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Pioneers in Alzheimer's Disease: People with Down Syndrome

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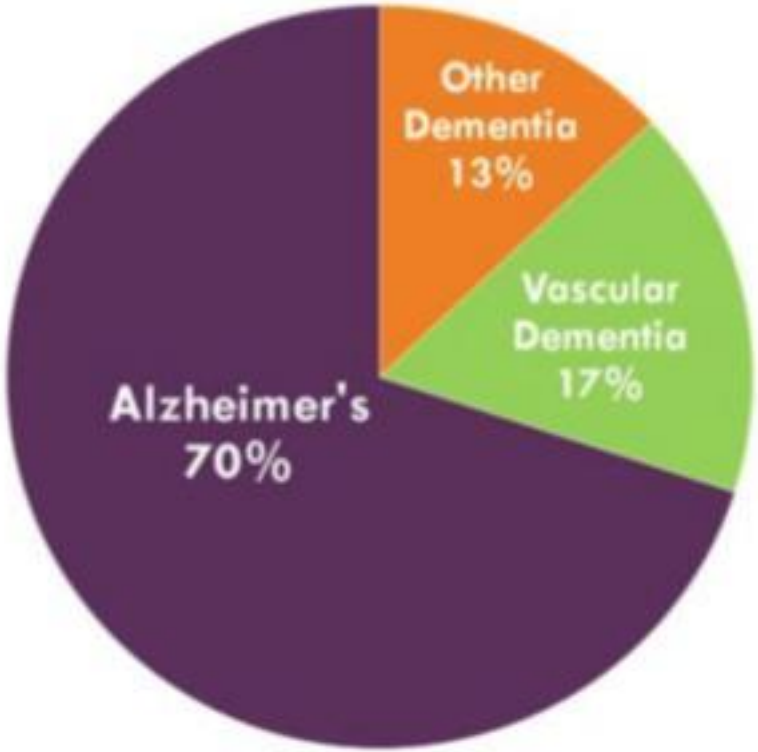
Objectives

- Understand Alzheimer's disease
- Realize the connection between Alzheimer's disease and Down Syndrome
- Learn about the research in detecting & preventing AD in DS

- **Histopathologische Untersuchungen über Entstehung und Wesen der senilen Plaques** (Histopathological studies on the origin and nature of senile plaques) **- F. Struwe, 1929**



70%

of all dementia cases are caused by Alzheimer's Disease

Source: Alzheimer's Disease Facts and Figures.. Alzheimer's Association. 2017, Alzheimer's Research UK

5.7 MILLION

Americans are living with Alzheimer's

BY 2050, this number is projected to rise to nearly

14 MILLION

1 in 3

seniors dies with Alzheimer's or another dementia.

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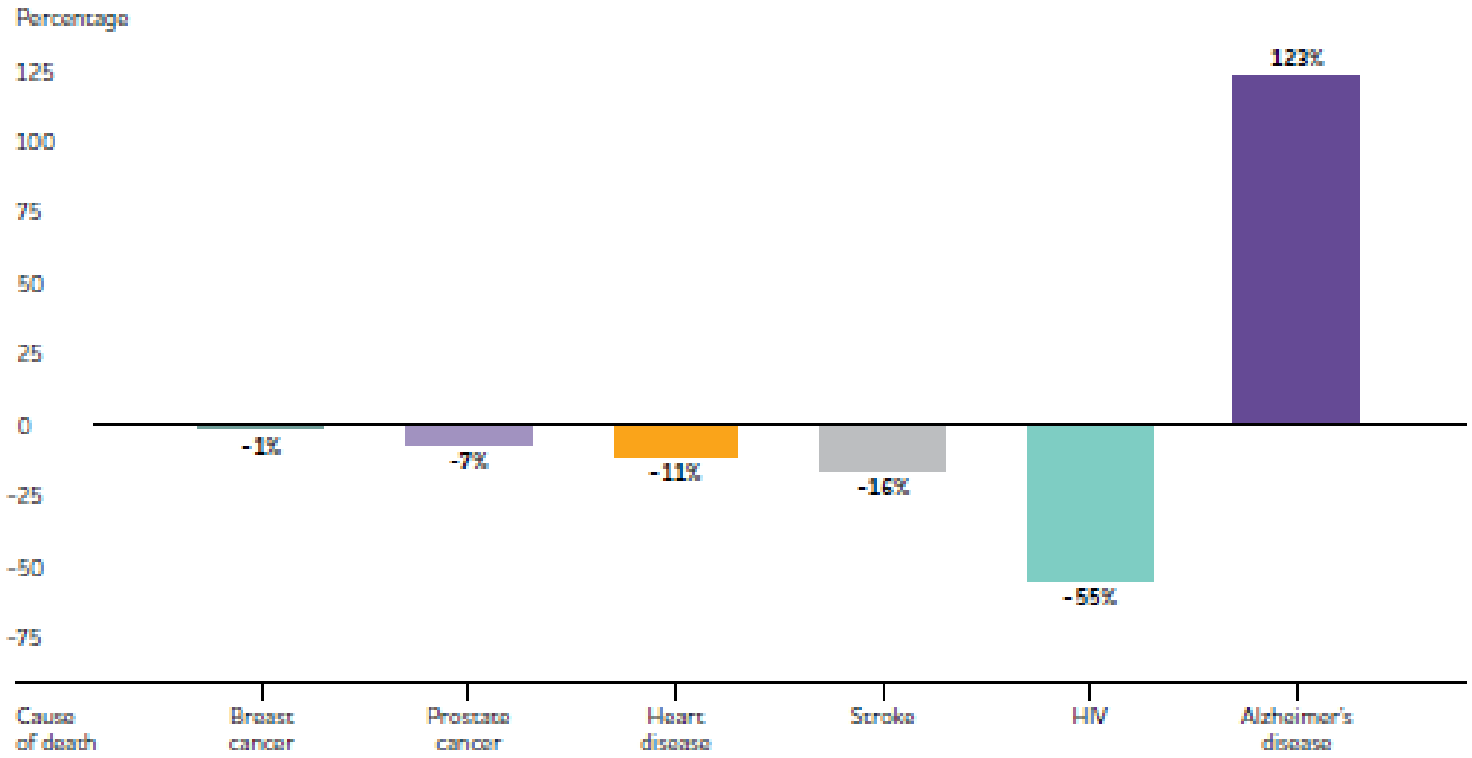
FIGURE 5

Percentage Changes in Selected Causes of Death (All Ages) Between 2000 and 2015



Created from data from the National Center for Health Statistics.[233,243]

It kills more than breast cancer and prostate cancer

COMBINED

ALZHEIMER'S DISEASE IS THE

6TH

leading cause of death in the United States

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Down Syndrome and Dementia

J Neurol (2017) 264:804–813

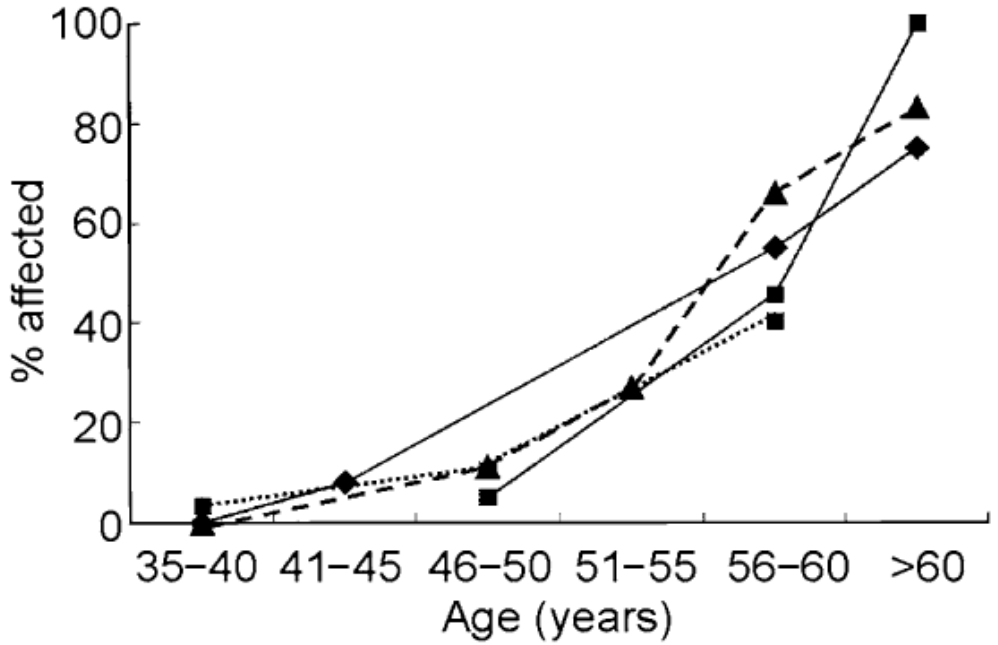

Fig. 1 Age-specific prevalence of dementia in adults with Down's syndrome [9]. *Line with filled diamond* data from Lai and Williams [6]; *dot with triangle* data from Visser et al. [7]; *line with filled square* data from Lai et al. [11]; *line with filled dot* data from Holland et al. [8]

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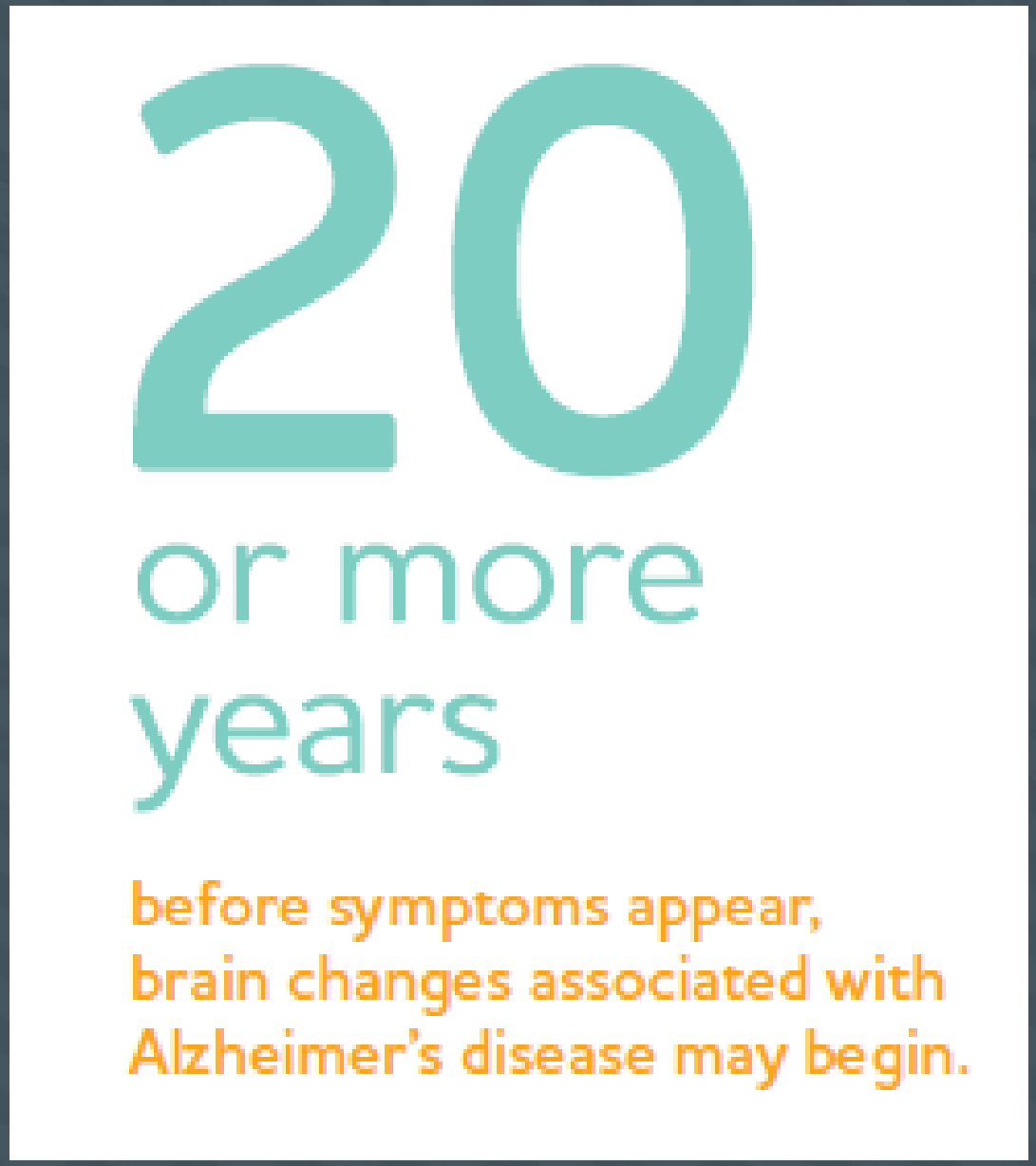

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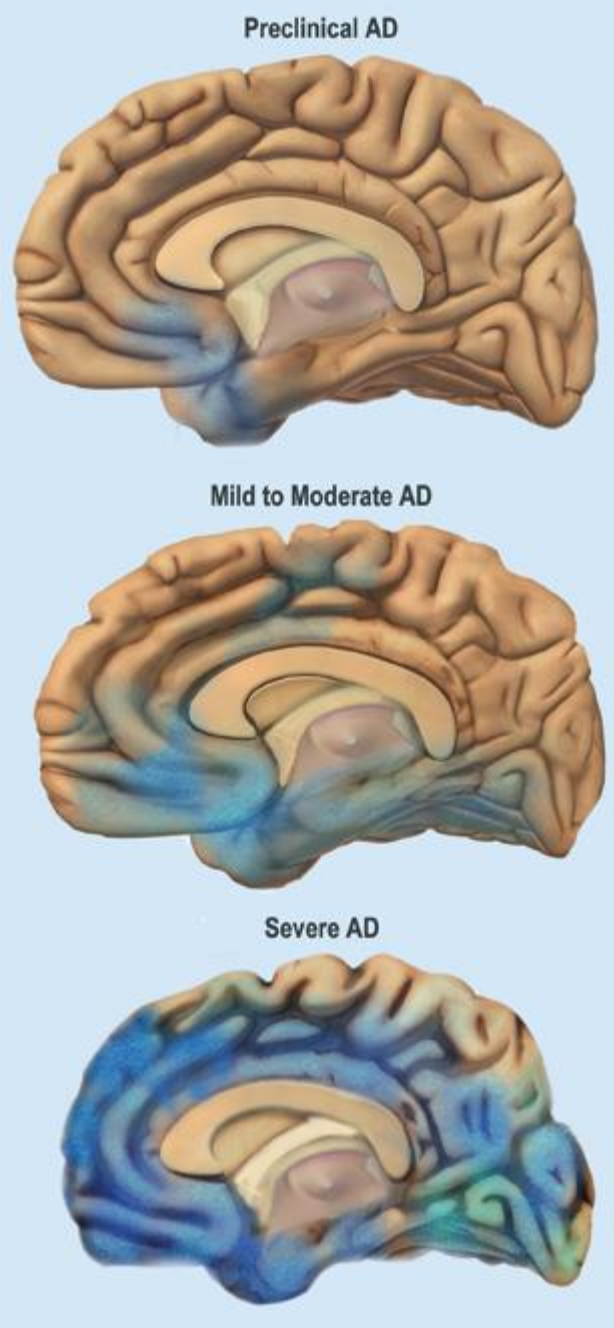
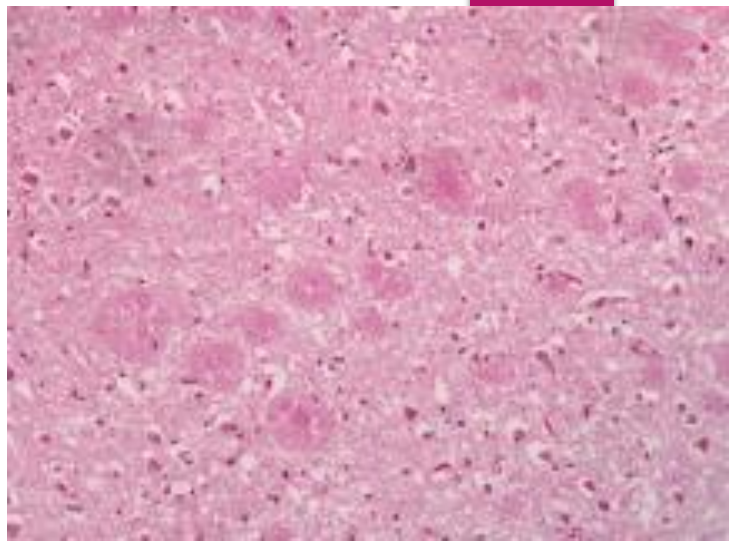
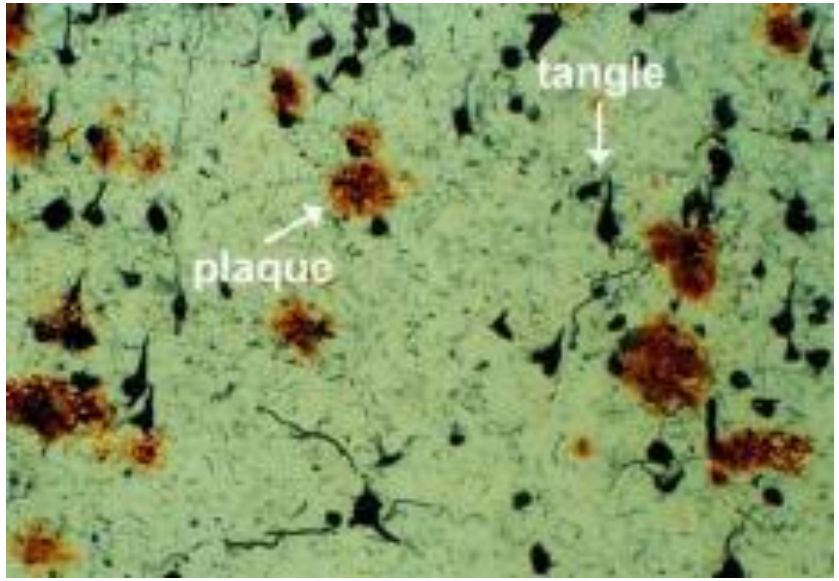
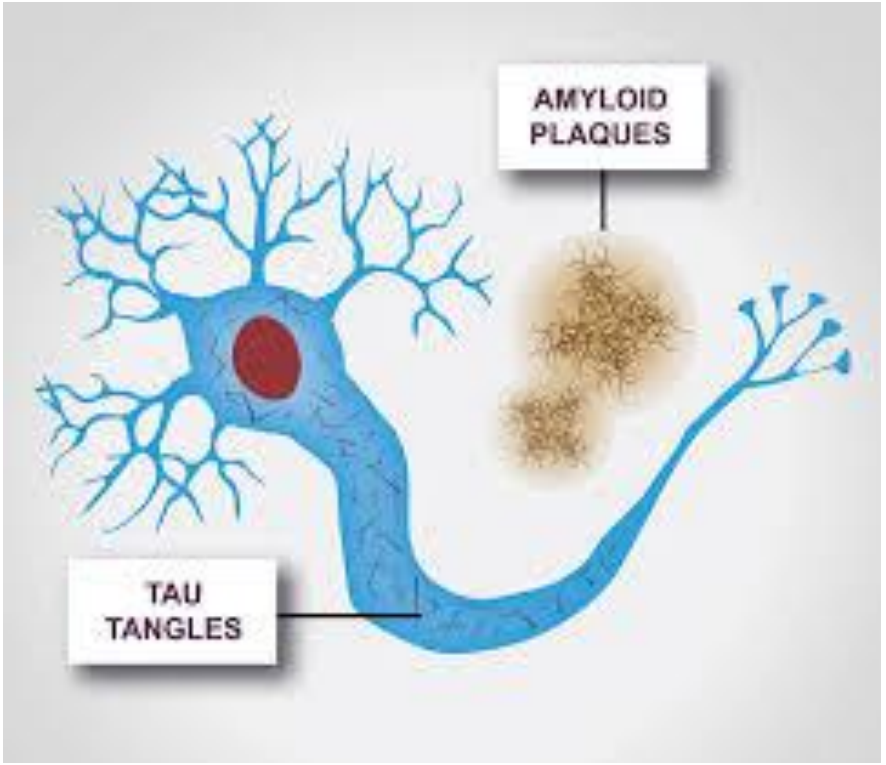


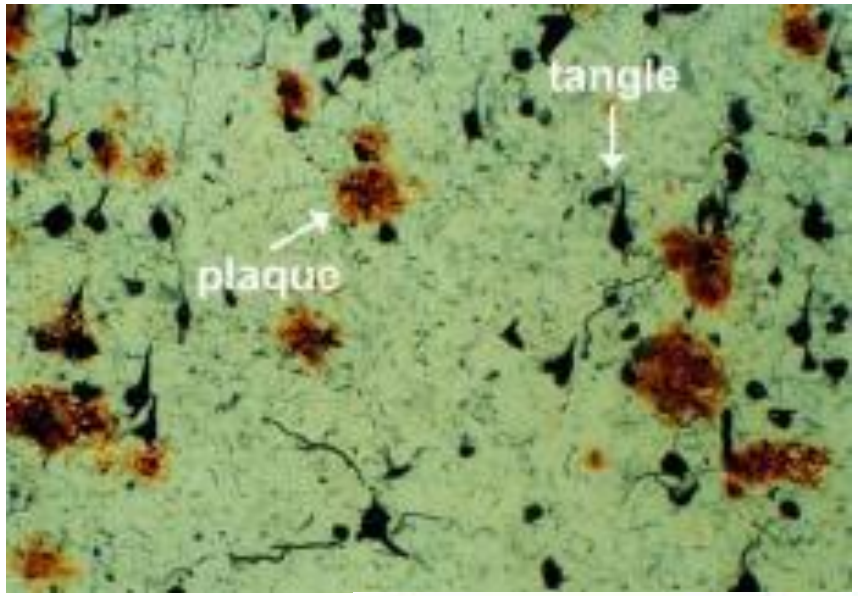
Soluble forms of Aβ42
(beta amyloid)

accumulate into plaques
to drive healthy neurons
into the diseased state



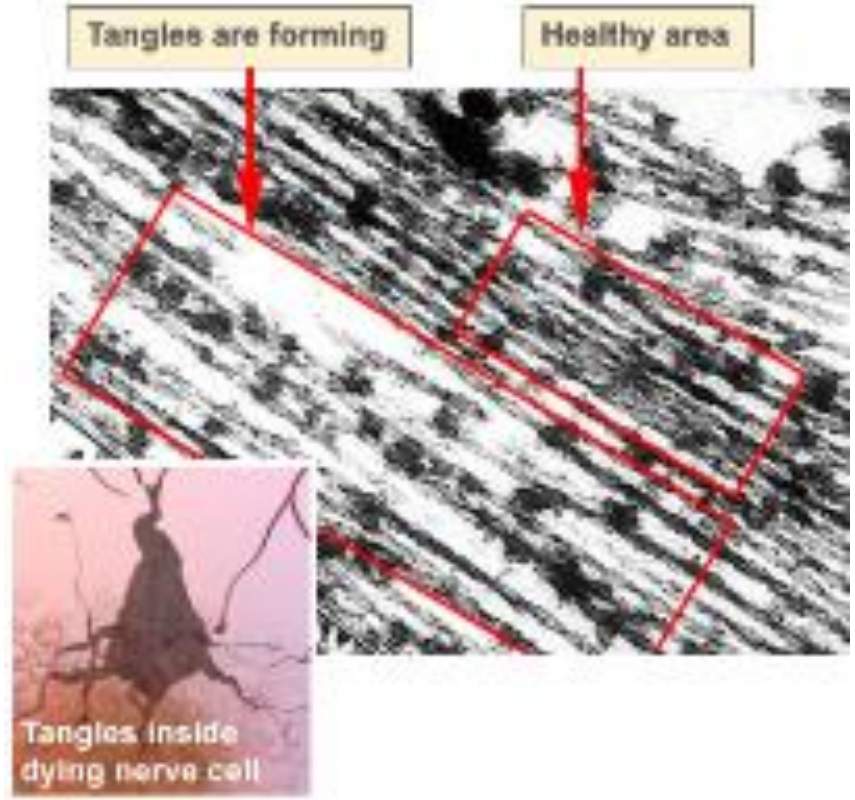


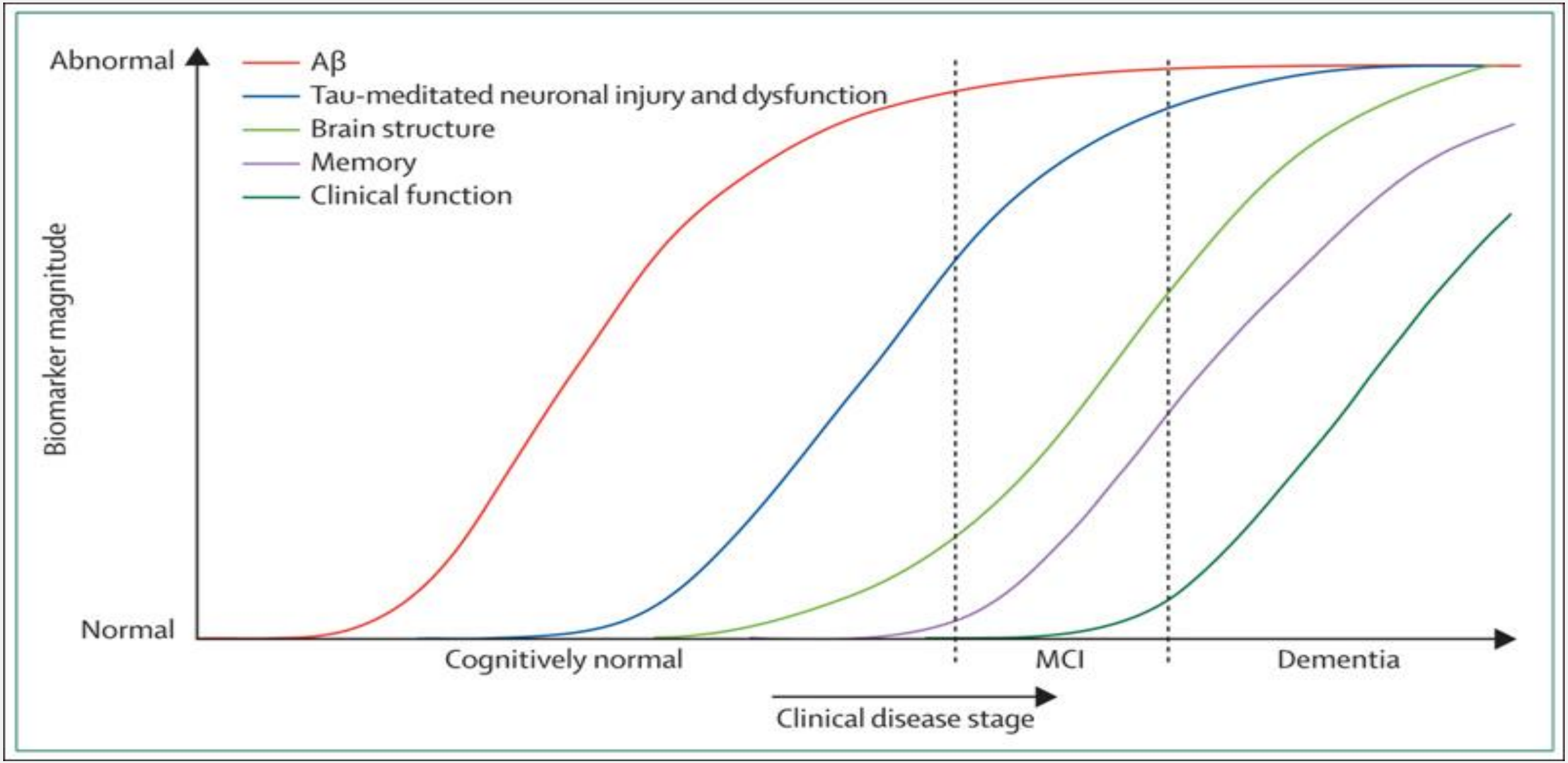


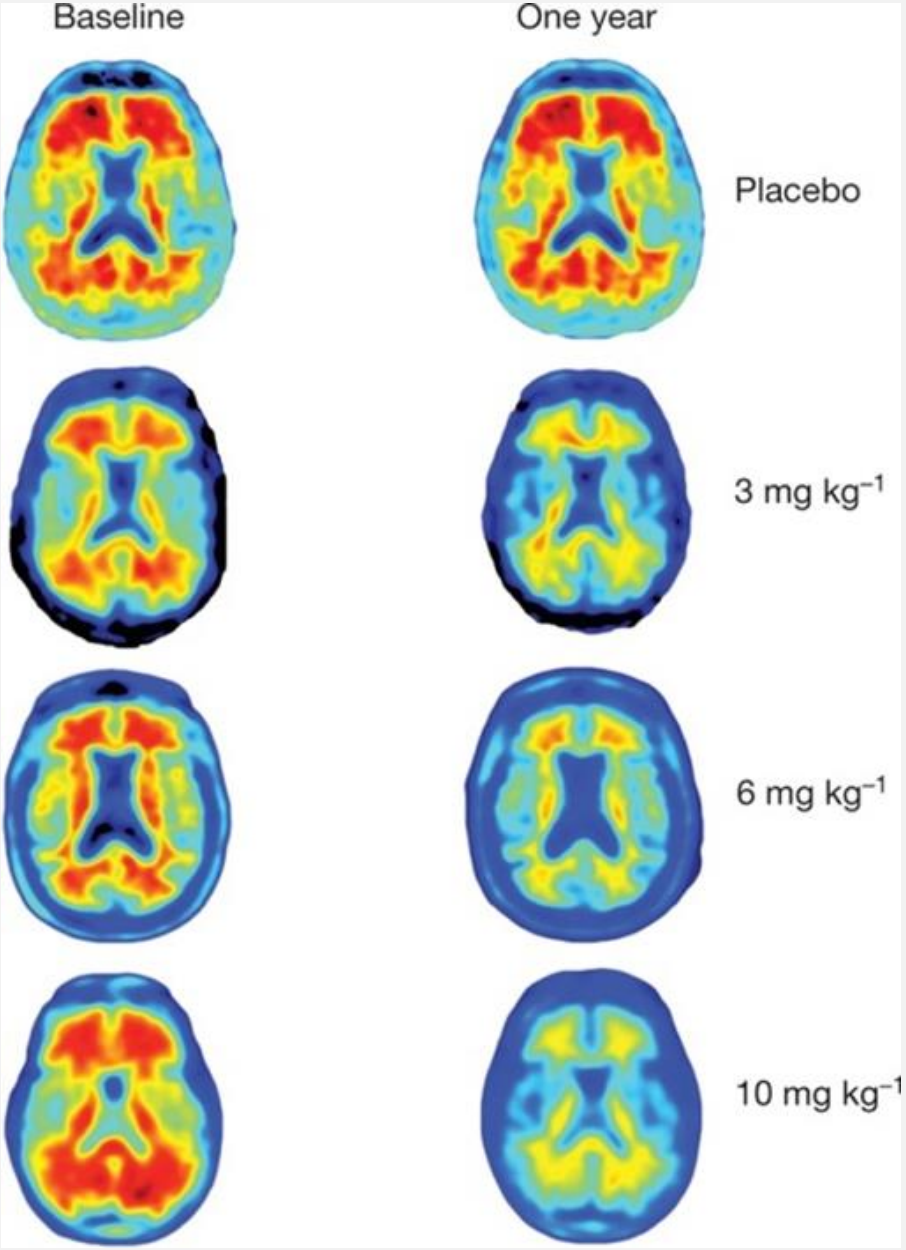


Tau accumulate into tangles inside neurons

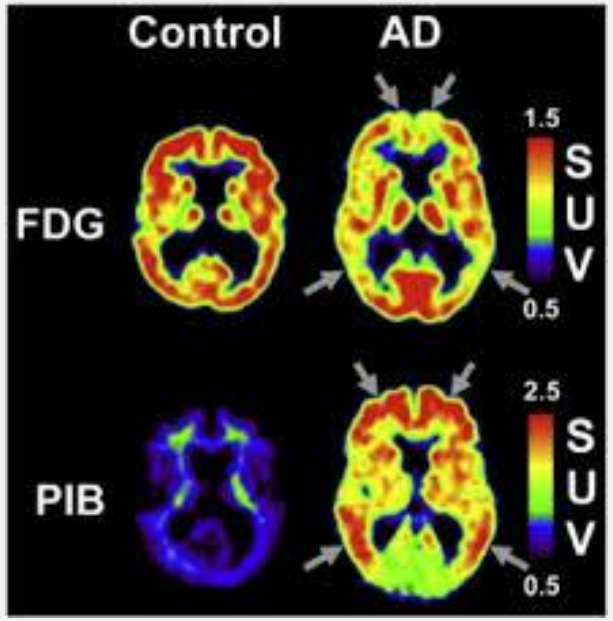
to drive healthy neurons into the diseased state

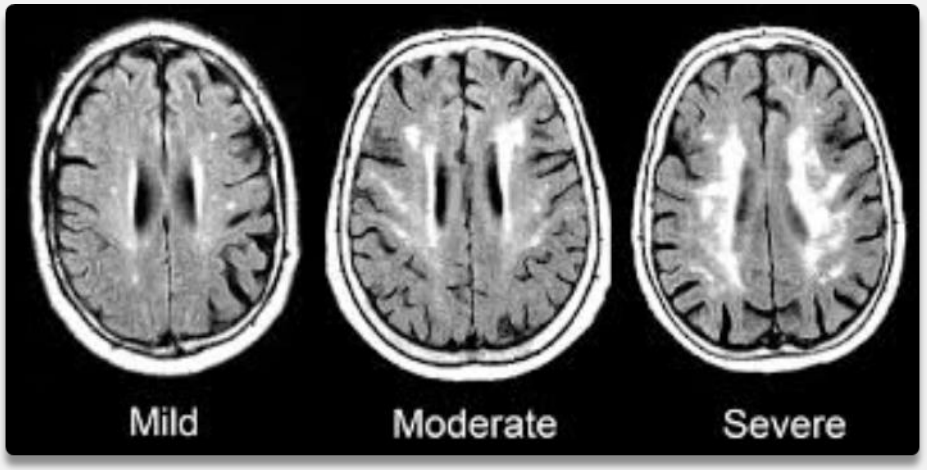



Abnormal
Aβ
Tau-meditated neuronal injury and dysfunction
Brain structure
Memory
Clinical function
Biomarker magnitude
Normal
Cognitively normal
MCI
Dementia
Clinical disease stage



Amyloid scan





MRI

Spinal Fluid

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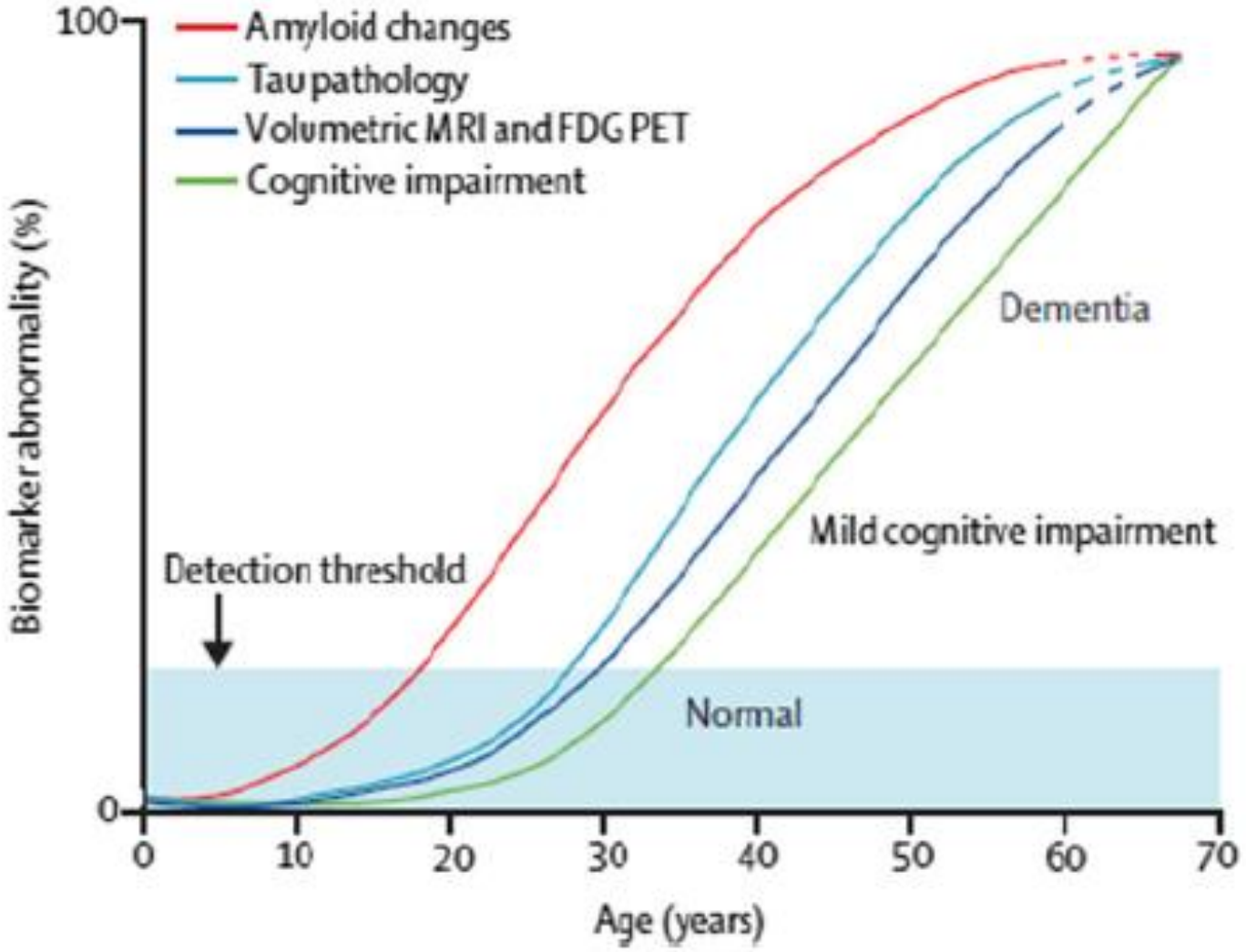
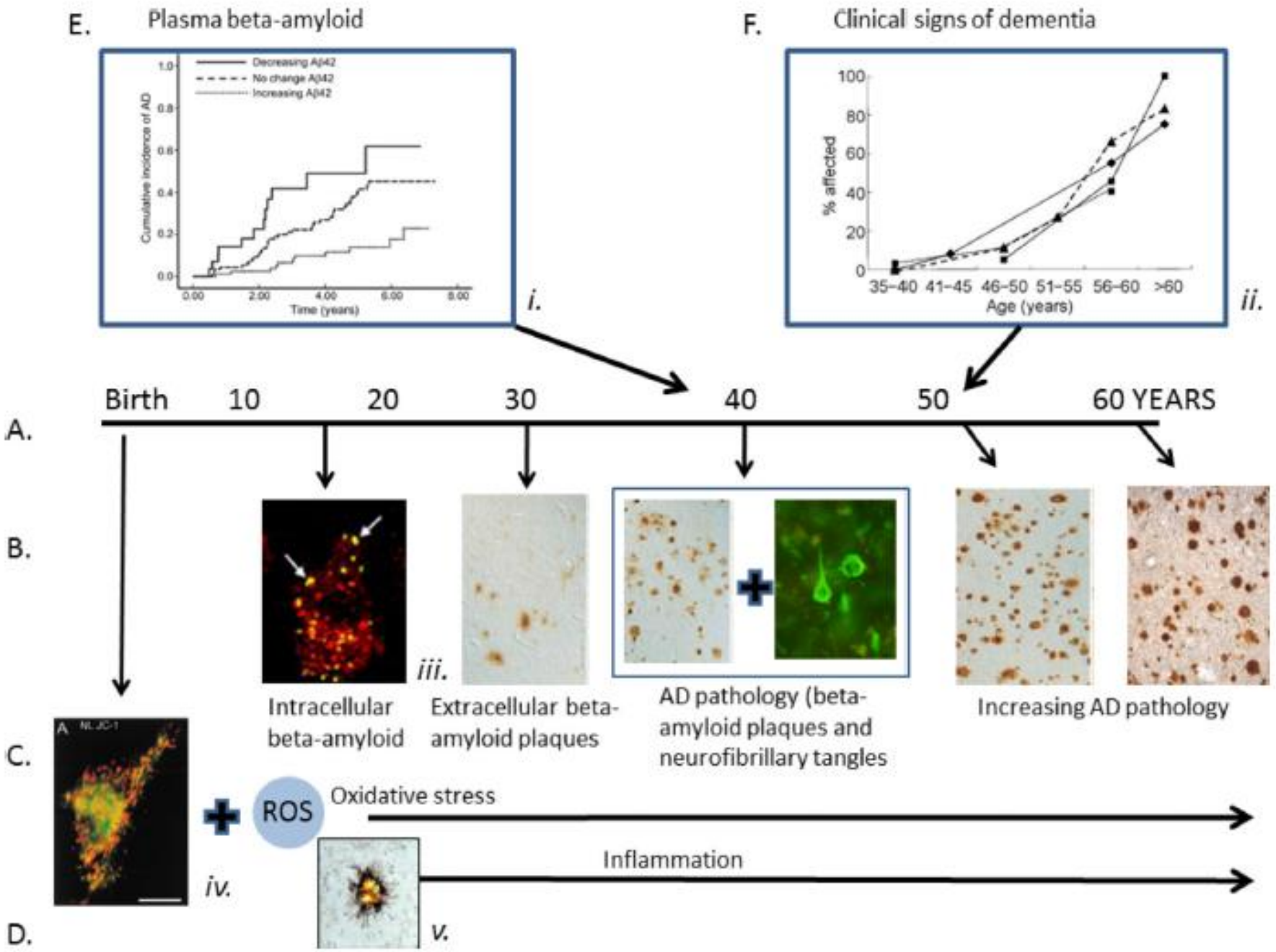


Fig. 2 Hypothetical model for development of dementia in people with Down's syndrome [81]

DS Has Been Moving AD Research Forward

- AD neuropathology found in DS after 30-40 years of age
- Mapped ADAD to Chromosome 21
- AD pathogenesis in DS: the amyloid cascade hypothesis
  - the depositions of amyloid, the amyloid precursor protein (APP) and presenilin genes are central to the promotion of the amyloid cascade hypothesis
  - the observations in DS and the high risk of early onset AD have provided important support for this hypothesis, given that the gene for APP is located on chromosome 21 and inherited in triplicate by people with DS
- Apolipoprotein E genotype
  - When ApoE4 (e4) is present in DS, the risk for AD is even higher, with a two-fold increase in the amyloid load deposited in the brain
  - In contrast, when e2 allele is present, it is associated with increased longevity and the absence of dementia



Dementia in DS

- Characterized by global neuropsychological deficits
  - Retention of some basic language skills
- Earliest manifestations of dementia in DS appear to involve changes in personality and behavior
- Pragnosia or socially deficient communication may be an early sign of frontal lobe dysfunction in DS and may represent a striking change from previous well developed social capacities in the disorder
- Rule out depression, thyroid disease, seizures

UCSD link:
https://medschool.ucsd.edu/som/neurosciences/CENTERS/DOWN-SYNDROME-CENTER/pages/default.aspx

“Diagnosing Alzheimer's Disease - On Our Mind” Video:
https://www.youtube.com/watch?v=MT9pvnYzjIs

Down Syndrome Biomarker Initiative (DSBI)

- Natural history study
  - 12 subjects with DS
    - 4 non-demented subjects between ages 30-40
    - 4 non-demented subjects between ages 40-50
    - 4 demented subjects 50-60 years old.

- Rate of decline as measured by cognitive, functional and behavioral tests
- Rate of conversion will be evaluated among all age groups
- Rate of volume change of whole brain, hippocampus, and other structural Magnetic resonance imaging (MRI) measures.
- Rates of change of glucose metabolism as measured by fluorodeoxyglucose positron emission tomography (FDG-PET) imaging
- Extent of amyloid deposition as measured amyloid PET imaging
- Rates of change on retinal amyloid measures.
- Correlations among biomarkers and cognitive change.
- Correlations of Tau deposition as measured by 18F-AV-1451 PET (Tau) imaging with other biomarkers
- Biospecimen Retention: Samples With DNA, blood, urine, cerebrospinal fluid

https://medschool.ucsd.edu/som/neurosciences/CENTERS/DOWN-SYNDROME-CENTER/pages/default.aspx

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Neurodegeneration in Aging Down Syndrome

- 180 adults with DS & 40 full siblings
- Cognitive testing and MRIs and PET scans
- Age 25 years of age and older
- No evidence of MCI or dementia
- 4 visits over a 4 year period
  - Each visit will take approximately 2 days

https://niad-project.org/

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Alzheimer's Biomarkers Consortium of Down Syndrome (ABC-DS)

- a new initiative that aims to identify biomarkers that indicate AD is developing or progressing in people with DS
- Conducted by Neurodegeneration in Aging Down Syndrome (NiAD) and Alzheimer's Disease in Down Syndrome (ADDS)
  - funded by the National Institute on Aging (NIA) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), both part of NIH

University of North Texas Health Science Center Fort Worth, TX

Sid O'Bryant, Ph.D., Site PI

https://www.nia.nih.gov/health/abc-ds-information-patients-and-families

3 Star -- ACI-24 vaccine

- 24 adults with DS
- 35 to 45 yrs old
- Treatment lasts 12 months, with 12 months of follow-up

- designed to induce antibodies against beta-amyloid, thus reducing its accumulation in the brain while not triggering a larger immune system response
- 7 SC injections over 12 months

https://www.adcs.org/3-star-study/

Benefits to DS

- We can "work backwards" and identify the earliest and most sensitive clinical changes and noninvasive biomarkers that may signal the onset of AD
  - Detection and diagnosis is currently challenging

- Secondary prevention trials

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DOWN with Alzheimer's

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