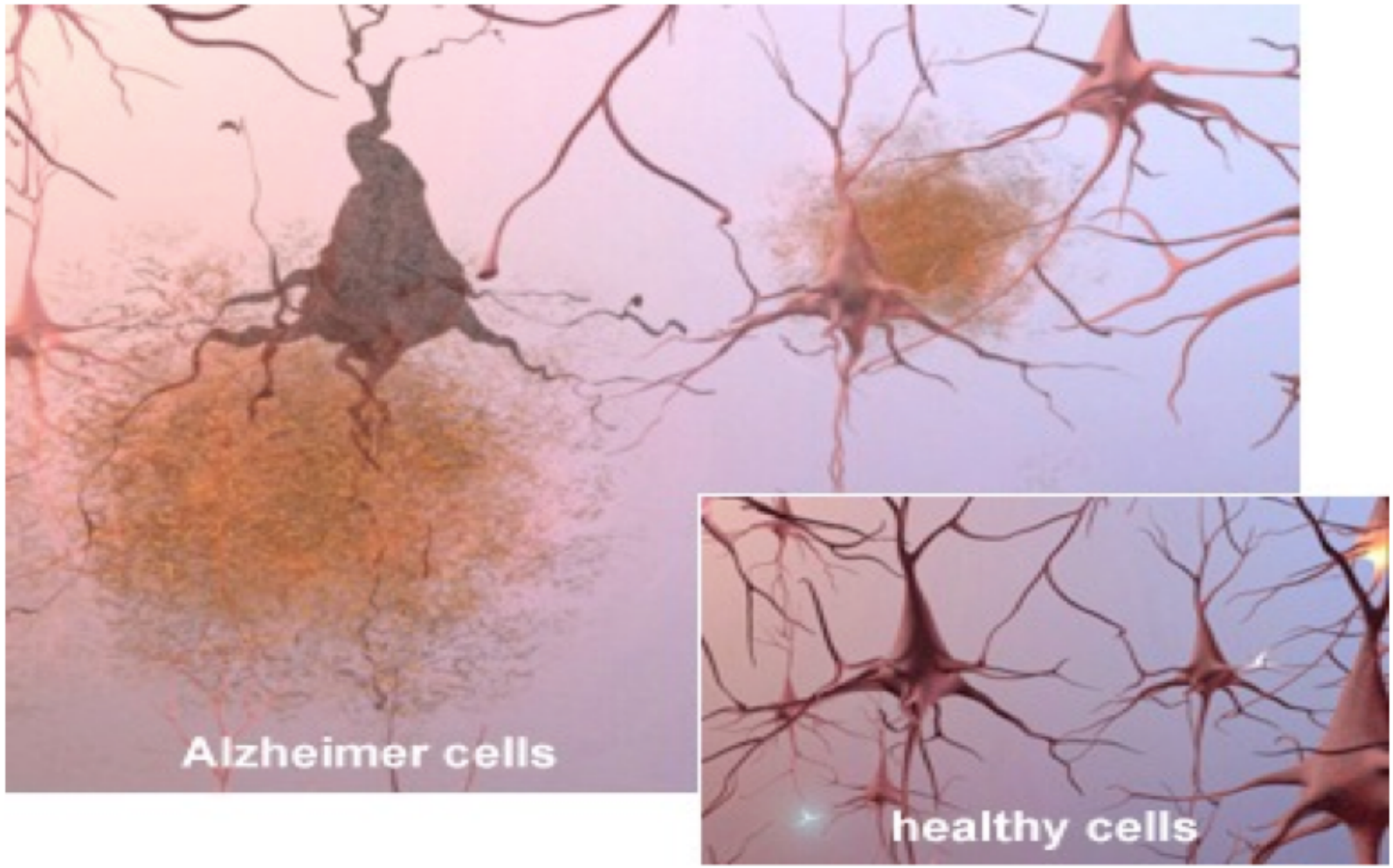


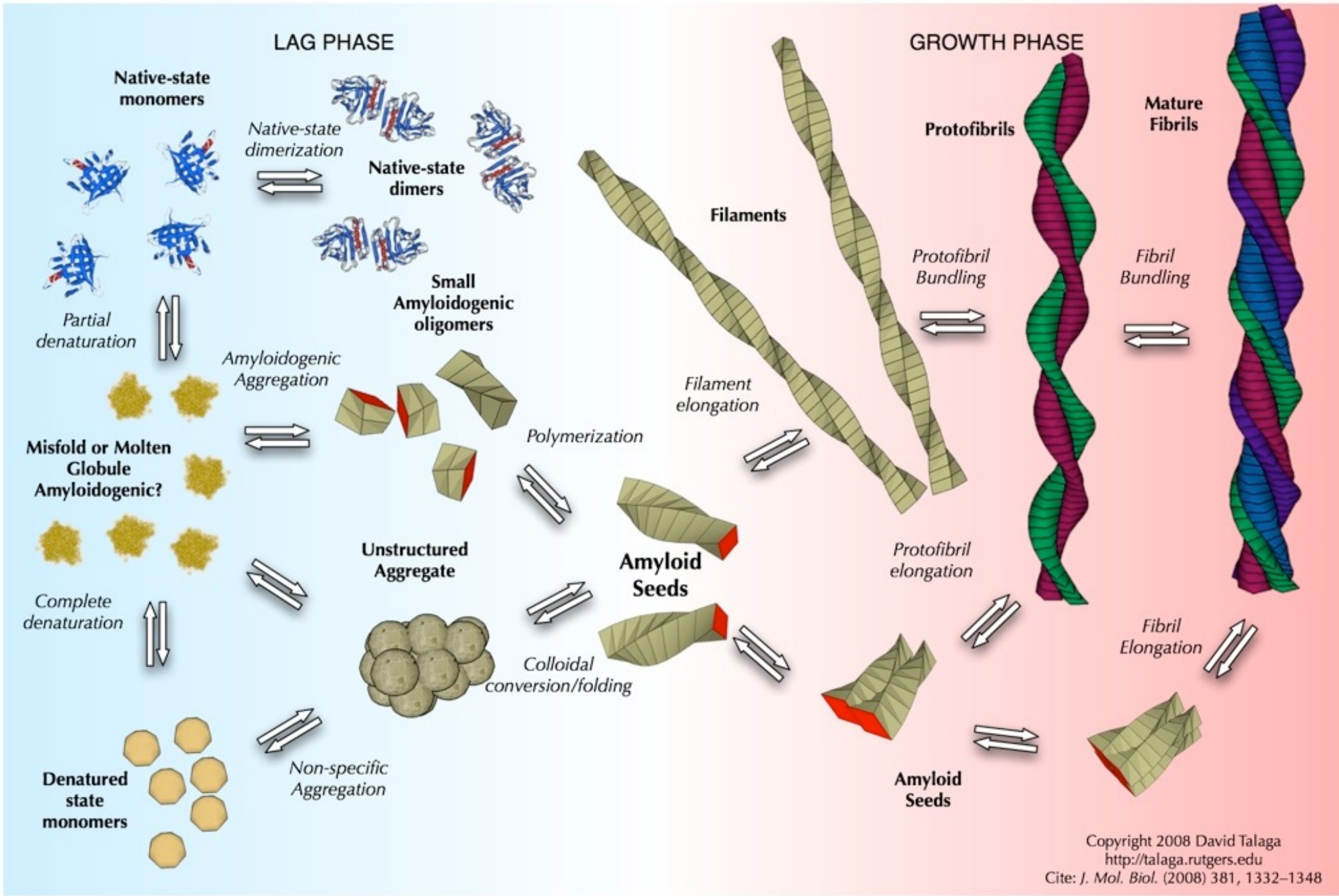
- β- and γ-secretase cuts APP to produce Aβ (39-43 amino acids long)
  - longer Aβ isoforms ($A\beta_{42-43}$) tend to cling together


endosome
synaptic vesicles
presynaptic terminal
transport
NT refilling?
uncoating
fission
constriction
invagination
lateral diffusion
active zone
fusion/ NT release
initiation/ clathrin-coat binding
Postsynaptic neuron
glial cell

The “Amyloidogenic” Pathway

- once enough Aβ has accumulated in the brain’s extracellular space, it starts to polymerize (aggregate)
- Aβ: soluble→oligomers→”diffuse” plaques→amyloid




LAG PHASE
GROWTH PHASE
Native-state monomers
Native-state dimerization
Native-state dimers
Small Amyloidogenic oligomers
Partial denaturation
Amyloidogenic Aggregation
Misfold or Molten Globule Amyloidogenic?
Polymerization
Filaments
Filament elongation
Protofibrils
Protofibril Bundling
Mature Fibrils
Fibril Bundling
Unstructured Aggregate
Amyloid Seeds
Protofibril elongation
Complete denaturation
Colloidal conversion/folding
Fibril Elongation
Denatured state monomers
Non-specific Aggregation
Amyloid Seeds
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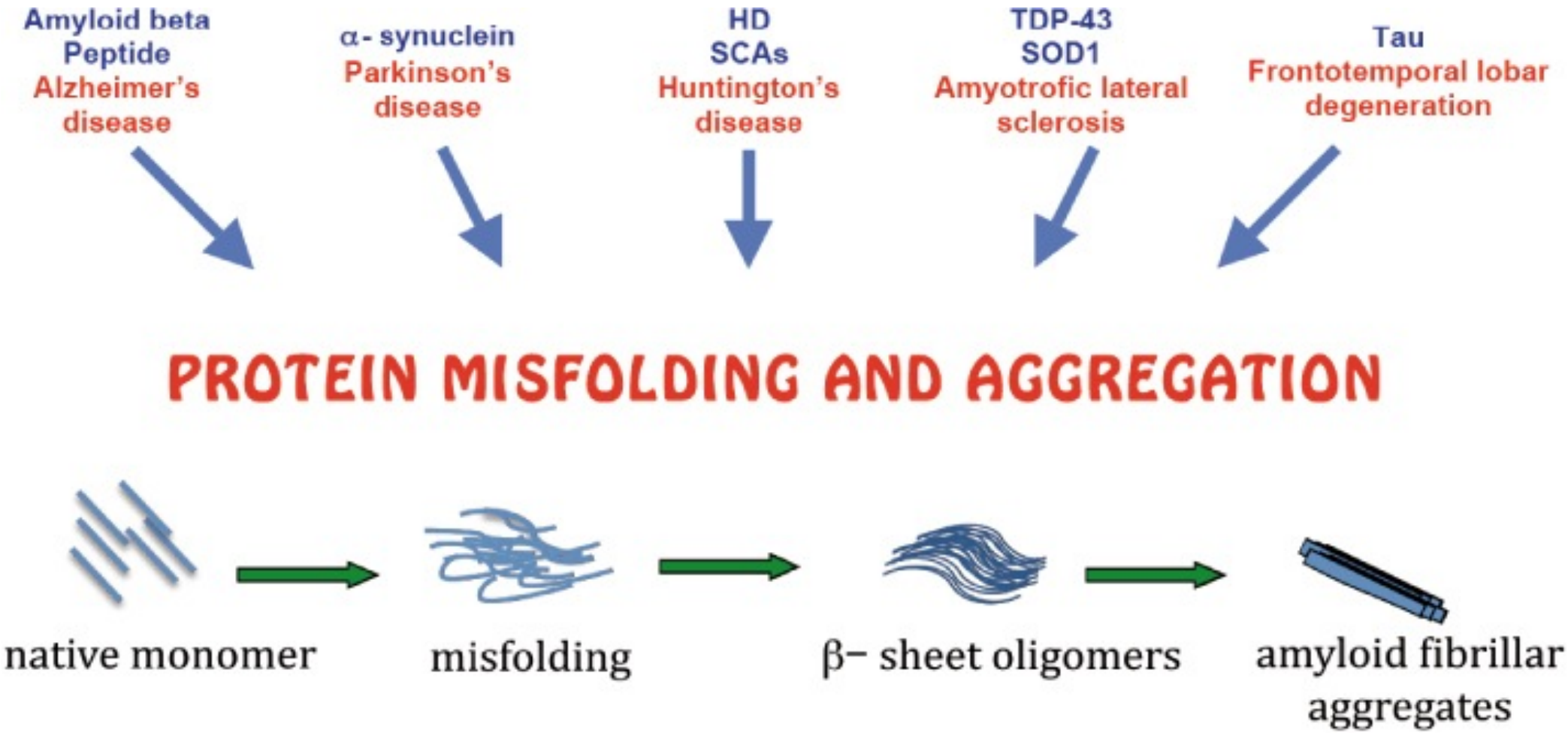
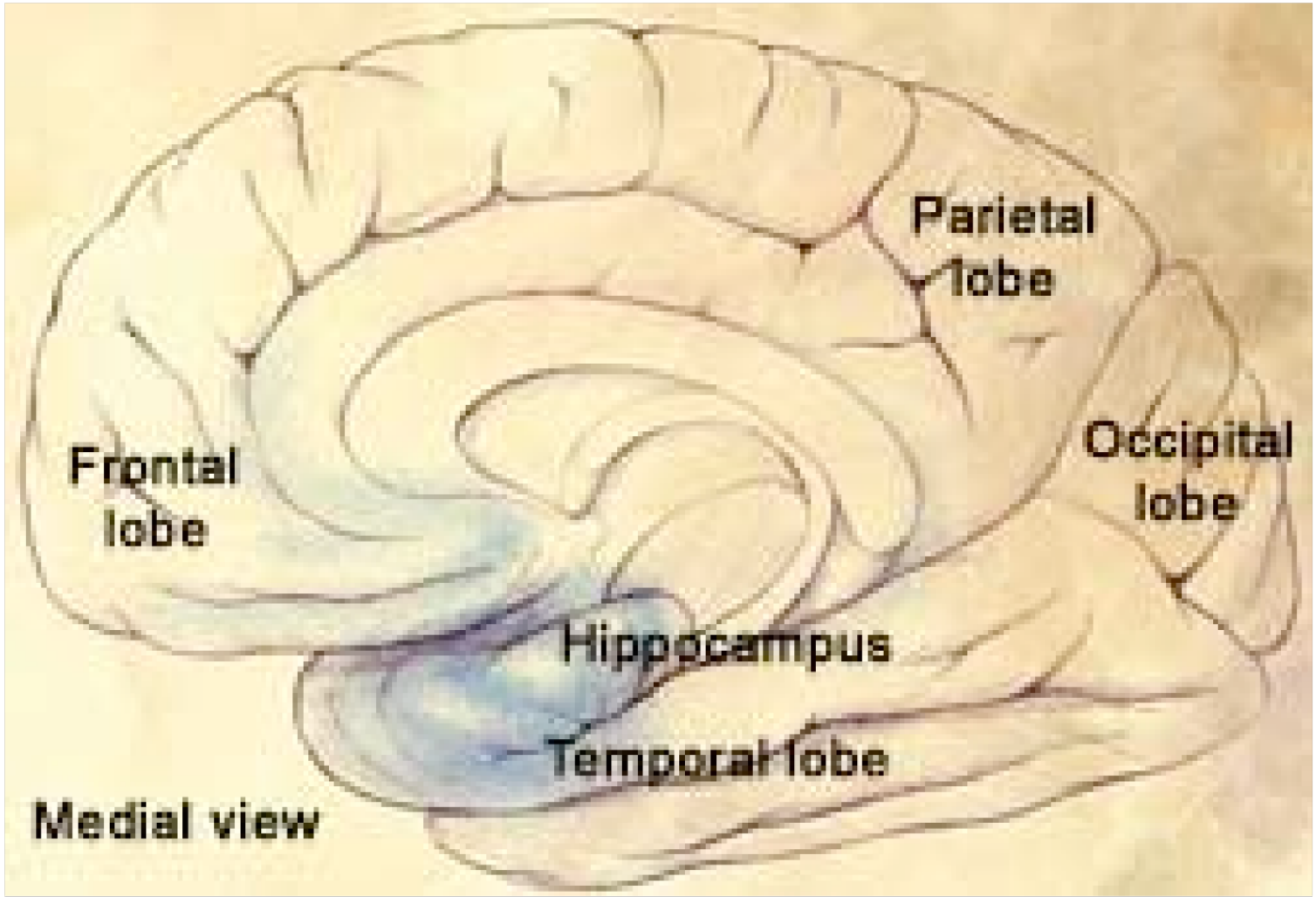
http://talaga.rutgers.edu
Cite: J. Mol. Biol. (2008) 381, 1332–1348


Amyloid beta
Peptide
Alzheimer's
disease
α- synuclein
Parkinson's
disease
HD
SCAs
Huntington's
disease
TDP-43
SOD1
Amyotrofic lateral
sclerosis
Tau
Frontotemporal lobar
degeneration
PROTEIN MISFOLDING AND AGGREGATION
native monomer
misfolding
β– sheet oligomers
amyloid fibrillar
aggregates

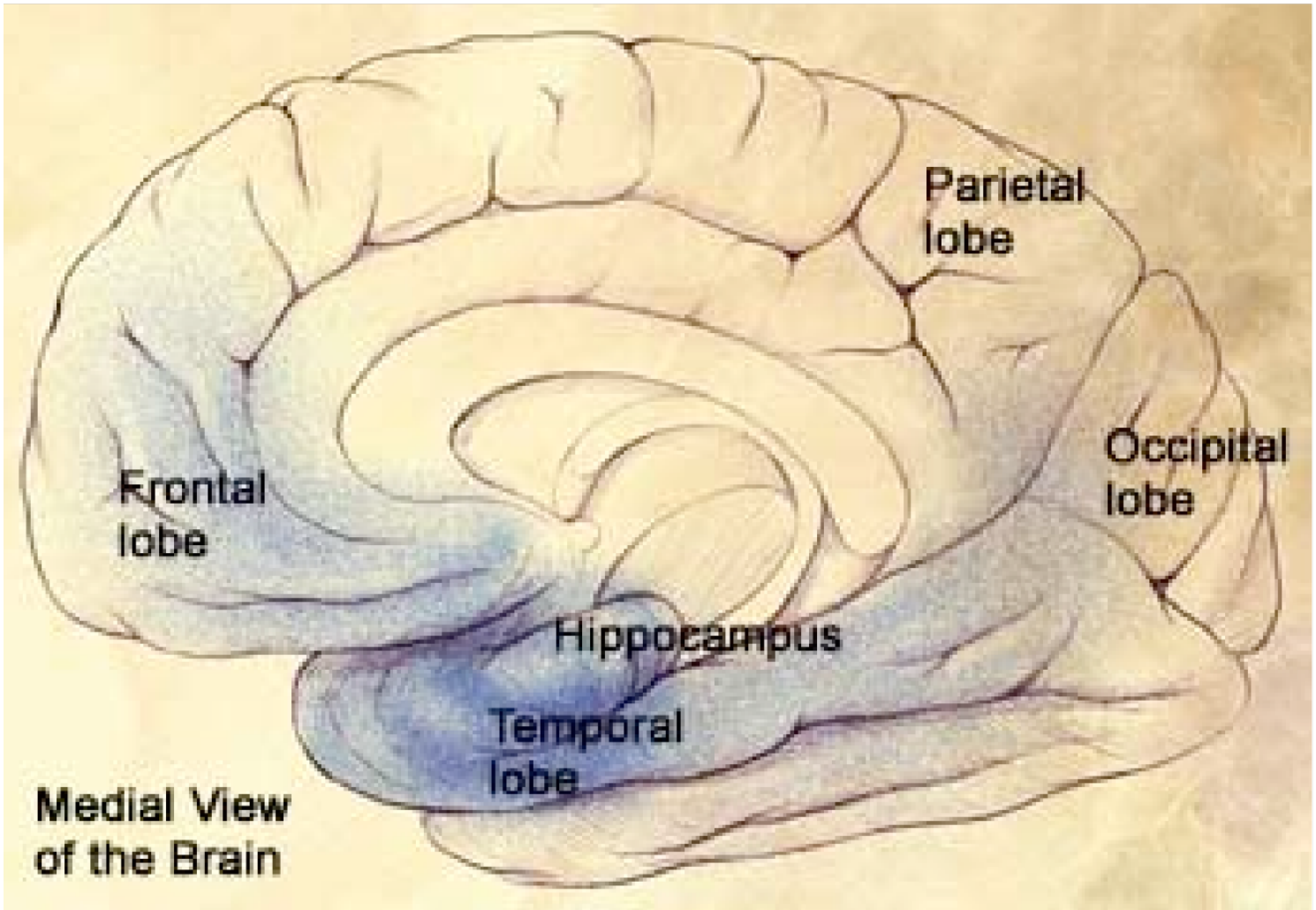
The “Amyloidogenic” Pathway

- deposition starts in hippocampus and then gradually spreads throughout the cortical and subcortical areas



The “Amyloidogenic” Pathway

- deposition starts in hippocampus and then gradually spreads throughout the cortical and subcortical areas



The “Amyloidogenic” Pathway

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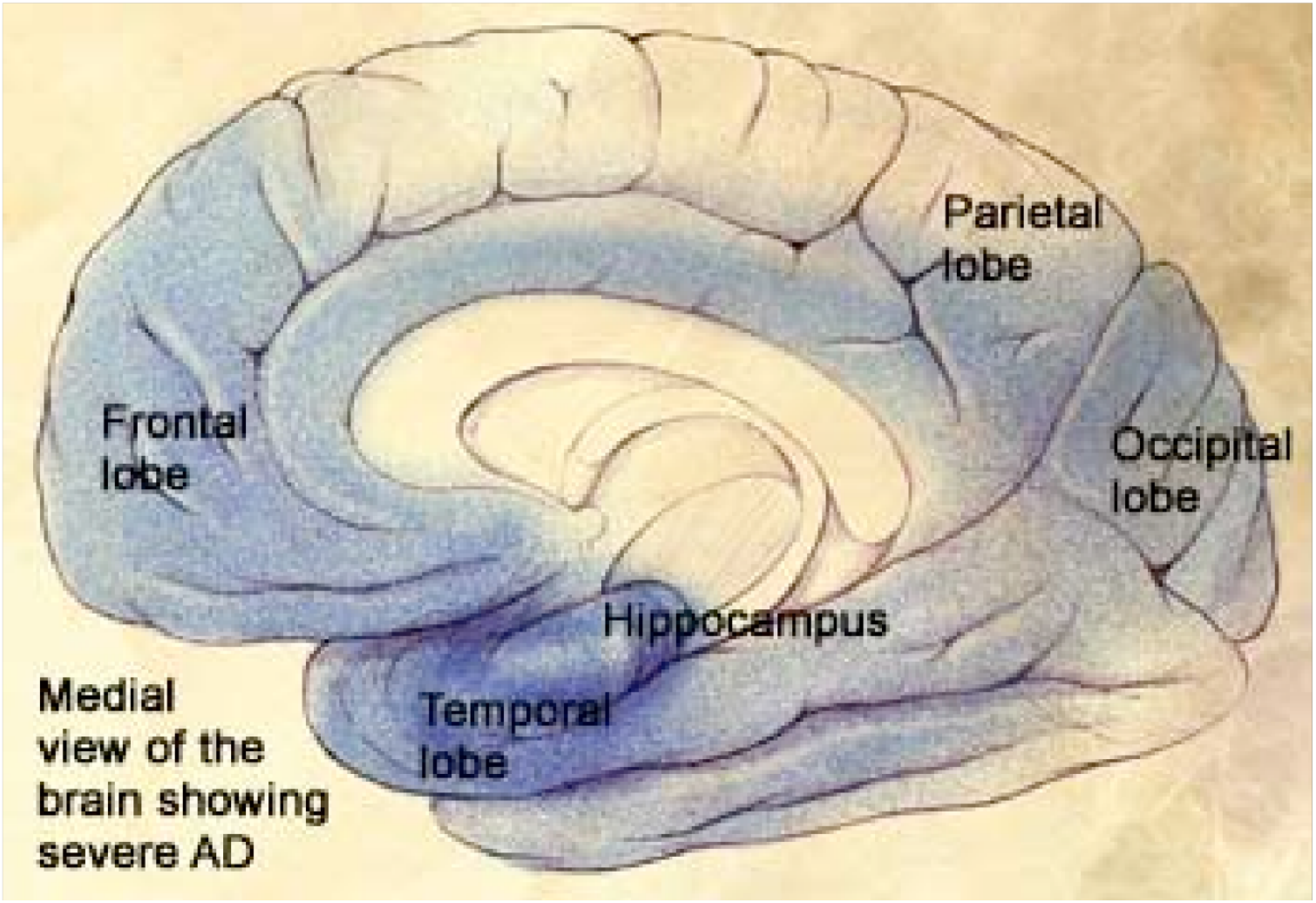
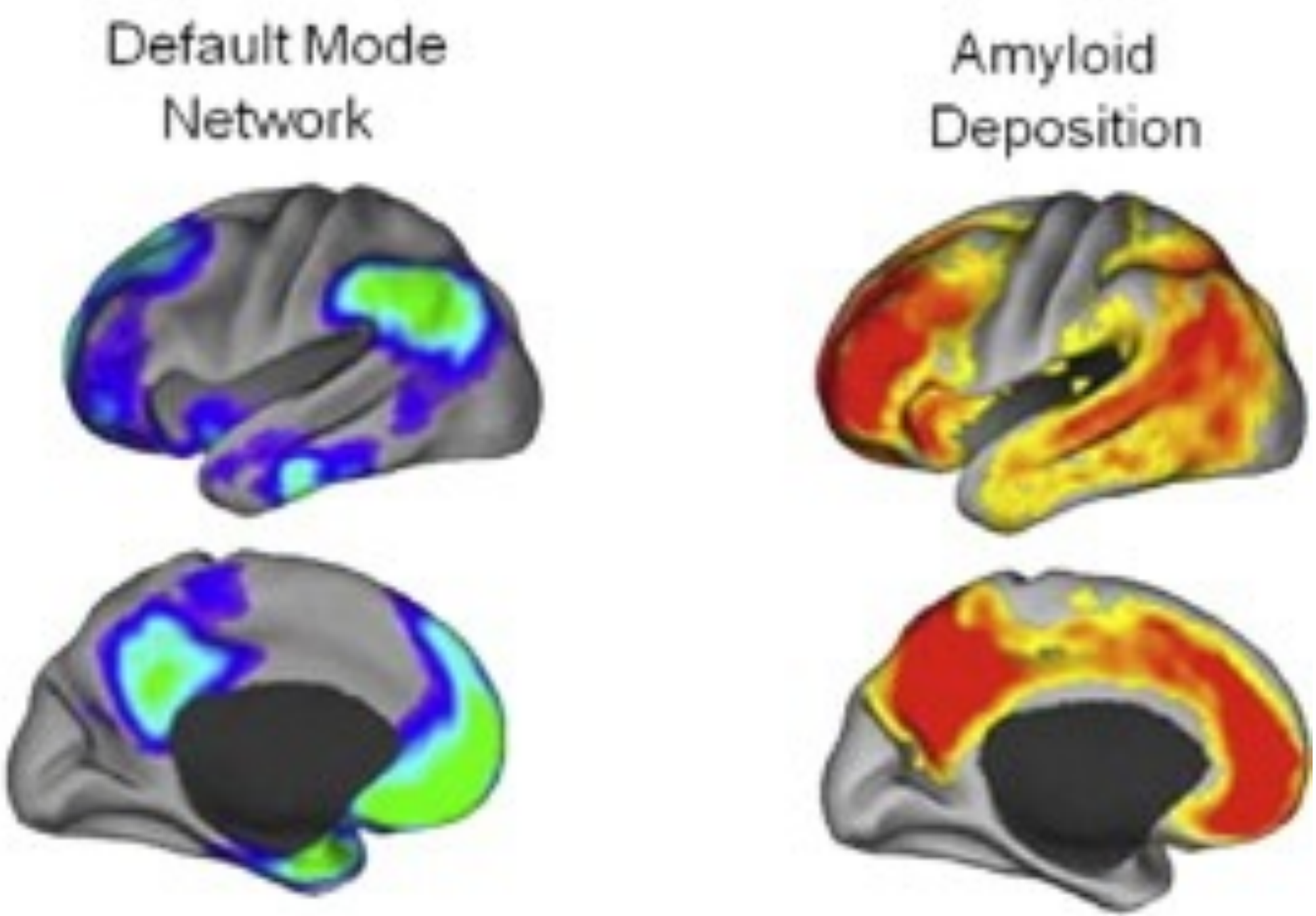
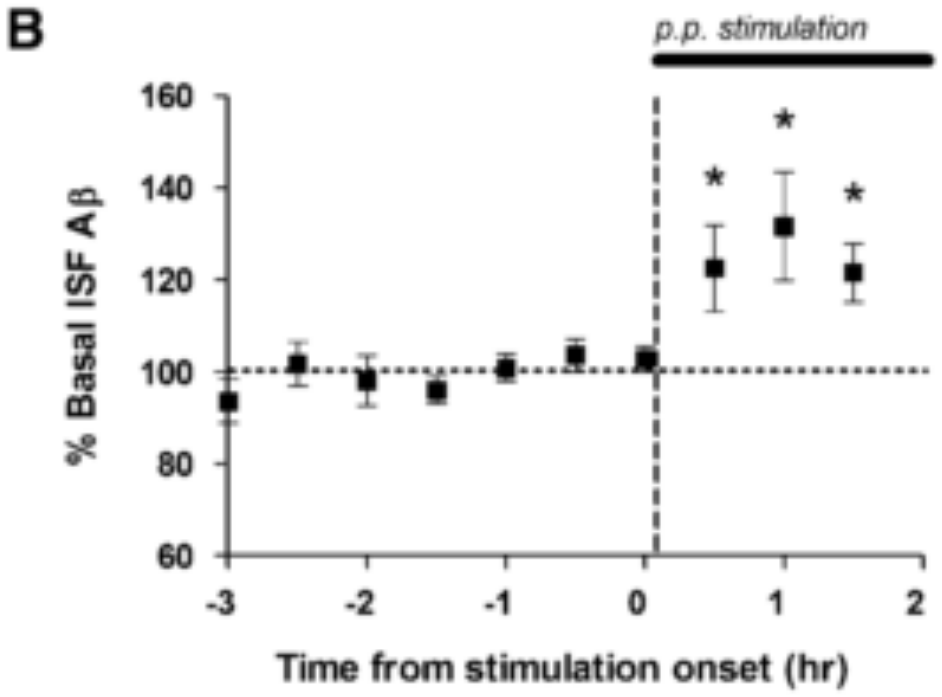


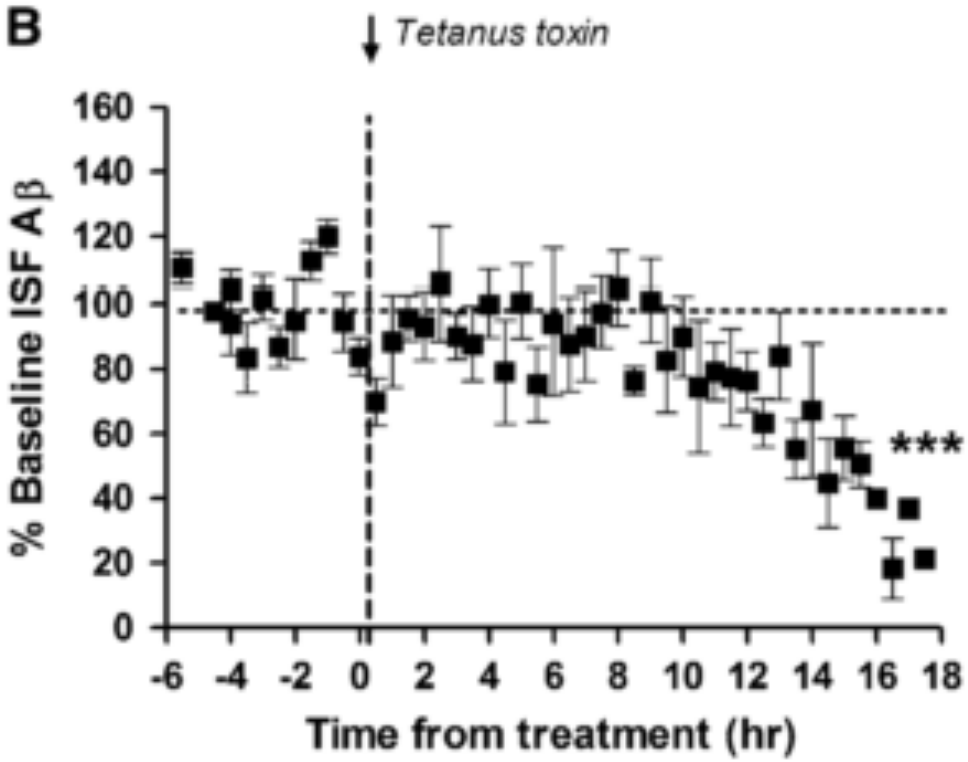
Plaque deposition is activity dependent



Increase activity > more Aβ made

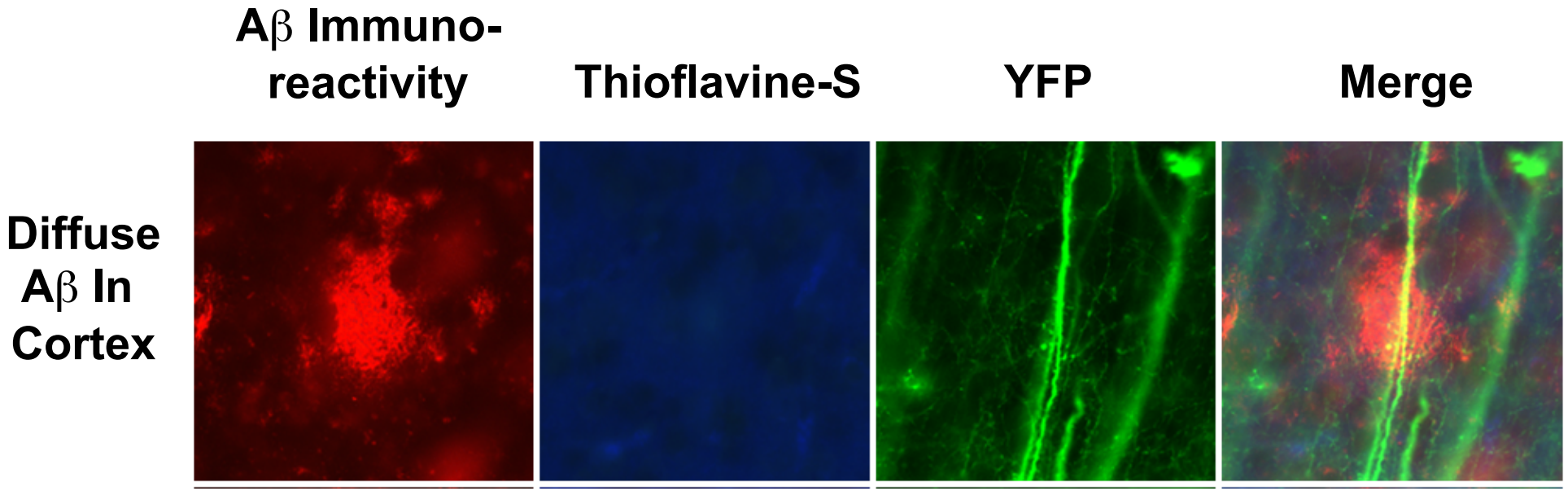


Decrease activity > less Aβ made



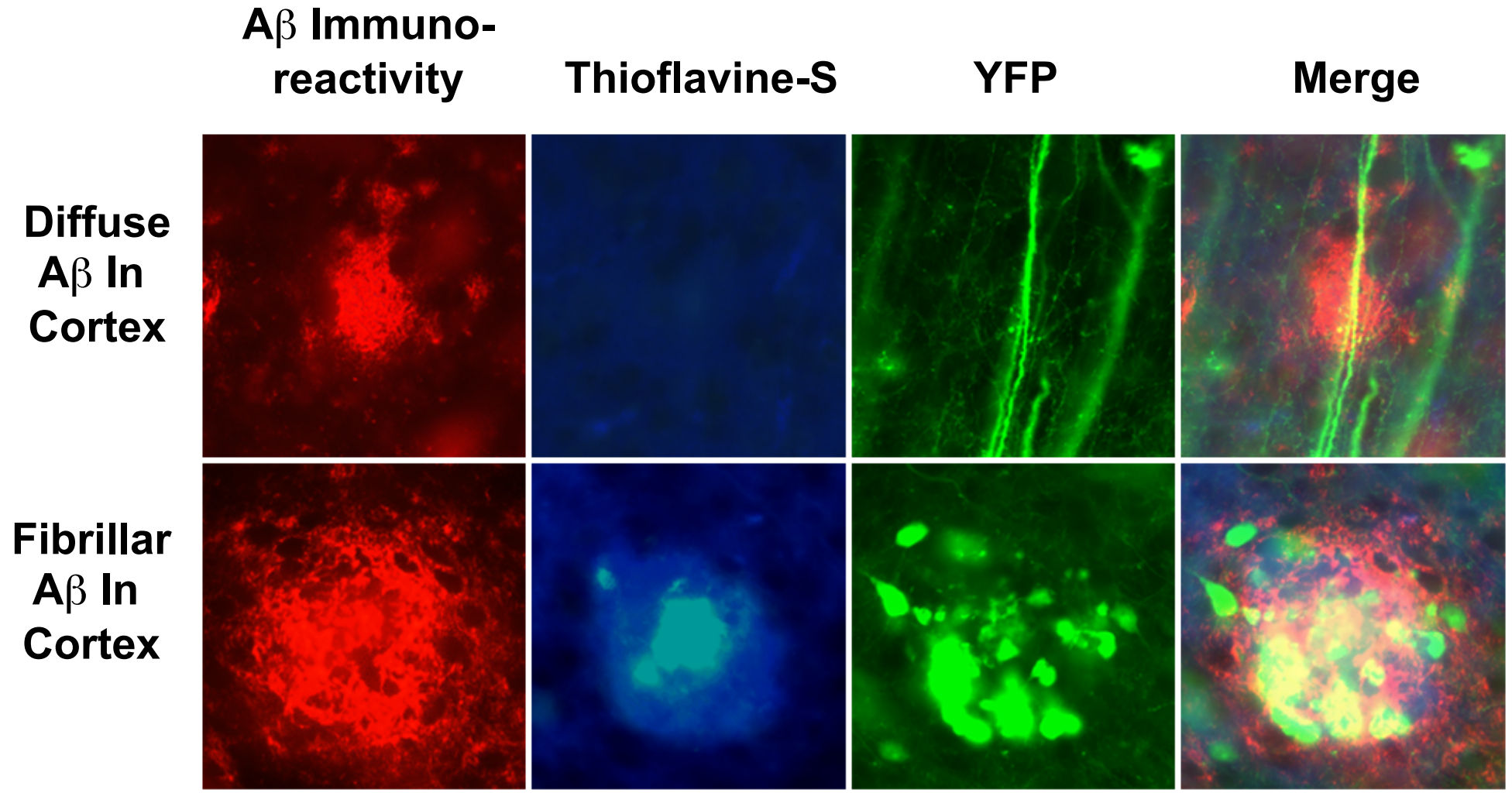
Aβ Toxicity

- initial, “diffuse” deposits of Aβ are not toxic

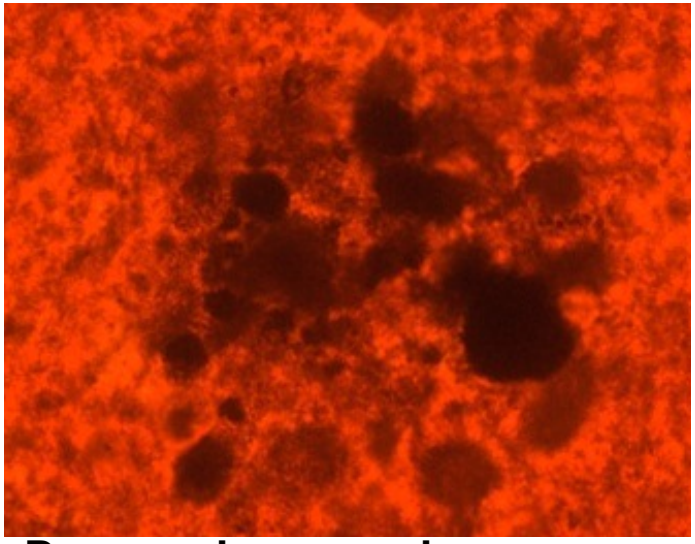


Aβ Toxicity

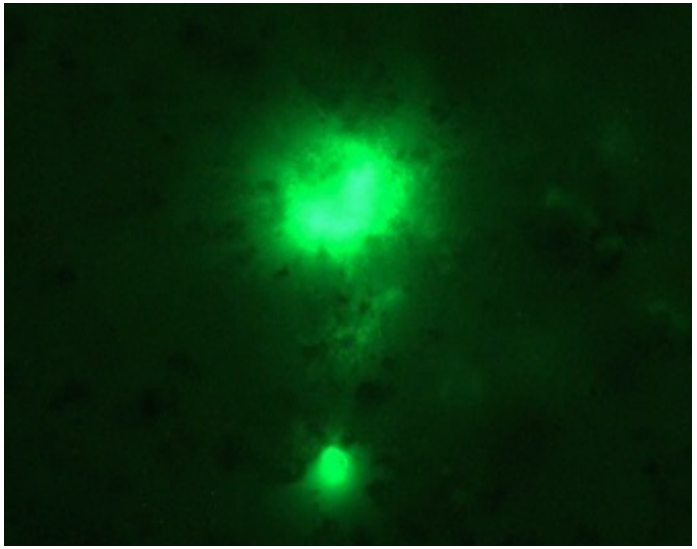
- initial, “diffuse” deposits of Aβ are not toxic
  - aggregated β-sheet Aβ (amyloid / fibrillar) is neurotoxic



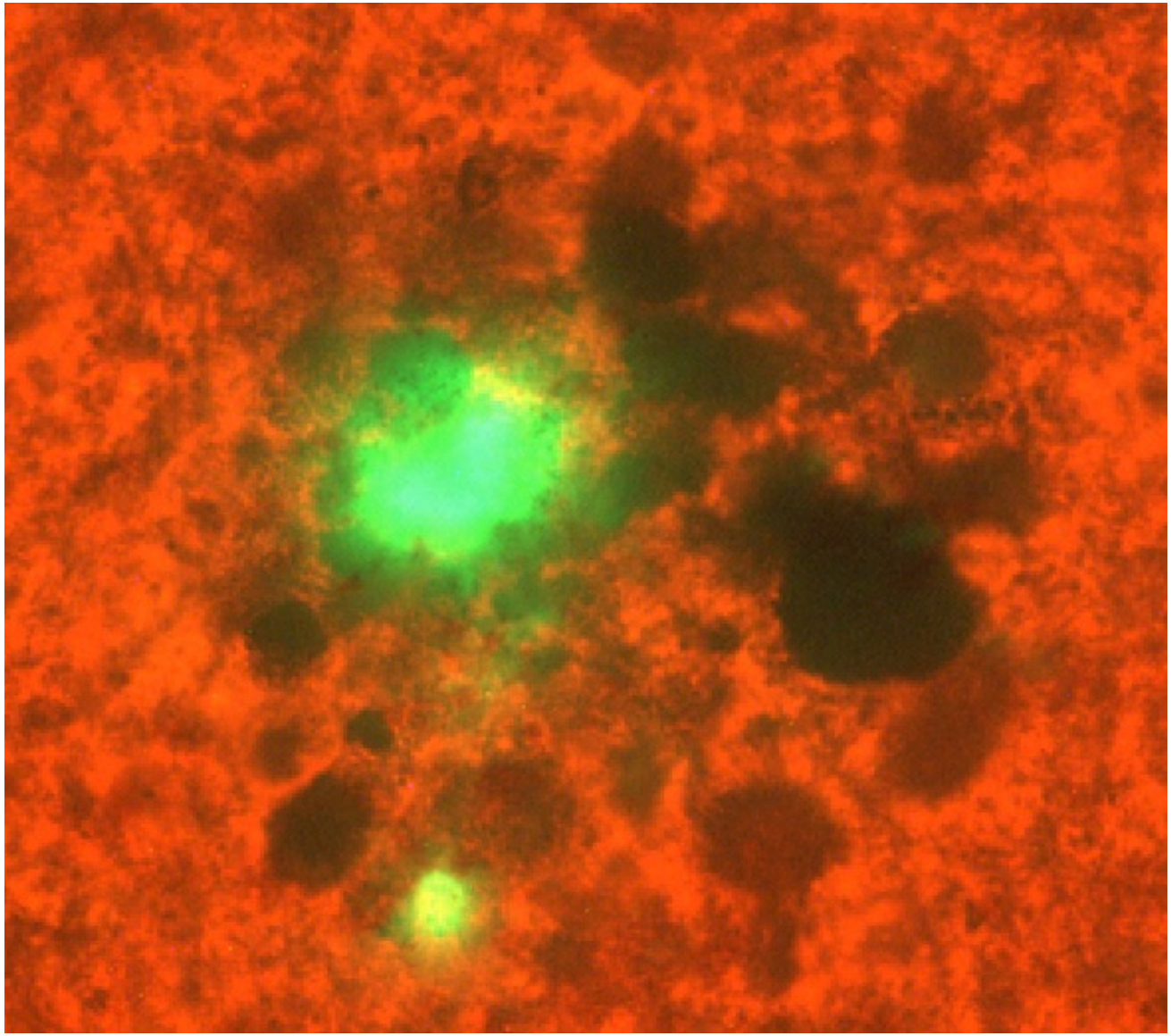
Aβ Toxicity



Damaged neuronal processes



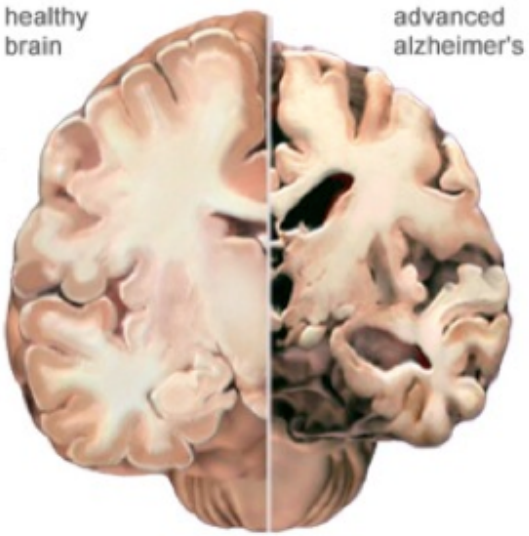
Amyloid plaque

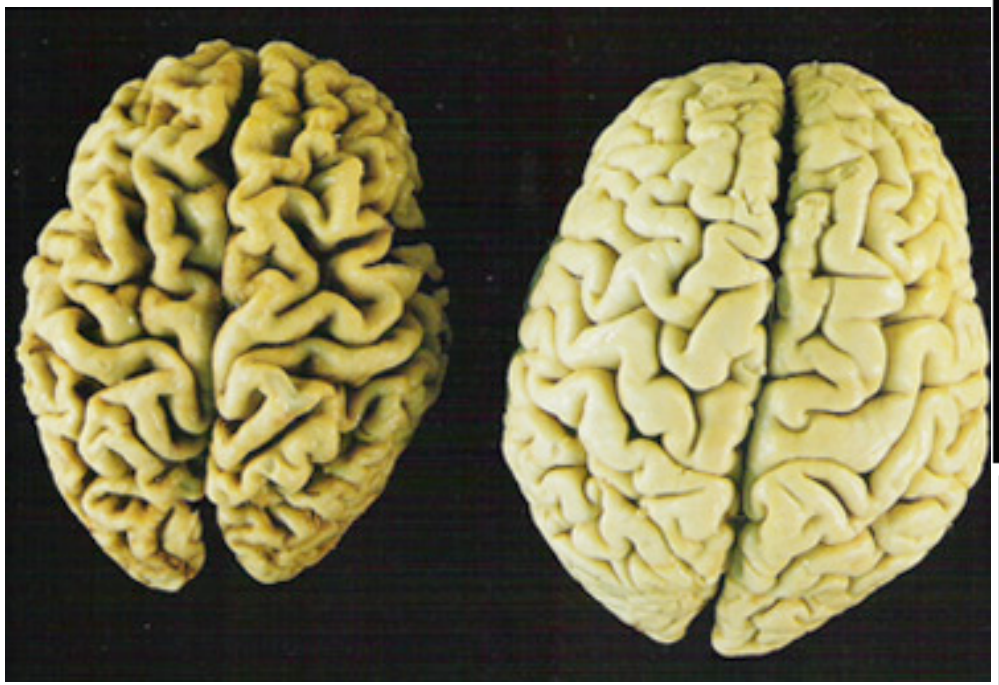


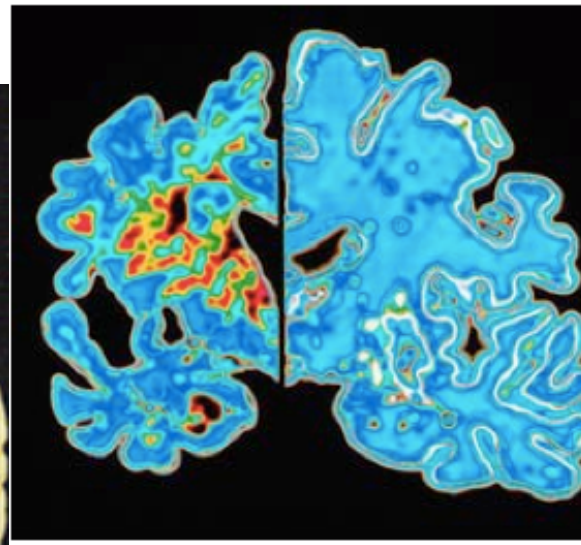
MERGED IMAGE

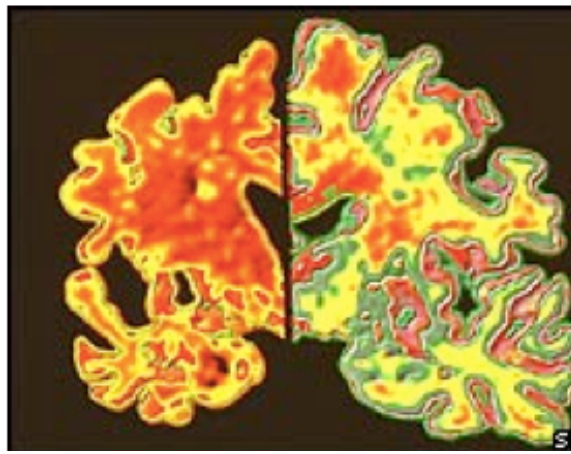
Alzheimer's Neuropathology

- like Parkinson's, symptoms are not observed until significant levels of neuropathology and neurodegeneration have accumulated







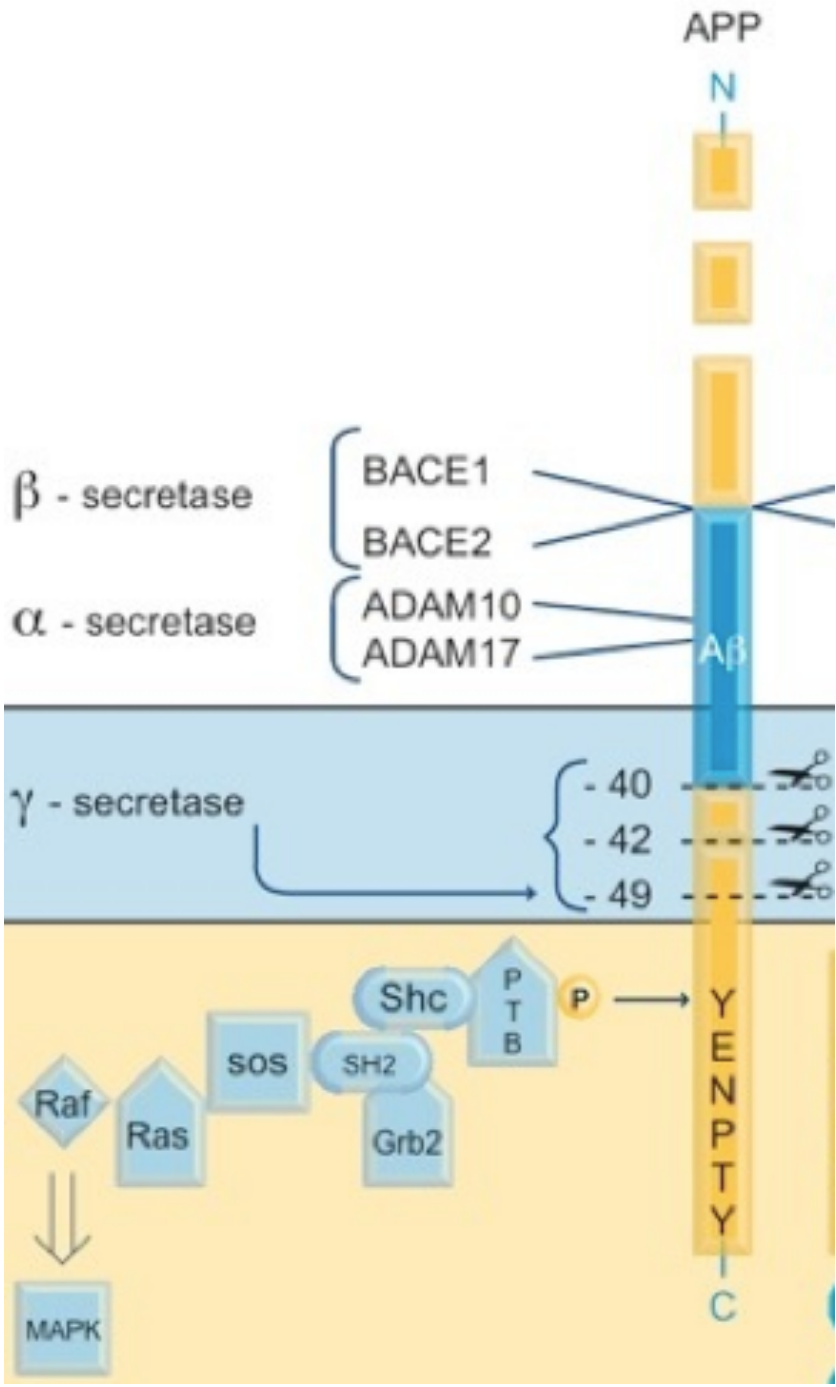


The “Non-Amyloidogenic” Pathway

- the α-secretase site lies <u>within</u>

  APP’s Aβ domain

- α-secretase cleavage:
  - <u>prevents</u> production of Aβ
  - <u>produces</u> sAPPα
    - neuroprotective



Mechanism of Aβ Toxicity

- Aβ can induce damage via oxidative stress
  - intracellular Aβ can enter mitochondria, inducing inflammation
  - Aβ interacts with other molecules within plaques and damages ACh receptors
    - damage can be prevented by treatment with antioxidants
- also, physical damage during the process of aggregation?

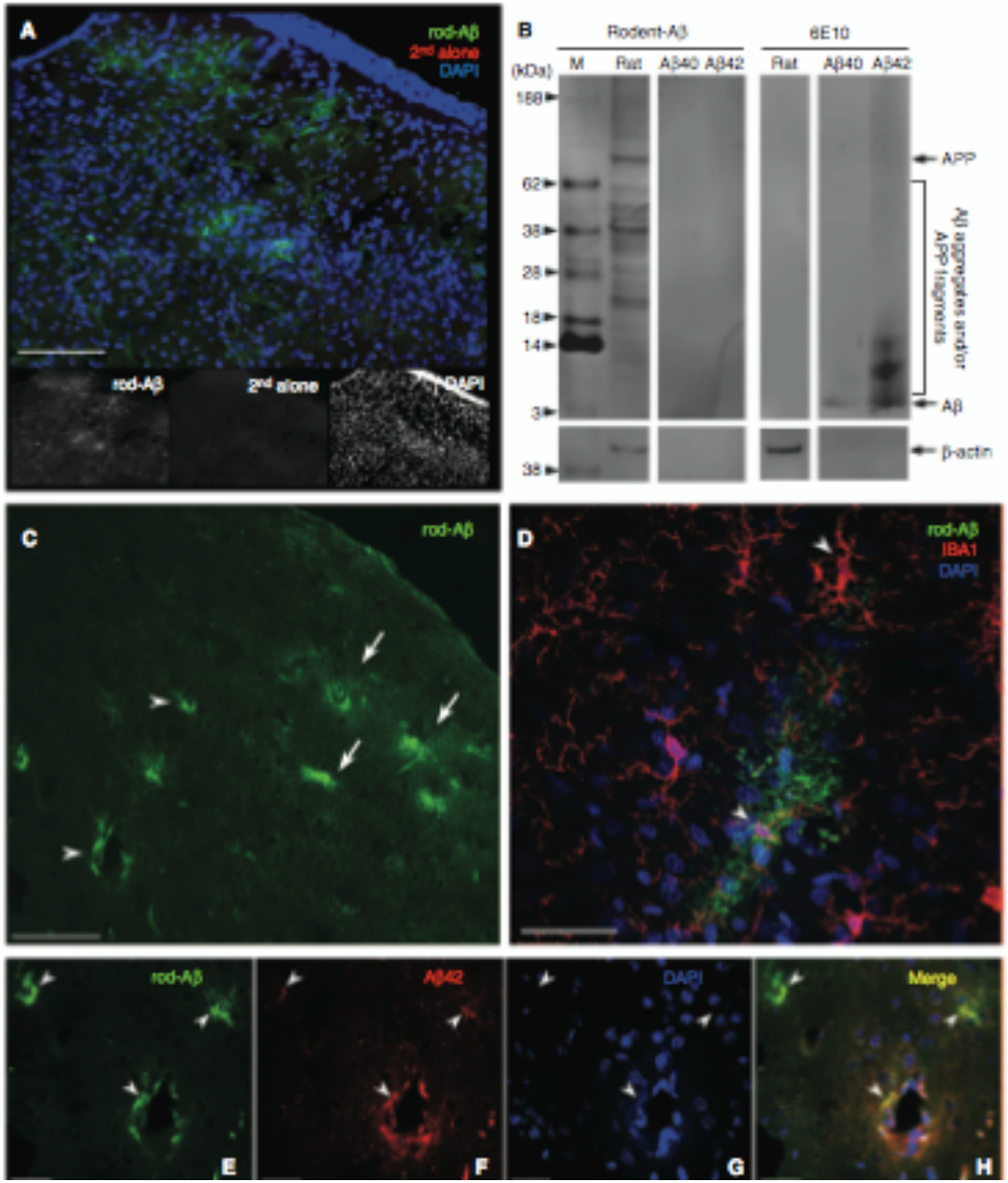
Risk Factors for AD

- most prevalent risk factor is aging
- other factors include genetics, brain injury, and diet
- mutations in *APP* and *PSEN* genes predispose individuals to develop *familial "early onset"* AD (~5-10%)
- only genetic risk factor for "sporadic" AD is *APOE*
  - 3 major alleles of the *APOE* gene: 2, 3, and 4

ORIGINAL ARTICLE

Early brain injury alters the blood–brain barrier phenotype in parallel with β-amyloid and cognitive changes in adulthood

Viorela Pop[1,5], Dane W Sorensen[1,2,5], Joel E Kamper[3], David O Ajao[2], M Paul Murphy[4], Elizabeth Head[4], Richard E Hartman[3] and Jérôme Badaut[1,2]



Genetic Risk Factors for AD

- Carriers of *APOE4* are more likely to develop AD
  - earlier and more pronounced Aβ deposition
    - gene dose-dependent
    - high cholesterol levels
- Carrying *APOE2* confers protection from AD

Apolipoprotein E4 Influences Amyloid Deposition But Not Cell Loss after Traumatic Brain Injury in a Mouse Model of Alzheimer's Disease

Richard E. Hartman,[1,2,3] Helmut Laurer,[4] Luca Longhi,[4] Kelly R. Bales,[5] Steven M. Paul,[5,6] Tracy K. McIntosh,[4] and David M. Holtzman,[1,2,3,7]

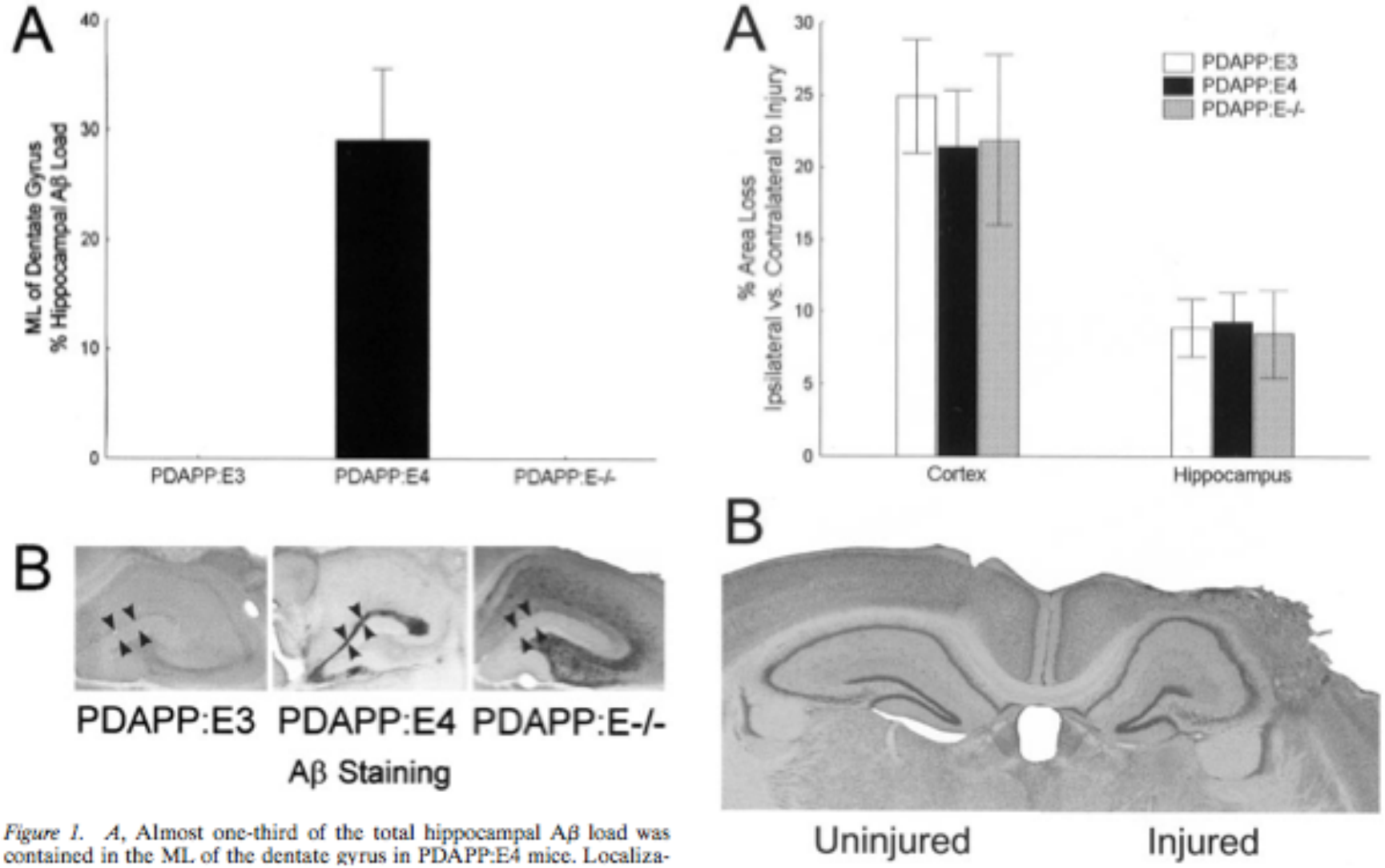


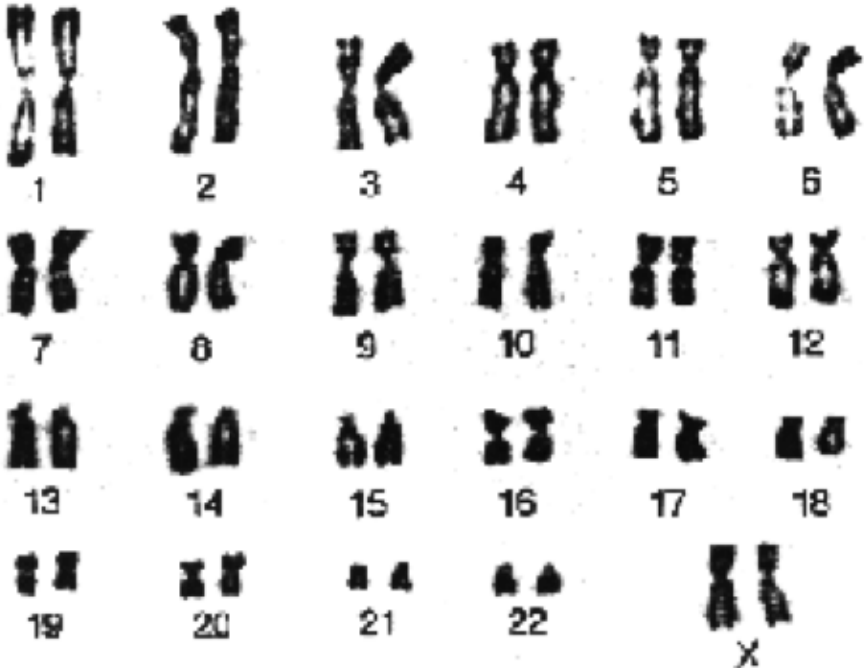
Figure 1. *A*, Almost one-third of the total hippocampal Aβ load was contained in the ML of the dentate gyrus in PDAPP:E4 mice. Localiza-

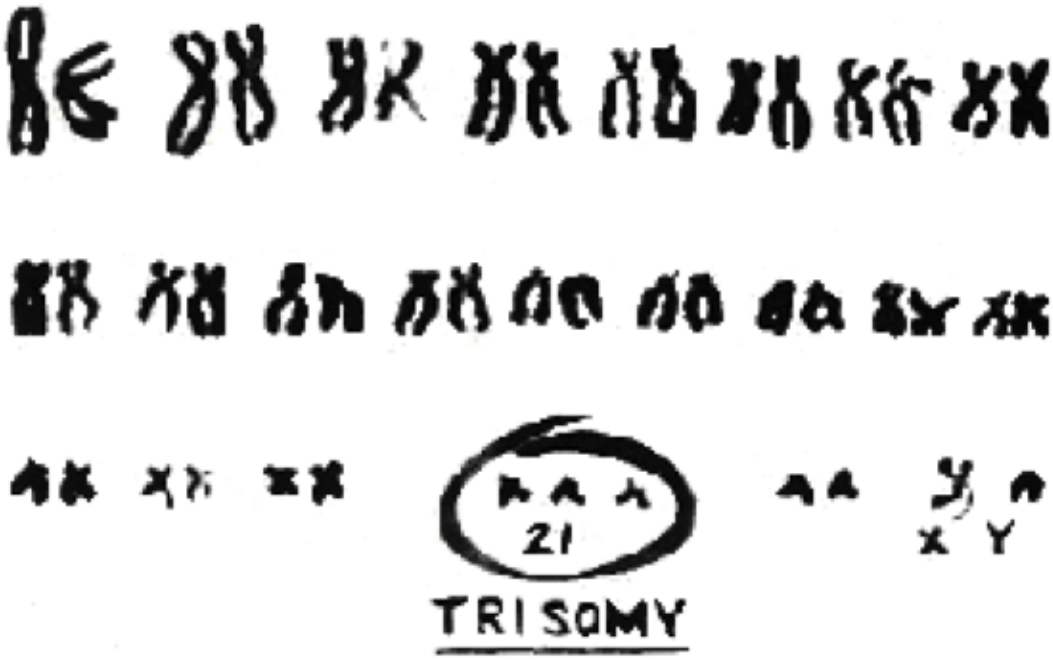
ACCUMULATION OF Aβ AS A CAUSATIVE FACTOR IN AD

- conditions that result in the accumulation of Aβ in the brain generally increase the risk of developing AD neuropathology
- Down syndrome (“Trisomy 21”) results from one extra copy of the 21st chromosome, which contains the *APP* gene

ACCUMULATION OF Aβ AS A CAUSATIVE FACTOR IN AD

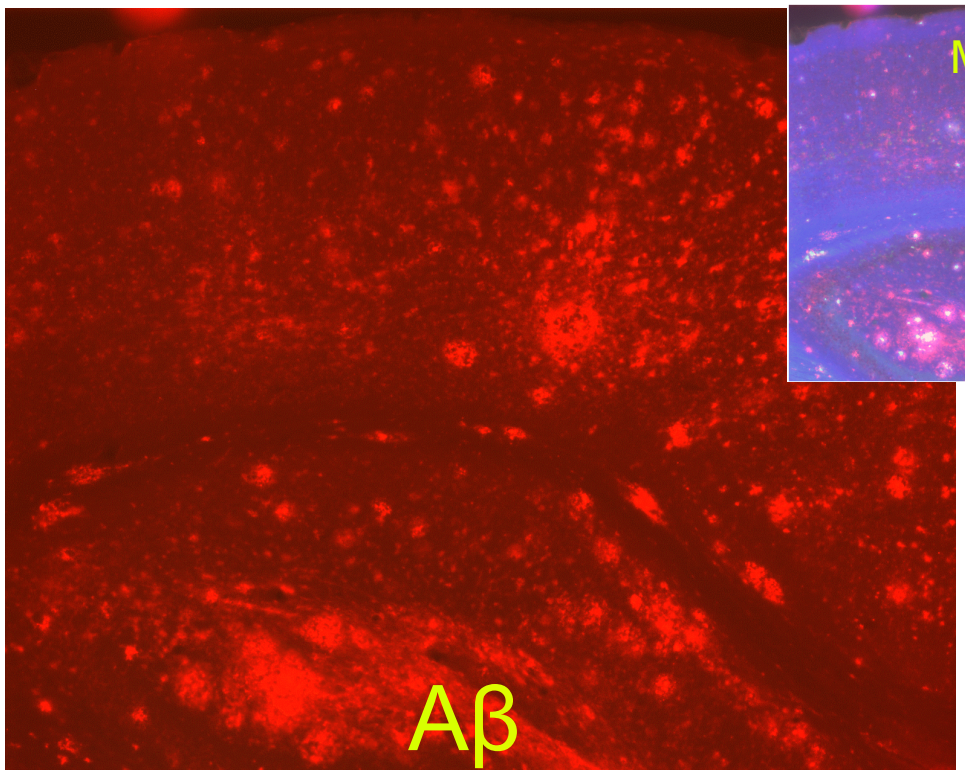
- The condition is associated with the production of ~50% more APP than normal
- leads to elevated Aβ production and deposition
  - “AD” dementia by around 50 years of age

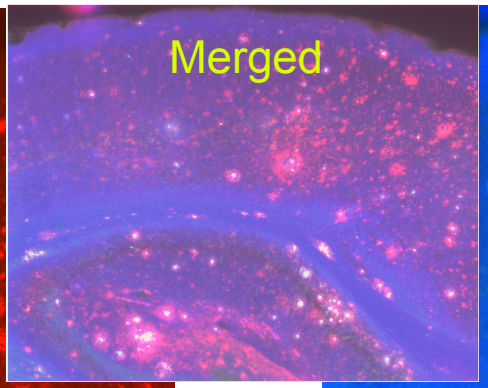


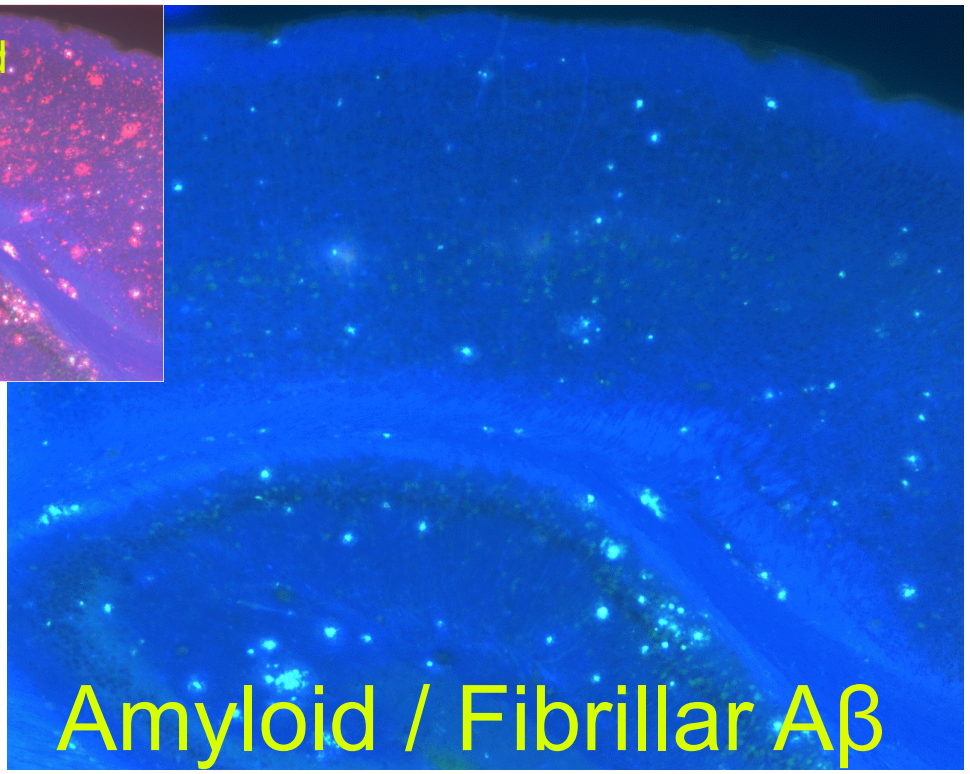


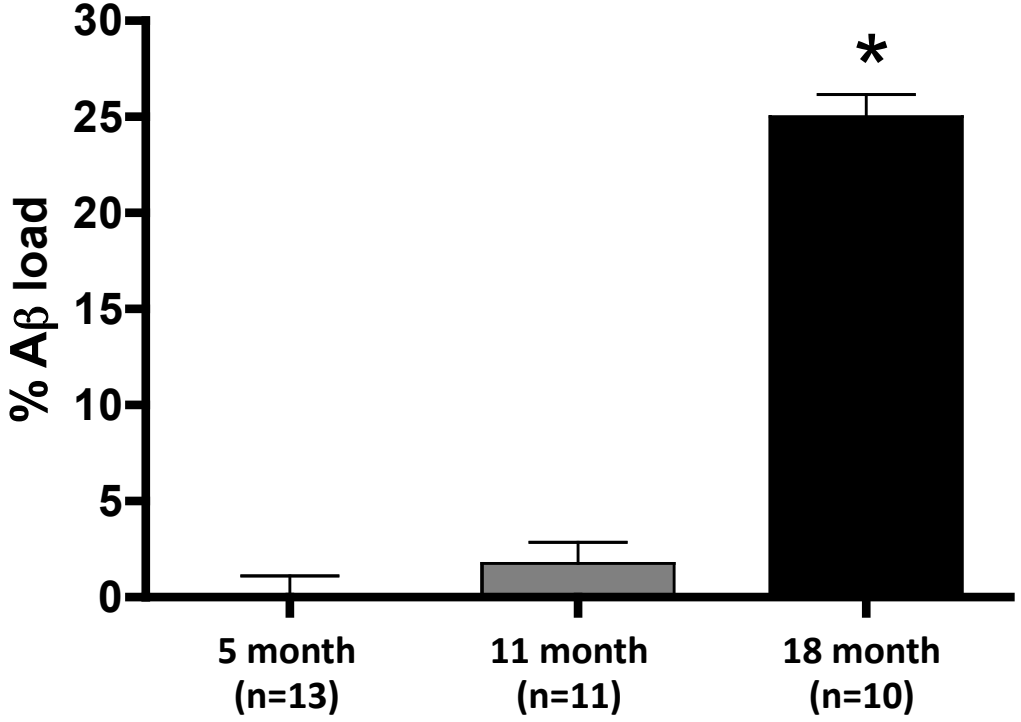
Animal Models of AD

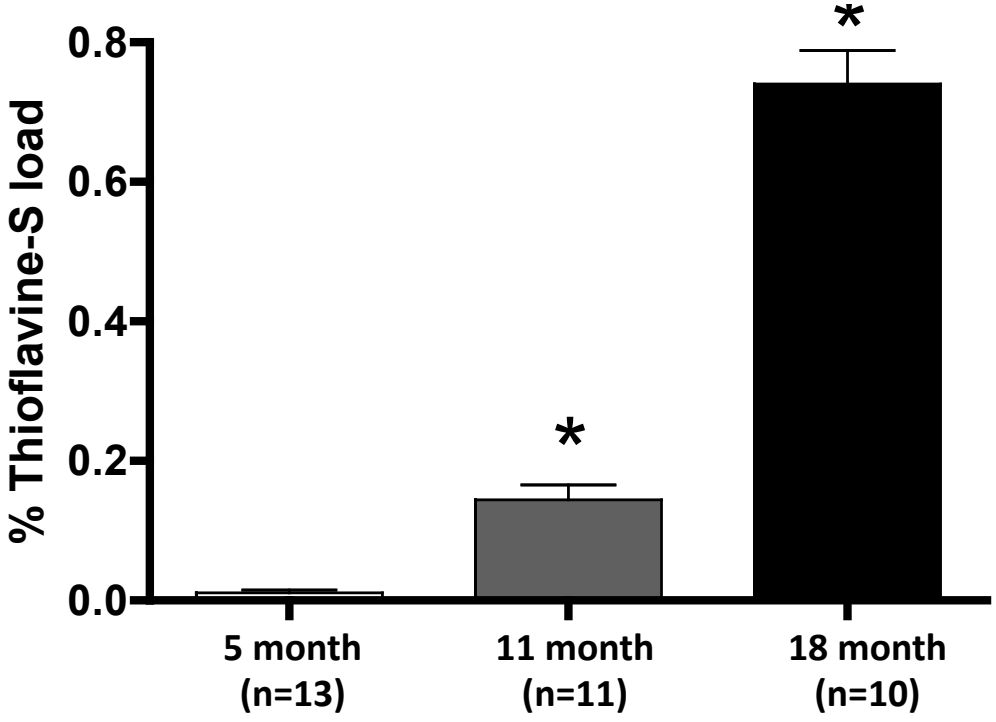
- *transgenic mice* express high brain levels of human APP
  - leads to development of age-related Aβ and, eventually, amyloid deposits
    - coincident with development of cognitive deficits


Aβ

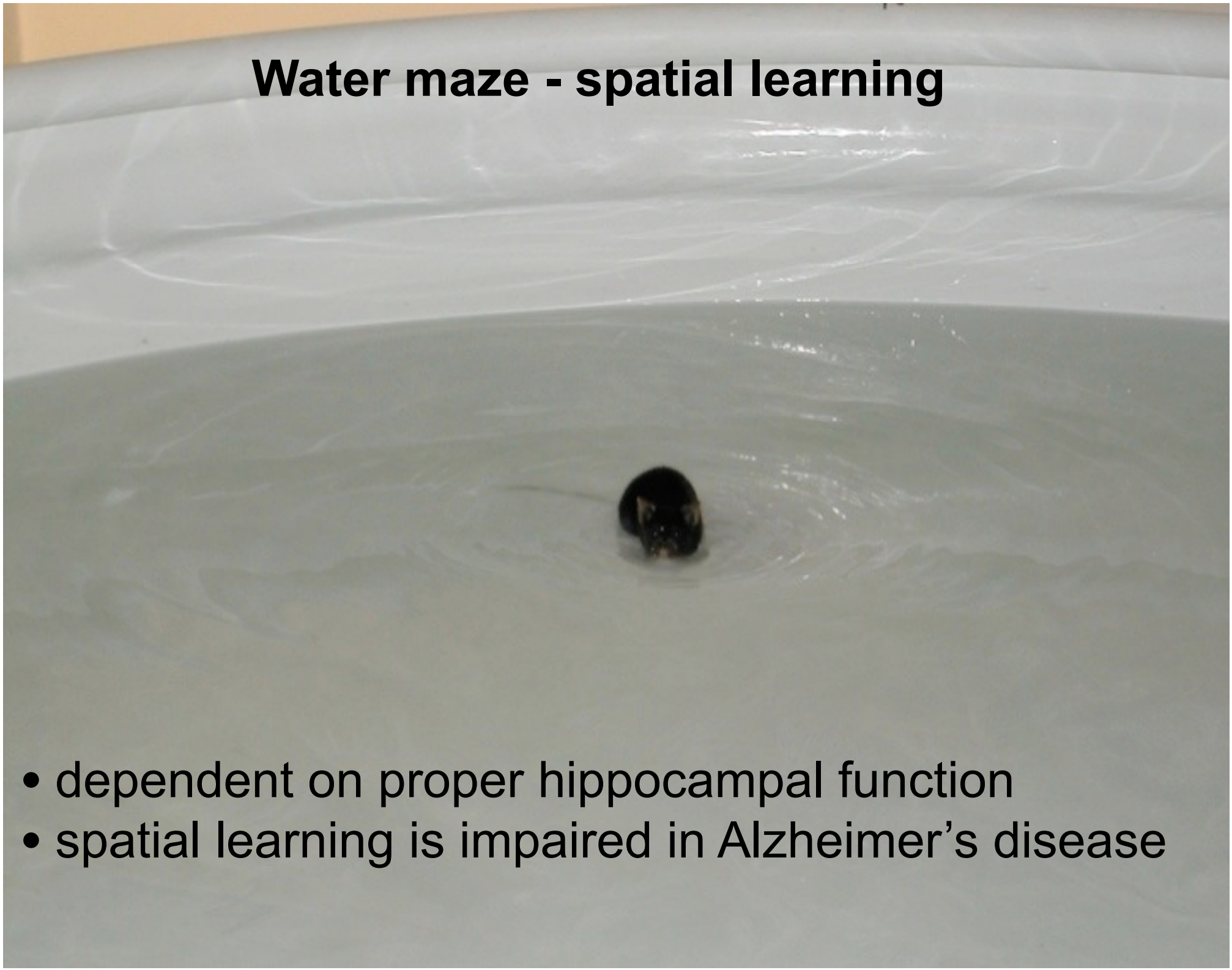

Merged


Amyloid / Fibrillar Aβ


% Aβ load
30
25
20
15
10
5
0
*
5 month
(n=13)
11 month
(n=11)
18 month
(n=10)

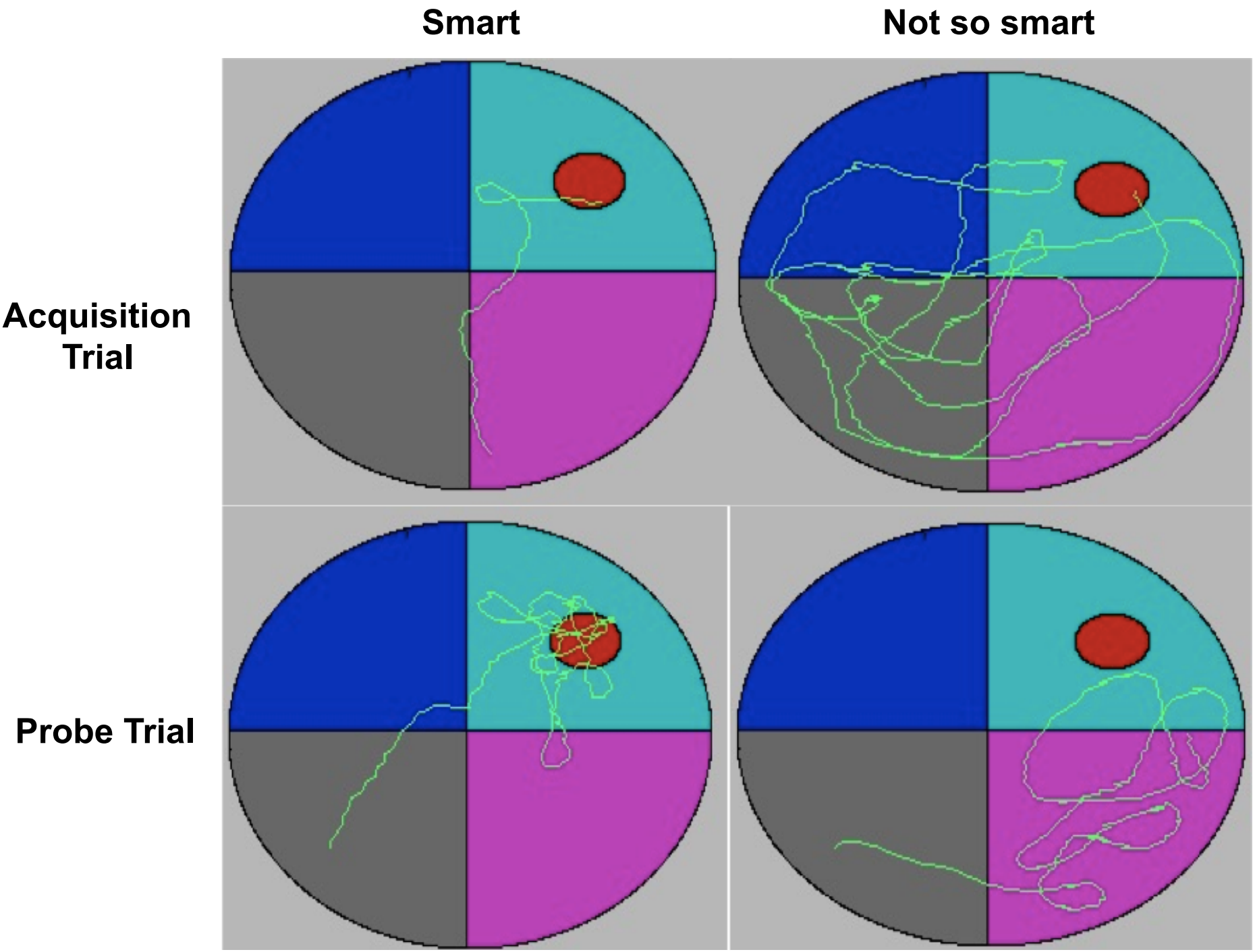

% Thioflavine-S load
0.8
0.6
0.4
0.2
0.0
*
*
5 month
(n=13)
11 month
(n=11)
18 month
(n=10)

Water maze - spatial learning

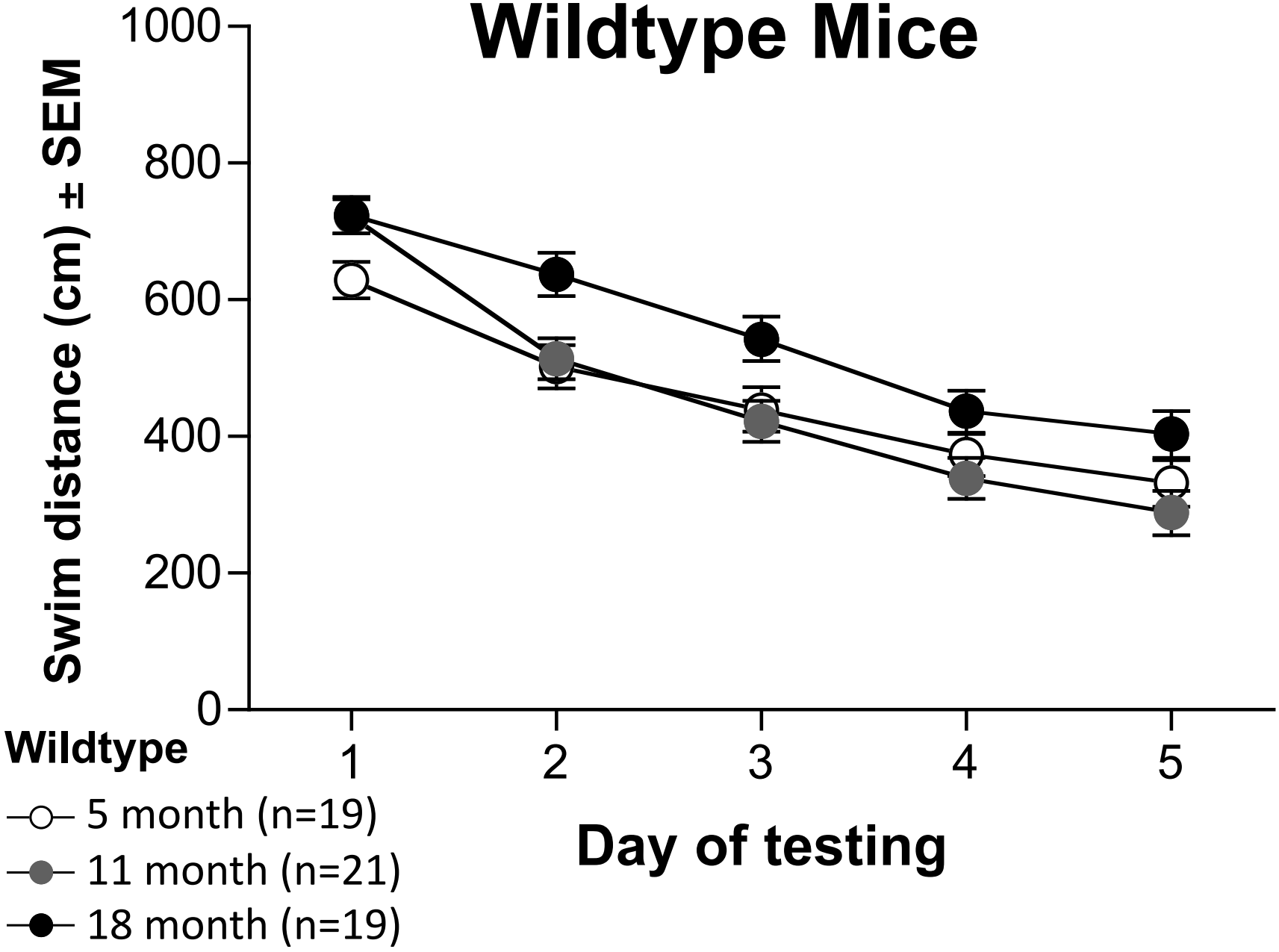


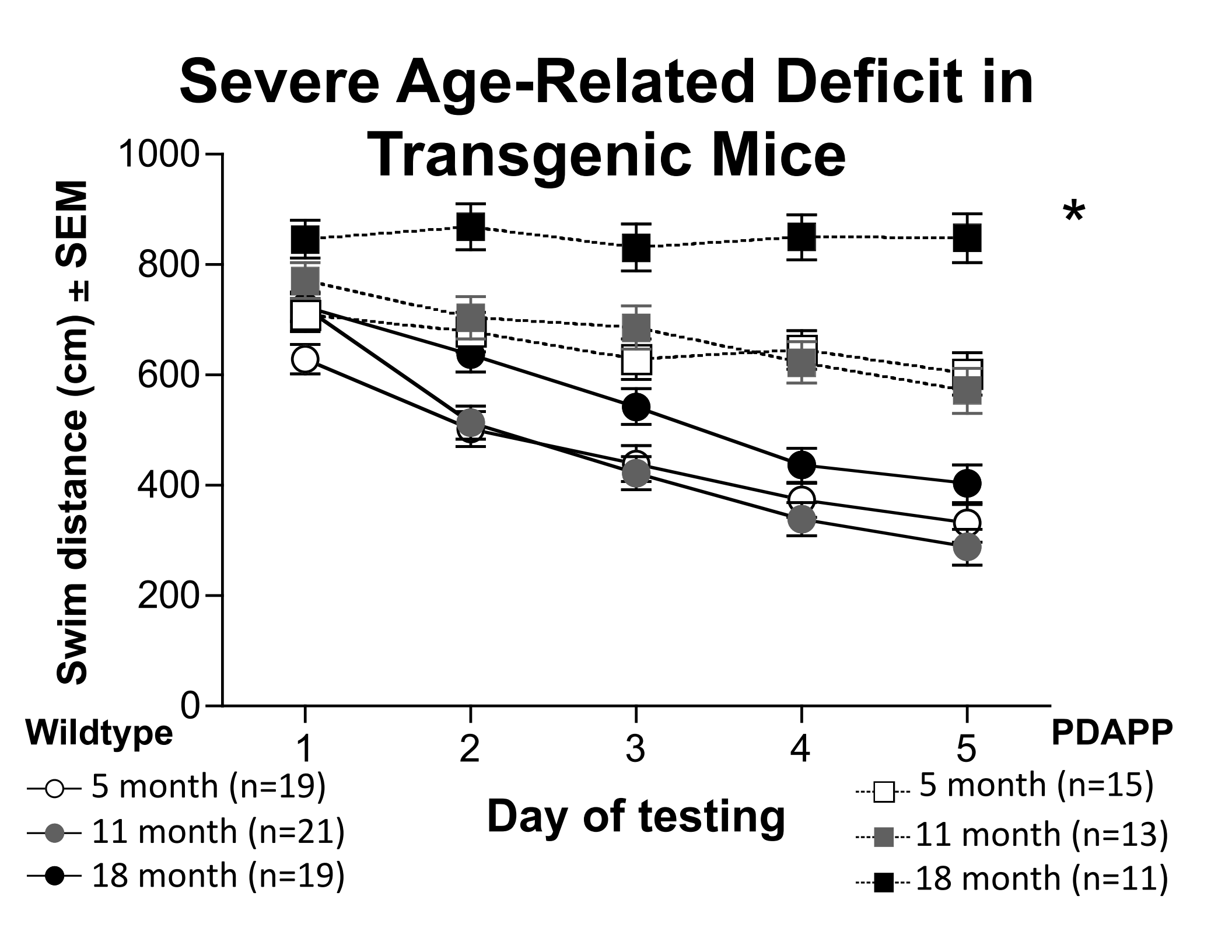
- dependent on proper hippocampal function
- spatial learning is impaired in Alzheimer’s disease

Spatial Learning: Submerged Platform

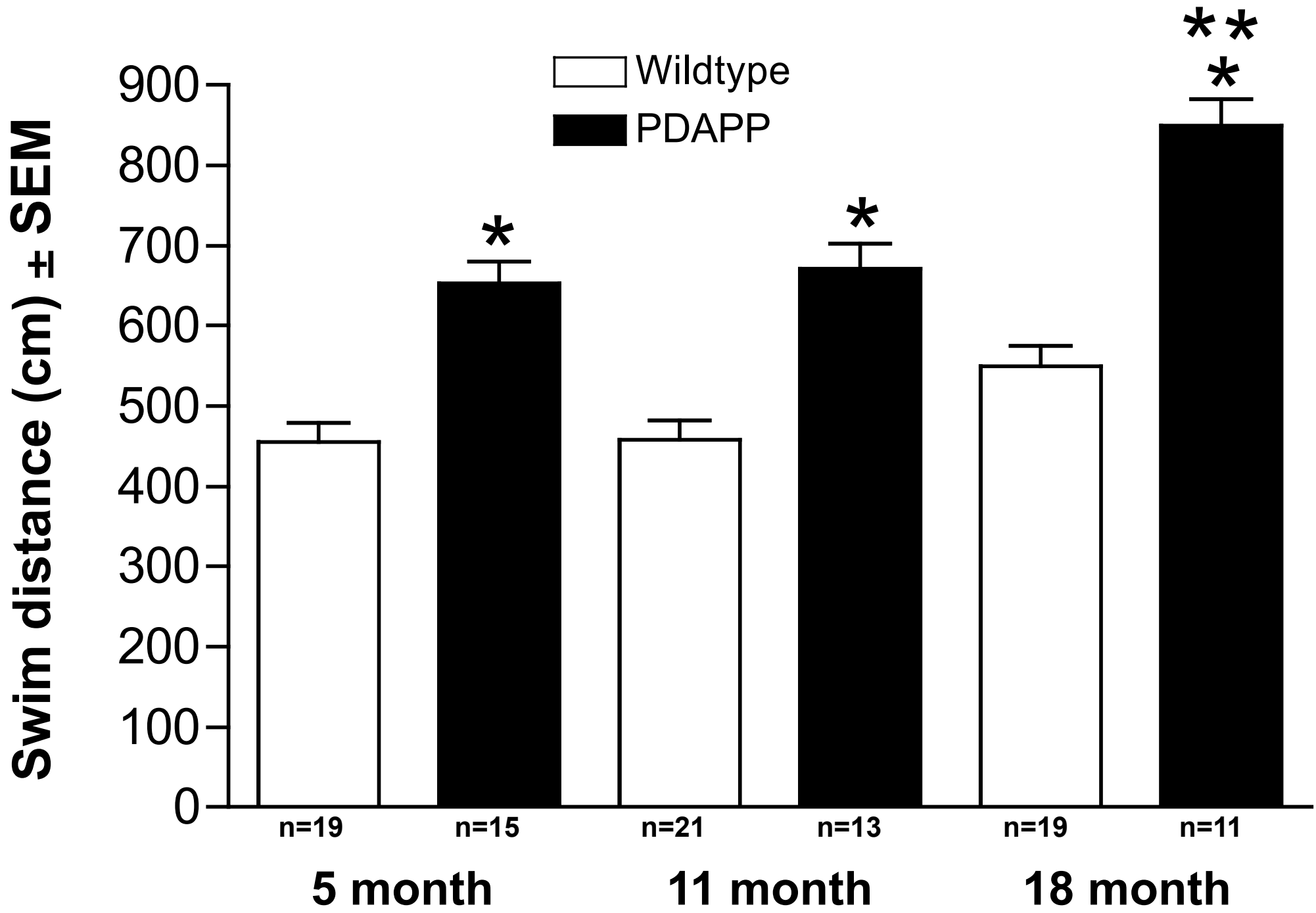


Subtle Age-Related Deficit in Wildtype Mice




Severe Age-Related Deficit in Transgenic Mice
Swim distance (cm) ± SEM
1000
800
600
400
200
0
1
2
3
4
5
Day of testing
*
Wildtype
PDAPP
5 month (n=19)
11 month (n=21)
18 month (n=19)
5 month (n=15)
11 month (n=13)
18 month (n=11)

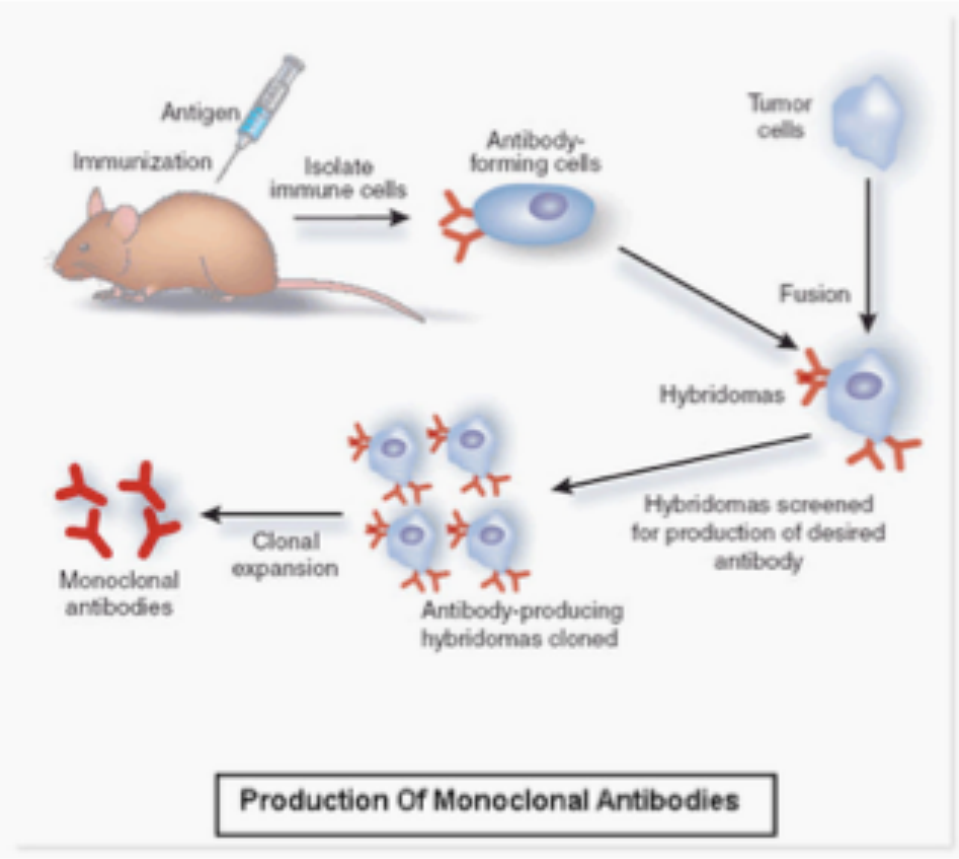
Spatial Learning: Severe Age-Related Deficit in PDAPP Mice



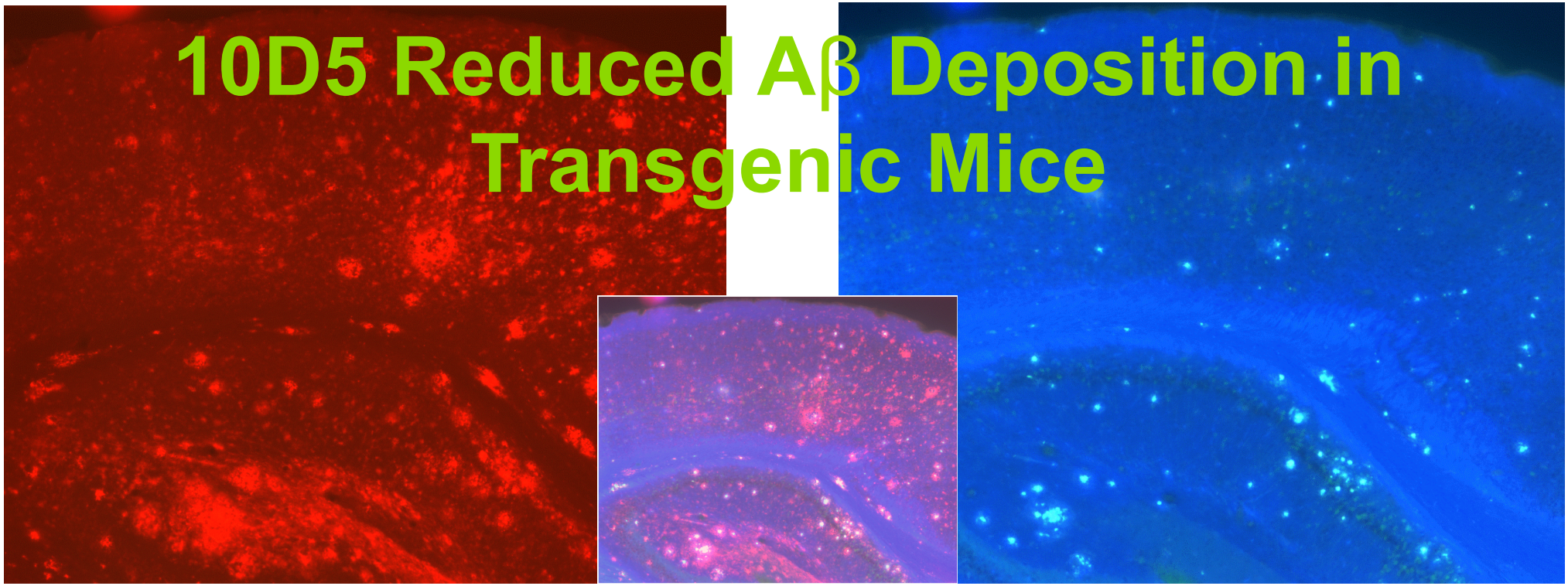
Is the Age-Related Deficit Due to Aβ?

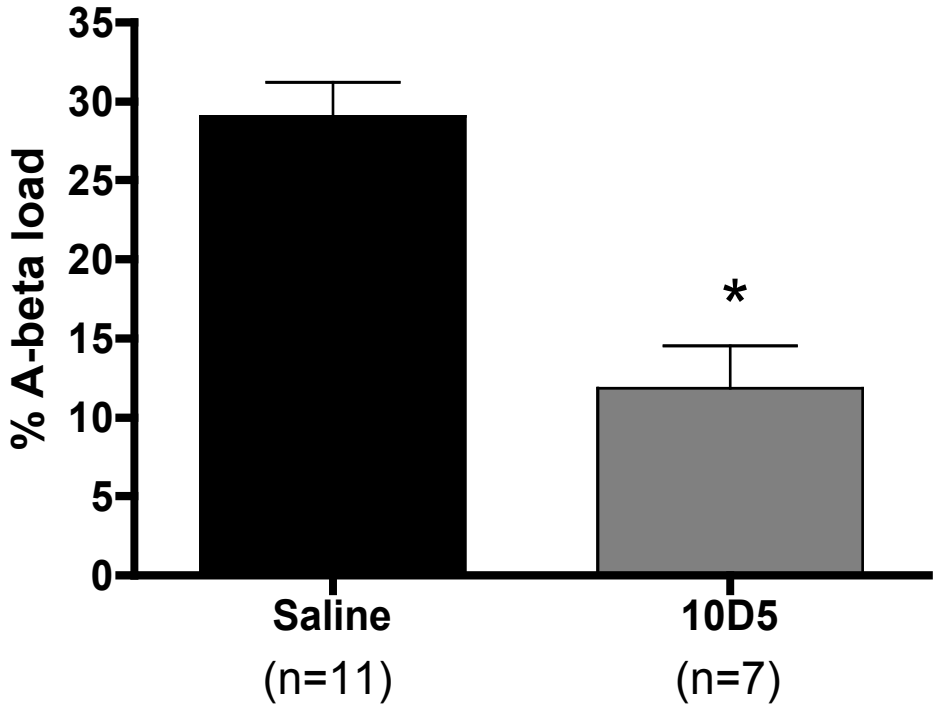
- 10D5 is a monoclonal antibody that targets Aβ

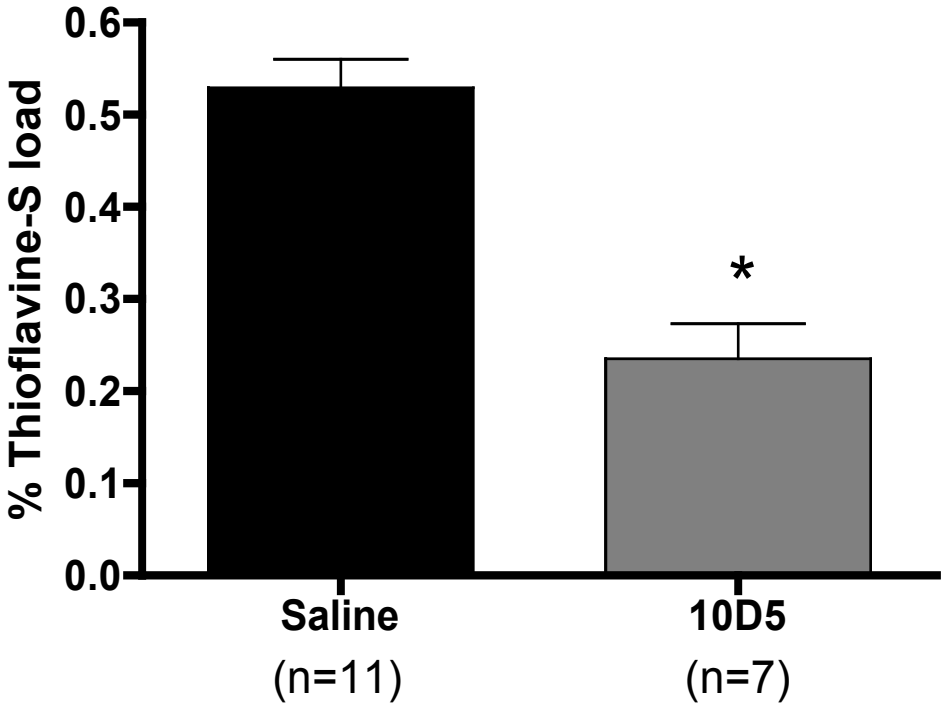
- Would treatment with 10D5 reduce plaque load and/or learning deficits in old transgenic mice?



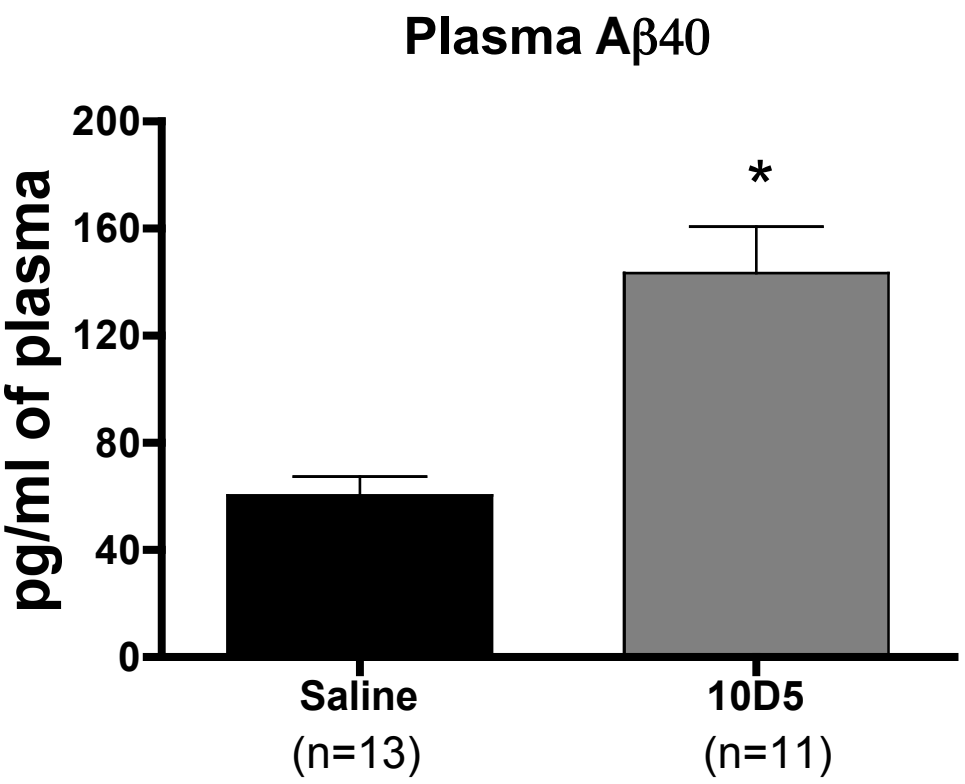
10D5 Reduced Aβ Deposition in Transgenic Mice

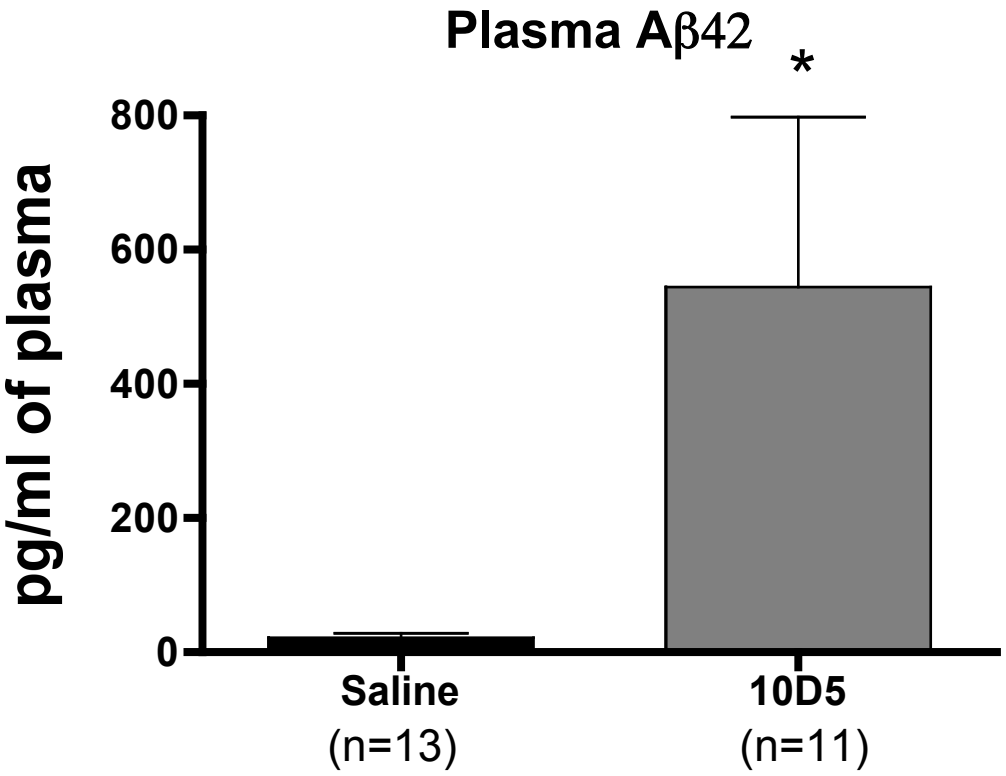




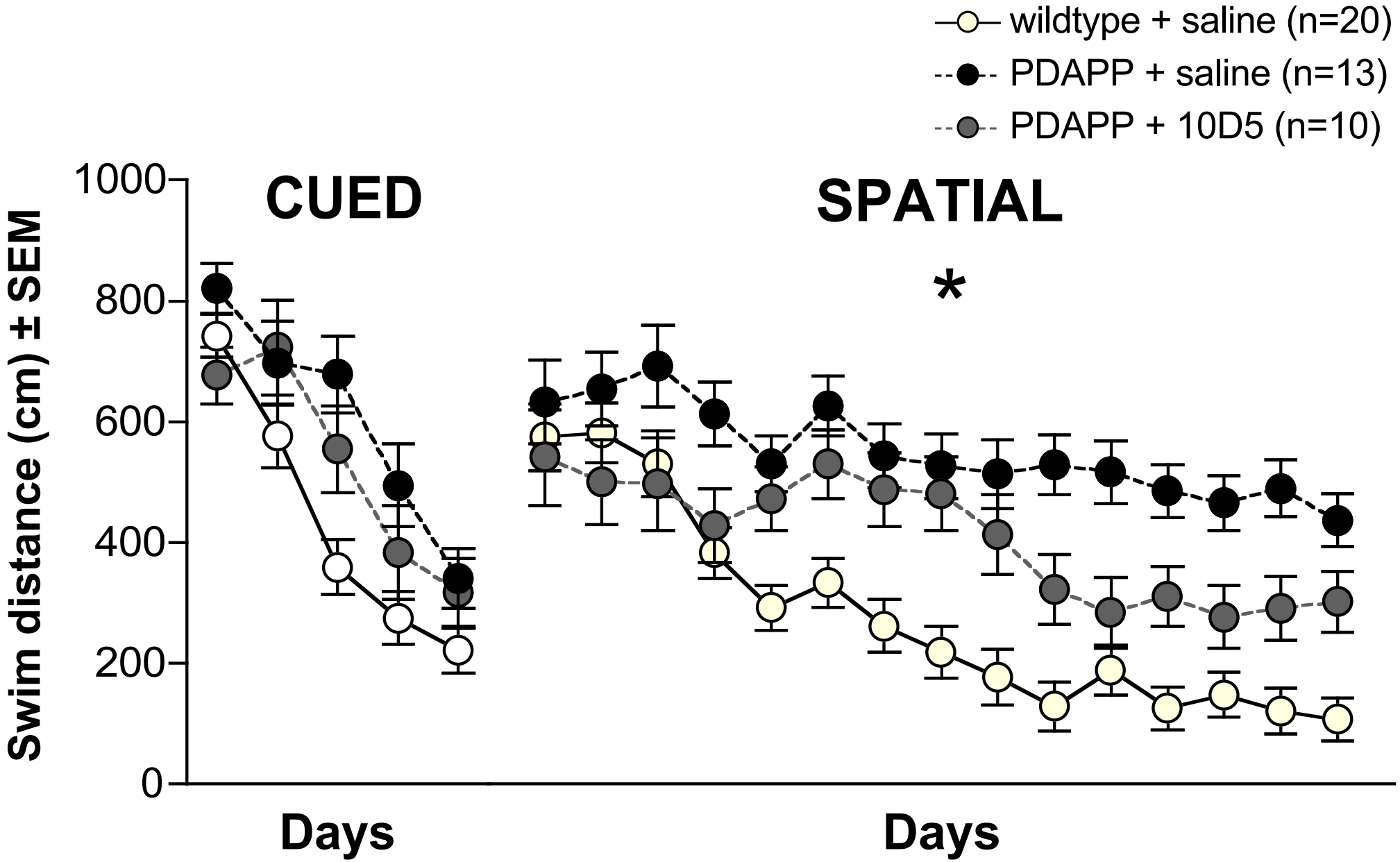


10D5 Increased Plasma Aβ Levels in Transgenic Mice

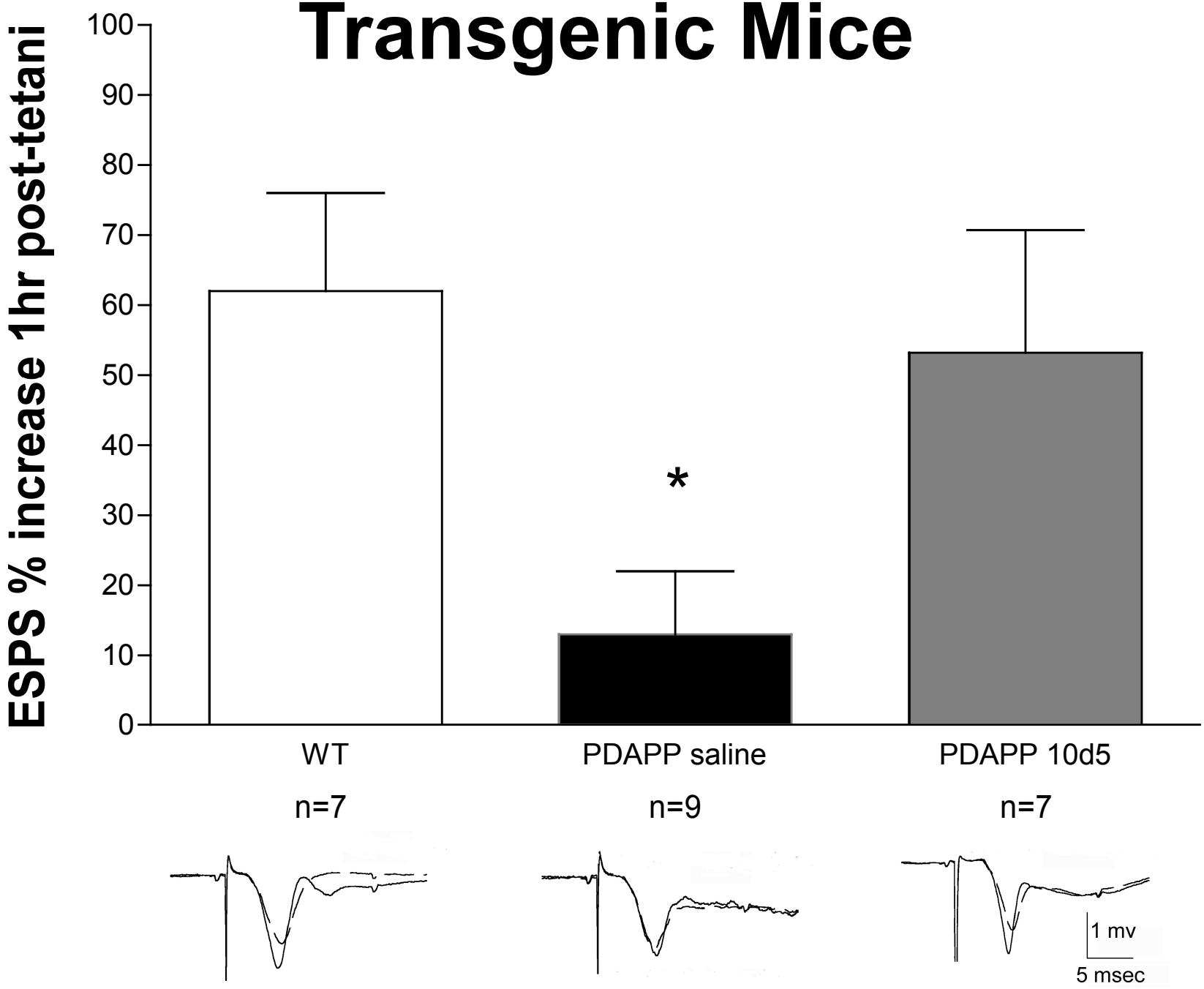




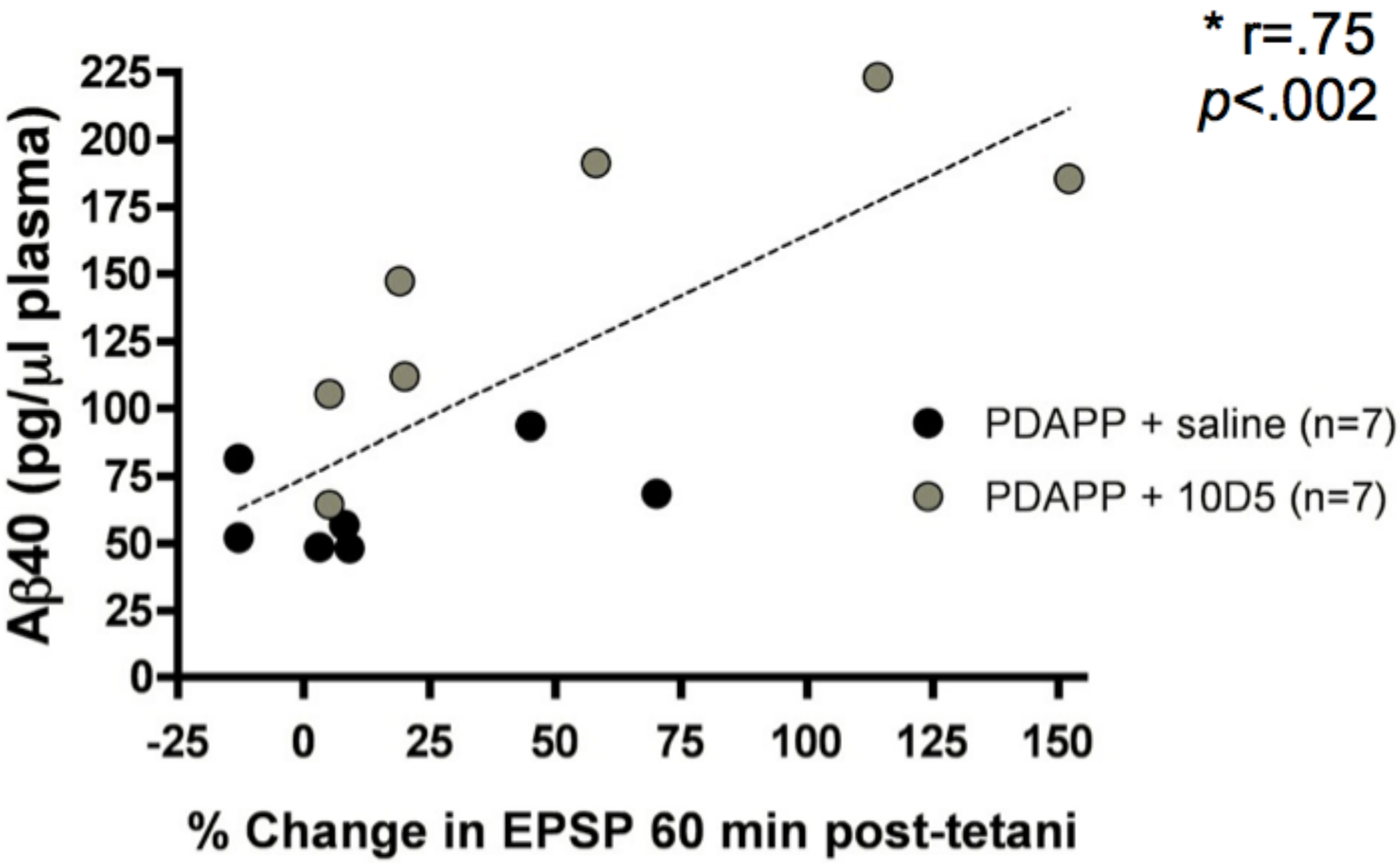
10D5 Reversed Spatial Learning Deficits in Transgenic Mice



10D5 Reversed LTP Dysfunction in Transgenic Mice



LTP Correlated with Plasma Aß



Alzheimer's treatments

- with age, more Aβ is produced, and less is cleared
  - accumulation of Aβ occurs slowly over the lifetime, most predominantly in the hippocampal formation

- pharmaceutical strategies for controlling AD include:
  - increasing levels of ACh
    - AChE inhibitors
  - blocking NMDA glutamate receptor channels
    - memantine

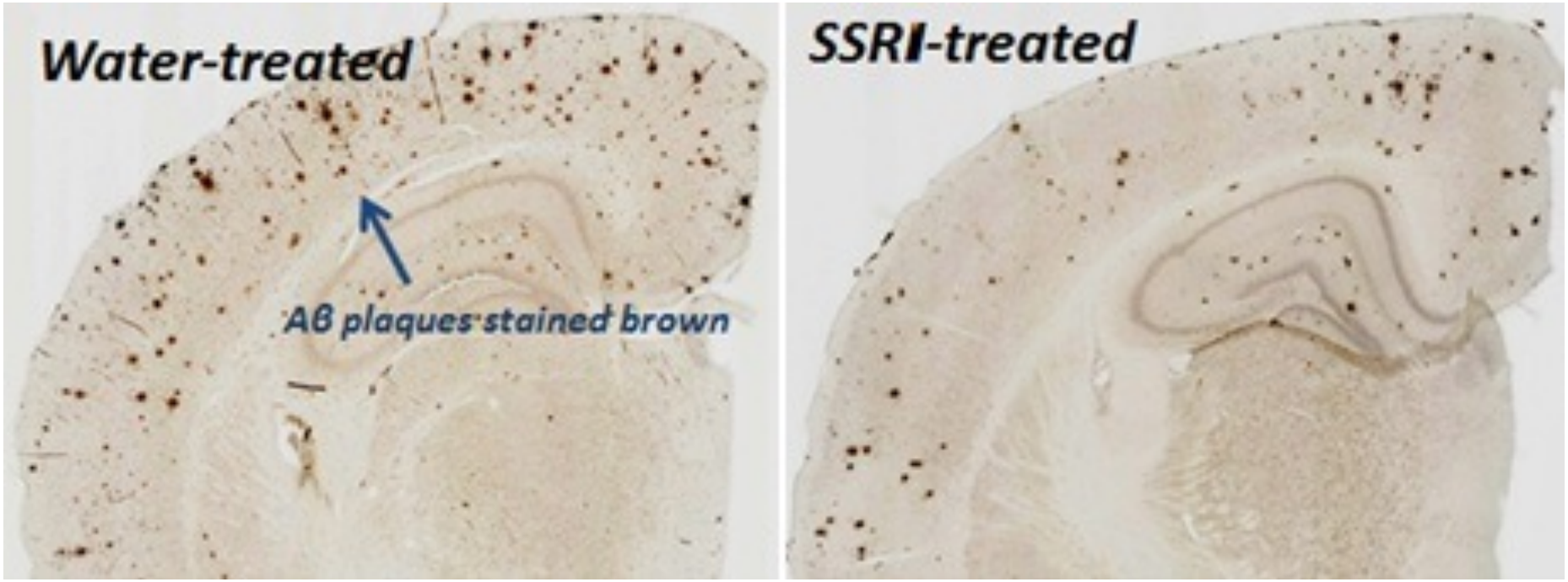
  - unfortunately, these treatments do not work very well

Antibodies such as 10D5 are in clinical trials

Also - SSRIs, nutrition

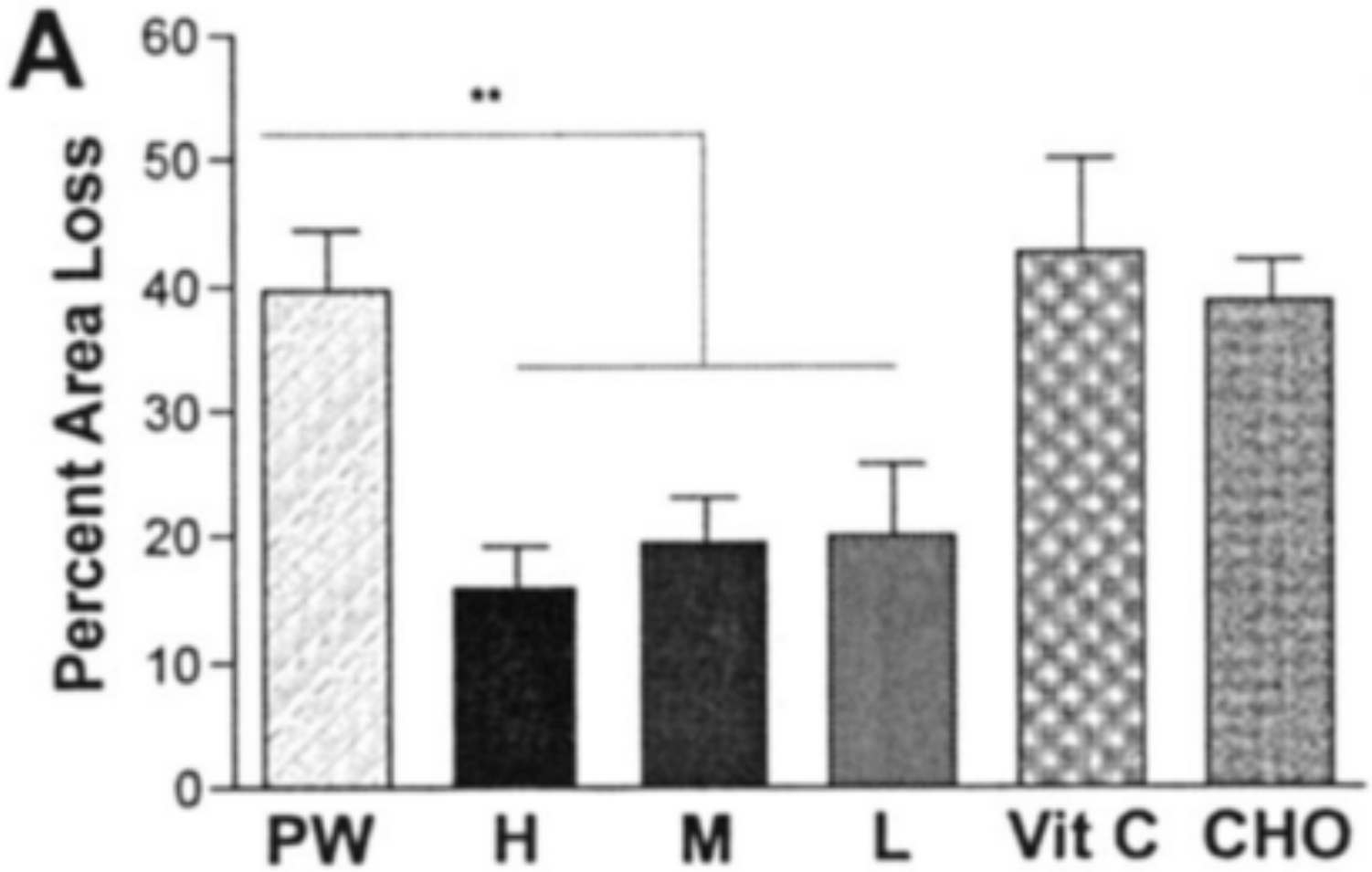
Alzheimer's treatments

- SSRIs activate 5HT receptors
  - binding of 5-HT to certain metabotropic receptors activates intracellular processes that "activate" and enzymes called extracellular-signal-regulated kinases (ERKs)
    - ERKs modulate enzymatic processing of APP
      - decrease gamma-secretase processing
      - increase alpha-secretase processing



Pomegranate and Stroke

• Loren et al. (2005) - when fed to pregnant mice, pomegranate juice protected neonatal offspring from subsequent hypoxic-ischemic brain injury



Pomegranate and Phytochemicals

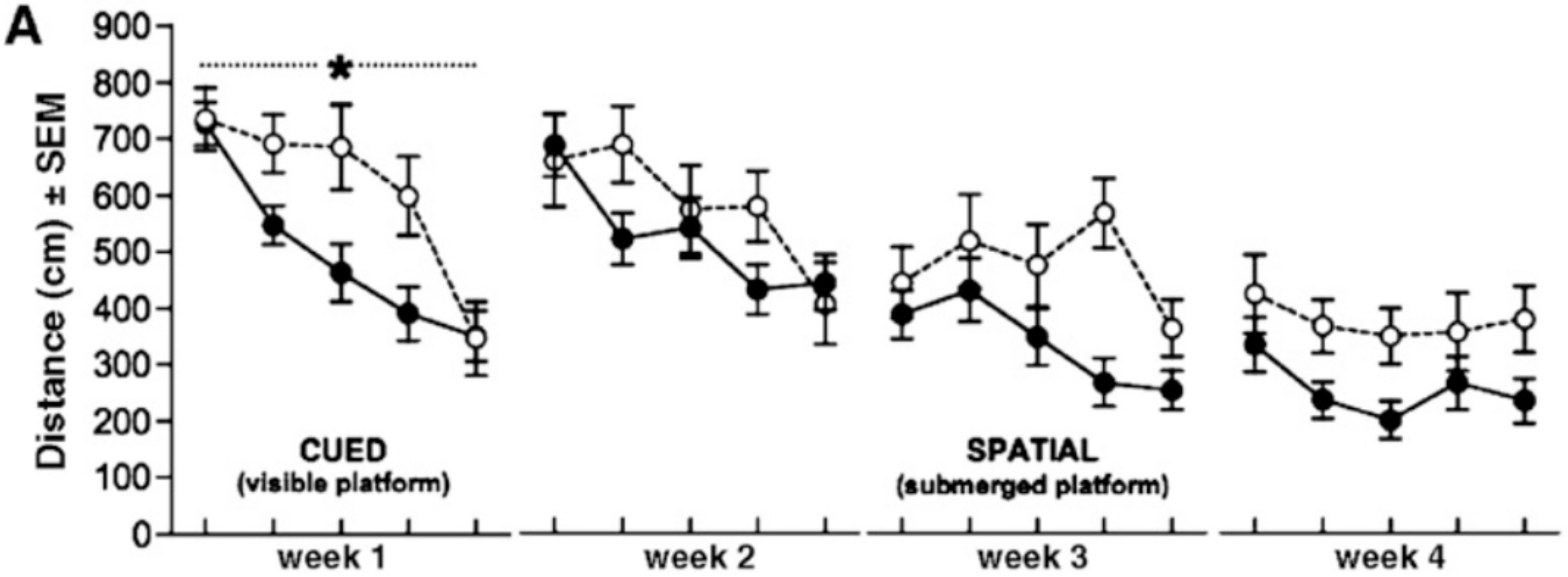
Pomegranates have been used as food and medicine for centuries. They contain very high concentrations of polyphenols (e.g., ellagic acid).

Diet Can Modulate the Risk of AD

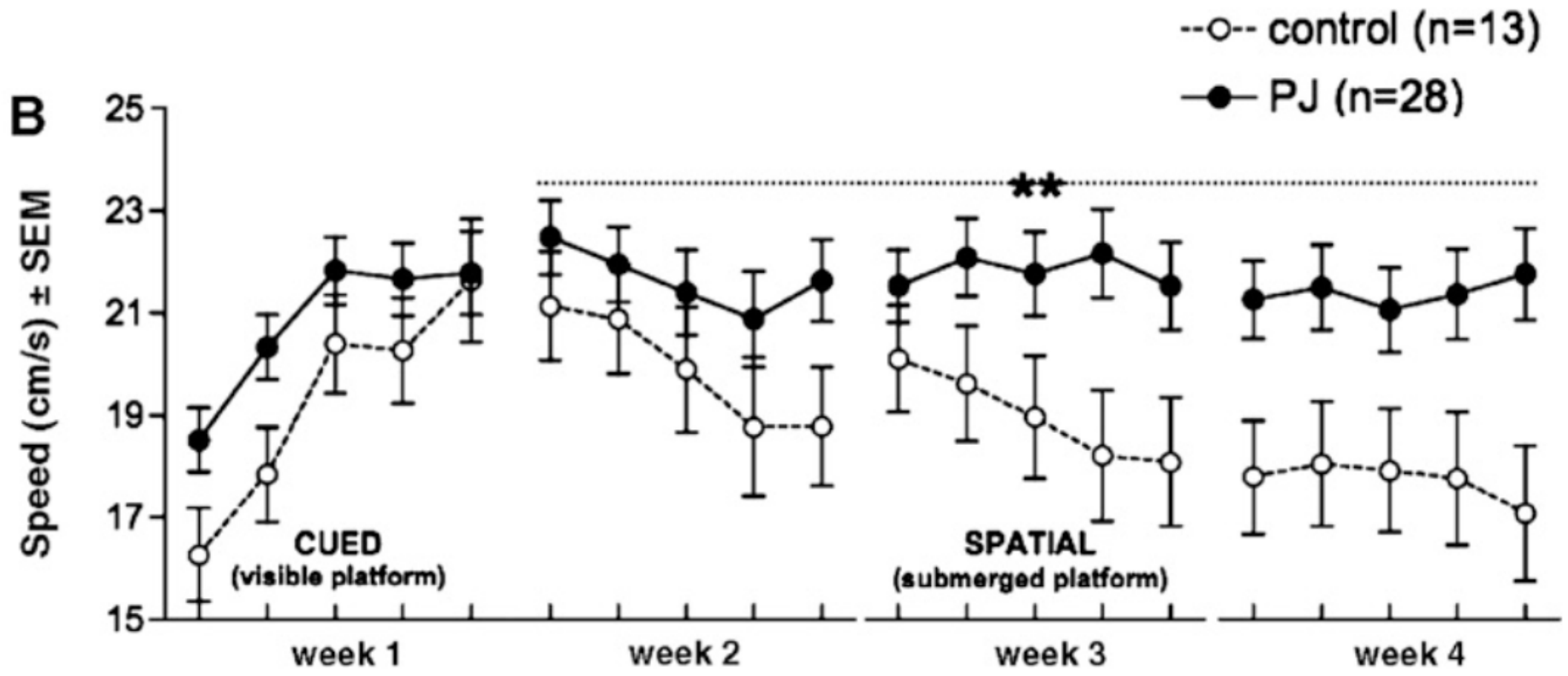
Dietary fruits and vegetables may decrease risk or slow progression of AD

- so….. pre-plaque transgenic mice were treated for 6 months (post-plaque) with either:
  - pomegranate juice - diluted to a human dose of ~1-2 cups / day
  - sugar water control

Pomegranate mice exhibited better spatial learning

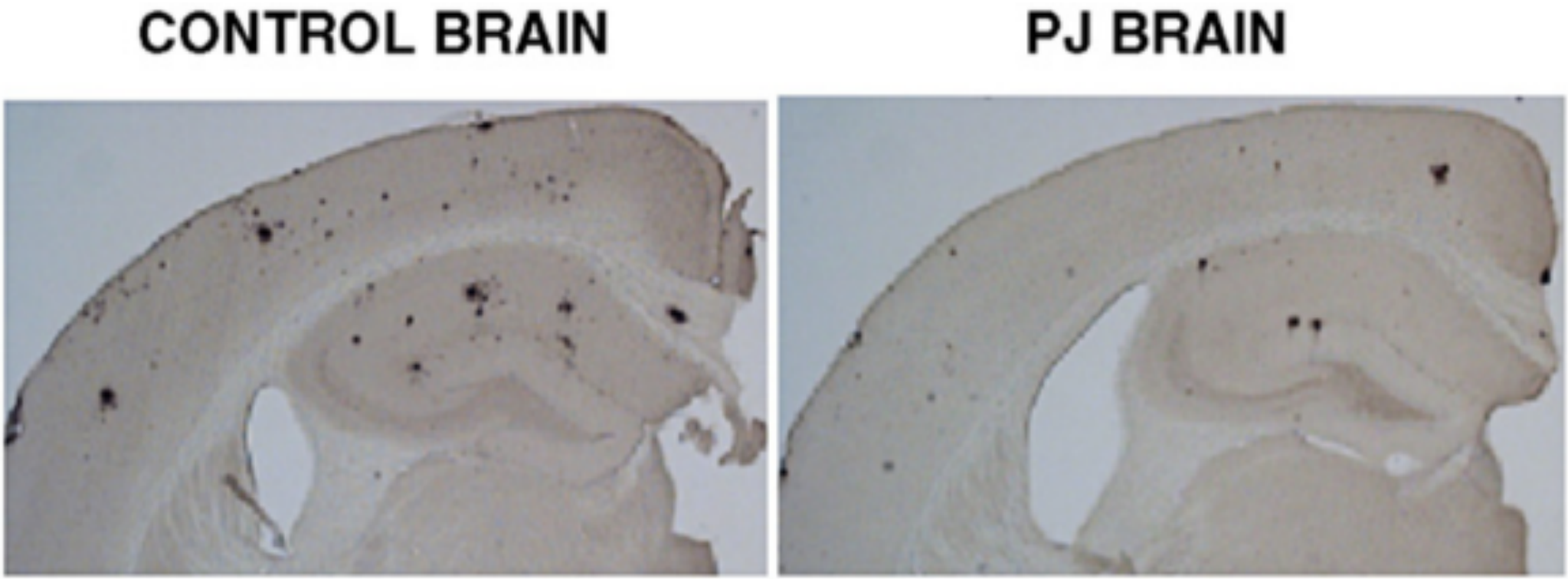


Pomegranate mice were also stronger swimmers



Pomegranate juice decreases amyloid load and improves behavior in a mouse model of Alzheimer's disease

Richard E. Hartman,[a,*] Aartie Shah,[b,c] Anne M. Fagan,[b,c] Katherine E. Schwetye,[b,c] Maia Parsadanian,[b,c] Risa N. Schulman,[d] Mary Beth Finn,[b,c] and David M. Holtzman[b,c,d,e,*]



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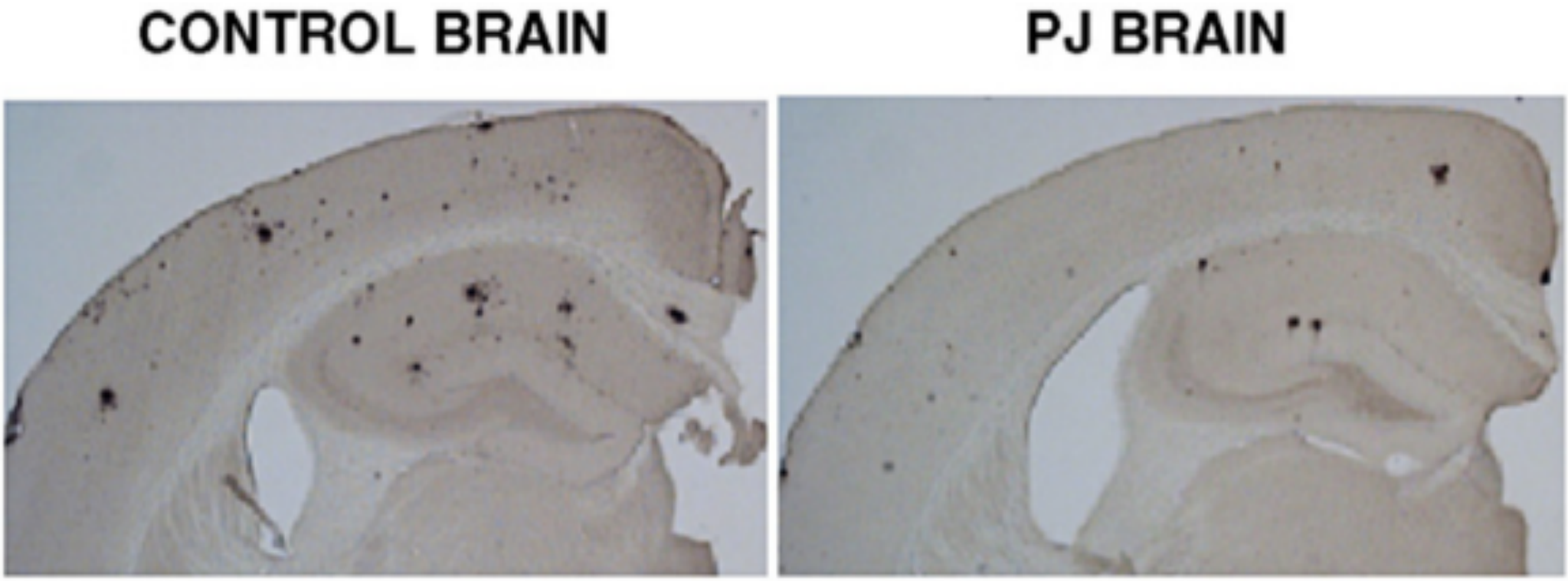

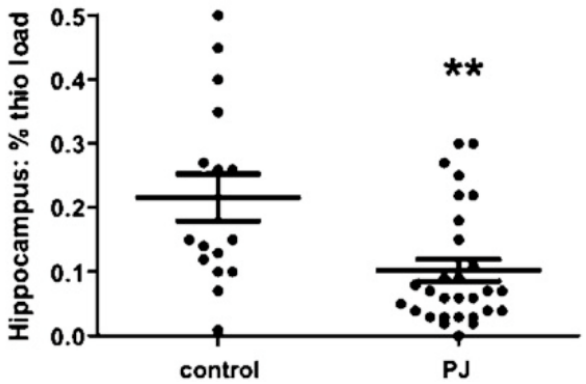

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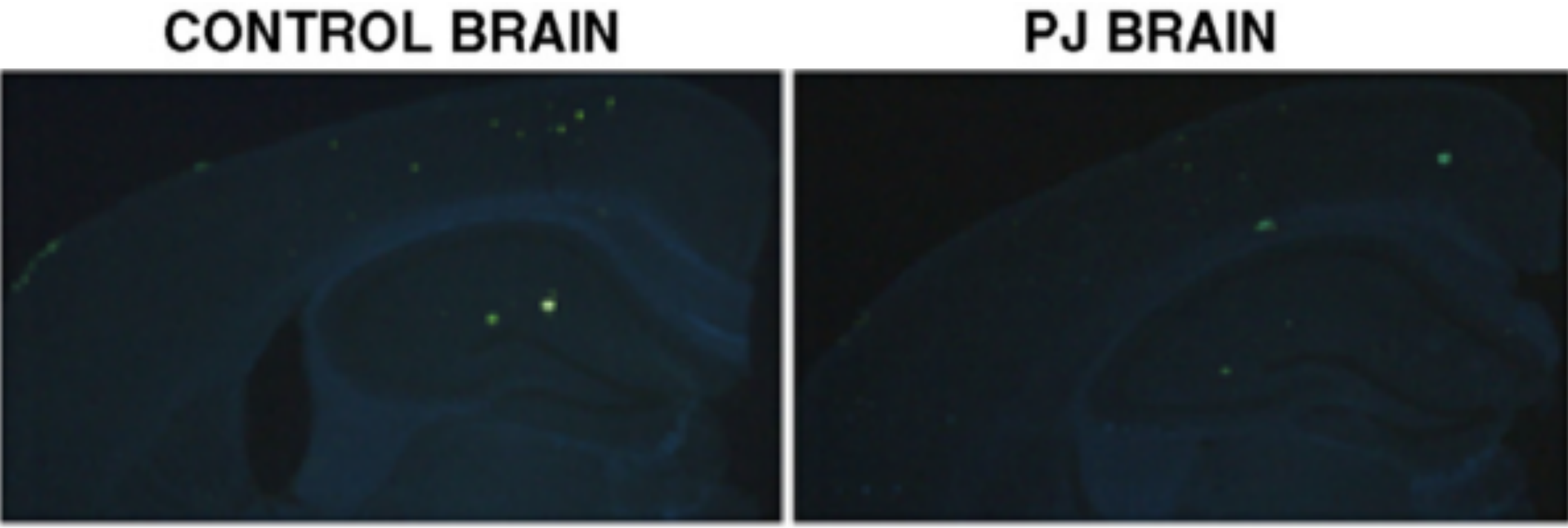
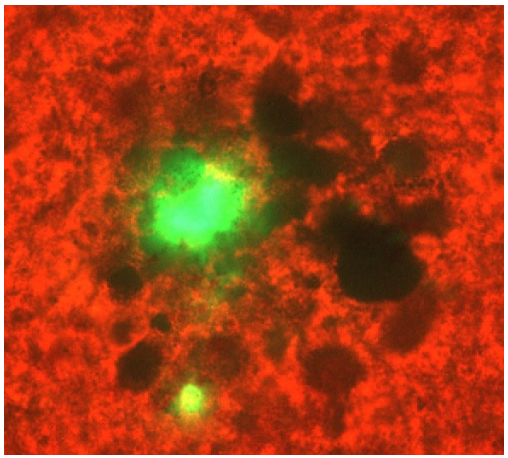
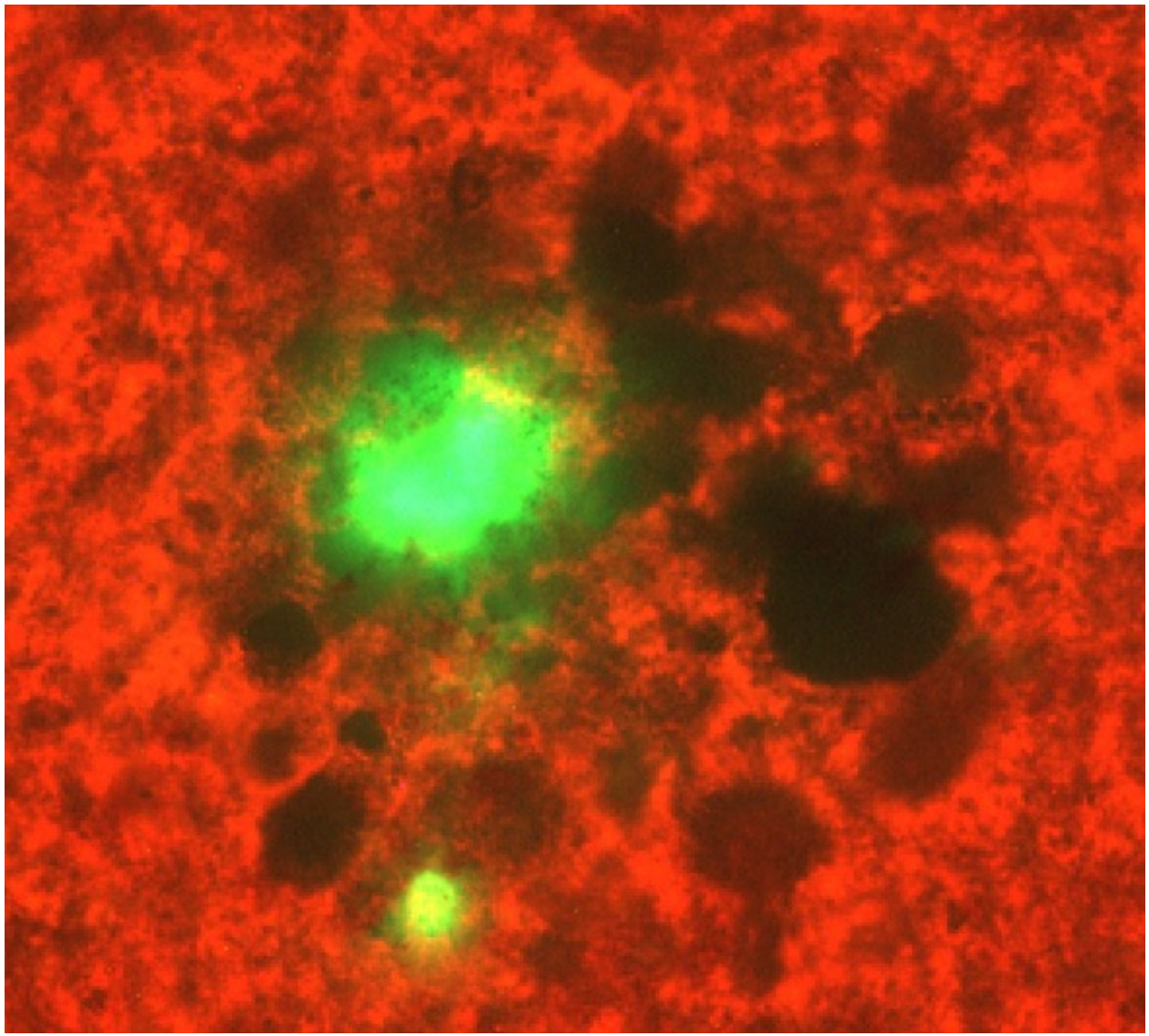


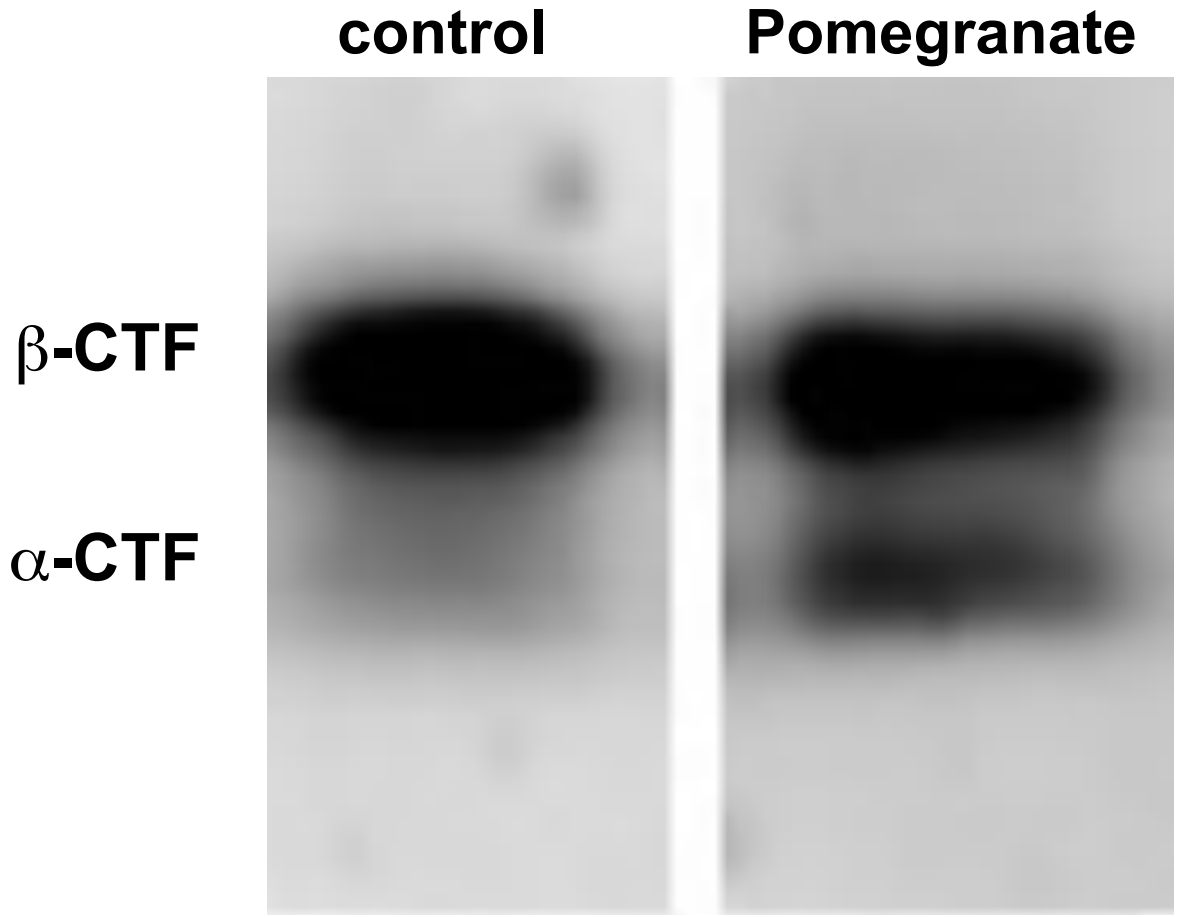


Pomegranate reduced amyloid toxicity



28% fewer swollen neuronal processes associated with each amyloid plaque

How?
Enhanced α−secretase processing of Aβ (ERK?)



→ less neurotoxic Aβ

→ more neuroprotective sAPP-α

Other potential pomegranate mechanisms

- antioxidant, anti-inflammatory, improved lipid profile, cardiovascular function, nitric oxide production, + ?
  - Kwak et al. (2005) showed that ellagic acid inhibits β-secretase
    → less neurotoxic Aβ

Summary

- Several lines of evidence suggest that:
  - gradual accumulation of Aβ in the brain causes downstream events leading to:
    - functional neuronal deficits
      - structural brain damage
        - behavioral impairments
          - eventually death

Summary

- So…. AD is related to abnormal buildup of brain Aβ
  - high levels of brain APP
  - and/or excessive amyloidogenic APP processing
    - induces neurotoxic events and even more Aβ accumulation
      - vicious circle of neurodegenerative decline
        - *"amyloid cascade"* hypothesis of AD

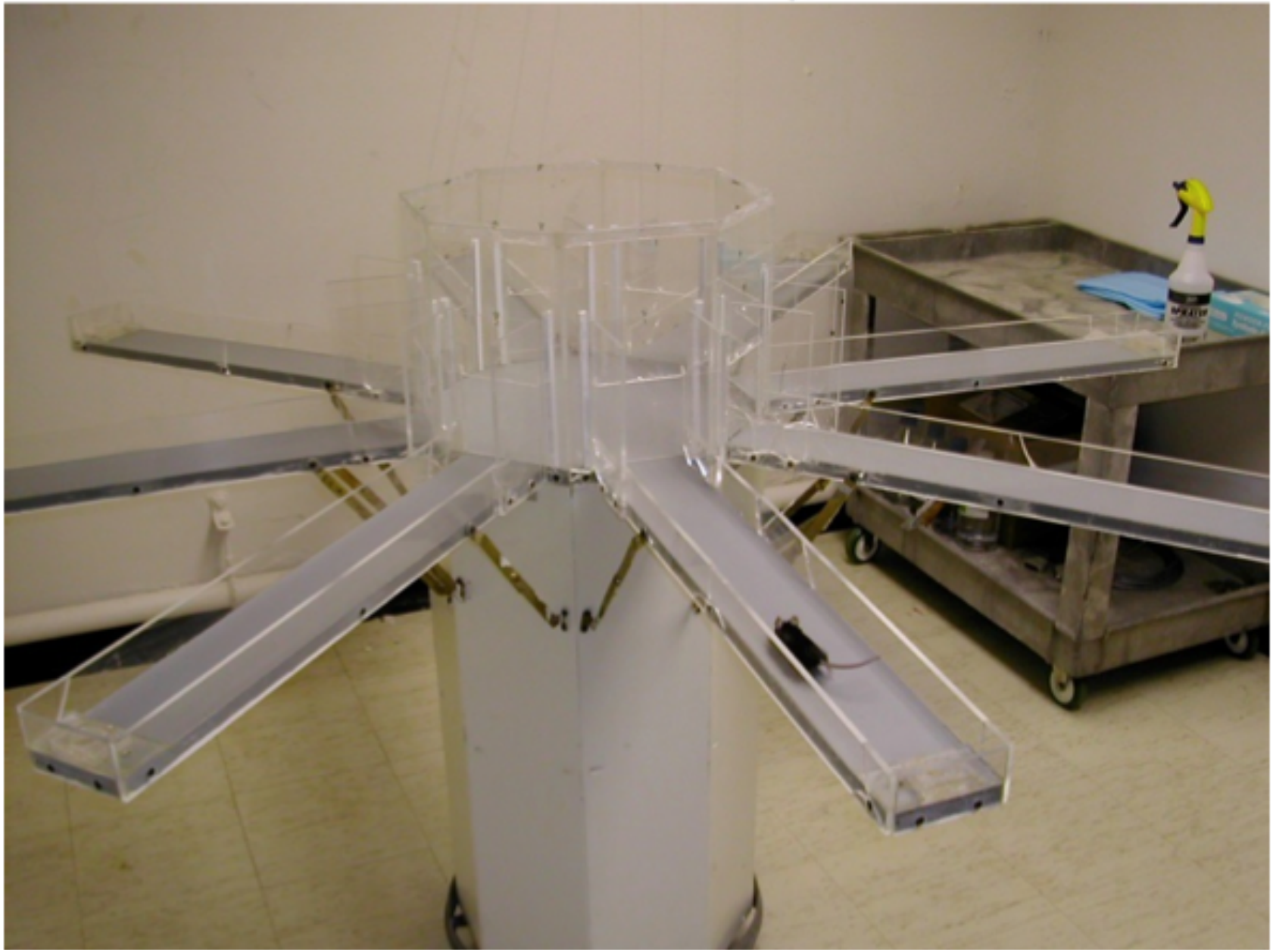
Summary

- treatments that lower levels of Aβ can prevent and reverse AD-like symptoms and pathology in transgenic mice
  - anti-Aβ antibodies decreased Aβ deposition and improved both cognitive performance and LTP in the hippocampus

Aβ accumulation is at least partially responsible for the age-related neuronal dysfunction that eventually disrupts cognitive performance

Behavioral Phenotyping of GFAP-ApoE3 and -ApoE4 Transgenic Mice: ApoE4 Mice Show Profound Working Memory Impairments in the Absence of Alzheimer's-like Neuropathology

R. E. Hartman,*,†,[1] D. F. Wozniak,*,†,[1,2] A. Nardi,* J. W. Olney,* L. Sartorius,‡ and D. M. Holtzman‡,§,[3]



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