Detection of Preclinical Alzheimer's disease: Implications for Prevention Trials

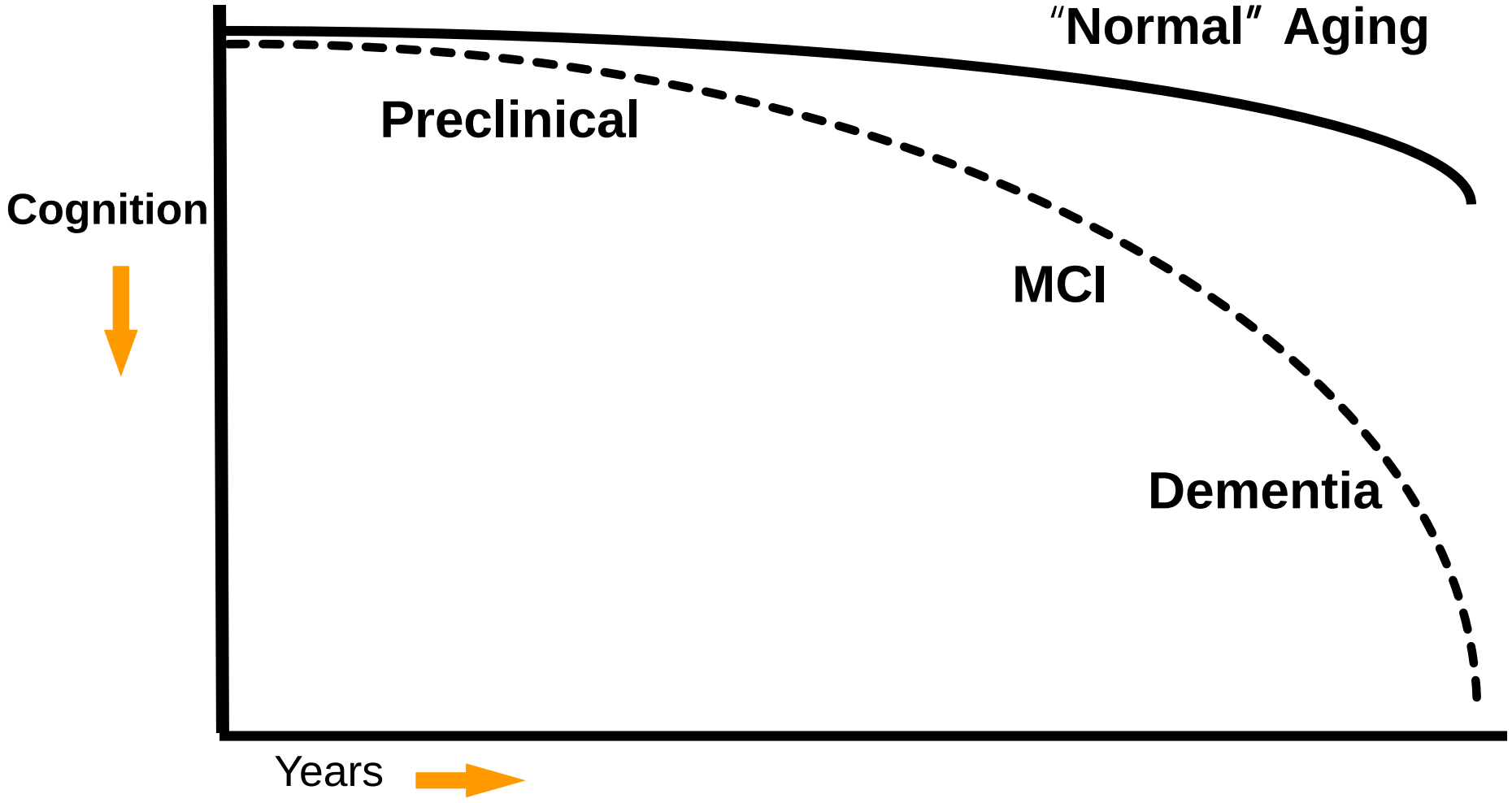
Reisa Sperling, MD

Brigham and Women's Hospital
Massachusetts General Hospital
Harvard Medical School

The A4 Study
NOW IS THE TIME

A4study.org

The continuum of Alzheimer's disease

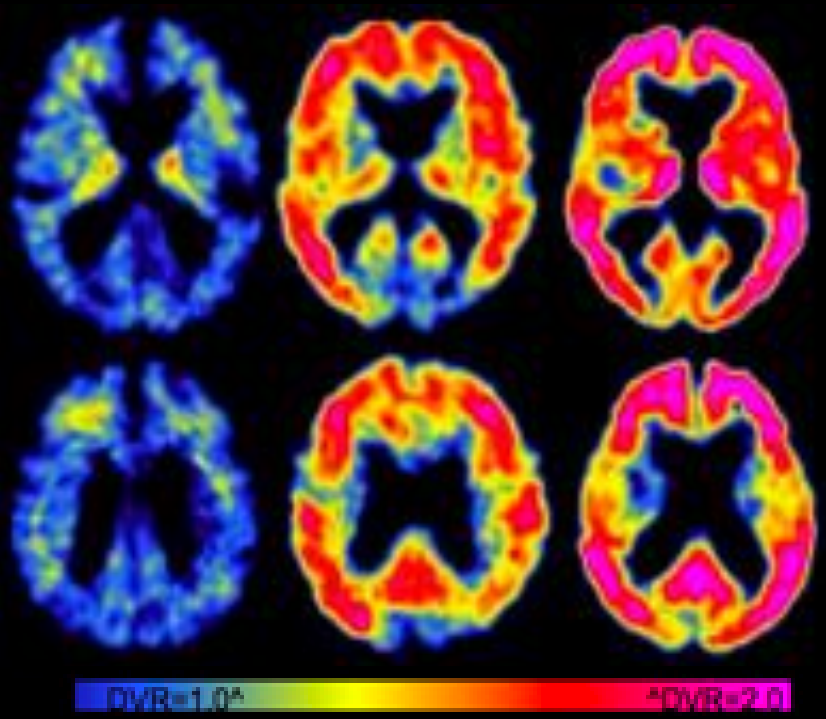


NIA-AA Preclinical Workgroup
Sperling R et al 2011

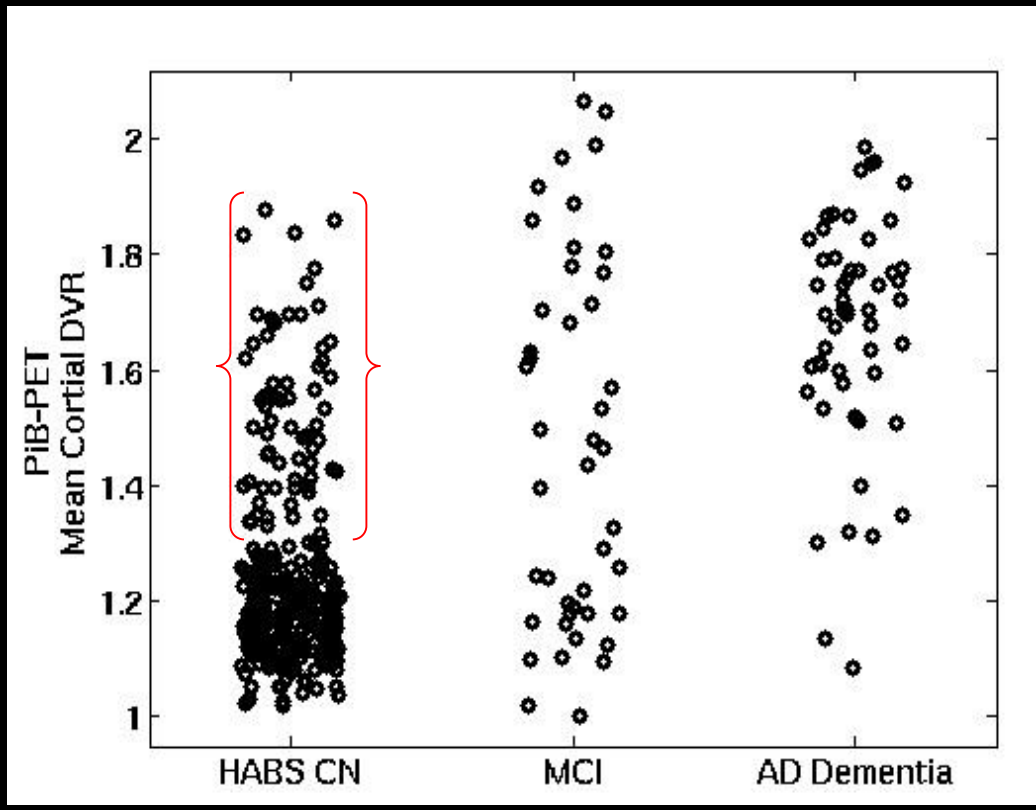
Rationale for Age-Biomarker-At-Risk Prevention Studies

- The pathophysiological process of AD begins well more than a decade before dementia
- Age is the greatest risk factor for AD
- One third of clinically normal older individuals harbor evidence of amyloid-β accumulation
- These "Aβ+ Normals" demonstrate "AD-like" structural and functional imaging abnormalities, subtle memory deficits, and faster rates of cognitive decline – an population at high risk for progression to AD dementia

PET Amyloid Imaging in Clinically Normal Older Individuals



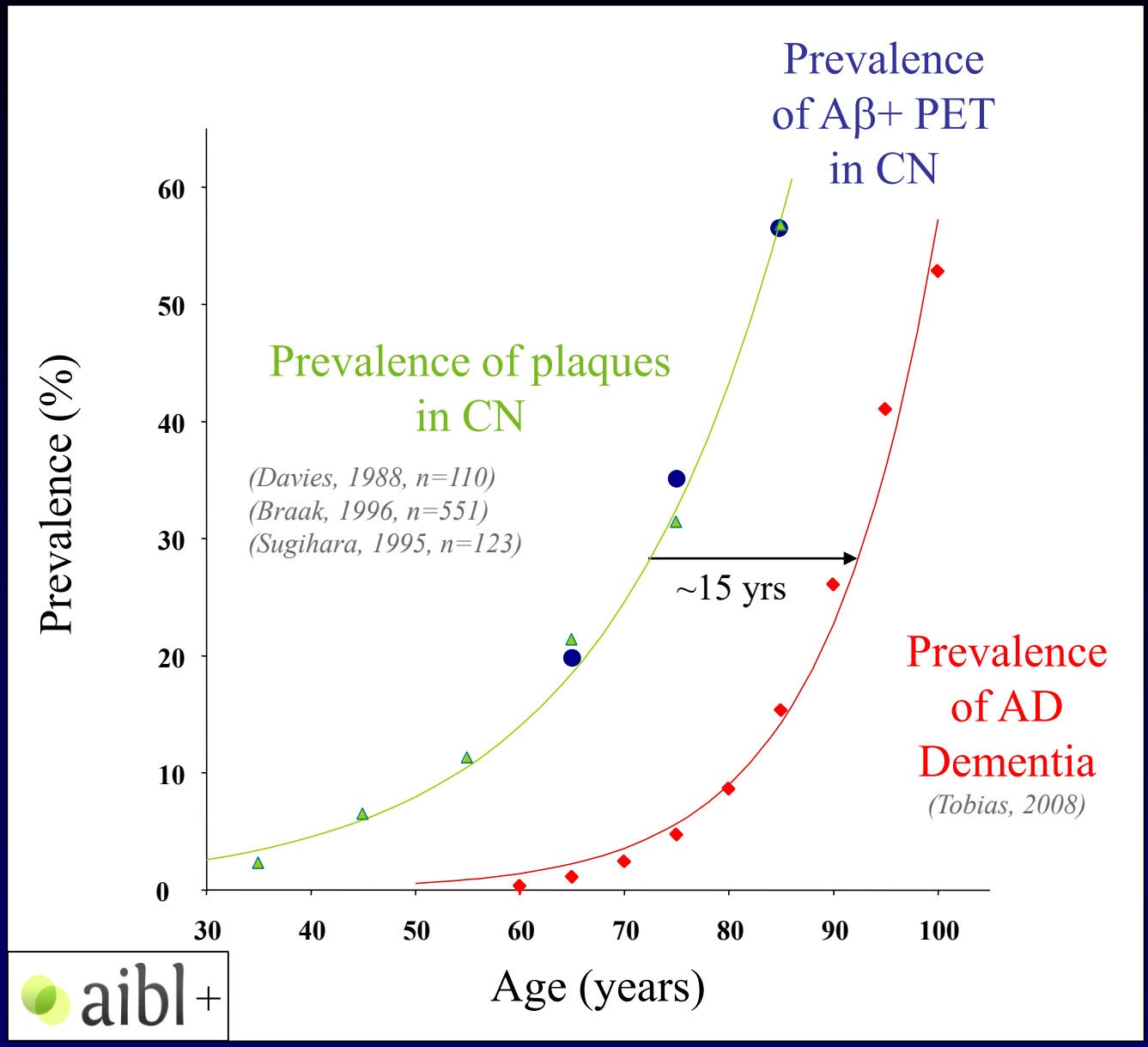
CN Aβ– CN Aβ+ AD Aβ+



Harvard Aging Brain Sudy

Sperling, Mormino, Johnson *Neuron* 2014

Preclinical Alzheimer's Disease



Adapted from Rowe C et al *Neurobiology of Aging* 2010

Staging Framework for Preclinical Alzheimer's disease

NIA-AA Preclinical Workgroup

Stage 0
No biomarker abnormalities

Stage 1
Asymptomatic amyloidosis
-High PET amyloid retention
-Low CSF $A\beta_{1-42}$

Stage 2
Amyloidosis + Neurodegeneration
-Neuronal dysfunction on FDG-PET/fMRI
-High CSF tau/p-tau
-Cortical thinning/Hippocampal atrophy on sMRI

Stage 3
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
-Evidence of subtle change from baseline level of cognition
-Poor performance on more challenging cognitive tests
-Does not yet meet criteria for MCI

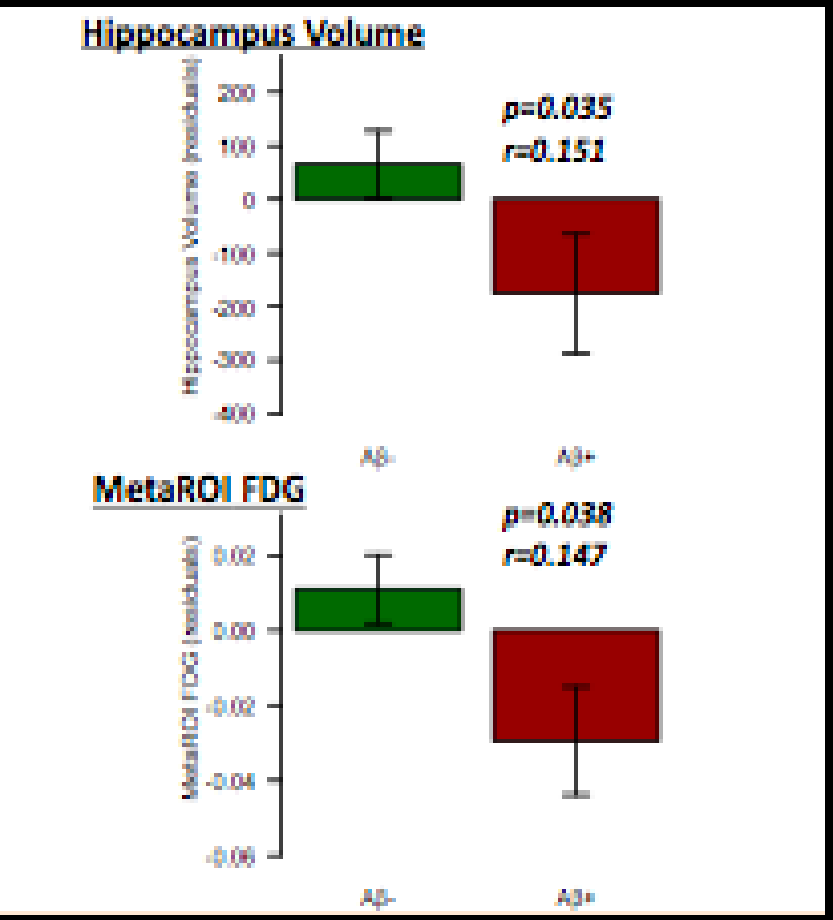
MCI ➔Dementia due to AD

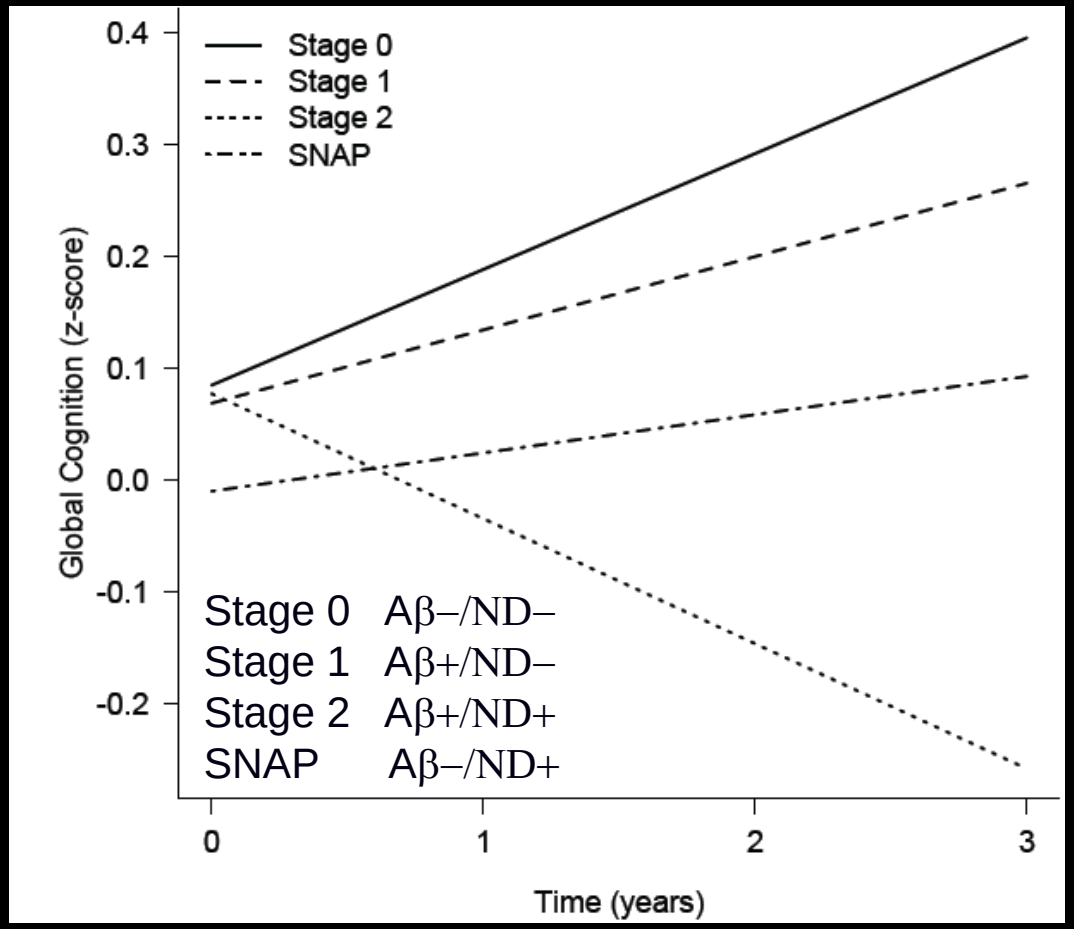
SNAP
Suspected non-Alzheimer pathology
- Neurodegeneration markers without evident amyloidosis

Sperling, Mormino, Johnson *Neuron* 2014
Adapted from Sperling 2011, Jack 2012

Relationship between markers of Amyloid β deposition and markers of neurodegeneration

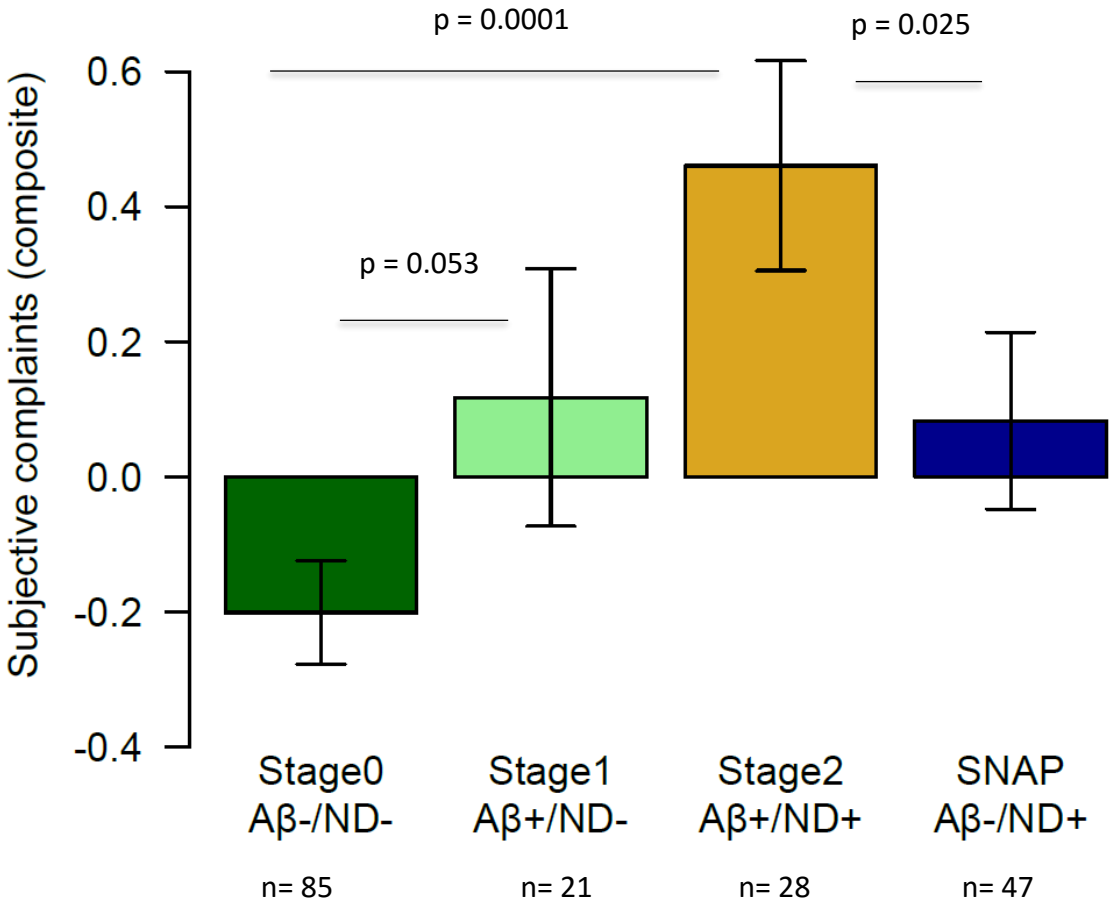
Harvard Aging Brain Study





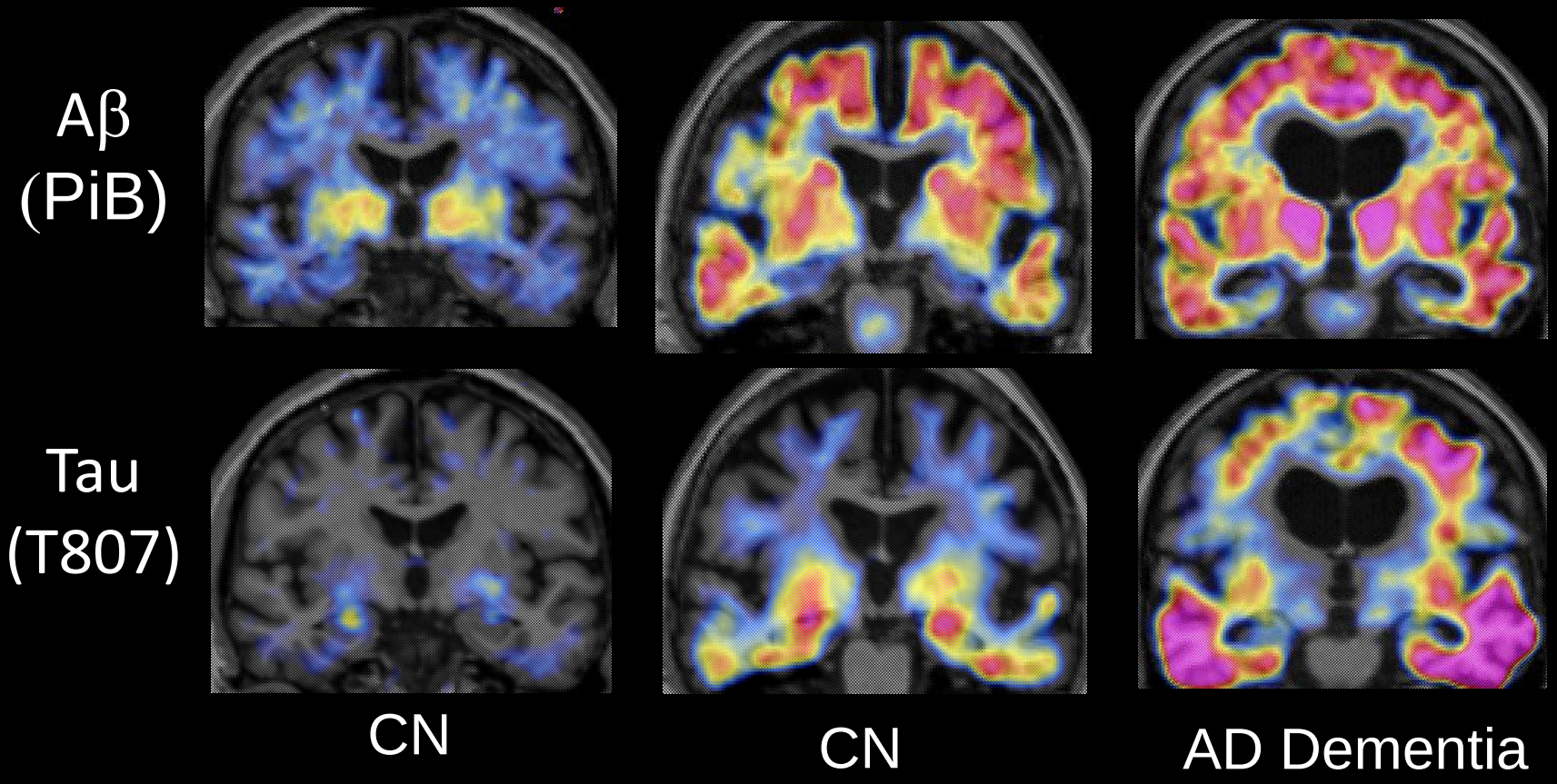
Mormino E et al *JAMA Neurology* 2014

Subjective cognitive concerns associated with advancing stages of preclinical AD



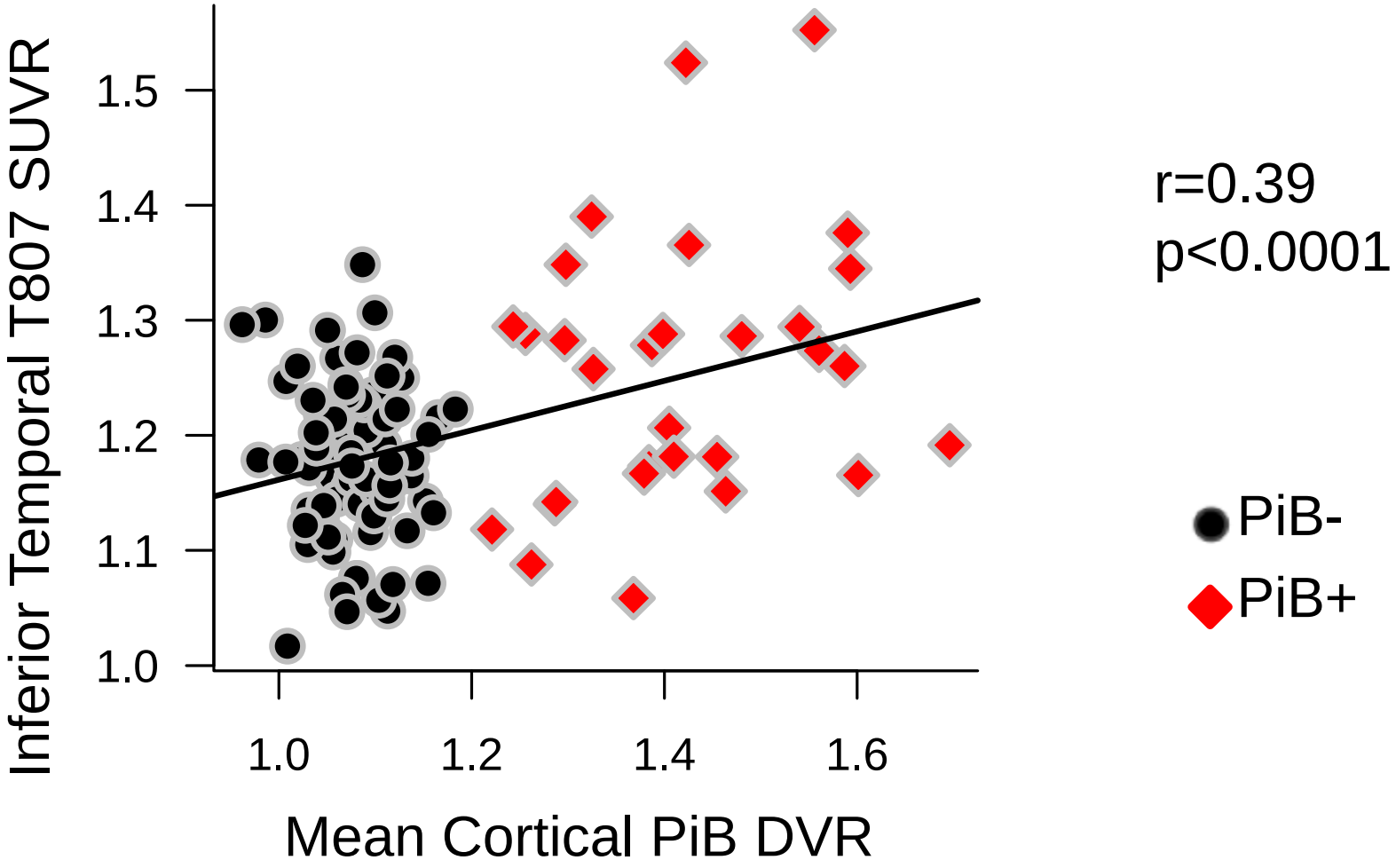
Amariglio et al. *Neurology* 2015

Amyloid and Tau PET Imaging



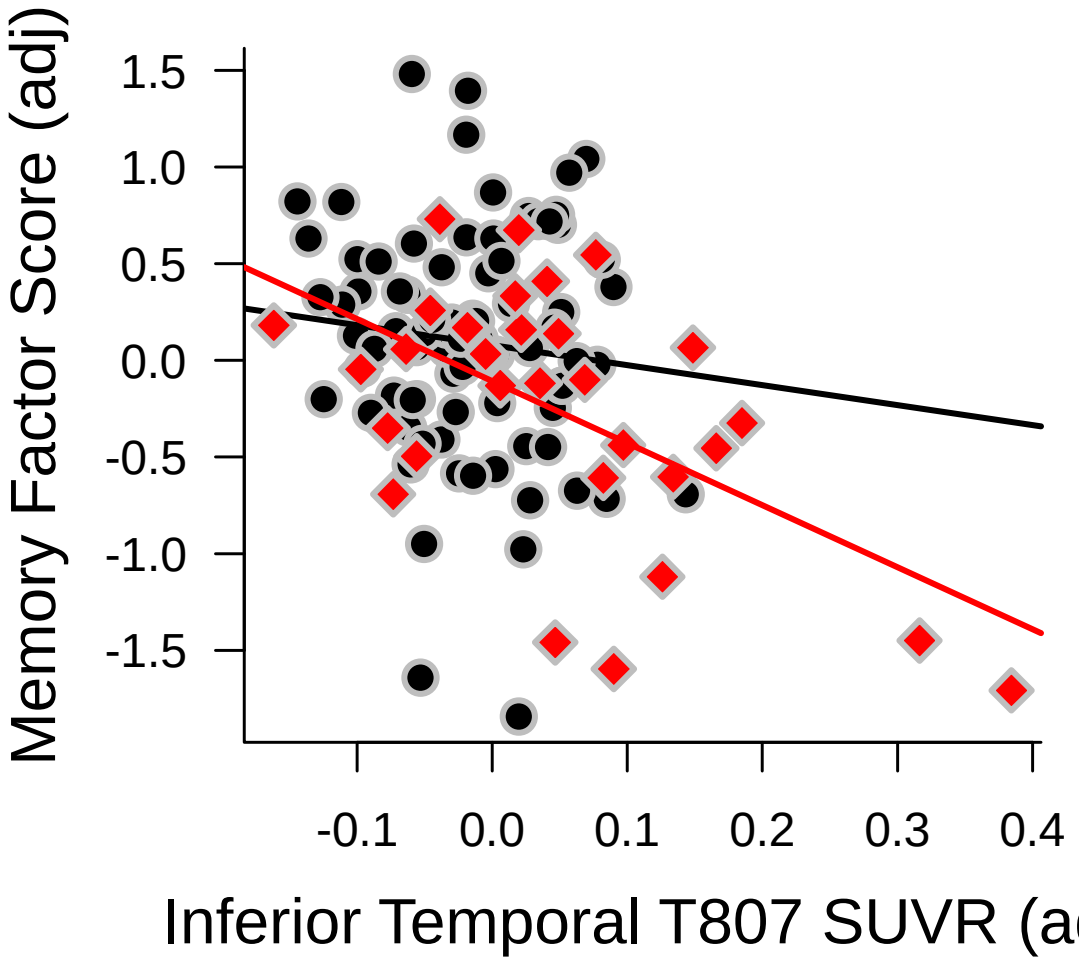
Sperling, Mormino, Johnson *Neuron* 2014

Higher Amyloid Burden Associated with Higher Tau Burden



Adjusted model for age, gender, education r=0.34; p=0.00013

Relationship of Tau and Memory by Amyloid Status

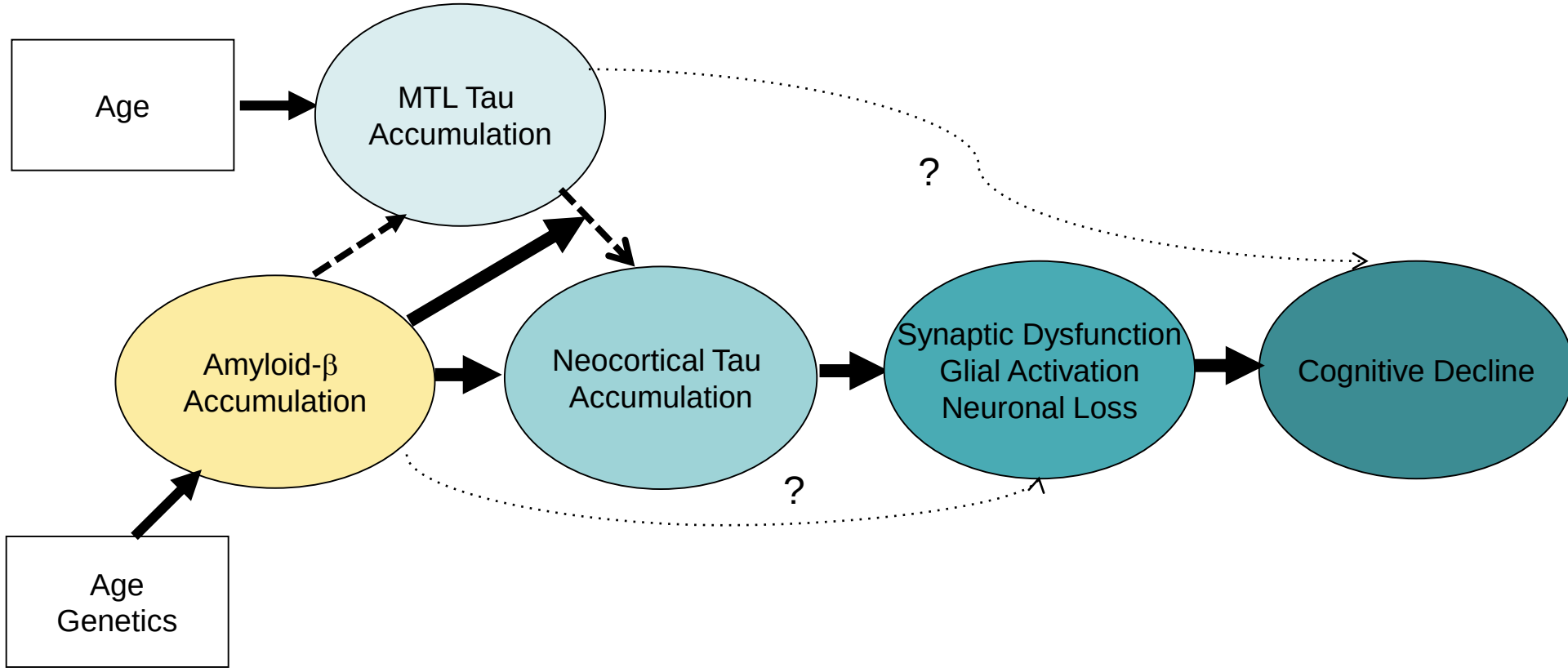


PiB- Slope= -1.07
r = -0.09
p=0.35

PiB+ Slope= -3.42
r = -0.52
p = 0.0014

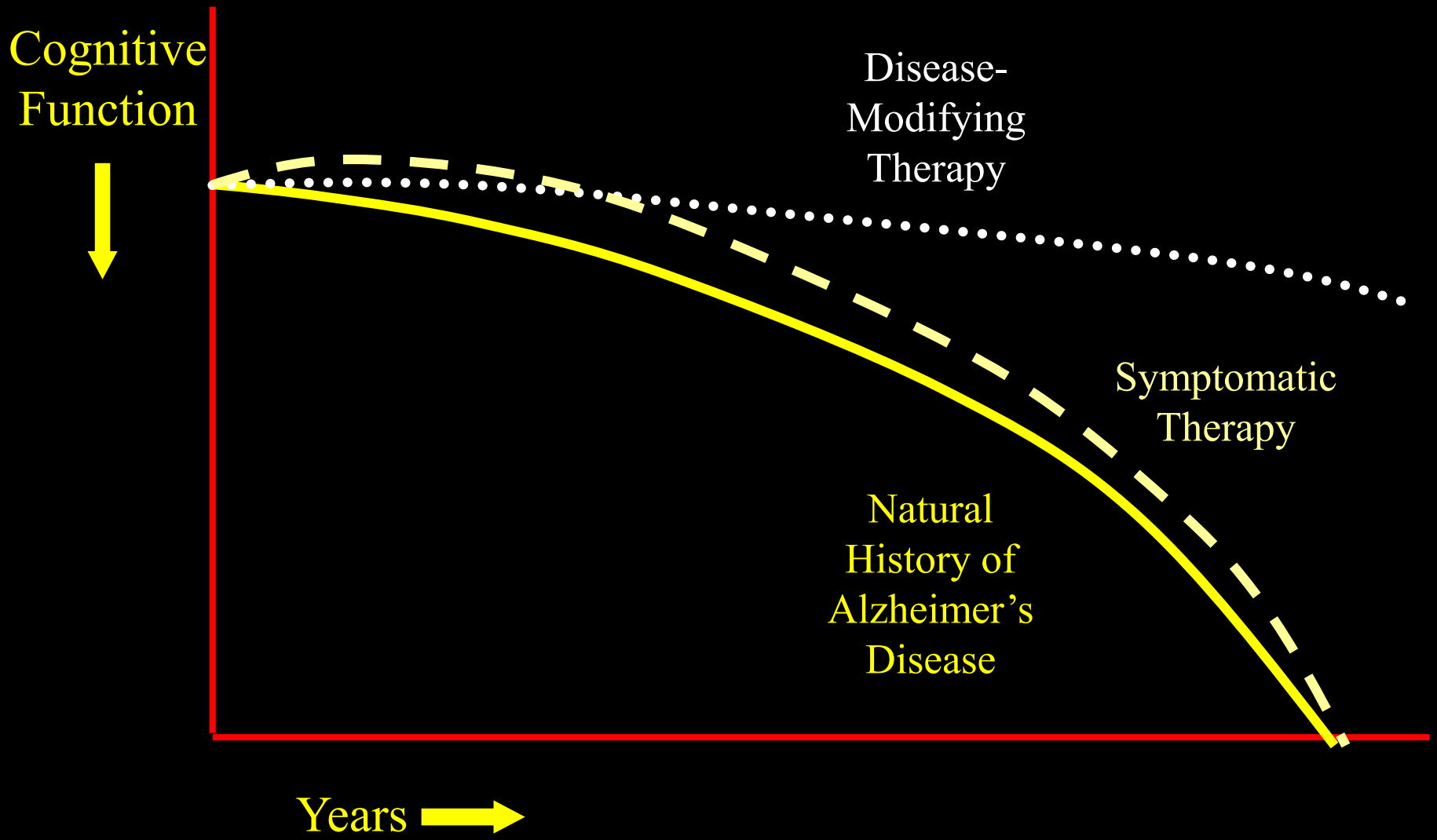
Interaction term
(PiB x T807)
p=0.089

Hypothetical Interaction of Amyloid and Tau in Preclinical AD



Sperling, Mormino, Johnson *Neuron* 2014

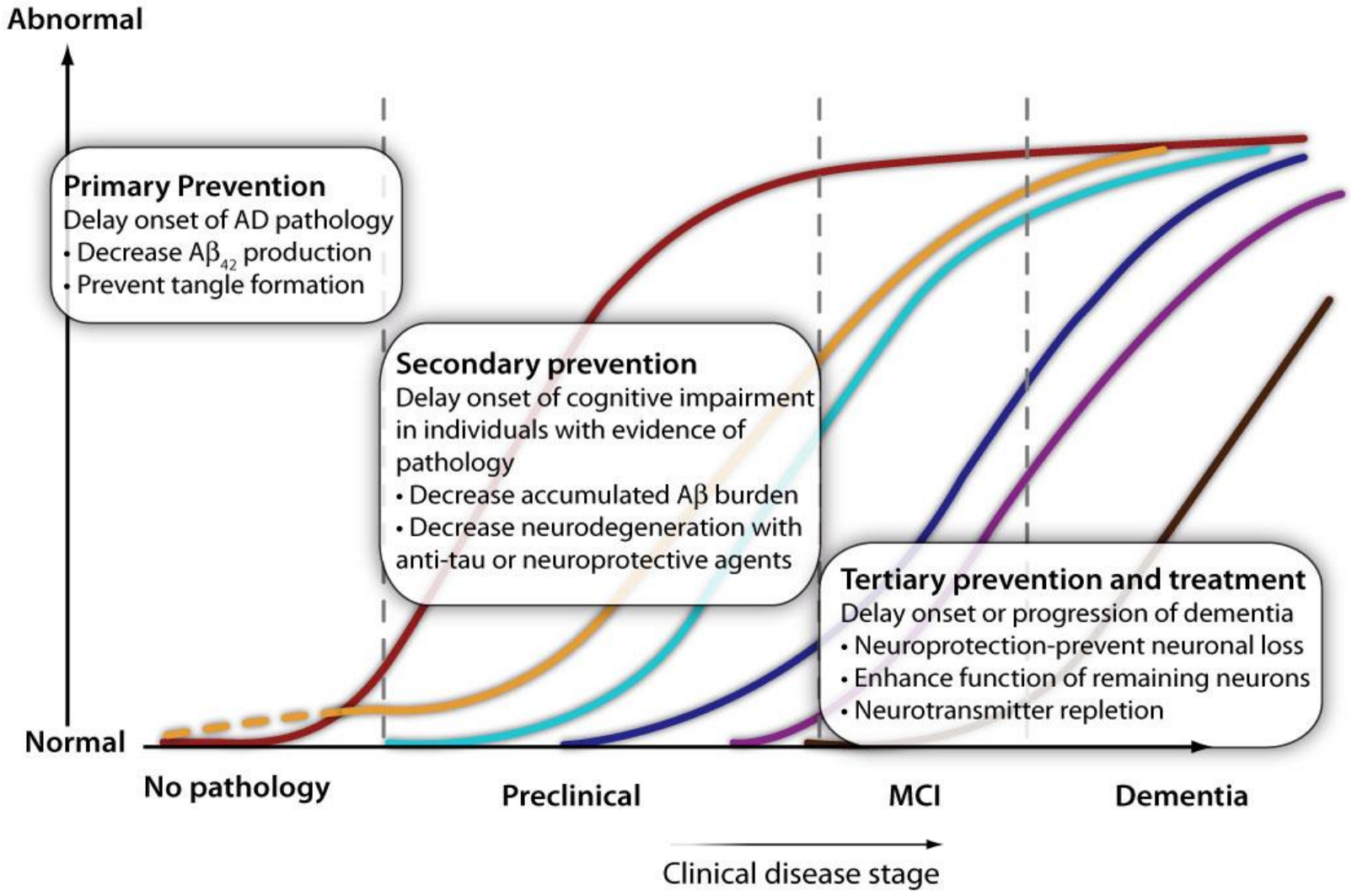
Treatment of Alzheimer's Disease



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?

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

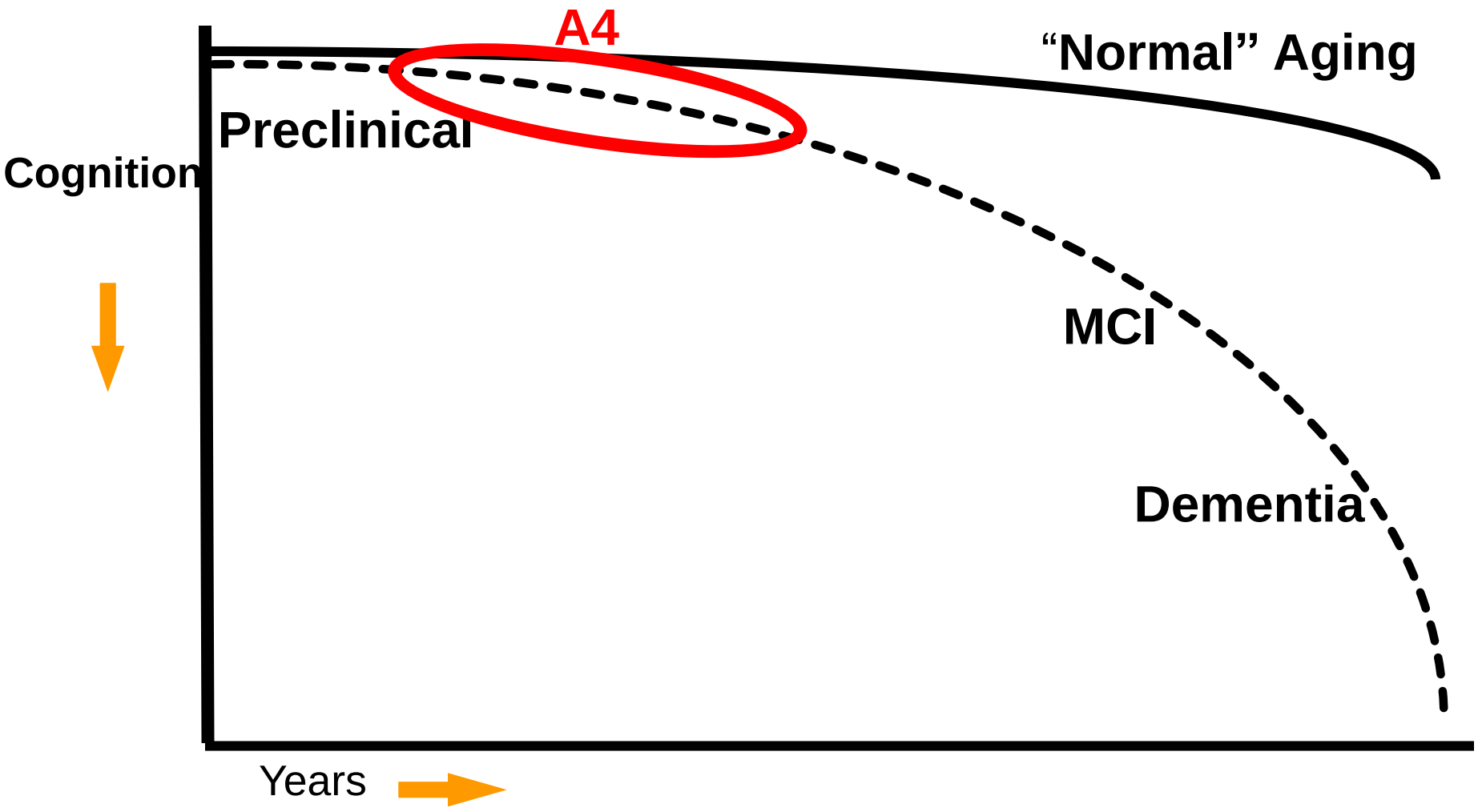


Sperling RA, Jack CR, Aisen P *Sci Transl Med* 2011

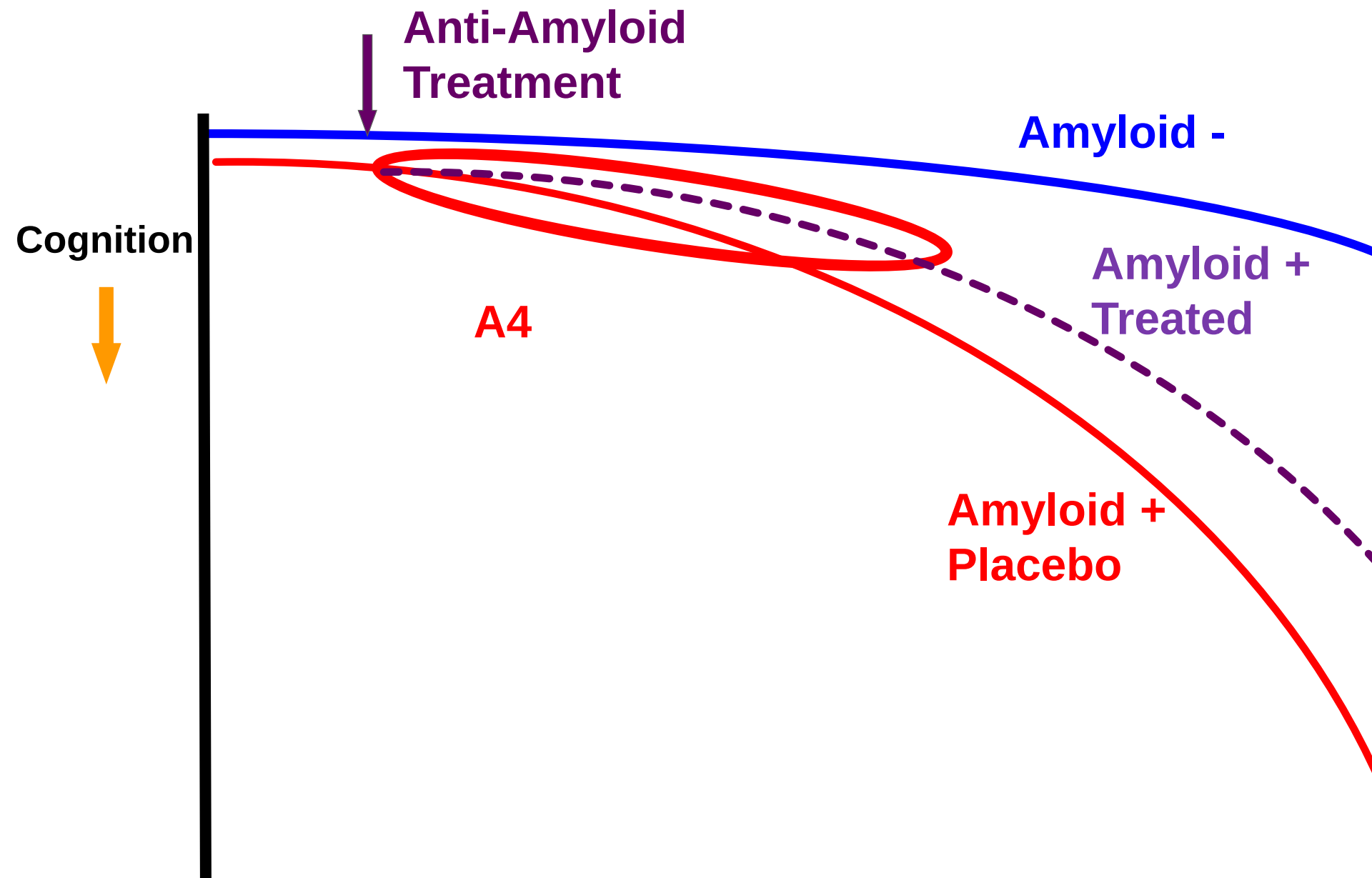
A4 Study Synopsis

- Secondary prevention trial in clinically normal older individuals (age 65-85) who have evidence of amyloid-β pathology on screening PET imaging
- Randomized, double-blind, placebo-controlled Phase 3 trial solanezumab vs. placebo for 168 weeks
- Trial N=1000+ (N=500+ per treatment arm)
- Observational cohort of Aβ negative "screen fails" – LEARN study (N=500)
- Ethics component – Disclosure of amyloid status

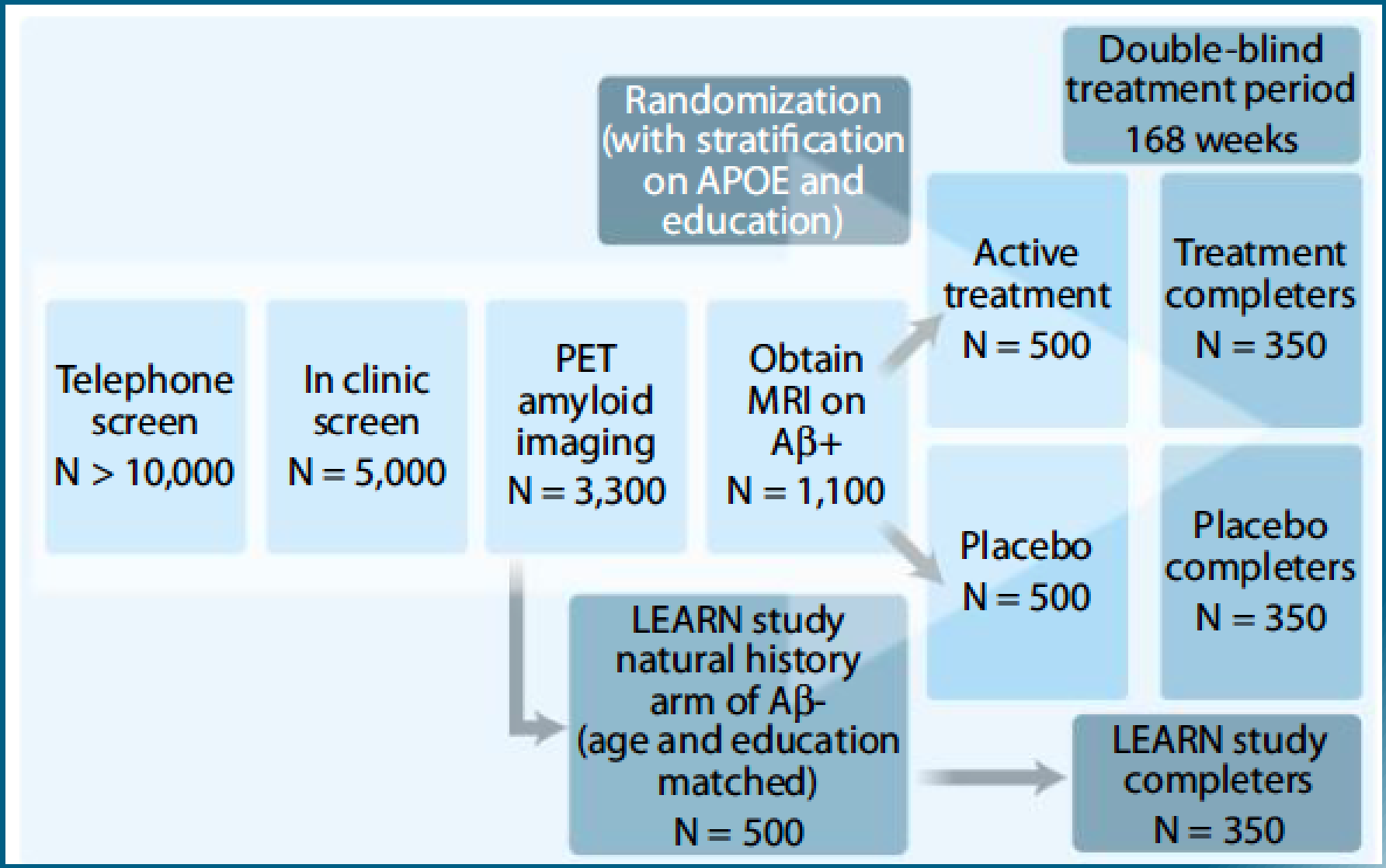
The continuum of Alzheimer's disease



The A4 Study


Anti-Amyloid
Treatment
Amyloid -
Cognition
Amyloid +
Treated
A4
Amyloid +
Placebo

A4 Screening and Randomization



Sperling R et al *Sci Trans Med* 2014

A4 Status as of Dec 1, 2015

- 63 sites enrolling in US, Canada and Australia
- Over 2700 participants screened/currently in screening process
- Current PET eligibility = 33%
- 378 participants randomized
- LEARN companion protocol launched
- 71 Tau PET images acquired

A4 Study - Anti-Amyloid Treatment in Asymptomatic AD

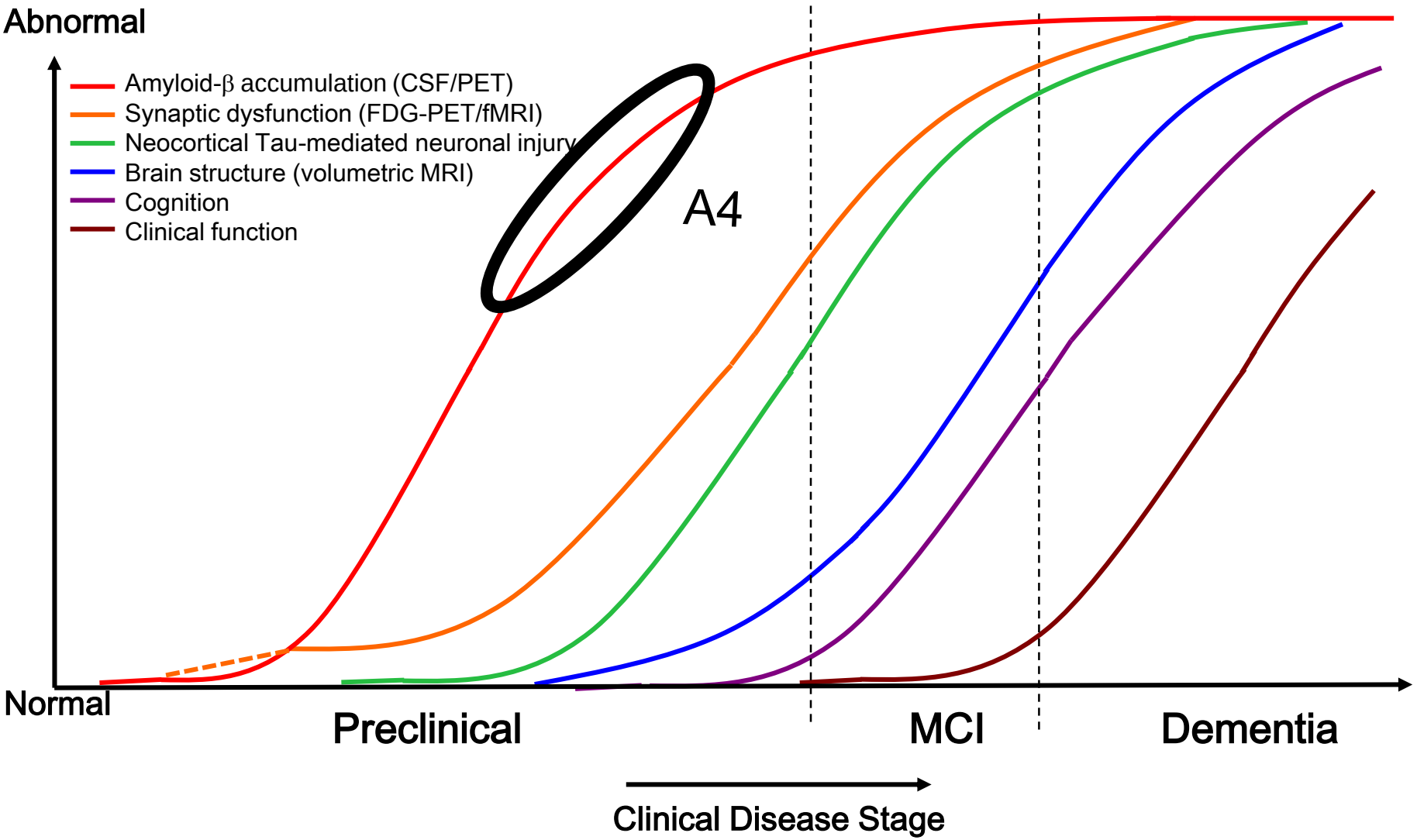
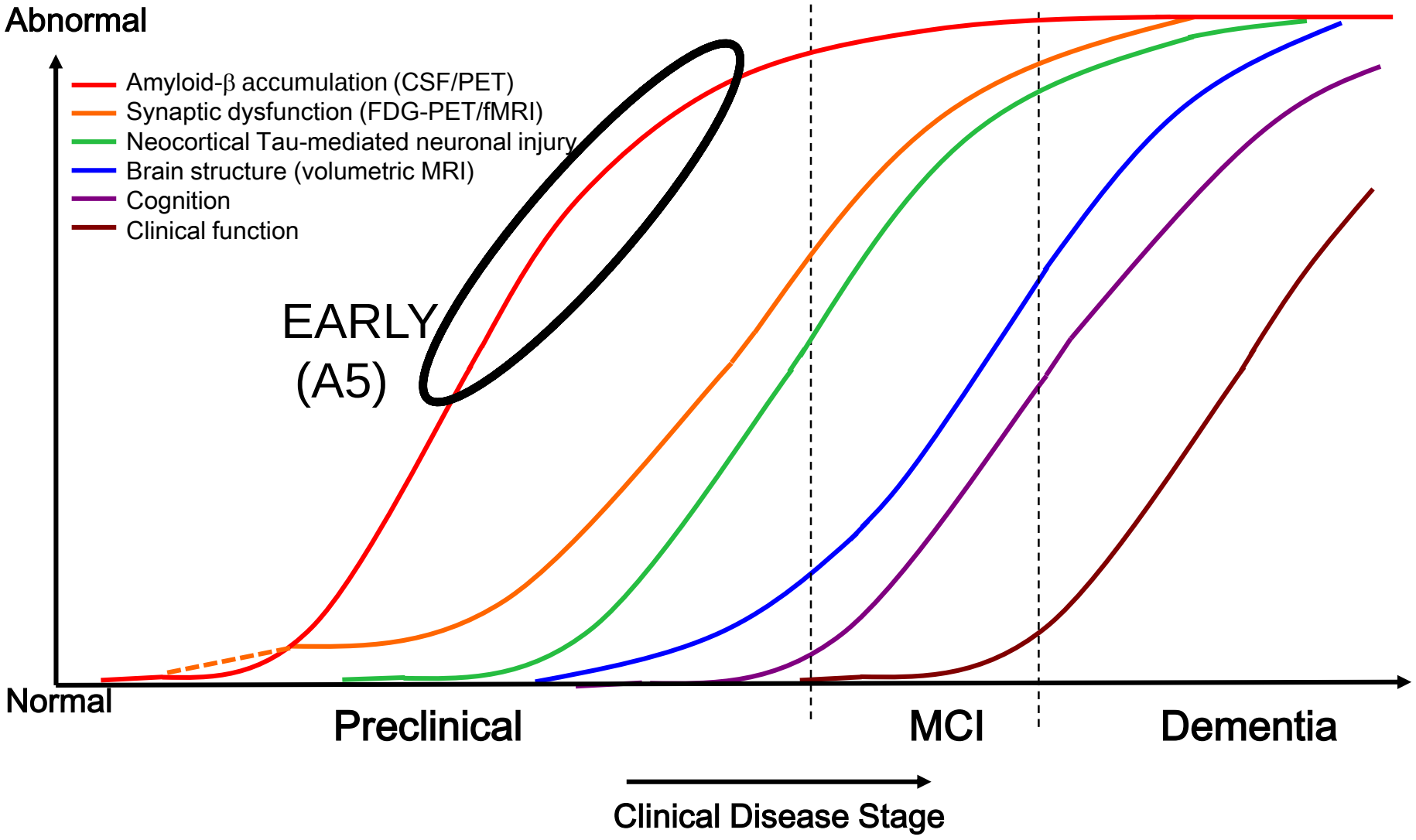


Figure adapted from Jack *et al.* 2010, Sperling *et a*l. 2011

EARLY Study (“A5”) – BACE inhibitor

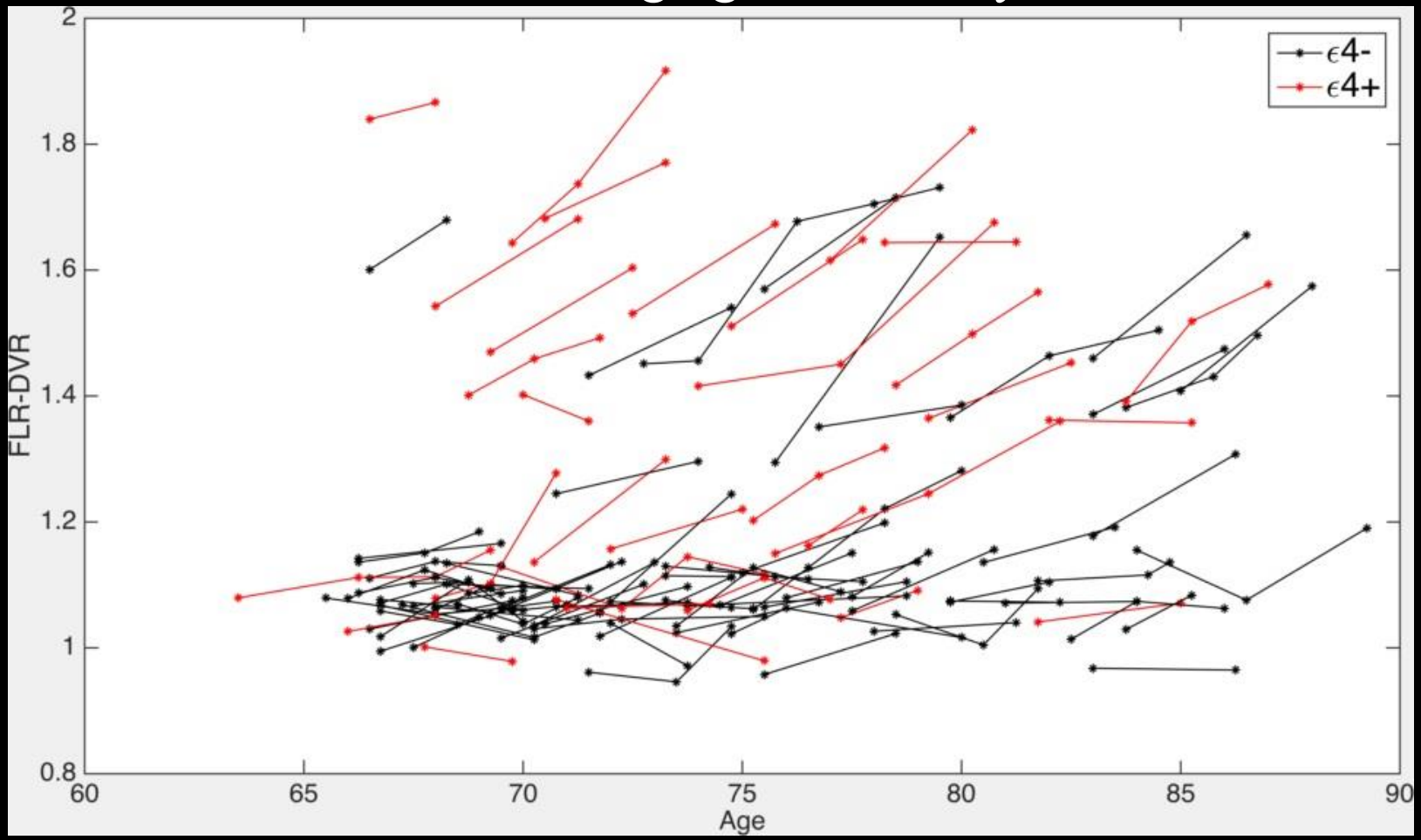


EARLY (A5) Trial

- Janssen sponsored trial of an oral BACE inhibitor with academic collaboration
- EARLY will be a global study - launching first in Europe, Australia, Asia, then US
- Amyloid eligibility by CSF or PET – same "amyloid positive" normals criteria as in A4
- Broader age range – 60-85 years old
  - Participants age 60-65 must have APOE risk factor
- Broader cognitive range than A4
- Longer trial – up to 4.5 years

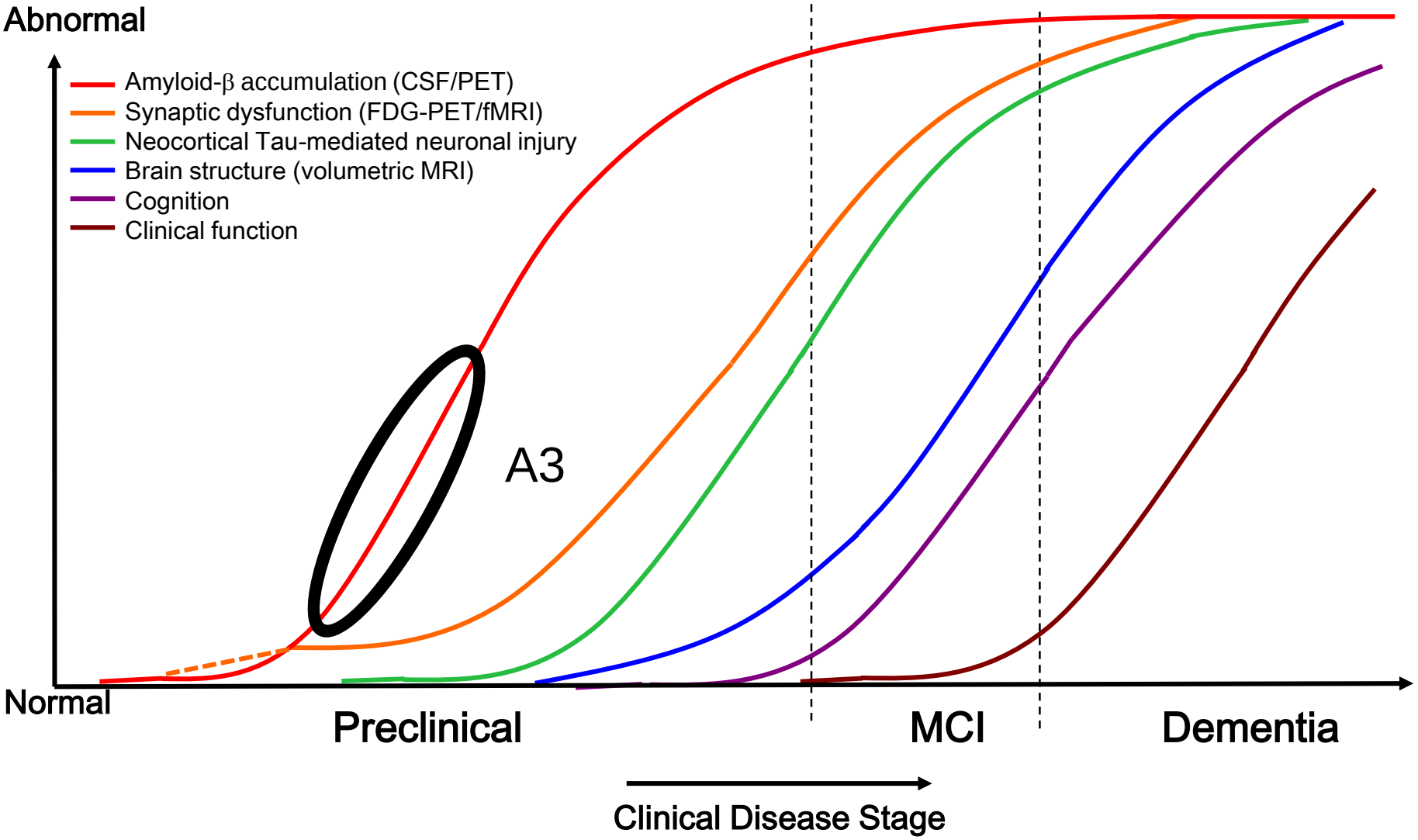
Longitudinal Amyloid-β Accumulation in Clinically Normal Elders

Harvard Aging Brain Study



Aaron Schultz and Keith Johnson HAI 2015

A3 Study = Ante-Amyloid prevention of AD
Getting closer to Primary Prevention!



A3 Study!

- A3 will leverage the A4 /A5 screening to identify people with "subthreshold" Aβ levels who are at high risk for continued amyloid accumulation
- Four year Phase IIb/IIIa 4 trial - BACE inhibitor
- Primary outcomes are biomarkers – rate of Aβ accumulation, tau spreading, MR atrophy
- Exploratory sensitive cognitive outcomes (iPAD)
- Public-private-philanthropic partnership (P4)
  - Currently have 5 interested industry partners
  - NIH grant will be submitted Dec 11th!

Encouraging history from other fields

- Cholesterol Wars in Cardiology
  - Good vs. bad cholesterol
  - Secondary prevention trials in familial hypercholesterolemia and in post-MI
  - Reduction of cholesterol estimated to have reduced cardiac morbidity and mortality by 28%
  - As in "A3" rationale, recommendations for treating cholesterol have steadily evolved to lower LDL
- Amyloid does not have to be "the" cause of AD, merely "a" critical factor that can impact the disease at the optimal time!

Thank you!

- Paul Aisen, ATRI at USC and ADCS at UCSD
- A4 Team at Eli Lilly, Avid, CogState
- Keith Johnson, Aaron Schultz, Dorene Rentz at Harvard Aging Brain Study
- Alzheimer's Association, Fidelity Biosciences, Accelerating Medicine Partnership (AMP)
- National Institute on Aging
- Fred Miller, GHR Foundation