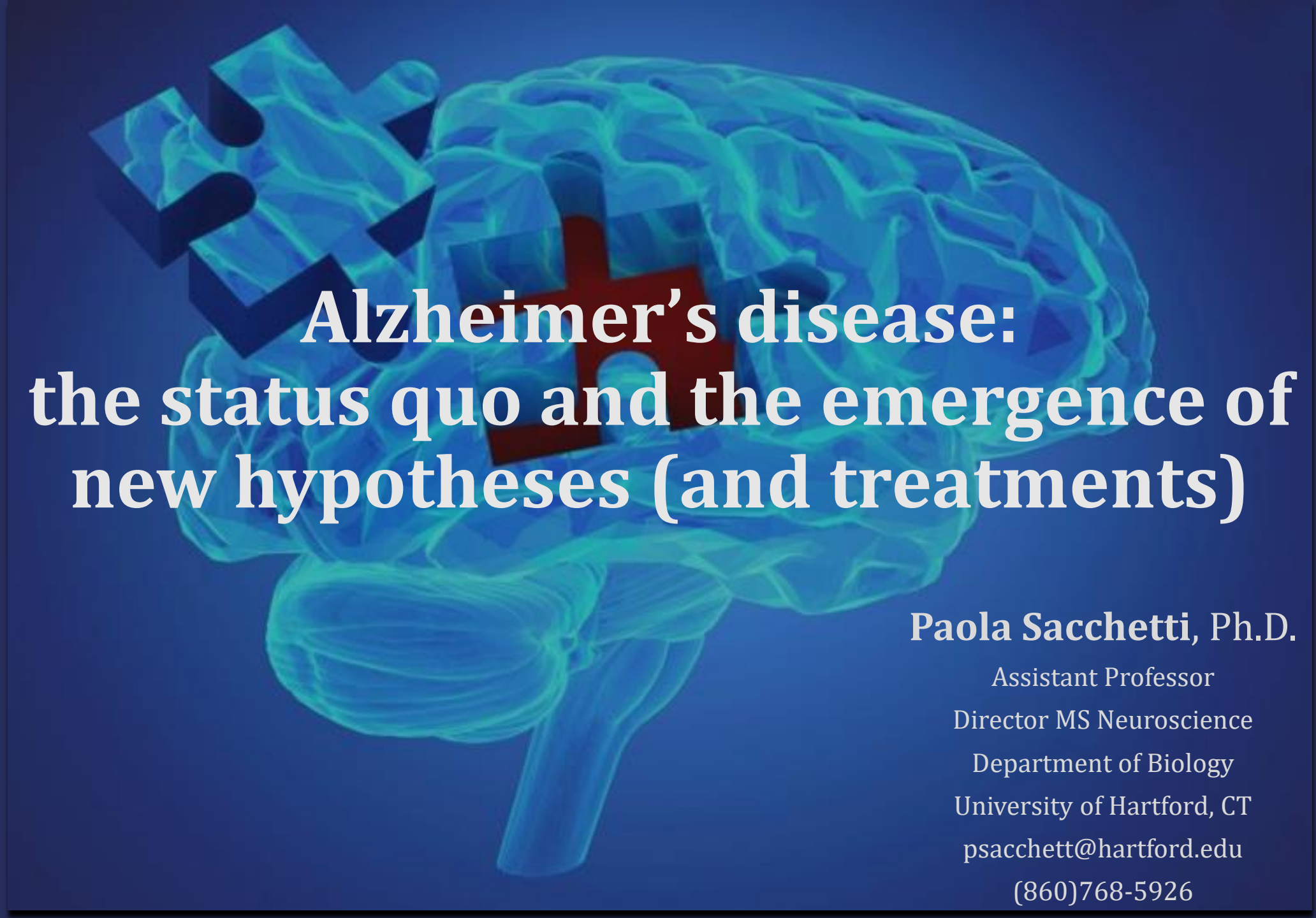

Alzheimer's disease: the status quo and the emergence of new hypotheses (and treatments)

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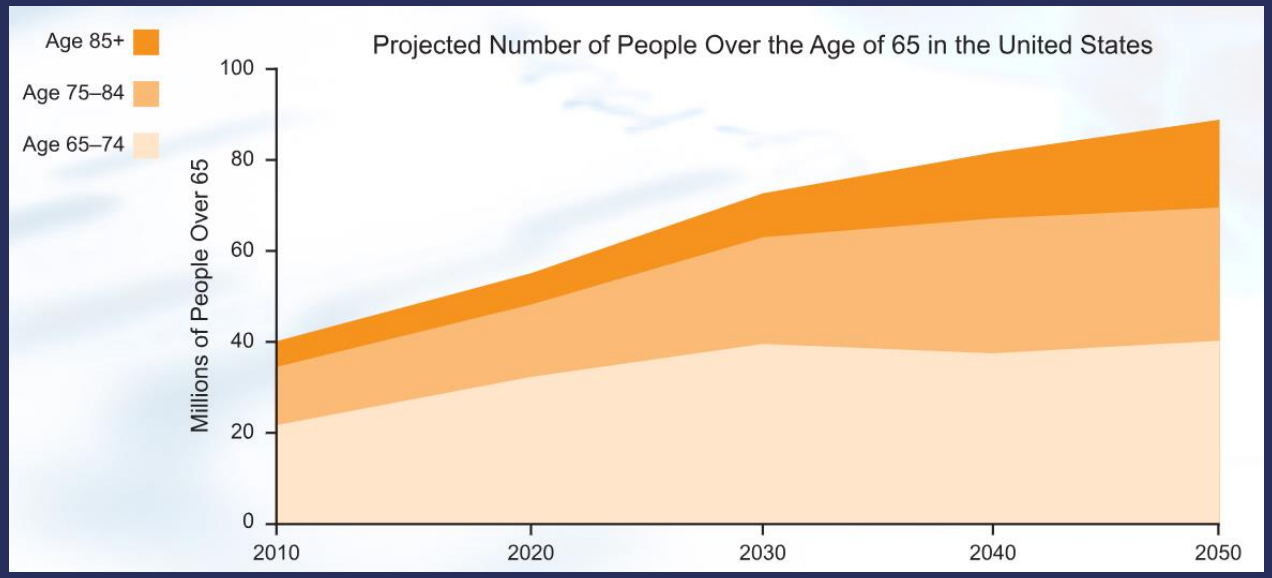
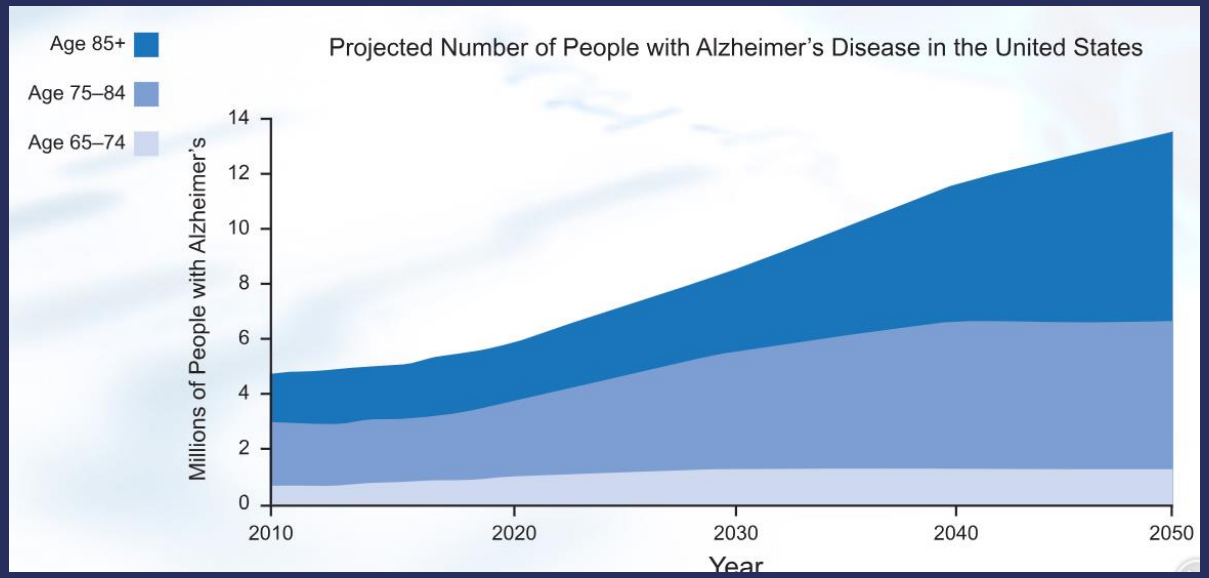
Today’s talk:

- ❑ Generalities about Alzheimer’s disease (AD)
- ❑ Pathology
- ❑ Beta amyloid hypothesis
- ❑ New hypotheses
- ❑ We, at UHart

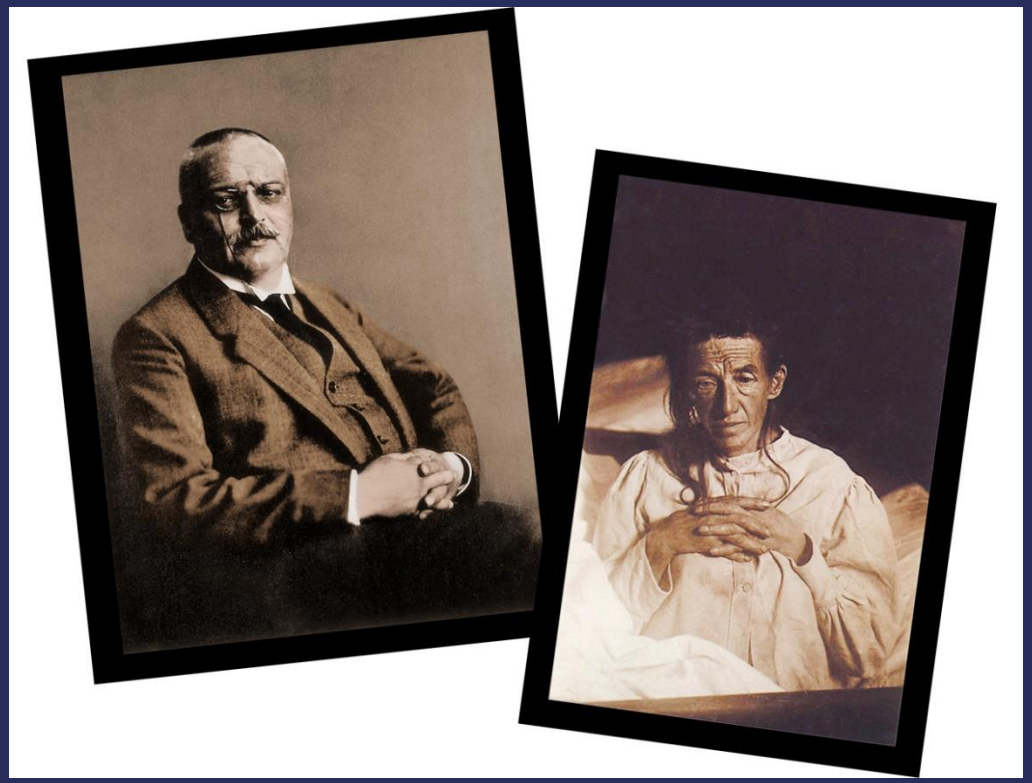
AD is the most prominent form of dementia

Incidence





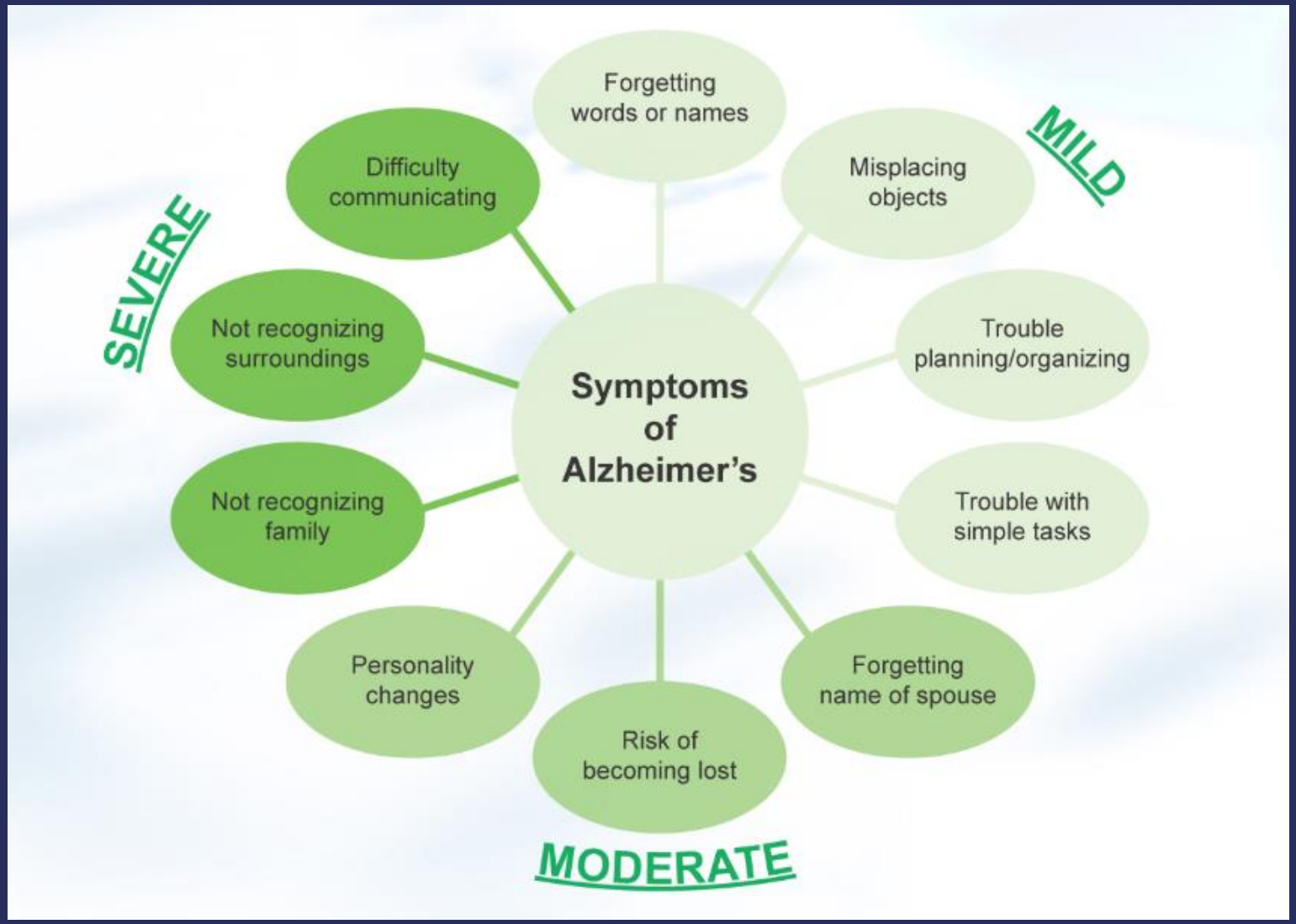
Alois Alzheimer (1864-1915)



1906 He reported “A peculiar severe disease process of the cerebral cortex” which affected a woman in her fifties, Auguste D., and caused memory loss, disorientation, hallucinations and ultimately her death (at 55).

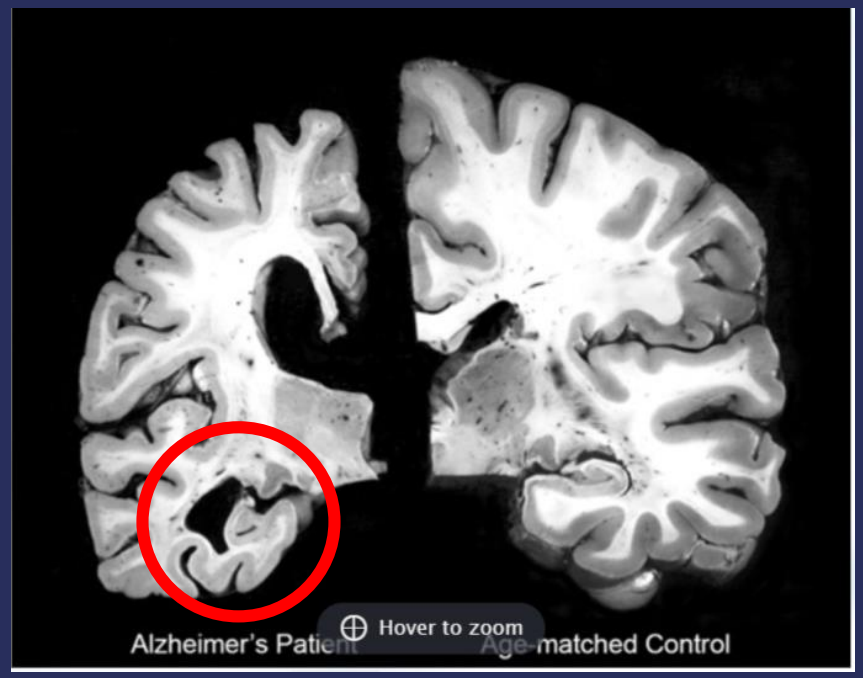
1907 His report noted distinctive plaques and neurofibrillary tangles in the brain histology.

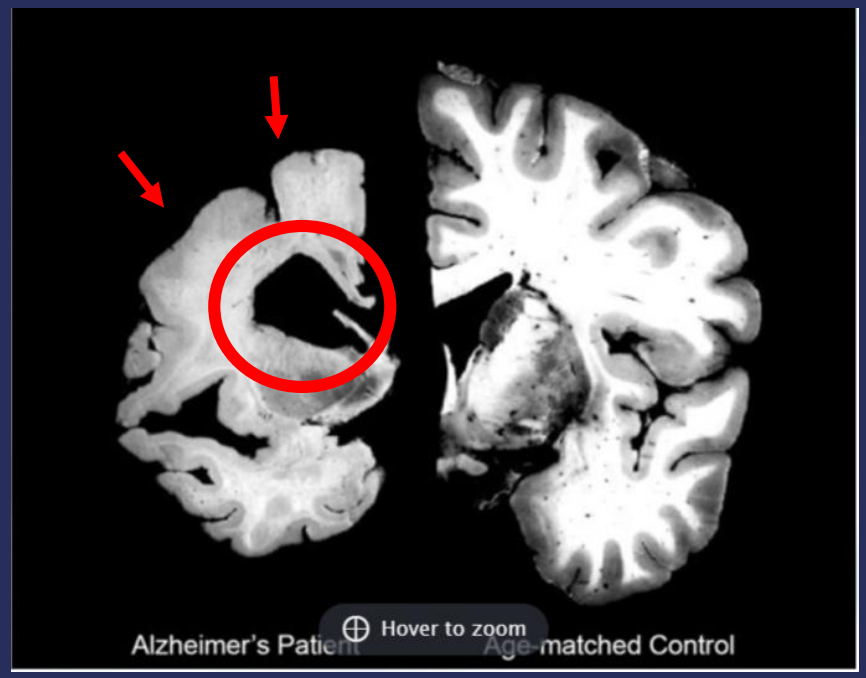
Symptoms of disease progression

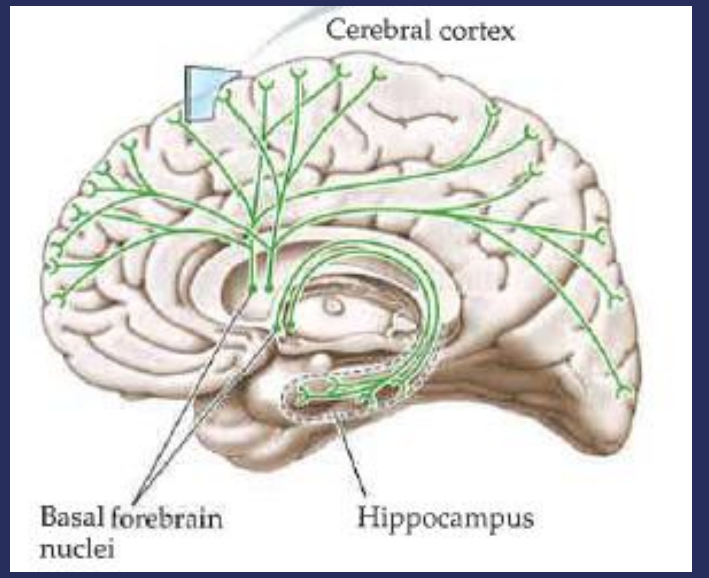


This is not normal aging

Pathology of the disease - structural changes







Purve 5th ed.

- Smaller size
- Decreased Cortex (atrophy)

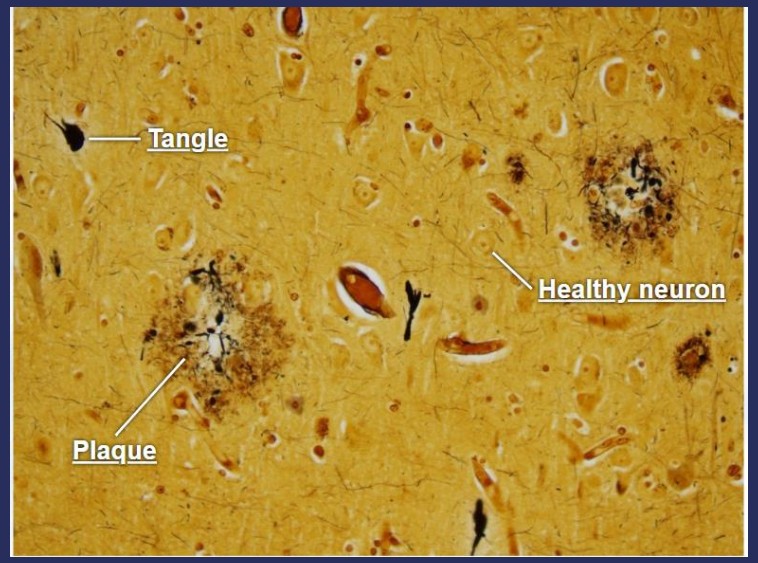
- Bigger ventricles
- Loss of Hippocampus & Entorhinal cortex

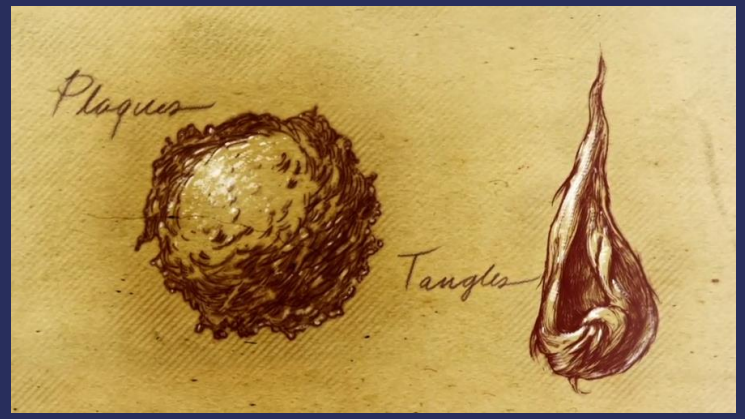
- Loss of Acetylcholine neurons

Davies P and Maloney, *Lancet* 1976
Bartus et al, *Science* 1982

HHMI interactive AD project

Pathology of the disease - Microscopic changes

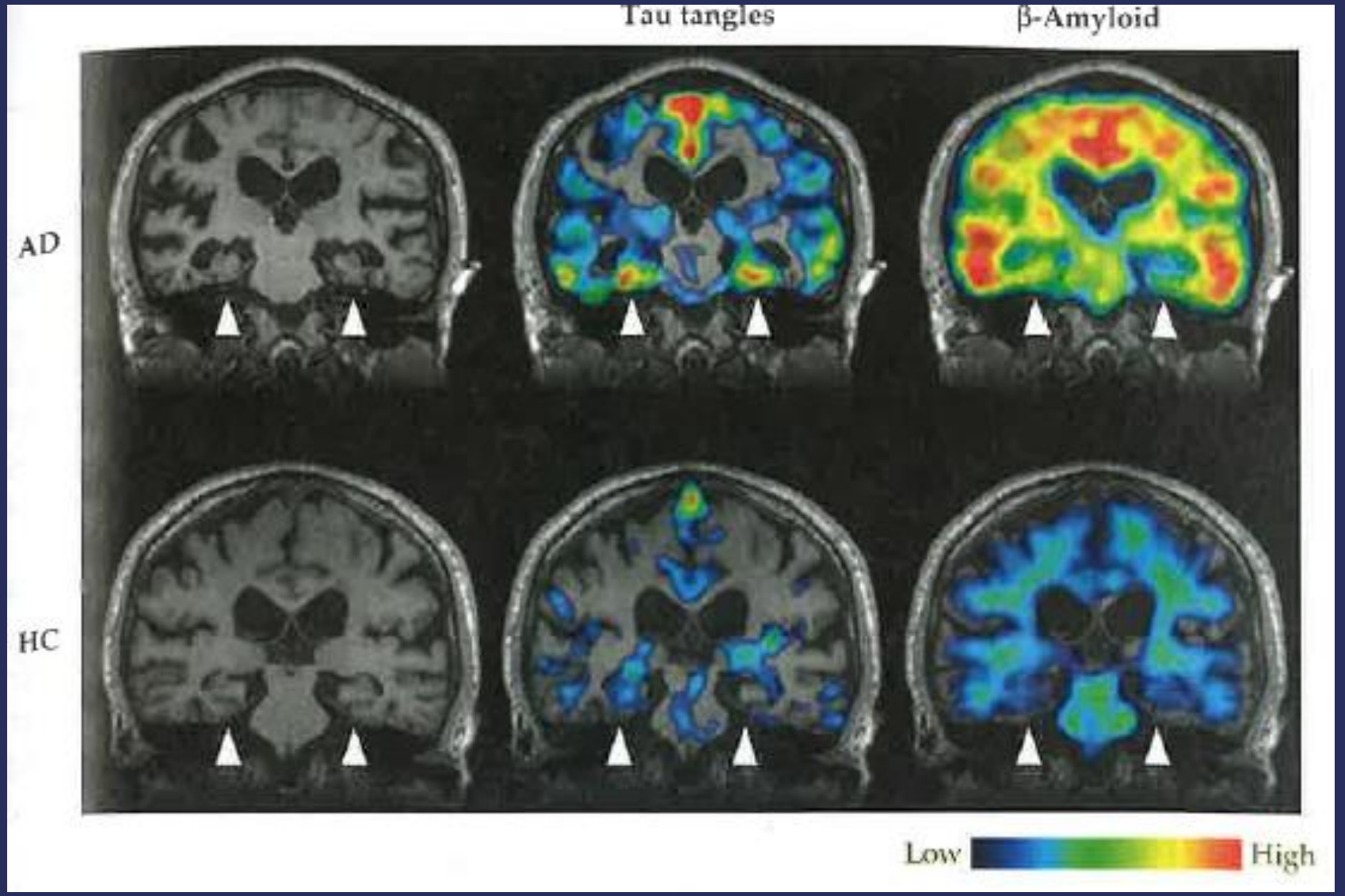




Plaques –
Extracellular deposits
Mostly composed of
Beta amyloid protein
Glenner and Wong, *BBRC* 1984

Tangles of neurofilaments
Intracellular deposits
Mostly composed of
Tau protein
Brion JP et al, 1985
Wood et al, *PNAS* 1986

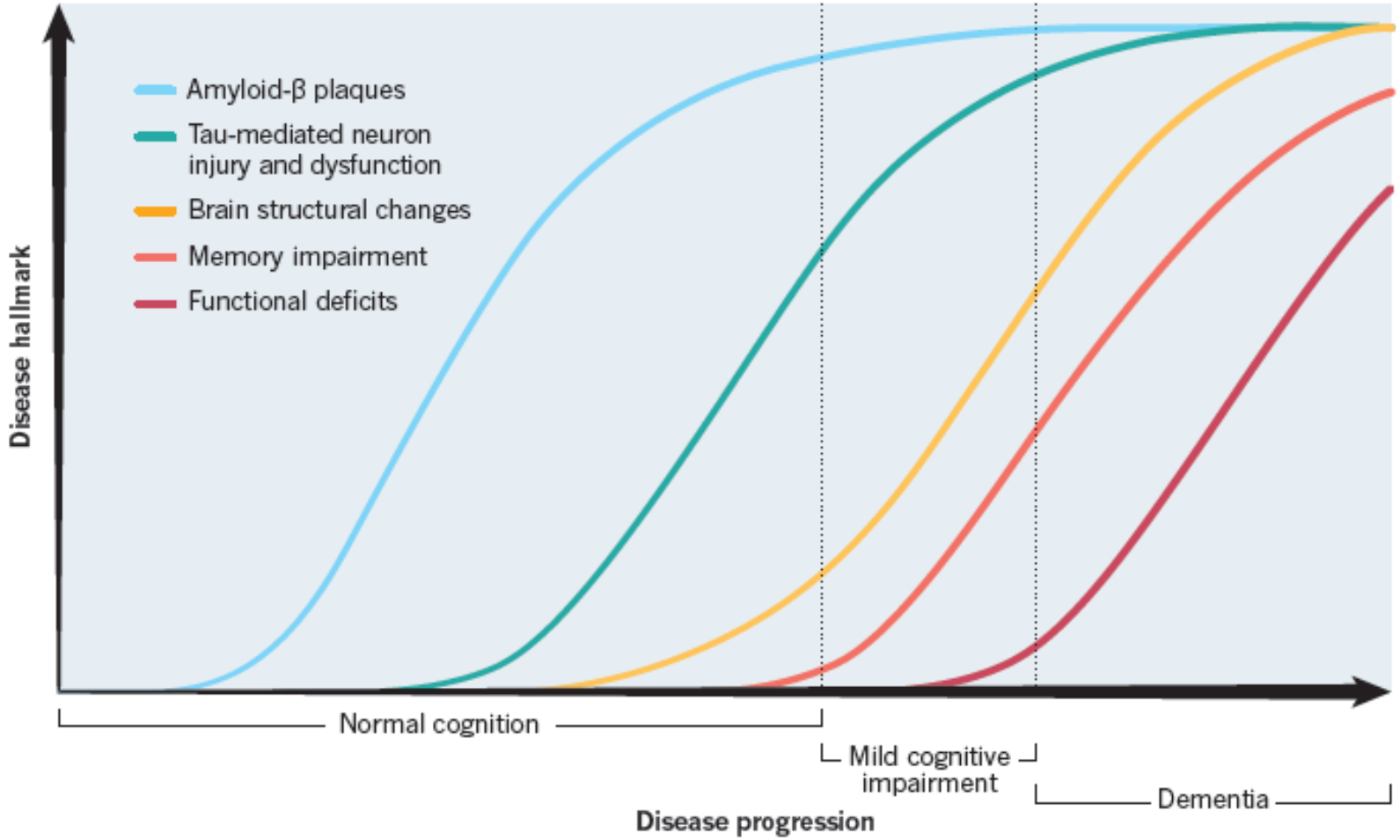
Distribution of toxic aggregates in AD brains



Purve 5th ed.

A SLOW MARCH

By the time that a person begins to experience the symptoms of Alzheimer's disease, the condition is already well-established in the brain. The accumulation of amyloid-β, generally thought to be the first step in disease progression, could precede symptoms by 10–15 years. Tau accumulation occurs later, much closer to the onset of neurodegeneration.



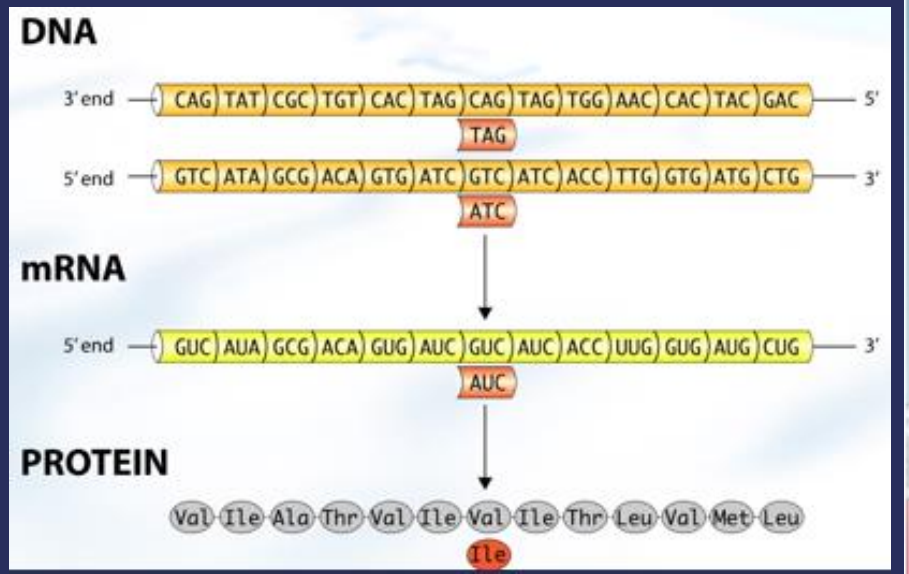
ADAPTED FROM REF. 1

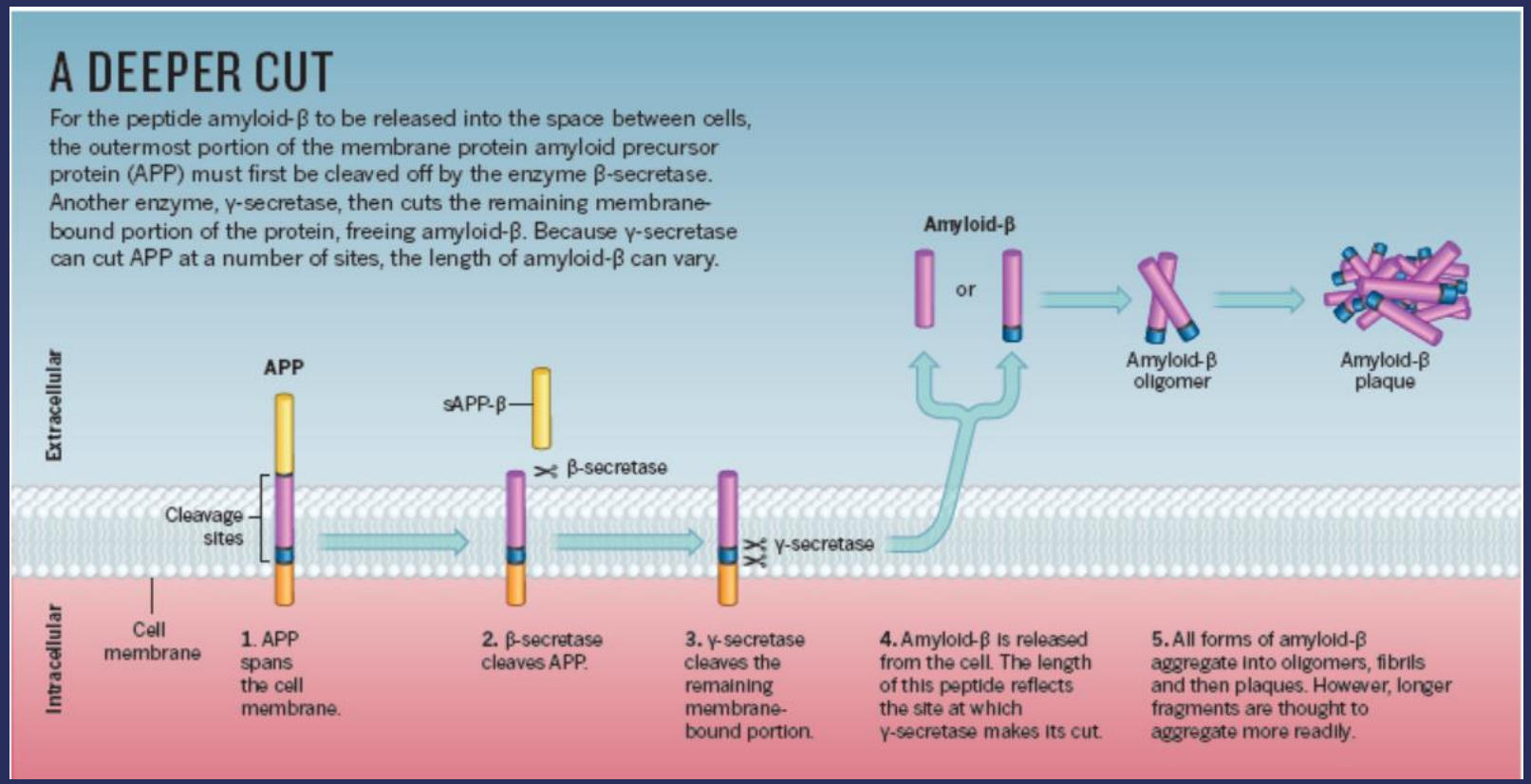
*Mild cognitive impairment is an abnormal decline in cognition that, unlike Alzheimer's disease, does not affect daily living. It is considered to be a precursor to the condition.

The Beta amyloid Hypothesis

From genetics – Familiar AD – mutations were identified

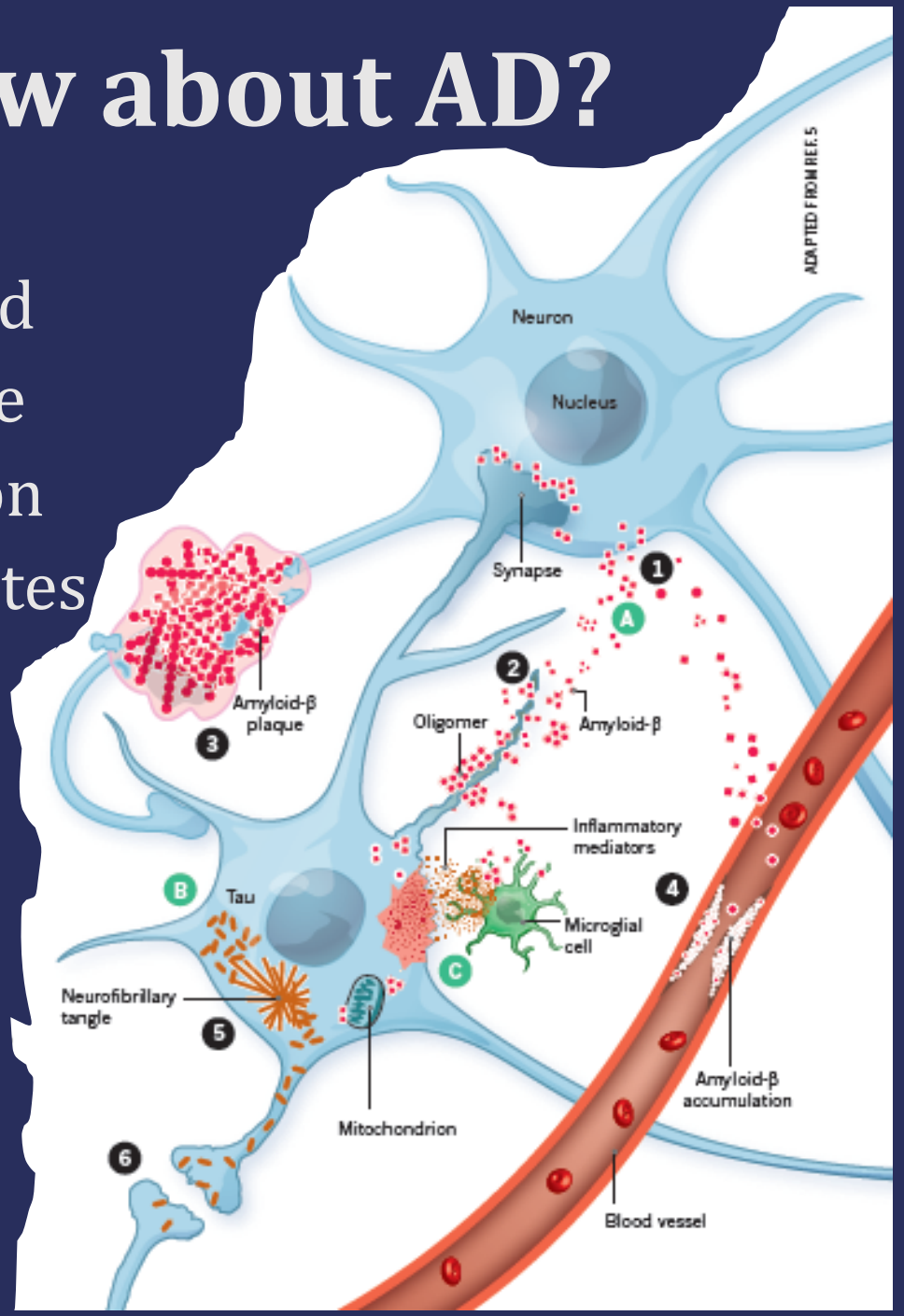
APP - amyloid precursor protein
gene on chromosome 21





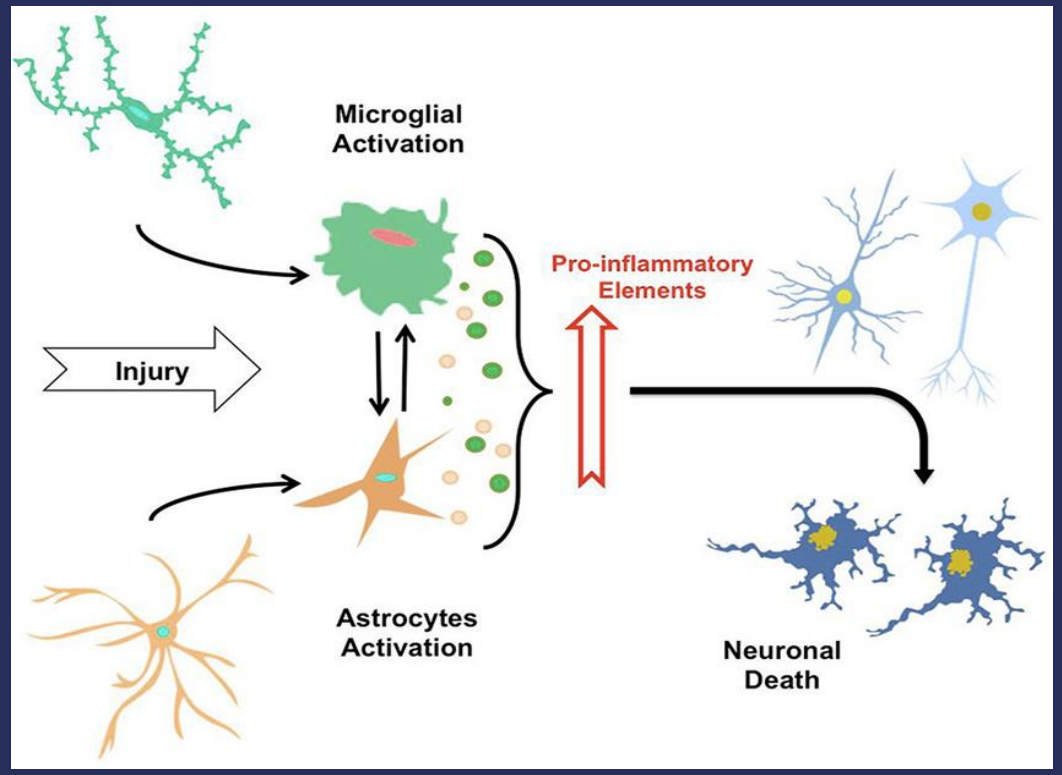
What do we know about AD?

- 1 - Beta Amyloid is cleaved
- 2-3 - Plaques form outside neurons and disrupt function
- 5 - Misfolded Tau aggregates inside neurons disrupting function
- 6 - Misfolded Tau can spread between neurons

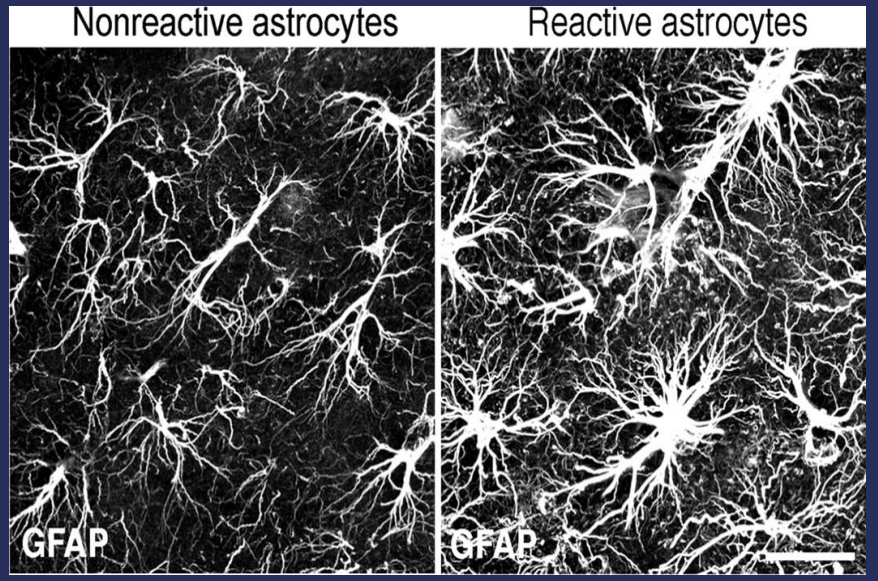


4 - Neuroinflammation Structural & functional changes in non neuronal populations in response to toxic aggregates

Pro-inflammatory activity in the brain



Neuroinflammation seen through activation of supporting **astrocytes** and resident immune cells - **microglia**



Current medications

Types of drugs approved by the FDA – symptoms relief:

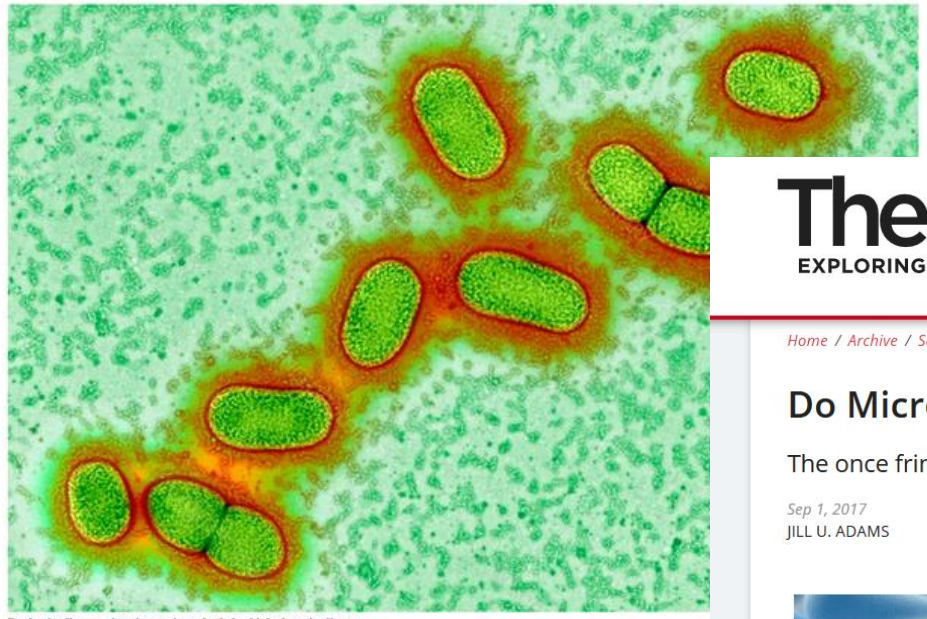
1. Cholinesterase inhibitors – "cholinergic hypothesis": increase acetylcholine in the brain to help with memory formation

2. N-methyl-d-aspartate receptor antagonists: oppose effects of excitatory neurotransmitter glutamate

- No new AD drugs have been approved by the U.S. FDA since 2003
- Trials are focused on anti-Aβ and anti-tau agents
- Failures of over 400 trials of these drug classes raise questions as to whether Aβ and tau proteins are biomarkers or causes

New hypotheses or unfollowed hypotheses

We may finally know what causes Alzheimer's – and how to stop it



P. gingivalis may be the main culprit in Alzheimer's disease
A. DOWSETT, PUBLIC HEALTH ENGLAND/SCIENCE PHOTO LIBRARY

TheScientist
EXPLORING LIFE, INSPIRING INNOVATION

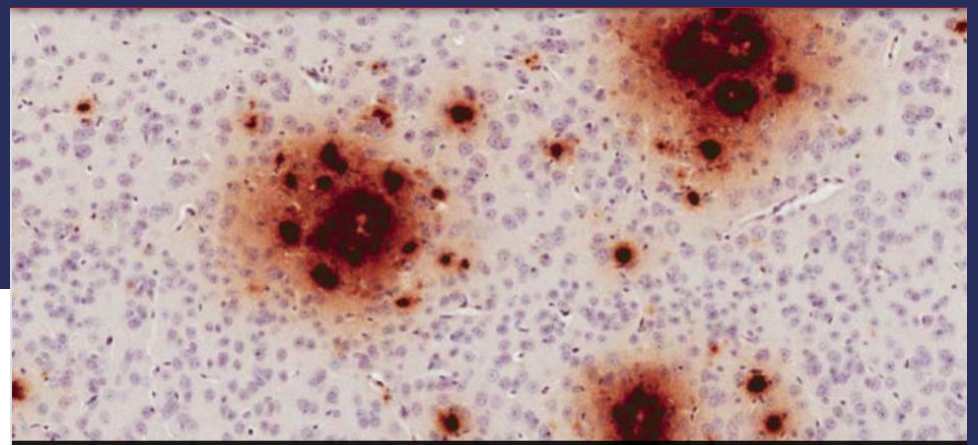
Home / Archive / September 2017 / Features

Do Microbes Trigger Alzheimer's

The once fringe idea is gaining traction among the scientific community.

Sep 1, 2017
JILL U. ADAMS

165 132



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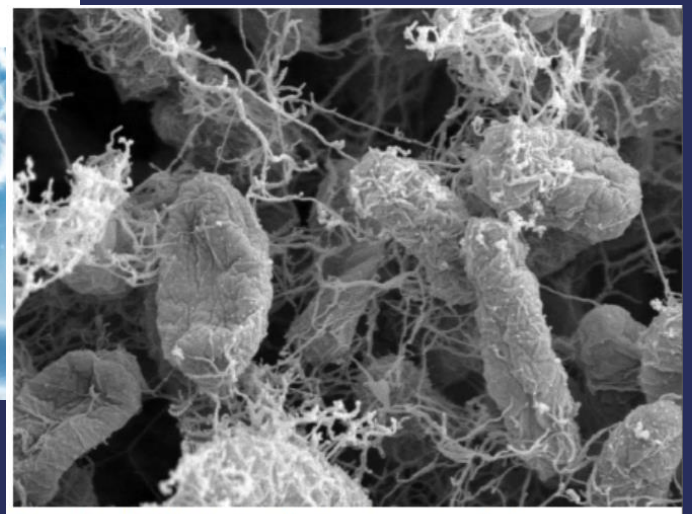
Herpes Viruses Implicated in Alzheimer's Disease



A mesh of amyloid-β fibrils entraps *Pseudomonas aeruginosa* bacteria.

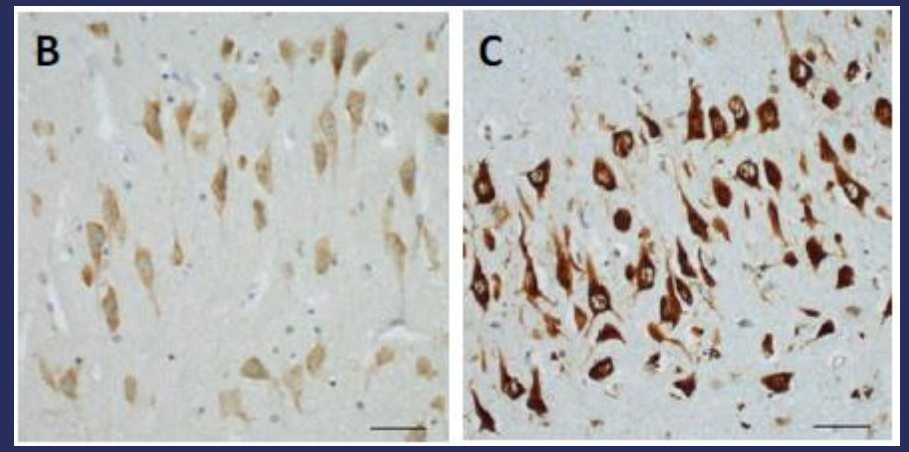
The link between chronic gum disease and AD

RESEARCH ARTICLE | HEALTH AND MEDICINE

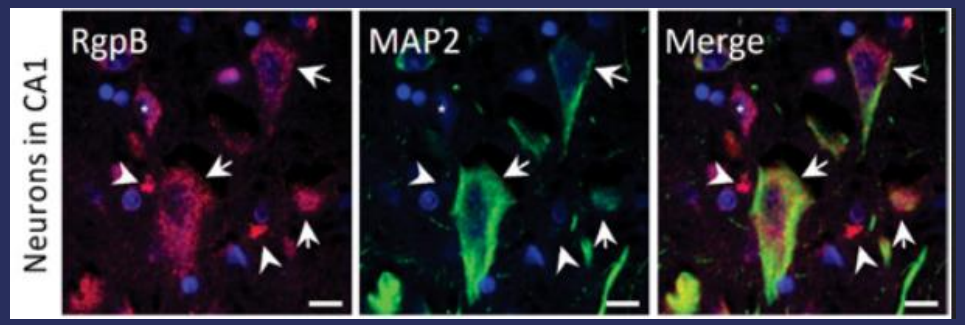
Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors

Stephen S. Dominy[1,*,†], Casey Lynch[1,*], Florian Ermini[1], Malgorzata Benedyk[2,3], Agata Marczyk[2], Andrei Konradi[1], Mai N...
+ See all authors and affiliations

Science Advances 23 Jan 2019:
Vol. 5, no. 1, eaau3333
DOI: 10.1126/sciadv.aau3333



Higher levels of an enzyme - gingipains, produced by the bacterium *Porphyromonas gingivalis,* have been found in the brains and CSF of AD patients



The link between chronic gum disease and AD

The enzyme was found to cause mice to develop signs of AD

- dying neurons in Hippocampus
- higher levels of β-amyloid protein

The enzyme damaged tau and induced it to aggregate.

A drug anti-gingipain enzyme reduced β-amyloid production and neuronal death, and markers of inflammation.

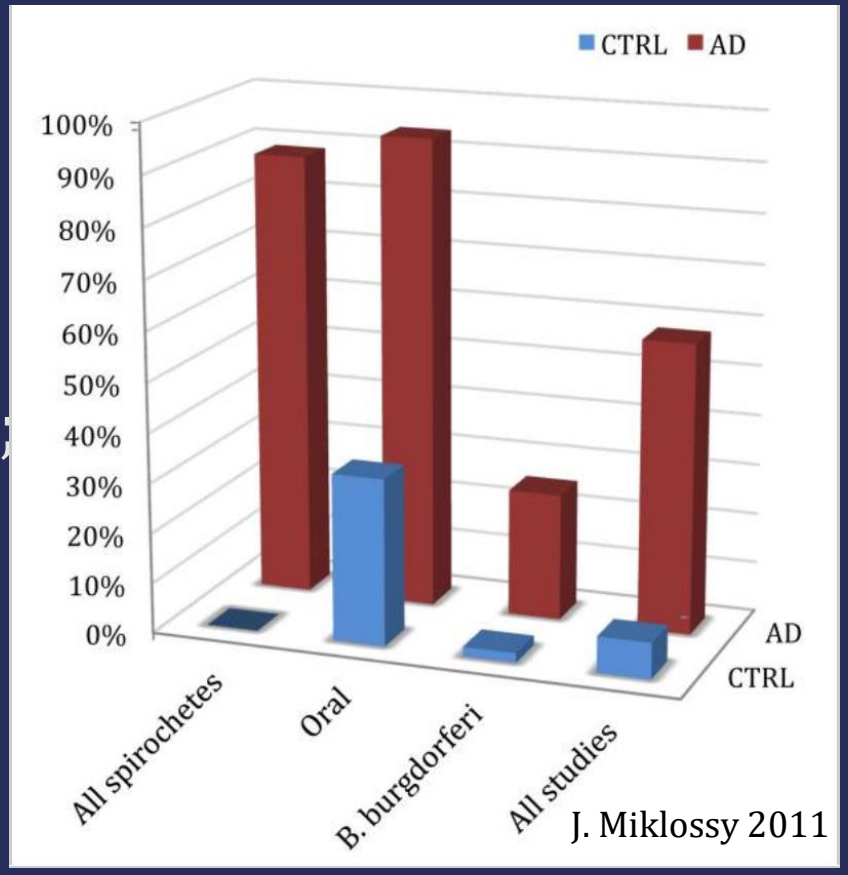
Spirochetes & AD

6 genera, some causing Lyme disease (*Borrelia burgdorferi*),
syphilis (*Troponema pallidum)*,
and gingivitis (several *Troponema*)

Polymicrobial biofilms formed over decades

Dementia observed in spirochetes-induced diseases;
identified in many AD brains

Exposure induces chronic inflammatory response,
Aβ plaques, cortical atrophy



J. Miklossy 2011

Herpes Virus Type I & AD

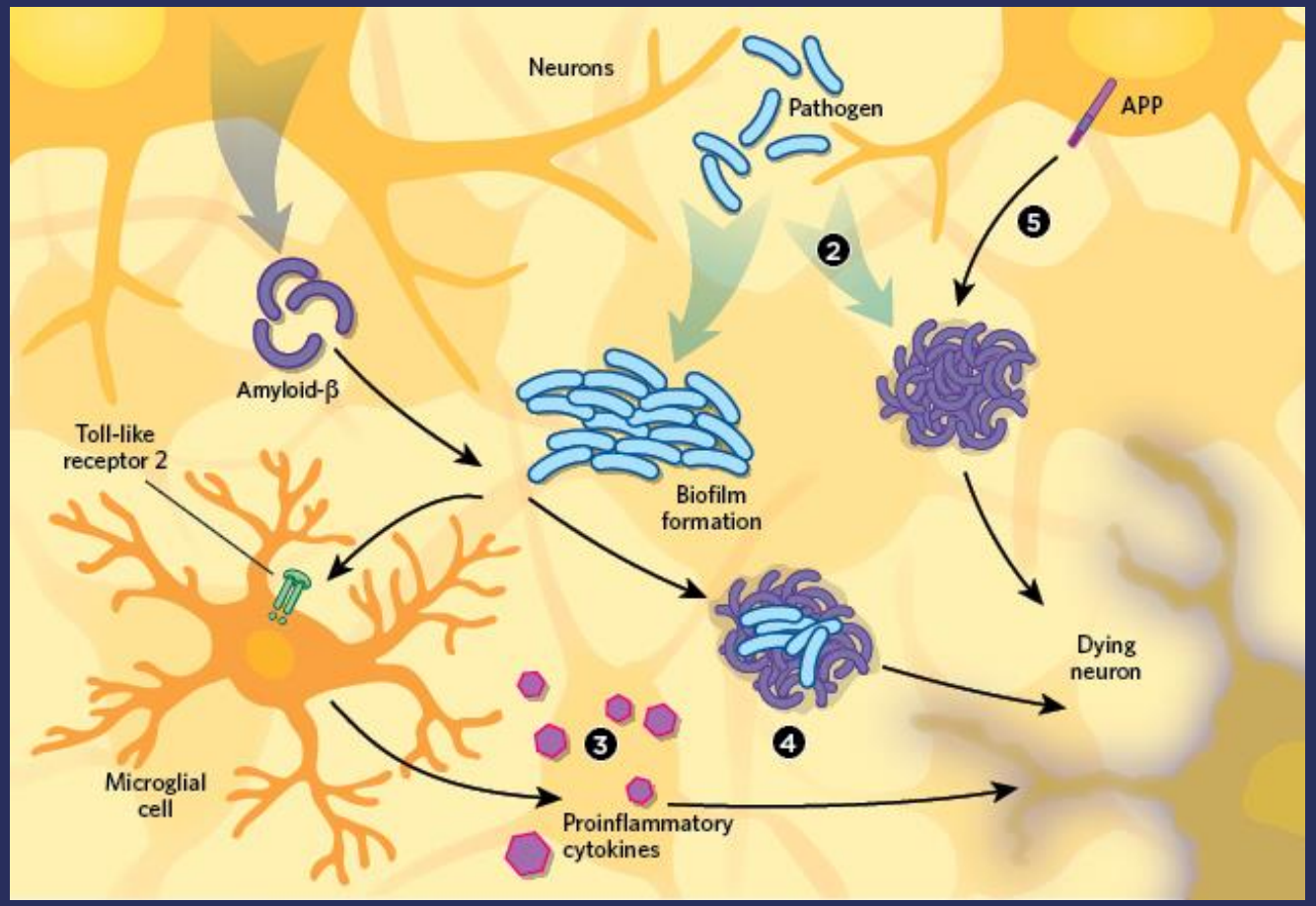
In 1,400 post-mortem AD brains, evidence of human herpes viruses 6A (HHV-6A) and 7 (HHV-7) in greater abundance in brain cortical regions

Amyloid-β could prevent HSV1 infection and can bind and aggregate the HSV1 and HHV6 viruses.

Mice that had genetically elevated amyloid-β expression, once infected with HSV1—which can cause encephalitis— were protected against encephalitis, but also had increased amyloid deposits. W.A. Eimer et al. *Neuron*, July 12, 2018.

A recent drug trial targeting the virus (VALZ-PILOT) has been launched [TrialsGov - Valacyclovir 2017]

Pro-inflammatory activity in the brain as a response to pathogens' attack



Amyloid plaques seen as an antimicrobial tool

J.U Adams The Scientist, 2017

“The Pathogen hypothesis”
Attention shifted to the microbiome

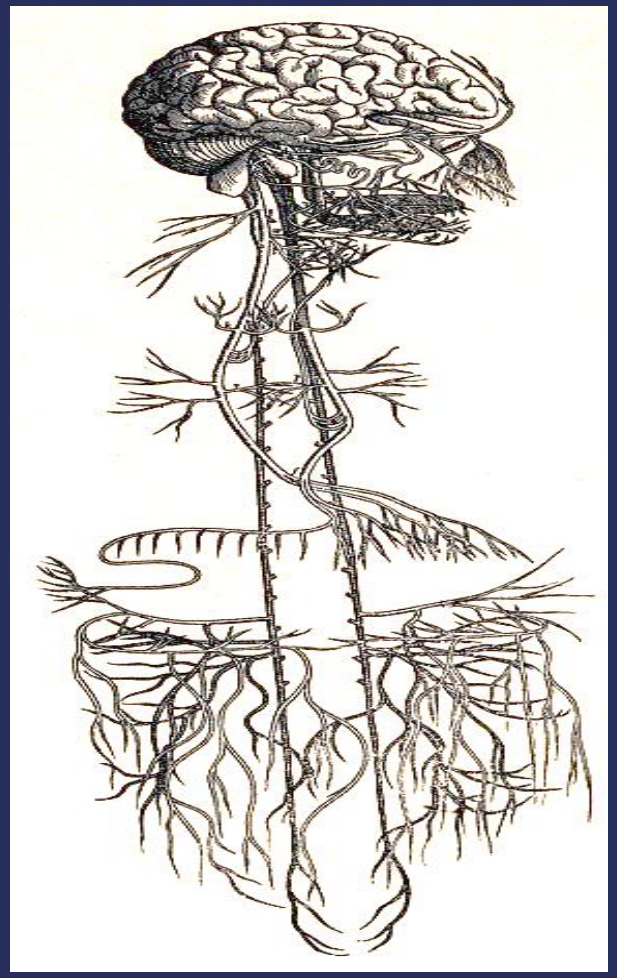
The brain microbiome contains hundreds of bacterial and fungal species

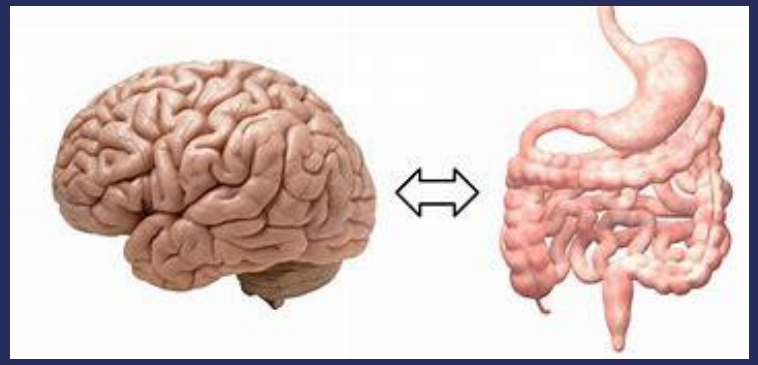
Comparing the brains of older and younger individuals with and without AD to identify viral residues.

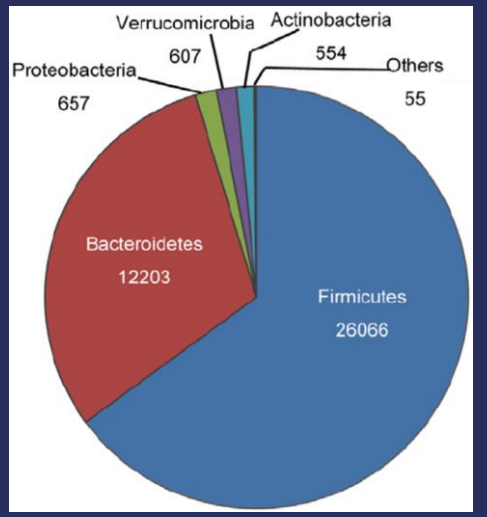
Preliminary evidence shows that the brain microbiome is shifted and is linked to pro-inflammatory activity.

Drs. Tanzi & Moir, Harvard-Mass General

Gut-Brain-Axis and AD dysbiosis

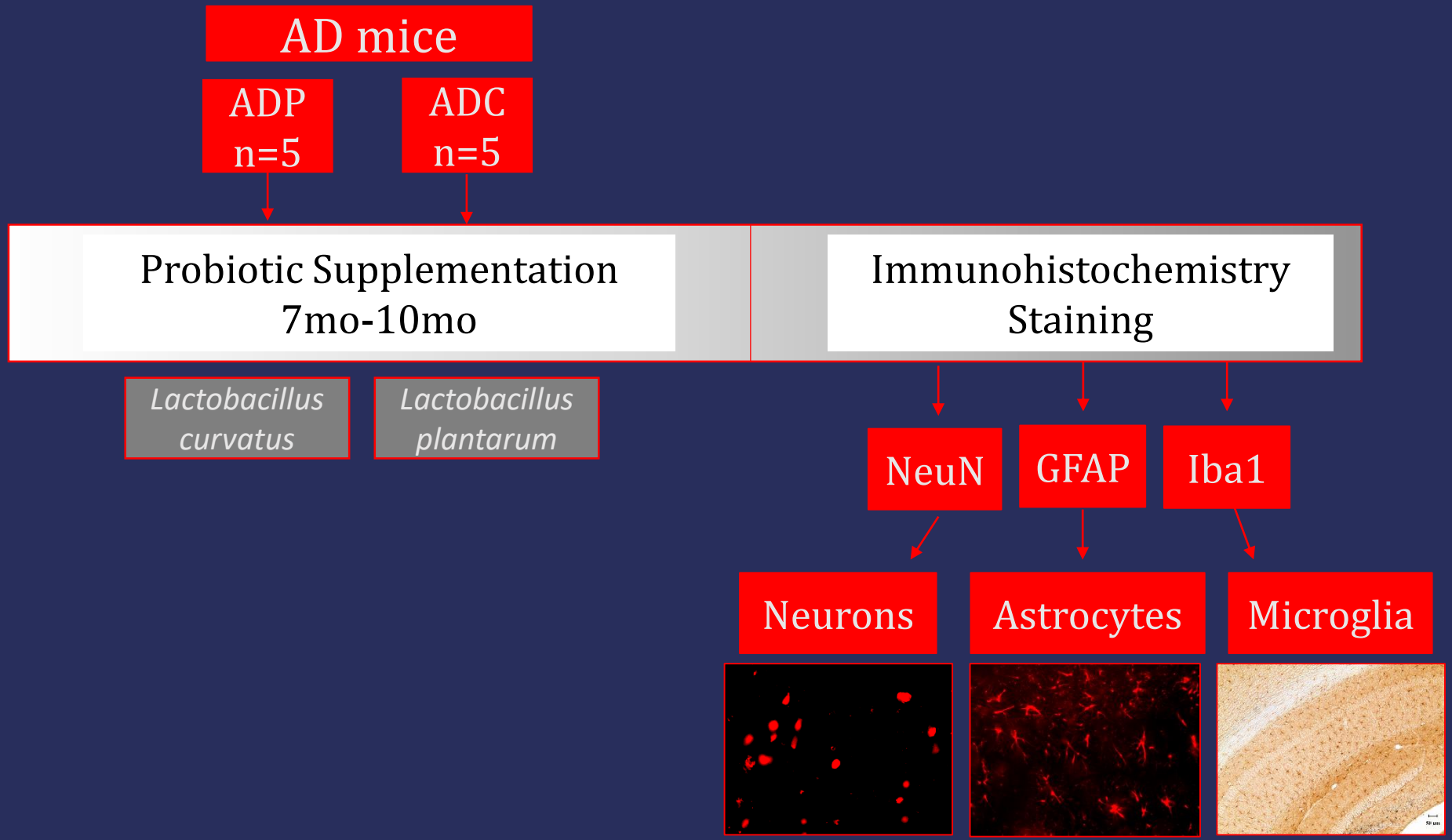






Dysregulation observed in AD

Can Probiotics Supplementation Alter AD Pathology?



Can Probiotics Treatment Alter AD Pathology in a Transgenic Mouse Model?

Aim 1:
Determine Effects of Probiotics on Neurons Death using NeuN+ Cell Counts

Aim 2:
Determine effects of Probiotics on supporting astrocytes using GFAP+ Cell Counts

Aim 3:
Determine effects of Probiotics on microglia using IBA1+ Cell Counts

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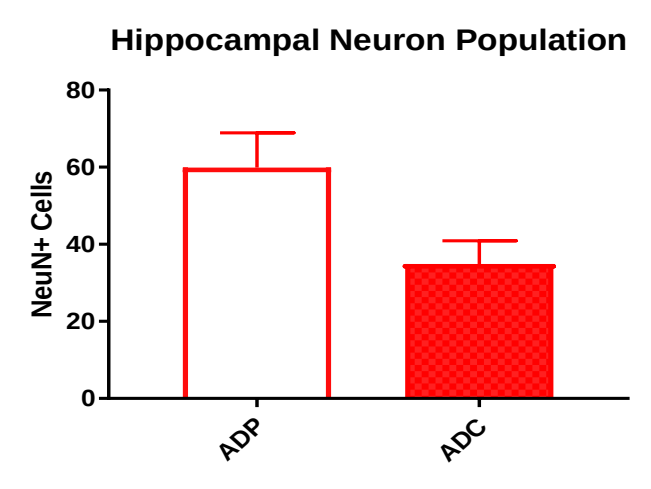

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Determine effects of Probiotics on supporting astrocytes using GFAP+ Cell Counts

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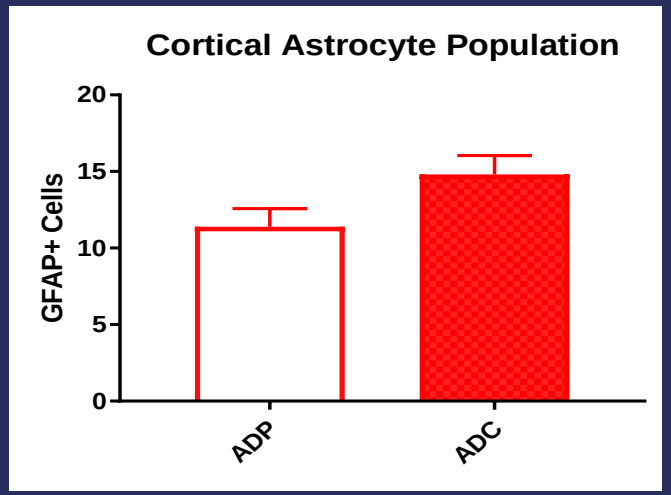

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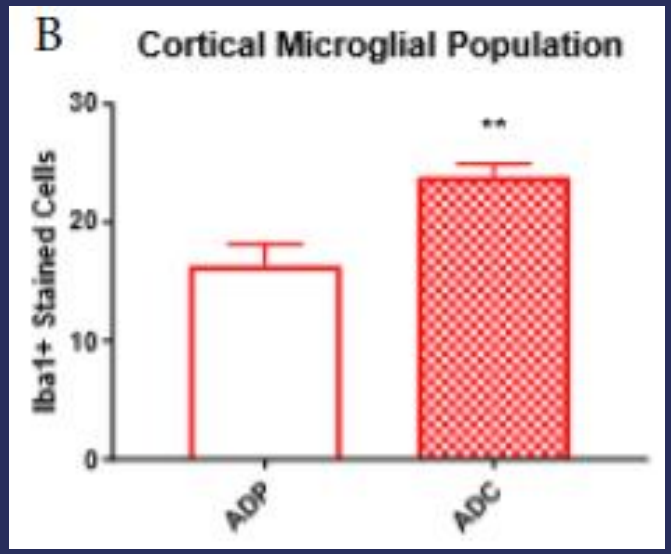
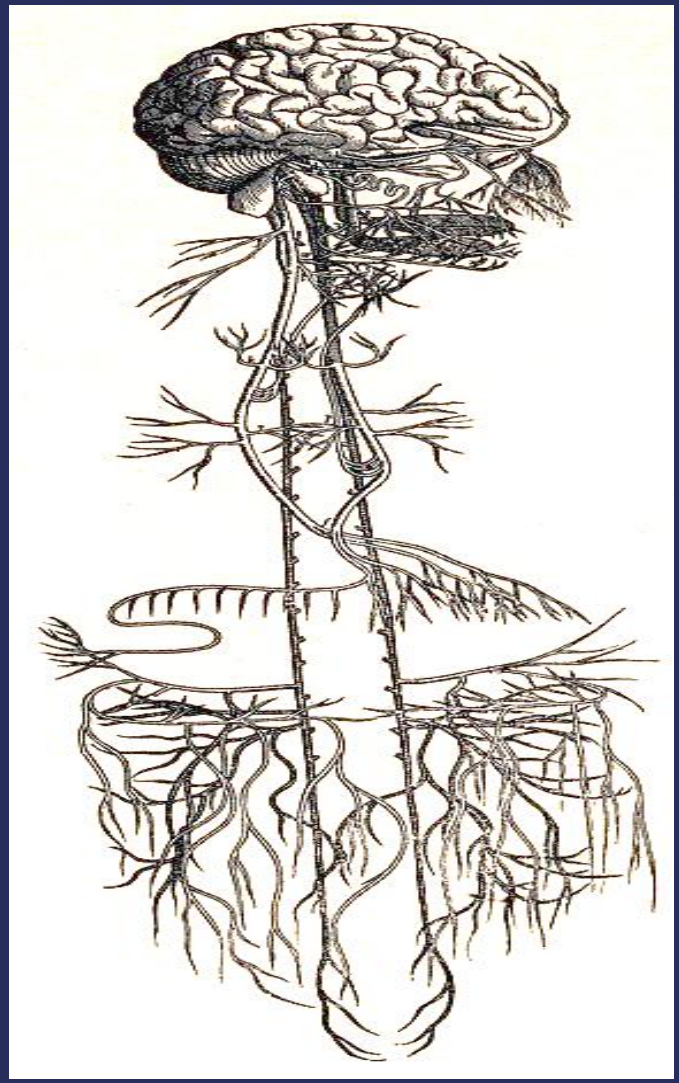


Possible therapeutics to combat neuronal loss

Possible therapeutics to combat neuroinflammation

Inexpensive, easy to administer therapeutics to combat costly, debilitating diseases

Can Probiotics Treatment Alter AD Pathology?



Acknowledgments

Probiotics

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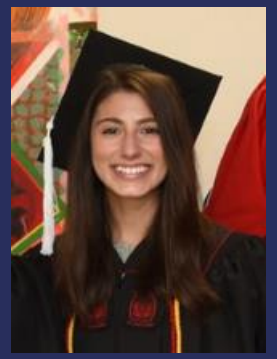
MSN ’18



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Ribicoff recipient

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