

# **The A4 Study**

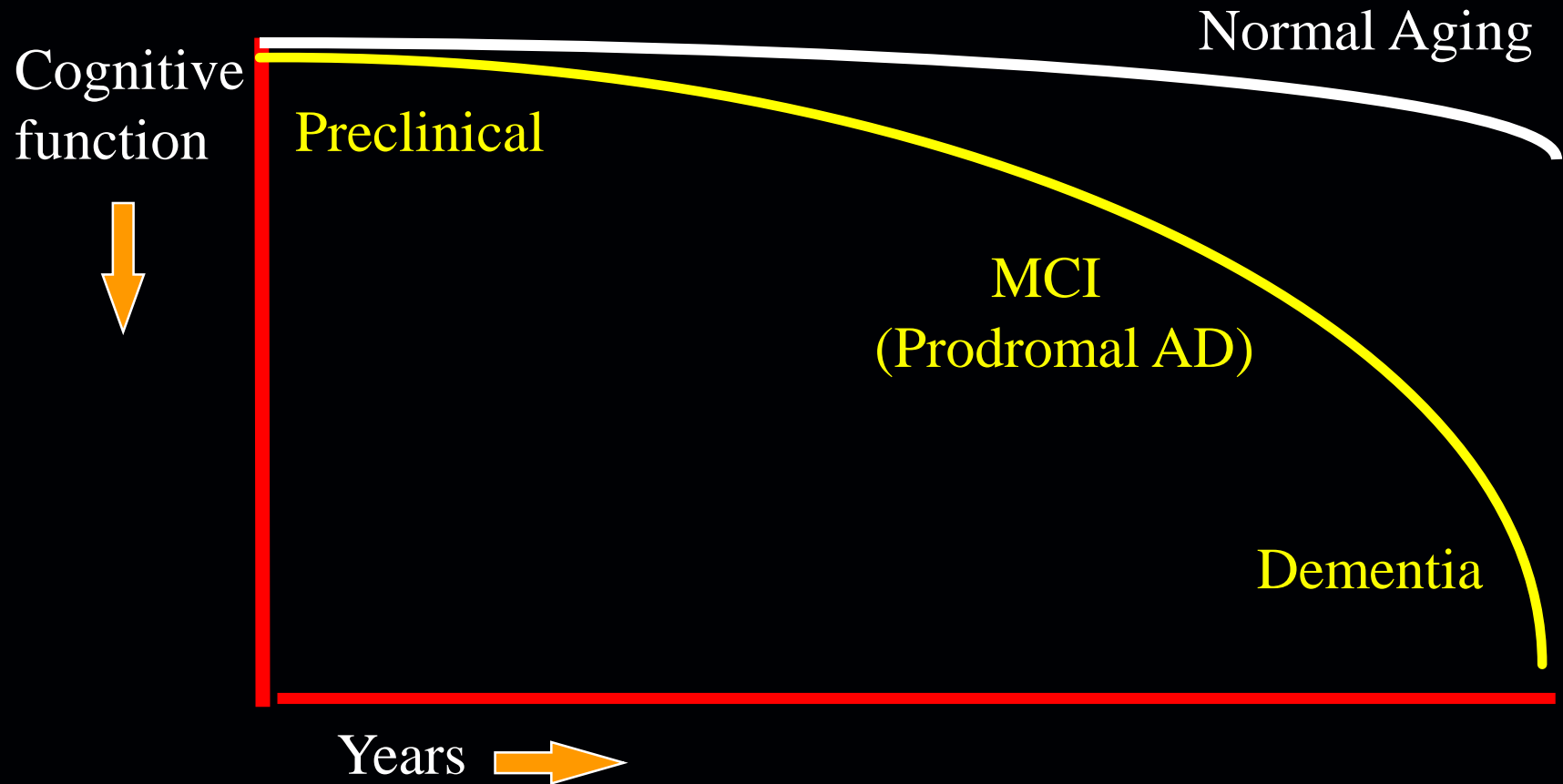
## **Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease**

**Reisa Sperling, M.D.**  
**Massachusetts ADRC**  
**Alzheimer's Disease Cooperative Study**

# Need for Earlier Intervention

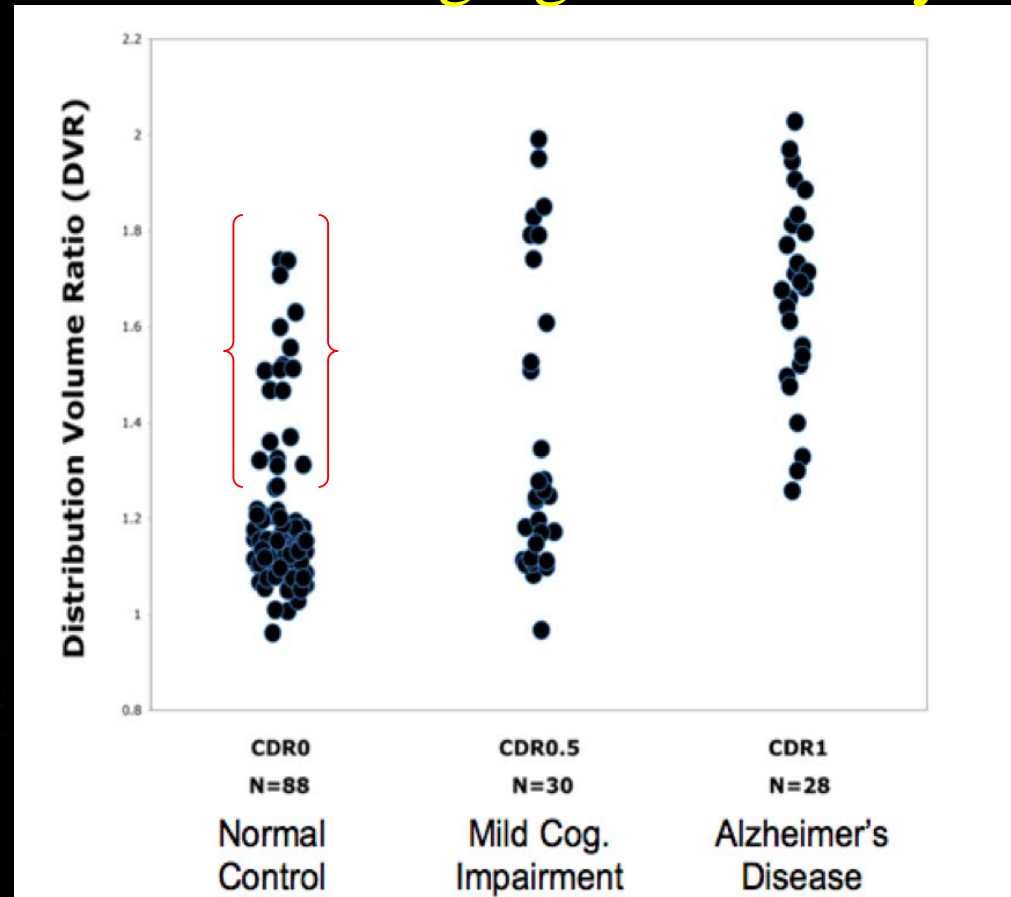
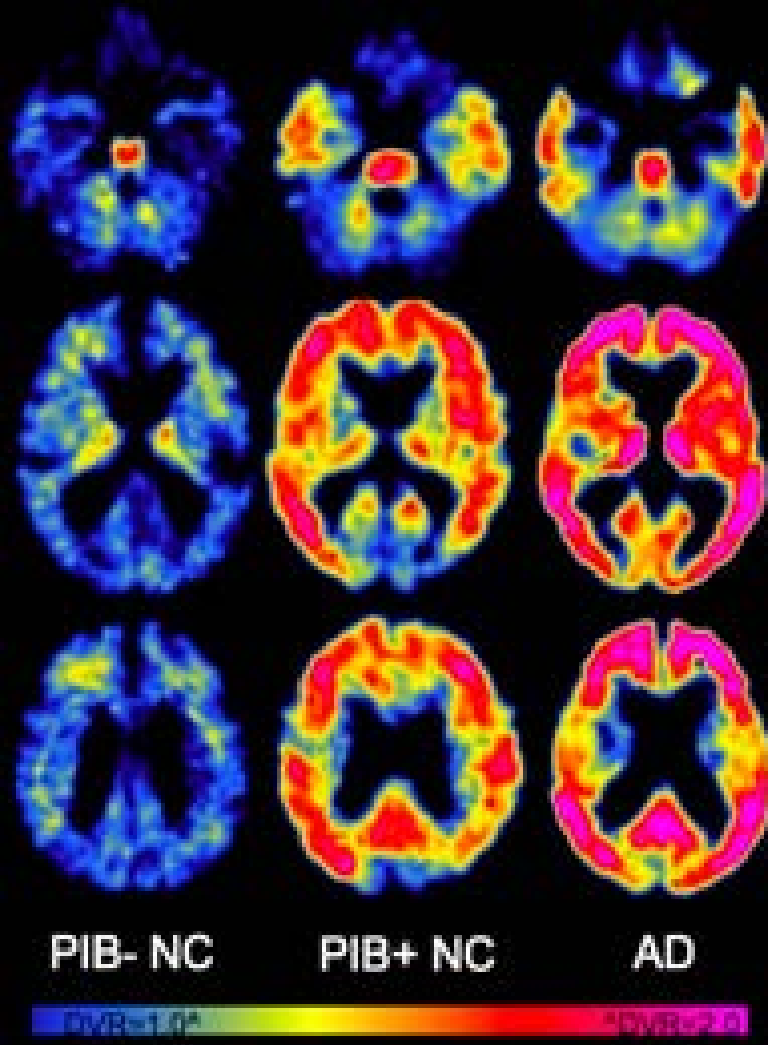
- Ten (maybe 9½) Phase III trial failures at stage of AD dementia over the past decade!
- Intervention prior to dementia (widespread irreversible brain cell loss) may have better chance of changing clinical course of the disease
- Delaying dementia by 5 years would reduce projected Medicare costs by nearly 50%
- Think about what happens in cancer, stroke, HIV, diabetes, osteoporosis .... if we wait to treat until after symptoms appear?

# The Continuum of Alzheimer's Disease

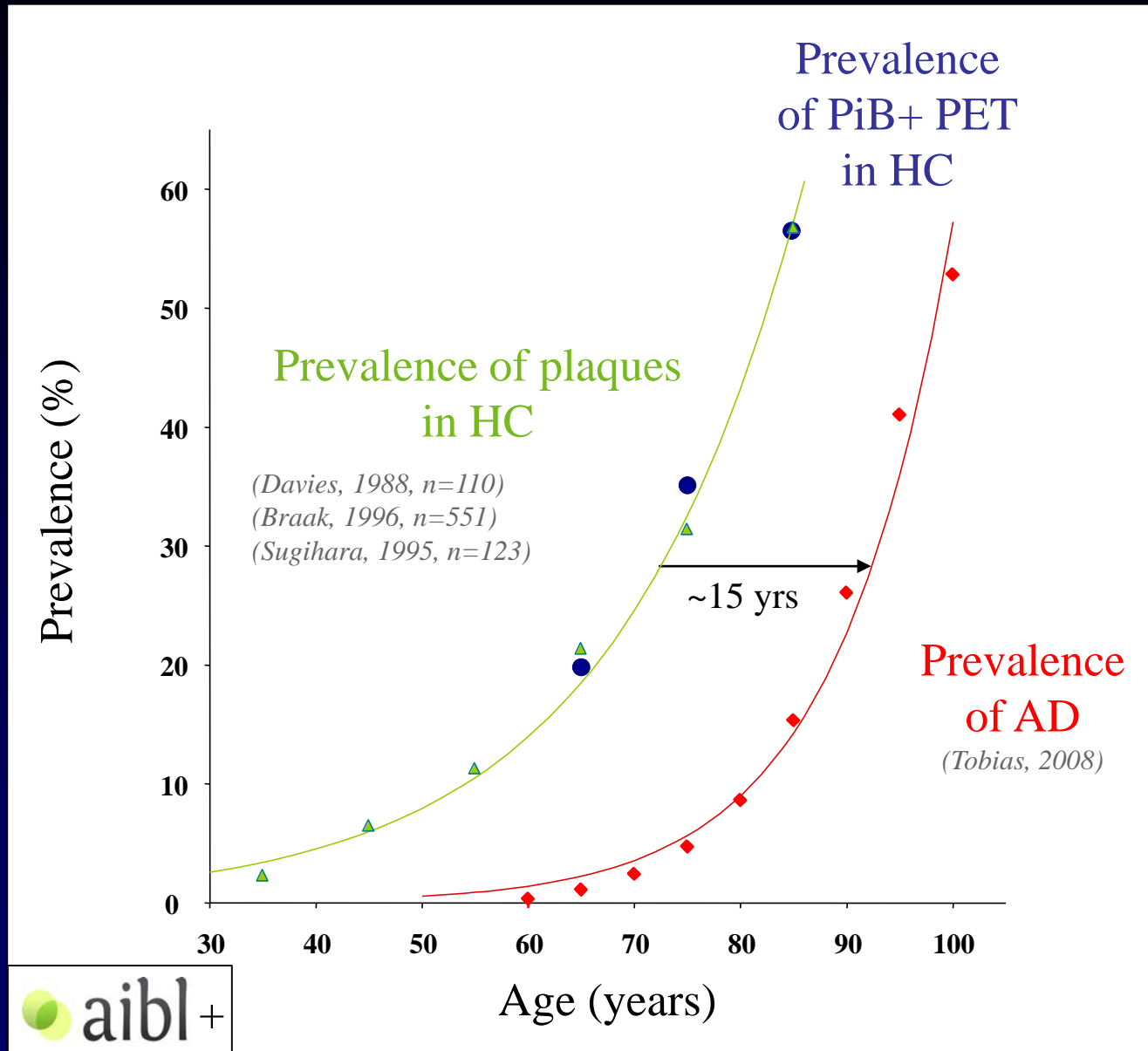


# PET Amyloid Imaging

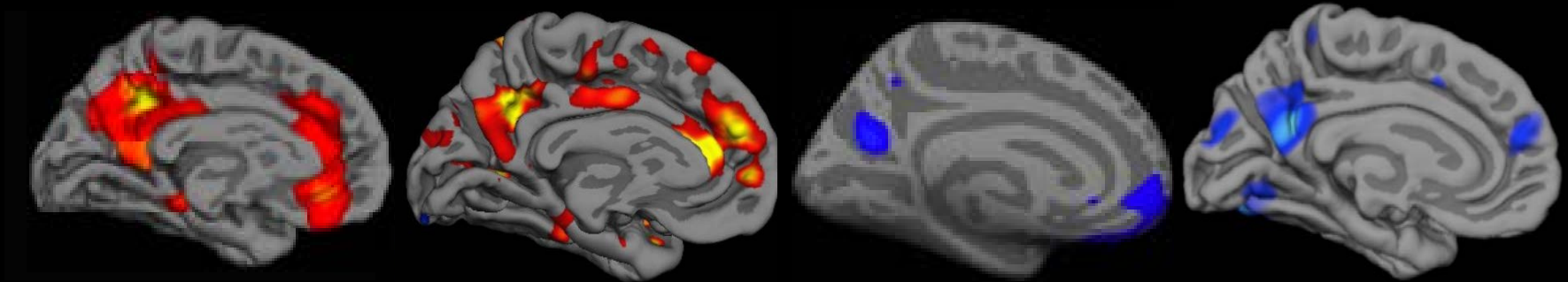
## Harvard Aging Brain Study



# Preclinical Alzheimer's Disease?



# Evidence of Amyloid-Related Alterations in Neural Function and Structure

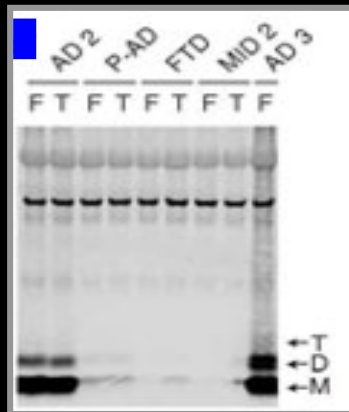


**PiB-PET**

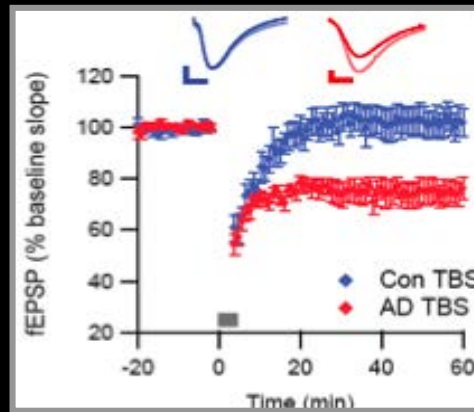
**fMRI**

**FDG-PET**

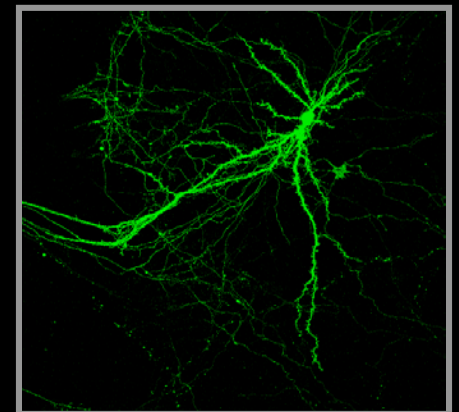
**vMRI**



**Molecular**

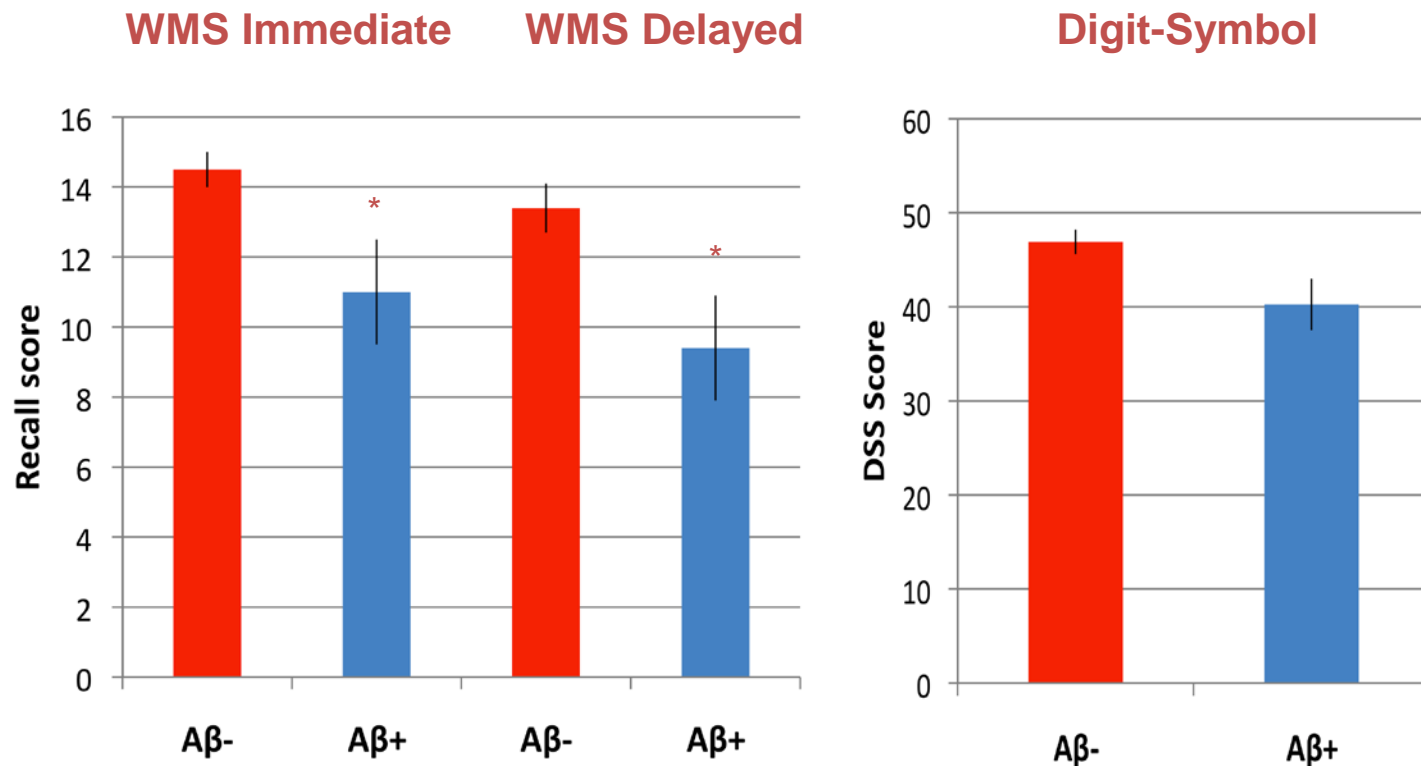


**Electrophysiological**

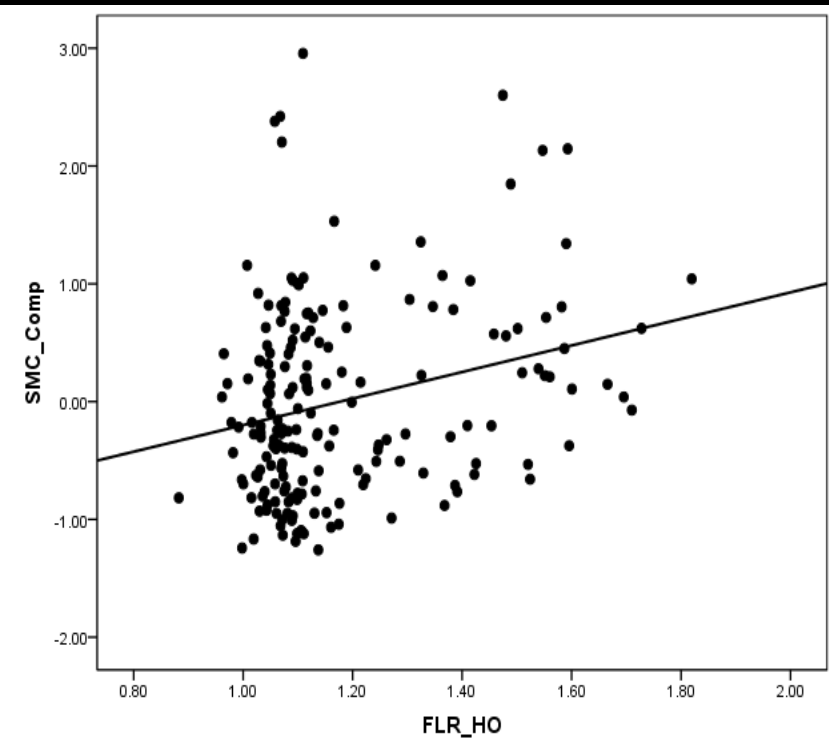


**Microscopic**

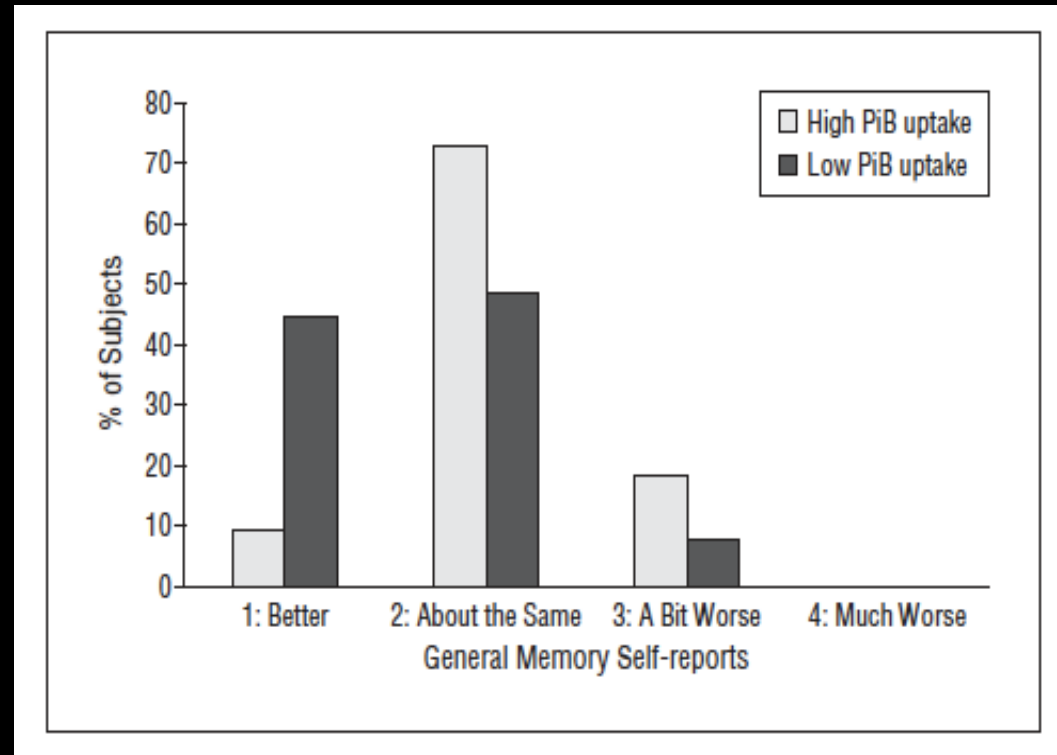
# Cognition in Amyloid Pos vs. Neg in HC > 70 years old



# Subjective memory concerns associated with amyloid burden among “normal” elderly



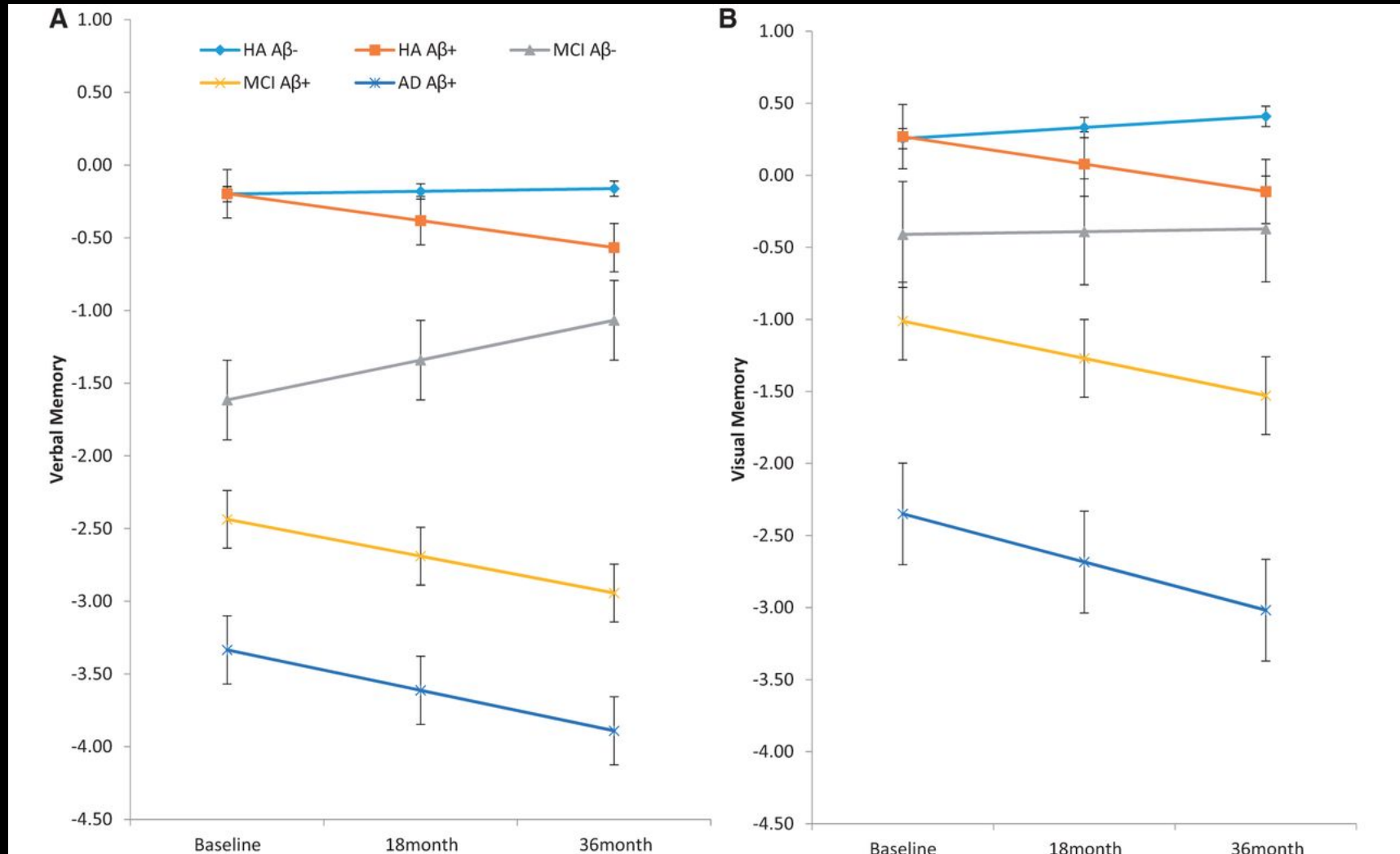
Amariglio R et al *Neuropsychologia* 2012



Perrotin A et al *Arch Neurology* 2012



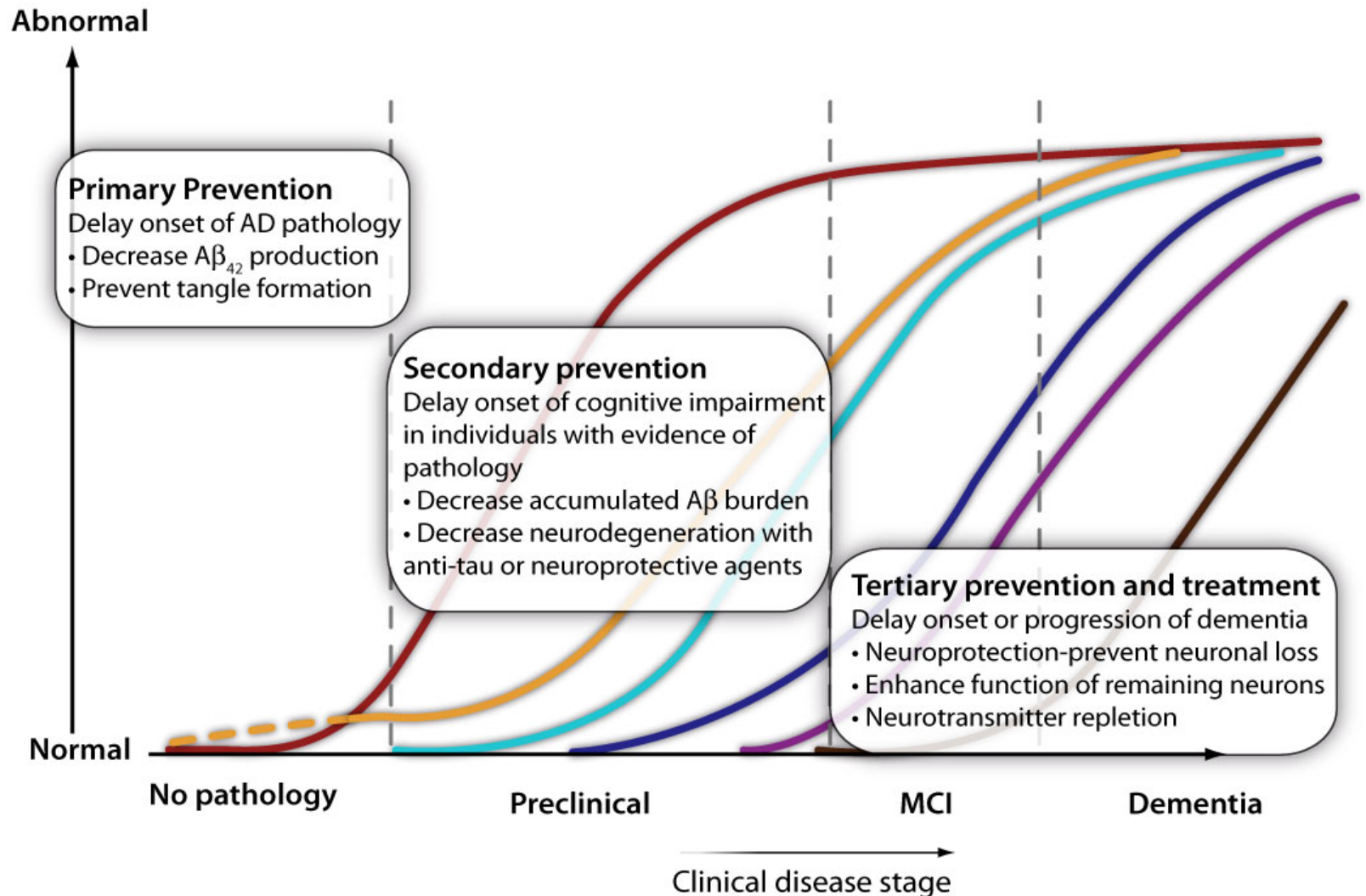
# Effect of amyloid on memory and non-memory decline from preclinical to clinical Alzheimer's disease



AIBL data

Lim Y et al *Brain* 2014

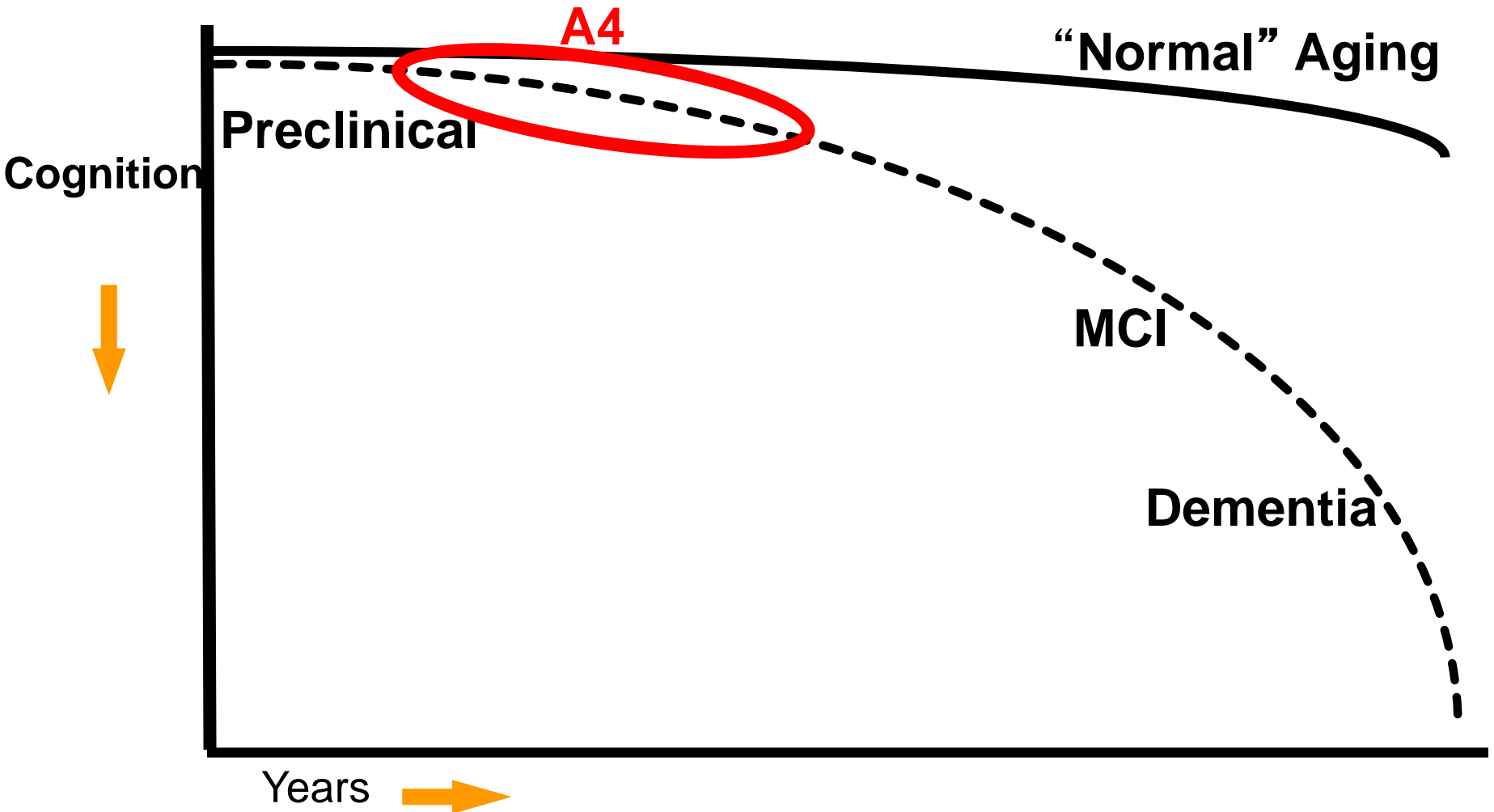
# Testing the Right Target and the Right Drug at the Right Stage of Alzheimer's Disease



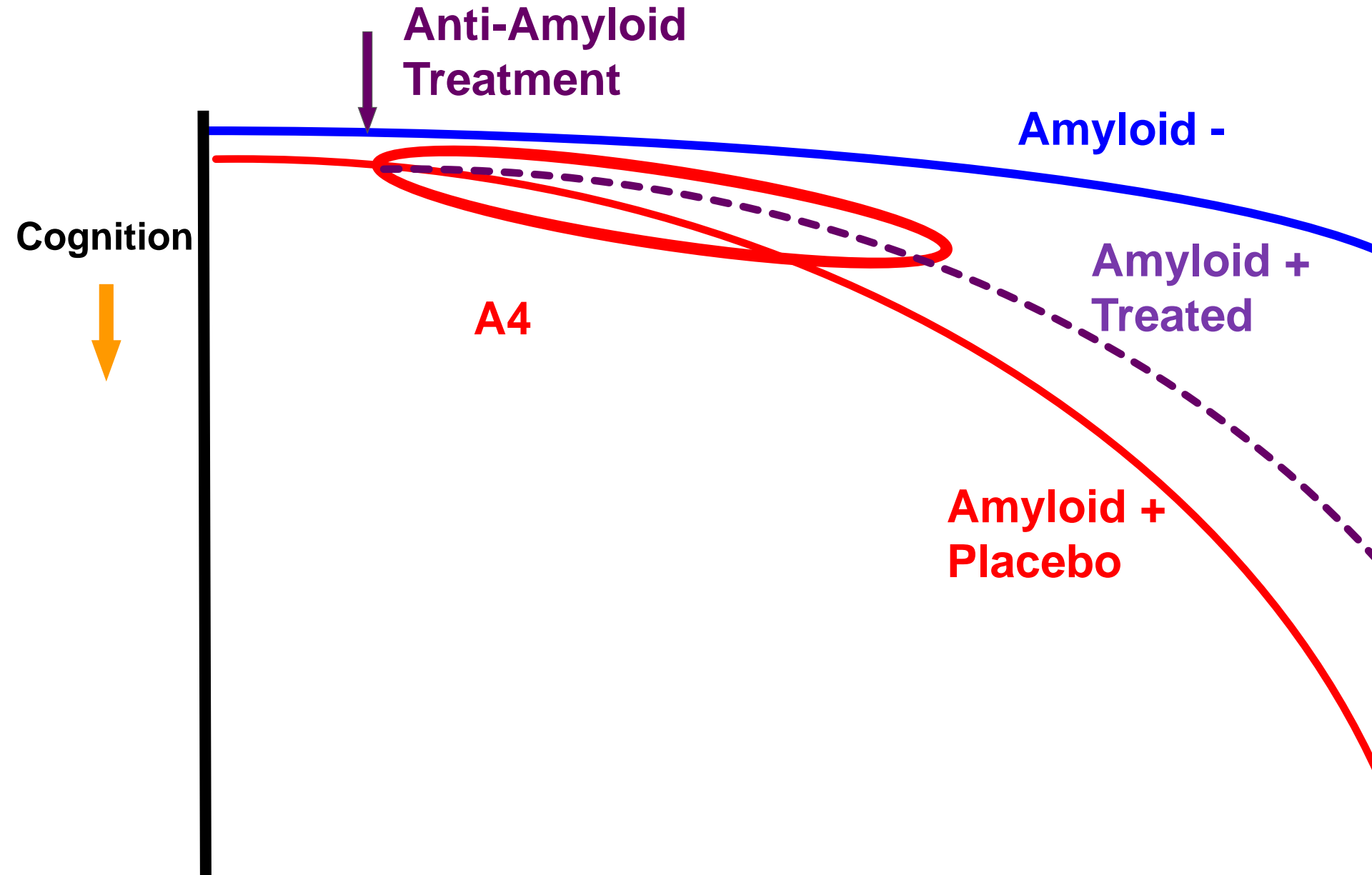
# A4 Study Synopsis

- Secondary prevention trial in clinically normal older individuals (age 65-85) who have evidence of amyloid- $\beta$  pathology on PET imaging
- Randomized, double-blind, placebo-controlled trial of solanezumab vs. placebo for 168 weeks
- Trial N=1000+ (N=500+ per treatment arm)
- Observational cohort of amyloid negative “screen fails” – LEARN study
- Ethics component – Disclosure of amyloid status

# The continuum of Alzheimer's disease



# The A4 Study



# A4 Eligible Participants

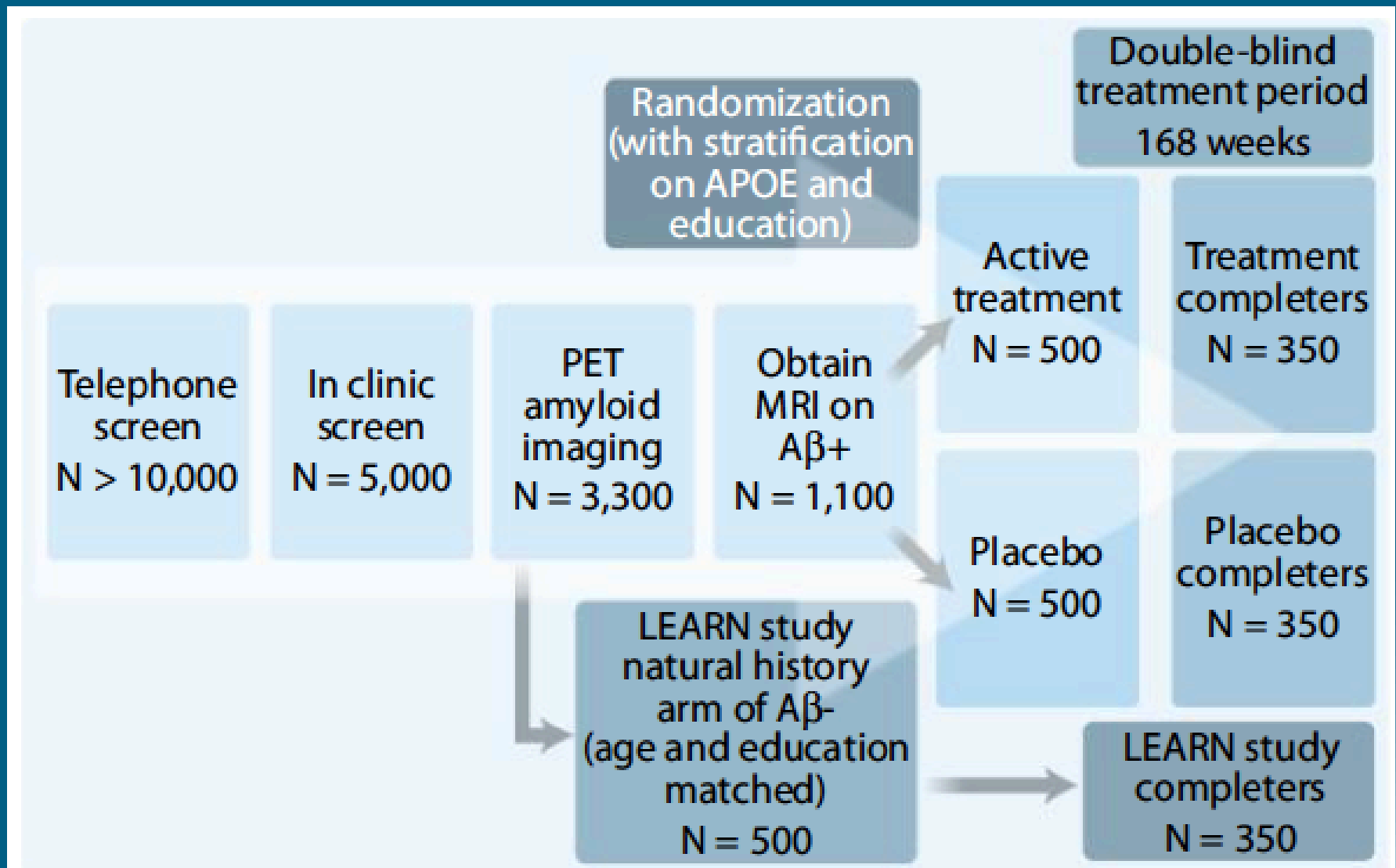
- Age 65 – 85 years; general good health
- One out of five from under-represented minority
- MMSE 27-30 (Education adjustment)
- CDR 0 – Will allow subtle subjective memory complaint if no evidence of impaired function
- Logical Memory II score of 15 – 8 for high education; 13 – 6 for low education
- Evidence of elevated amyloid accumulation on screening PET amyloid imaging

# LEARN Observational Cohort

## Longitudinal Evaluation of Amyloid Risk and Neurodegeneration

- Funded by the Alzheimer's Association and philanthropic foundations
- Selected from “screen fails” at Screening Visit 2
- 400 “Amyloid Negative” +100 “Amyloid Intermediate” or “Indeterminate”
- Matched on demographics to A4 treatment arms
- Will undergo same clinical and Imaging assessments - Tau imaging in a subset

# A4 Screening and Randomization





# A4 Primary Outcome - Cognitive

- Primary outcome – Rate of decline on ADCS Preclinical AD Cognitive Composite (PACC)
  - Free and Cued Selective Reminding Test
  - LMIIa paragraph – Delayed recall
  - Digit Symbol
  - Global cognition
  - MMSE
- Based on power calculations from ADNI, AIBL, ADCS-PI - A4 is powered to detect 30% slowing

# A4 Novel Outcome Measures

- “Patient” or Participant reported outcomes
  - Cognitive Function Index
  - C-PATH questionnaire and MAC-Q on iPad
  - Updated Instrumental ADL (Galasko)
- Impact of amyloid disclosure
  - Perception of time
  - Concern about developing AD dementia
- Computerized Cognitive Composite (C3)
  - CogState Card Playing tasks on iPad
  - Face-name and Pattern Separation

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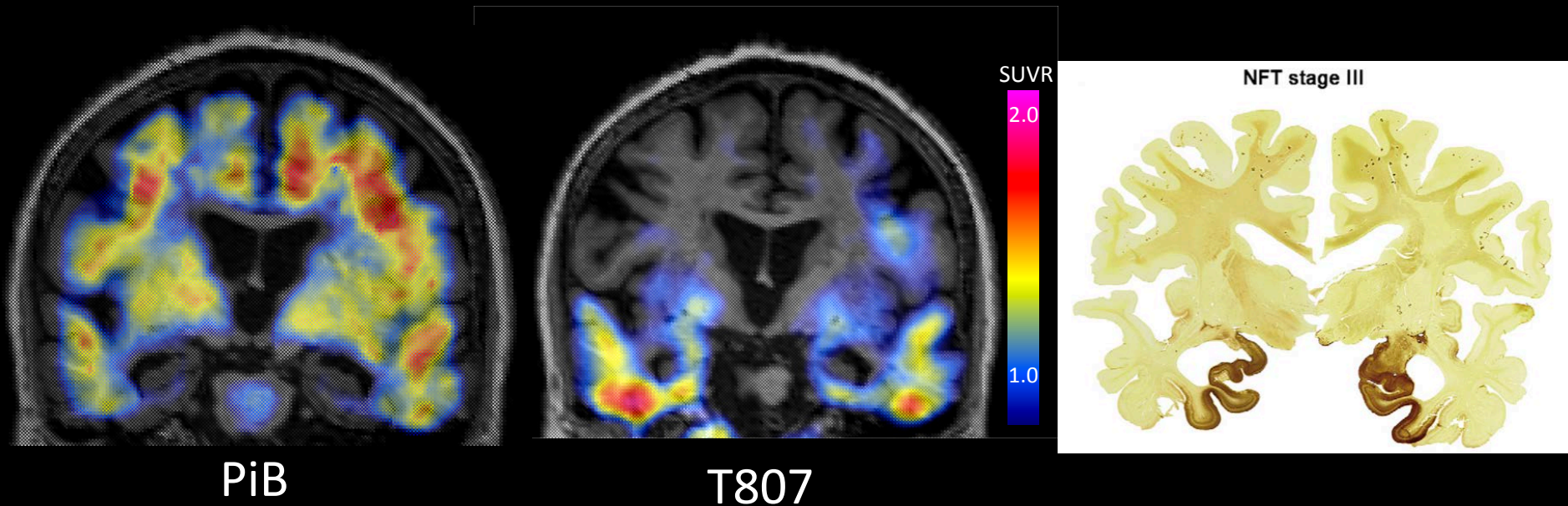
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# A4 Biomarker Outcomes

- PET amyloid imaging
  - Decrease in mean cortical SUVR
- CSF phospho-tau and tau (in subset)
- Volumetric MRI
  - Cortical thinning
  - Hippocampal atrophy
- Functional MRI
  - Task-free default network connectivity
- PET tau imaging

# Tau PET

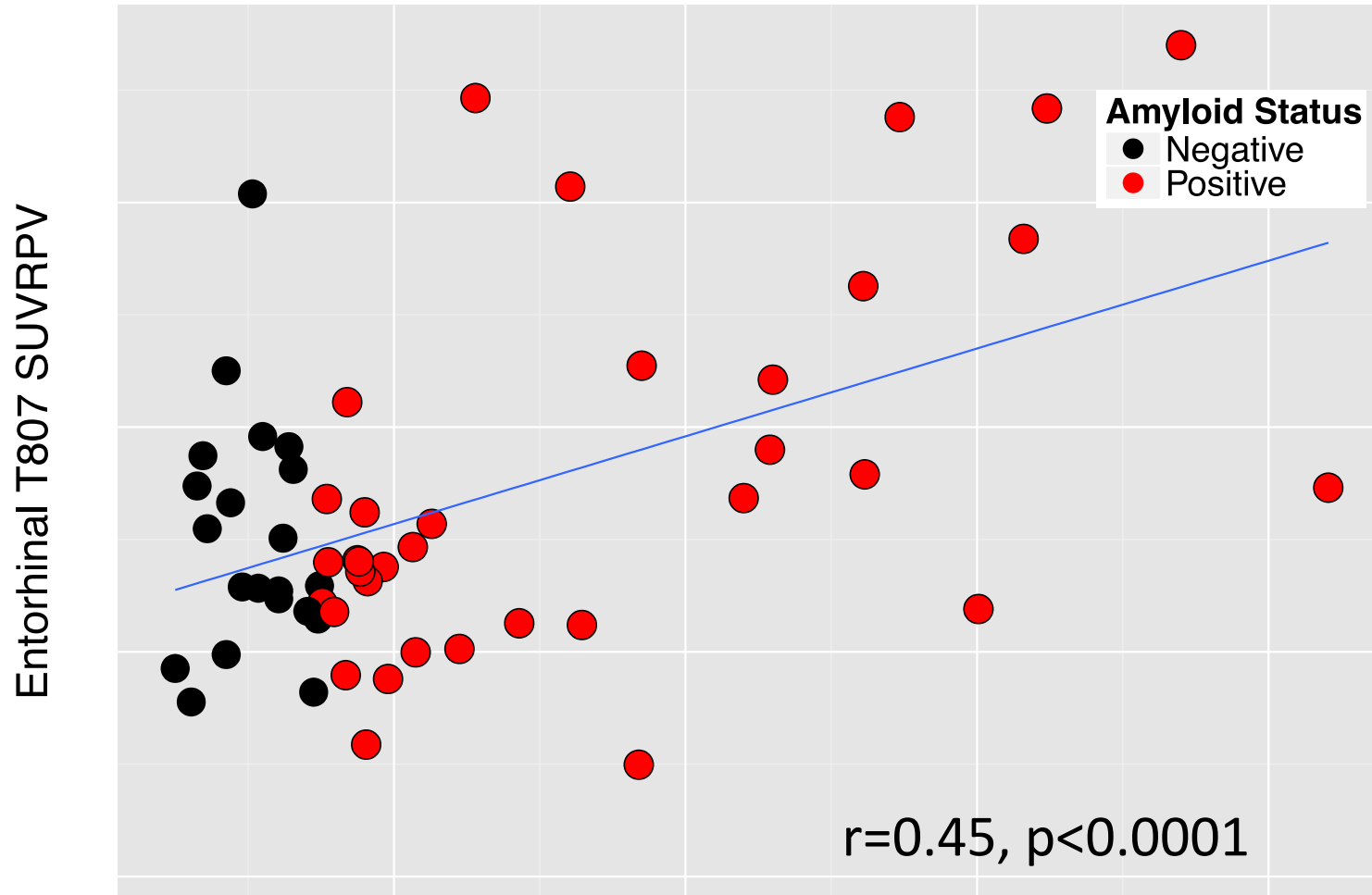
70 y/o MMSE =27



Keith Johnson CTAD 2013

# T807 Tau vs. PiB Amyloid- $\beta$

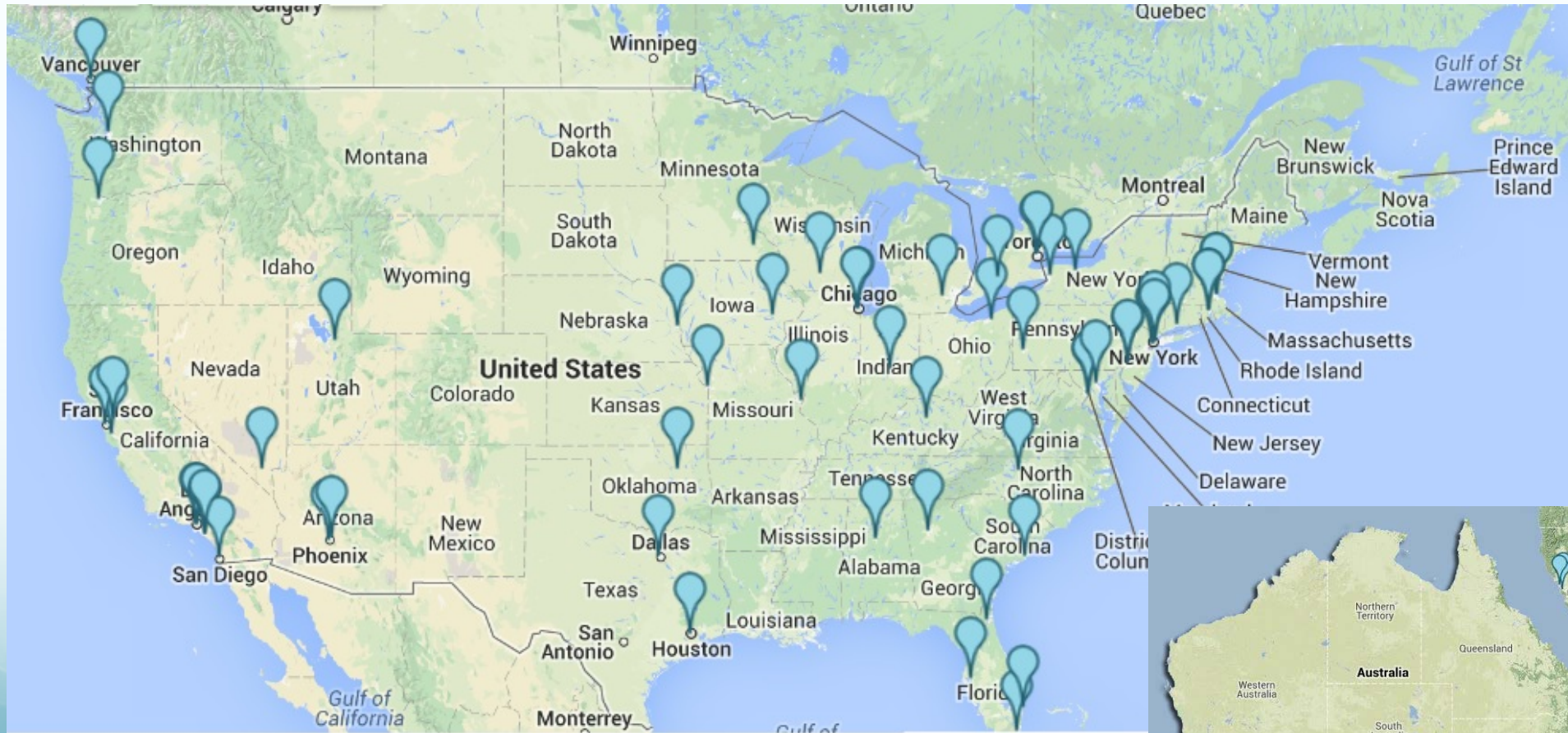
## Harvard Aging Brain Study



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# A4 Sites in US, Canada, and Australia



# A4 Recruitment



**A4Study.org**

**1-844-A4-STUDY**



# A4 is Enrolling!

- 46 sites with IRB approval
- 6 sites fully qualified to enroll
  - UCSD – Star site!!!!
  - Brown
  - Mayo Clinic
  - UC Irvine
  - Brown
  - Yale
  - Iowa
- Hope to have most sites up by this summer

# A4 Partnership

- A4 is funded through a public-private-philanthropic partnership (P4)
  - NIA, Eli Lilly, Avid, CogState, Alzheimer's Association, several philanthropic organizations
- All data from A4 study will be made available to the field
  - Screening data made available when enrollment complete, treatment data after regulatory submission
- Collaboration for Alzheimer Prevention
  - A4, DIAN, API, Fidelity, Alz Assoc, NIA

## A4 (and beyond...)

- A4 study intended as a platform to test the hypothesis that treatment during the preclinical stages of AD can slow cognitive decline and to determine if there is a “critical window” for successful anti-amyloid therapy
- A5 – Likely a beta-secretase inhibitor
- COMBAT – Combination Alzheimer Therapy
  - BACE inhibitor + Anti-A $\beta$  antibody
  - Anti-A $\beta$  + Anti-Tau

# A4 Acknowledgments

- Paul Aisen and ADCS
- Keith Johnson and Dorene Rentz from the Harvard Aging Brain Study
- Massachusetts ADRC
- A4 Study Team at Eli Lilly and Co.
- Collaboration for Alzheimer Prevention
- Alzheimer's Association
- National Institute on Aging

# Disclosures and Funding

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Foundation

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