The AT(N) Framework: Progression from Cognitively Unimpaired to Mild Cognitive Impairment

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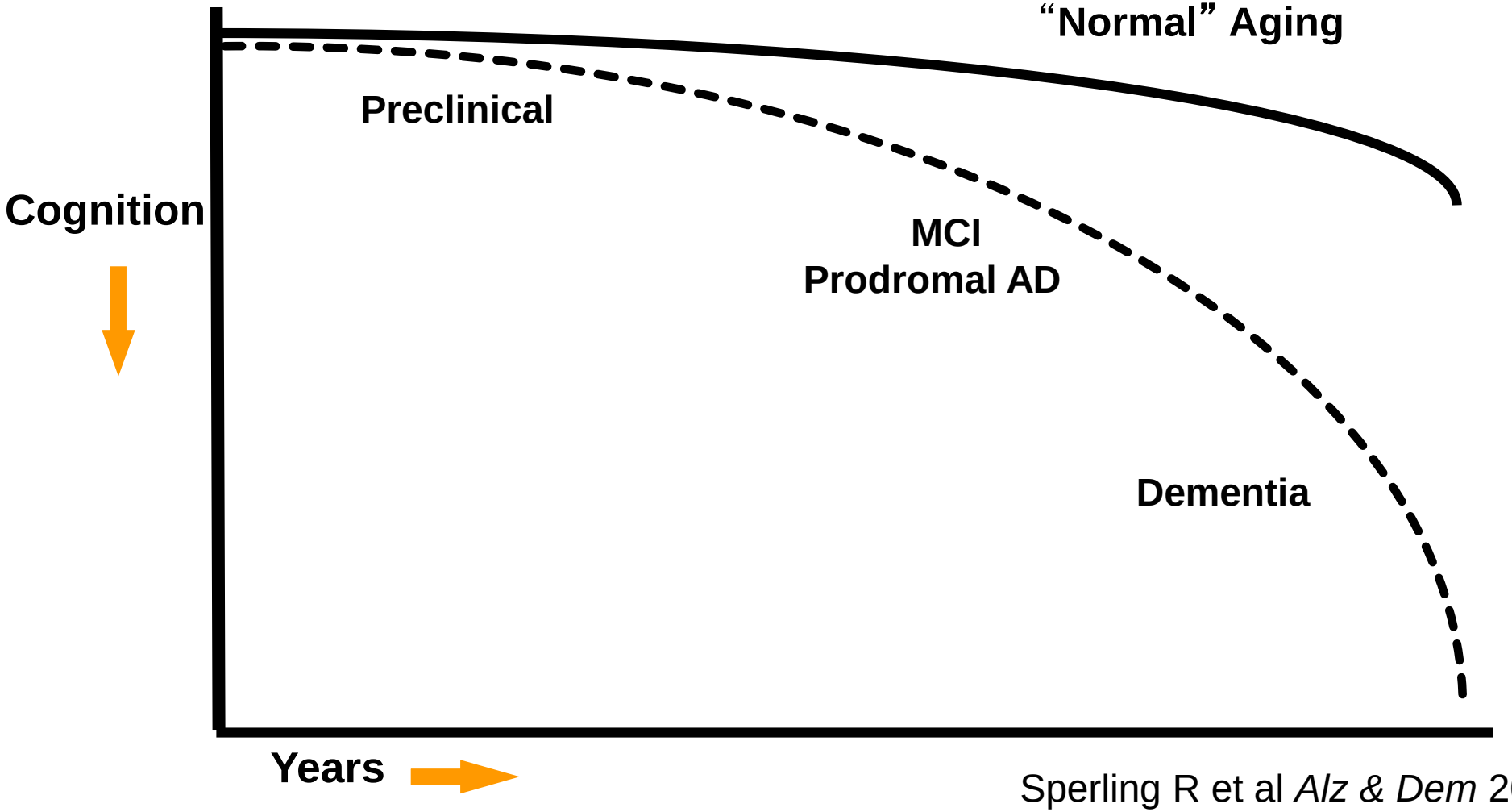
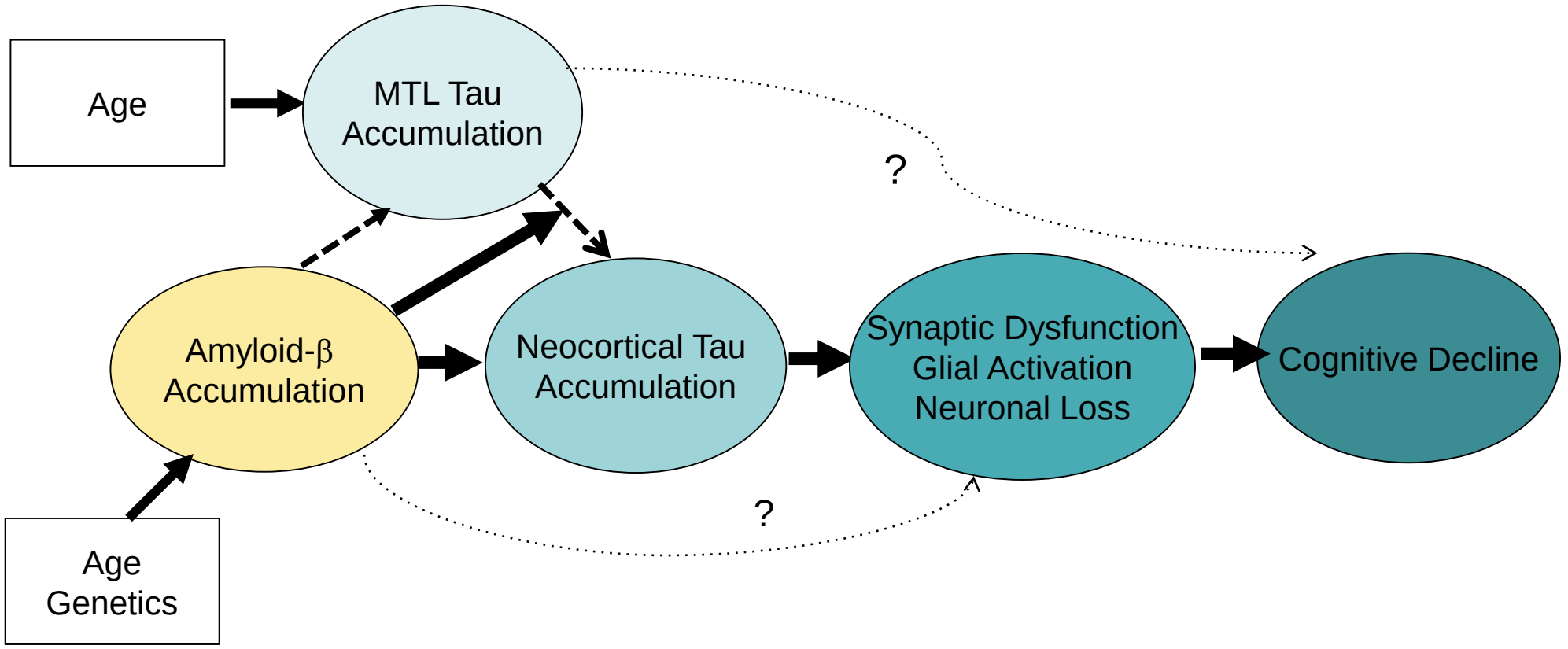
Eli Lilly, Janssen
Accelerating Medicines Partnership FNIH

The continuum of Alzheimer's disease



Sperling R et al *Alz & Dem* 2011
Jack C et al *Alz & Dem* 2018
NIA-AA Workgroup

Hypothetical Pathophysiologic Sequence in Preclinical AD

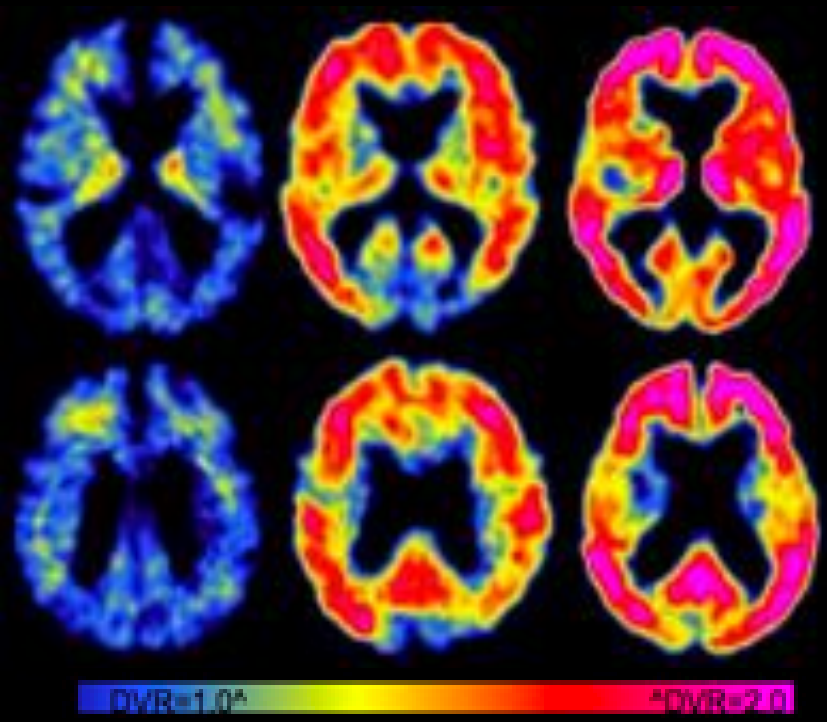


Sperling, Mormino, Johnson *Neuron* 2014

AT(N) Overview in Cognitively Unimpaired

- Evidence for “A” and especially “A” + “T” associated with cognitive decline
- Issues with dichotomizing A and T in cognitively unimpaired individuals
- Issues with (N) – heterogeneous measures of N, specificity for AD, measuring reserve vs. co-morbidities vs. AD progression
- Operationalizing criteria for next set of prevention trials

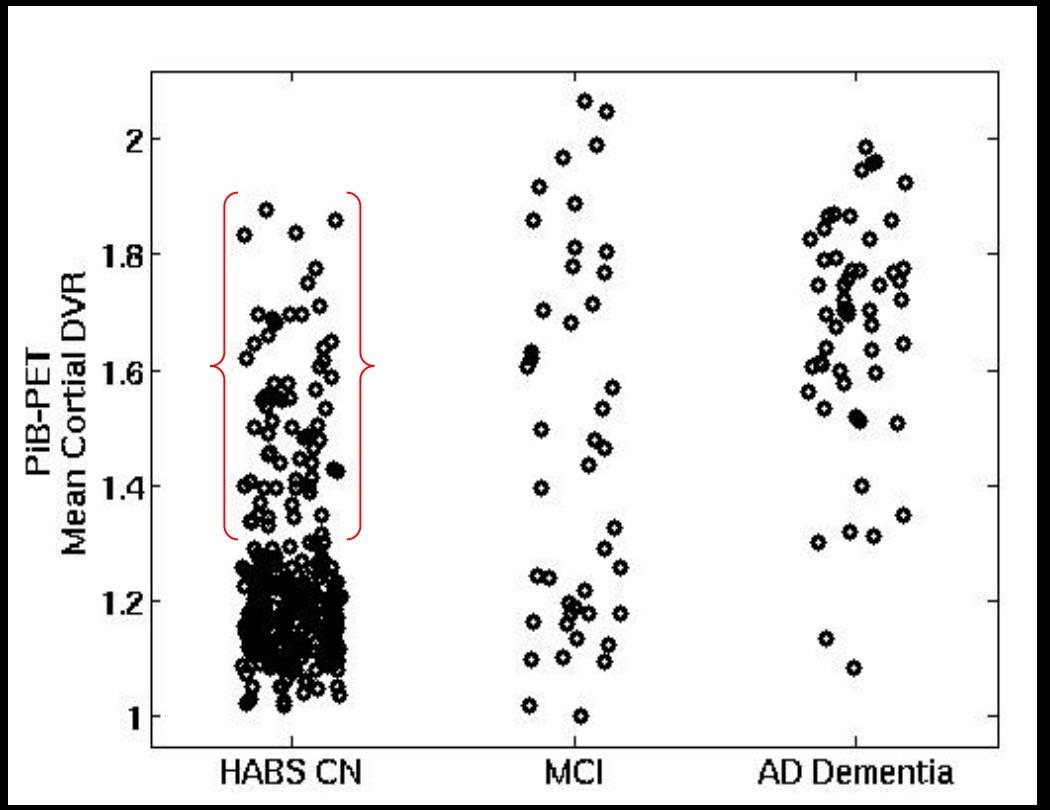
PET Amyloid Imaging Across the Spectrum of AD



CN Aβ–

CN Aβ+

AD Aβ+

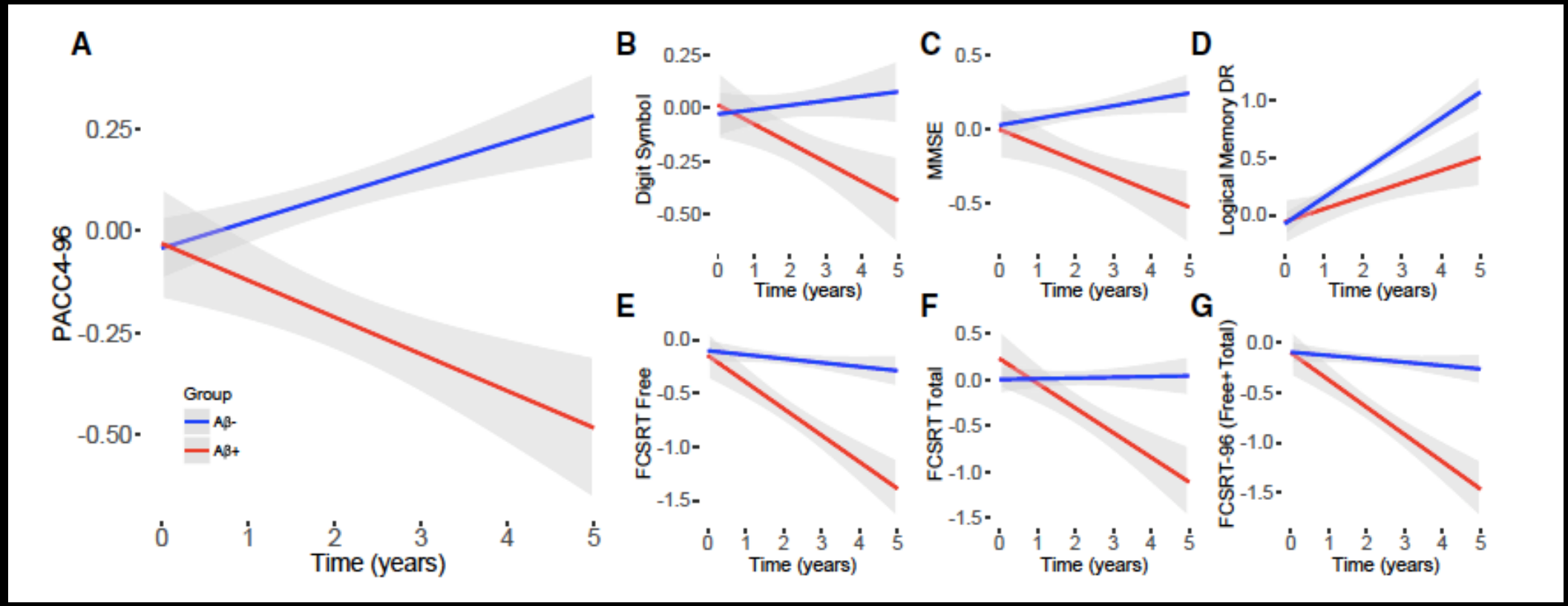


Harvard Aging Brain Sudy

Sperling, Mormino, Johnson *Neuron* 2014

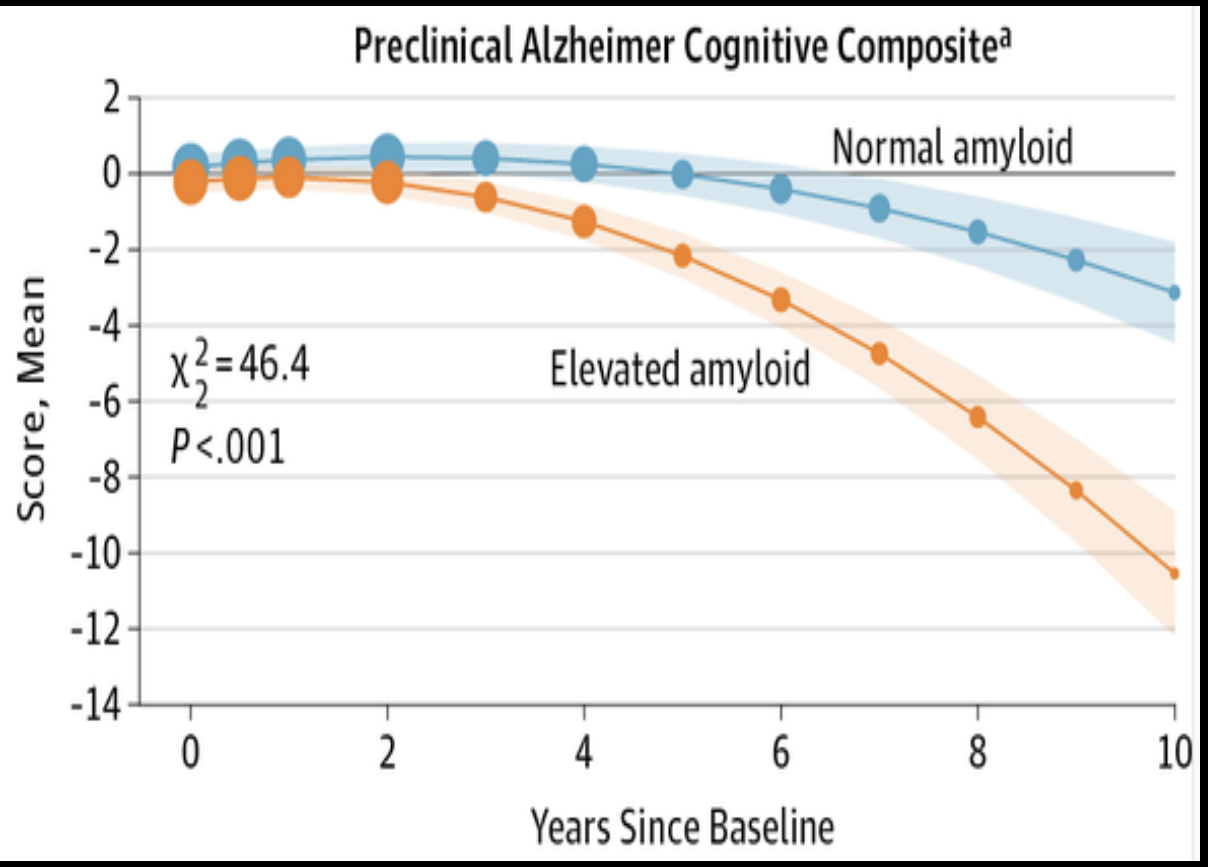
Preclinical Alzheimer Cognitive Composite

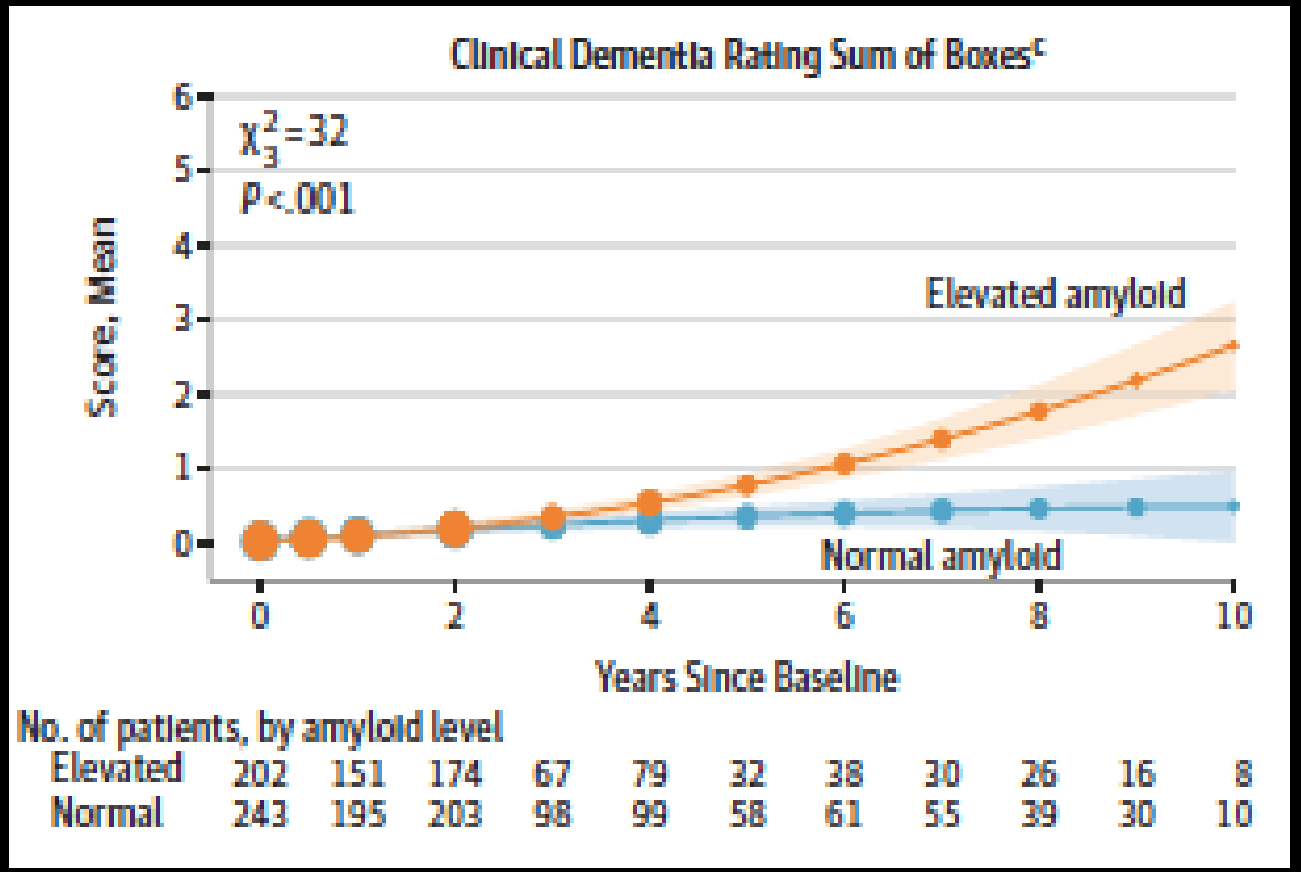
Harvard Aging Brain Study (n=277)



Mormino E et al. *Alz & Dementia* 2017

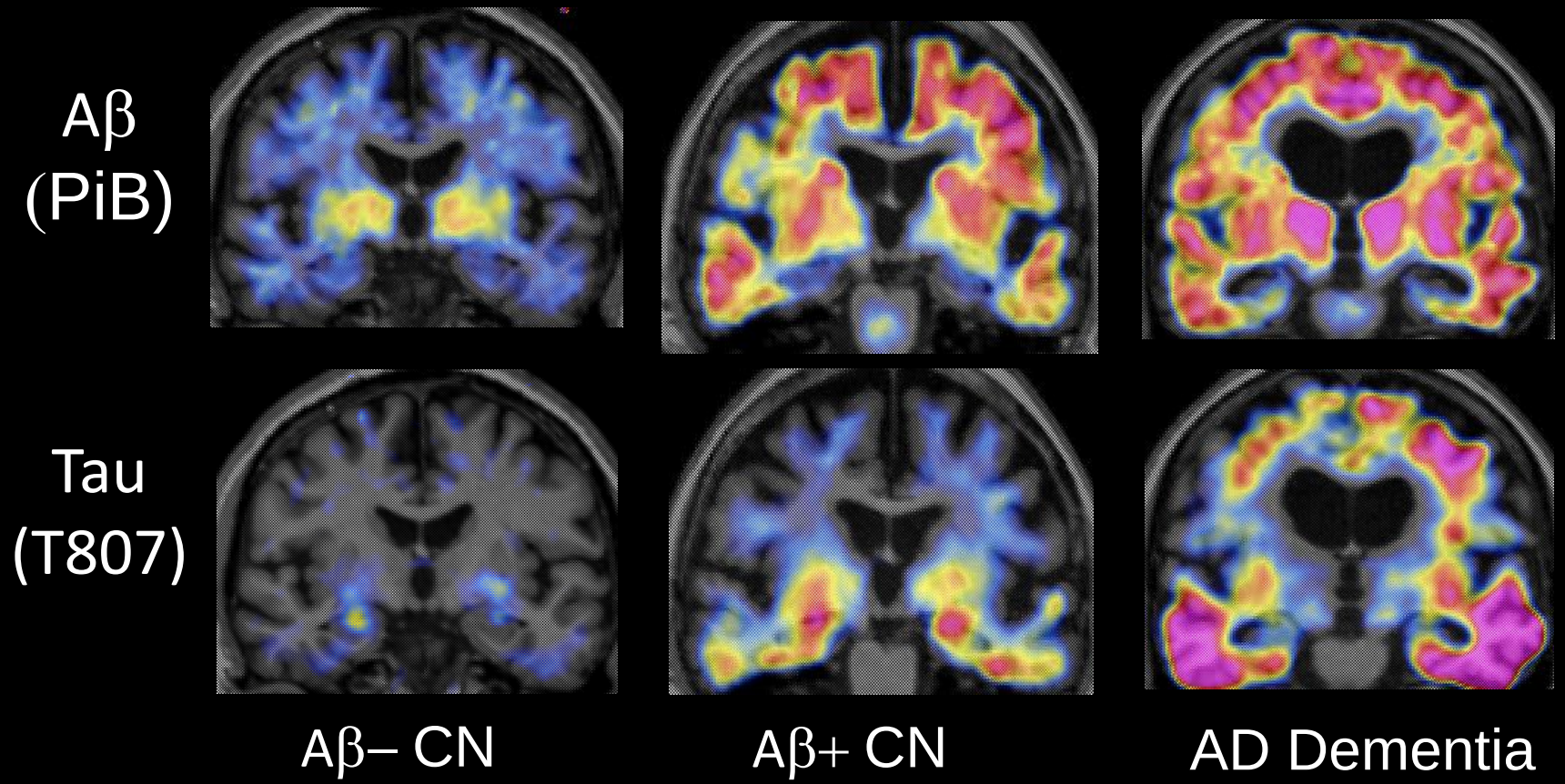
Cognitive Decline and Clinical Progression in A+ ADNI Normals





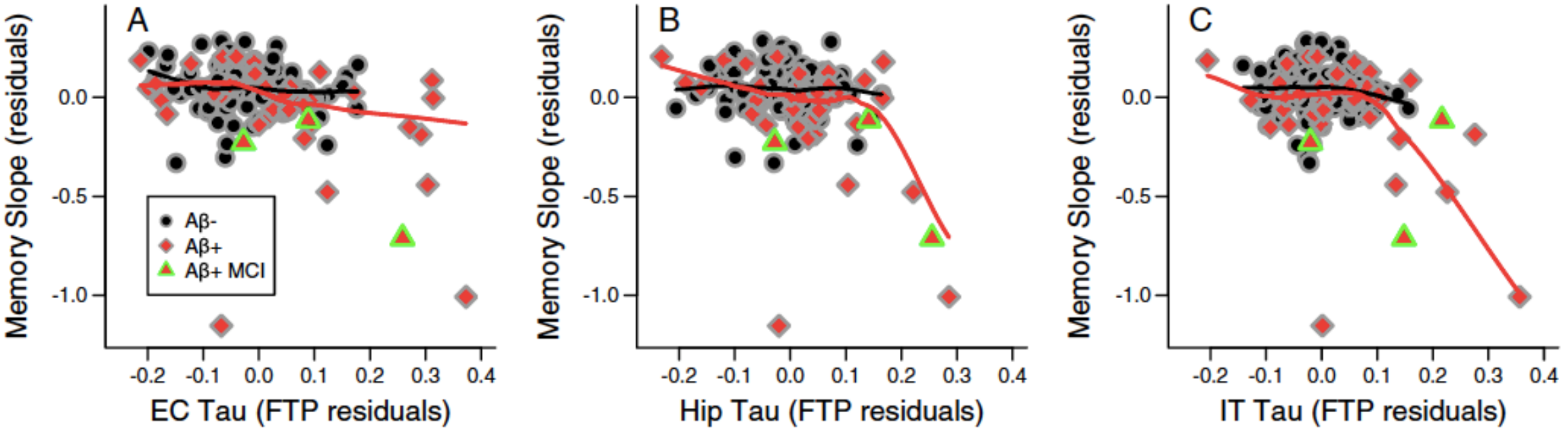
Donohue M., Sperling R et al. *JAMA* 2017

Amyloid and Tau PET Imaging



Sperling, Mormino, Johnson *Neuron* 2014

Imminent Prospective Longitudinal Memory Decline related to Tau in High Amyloid Normals

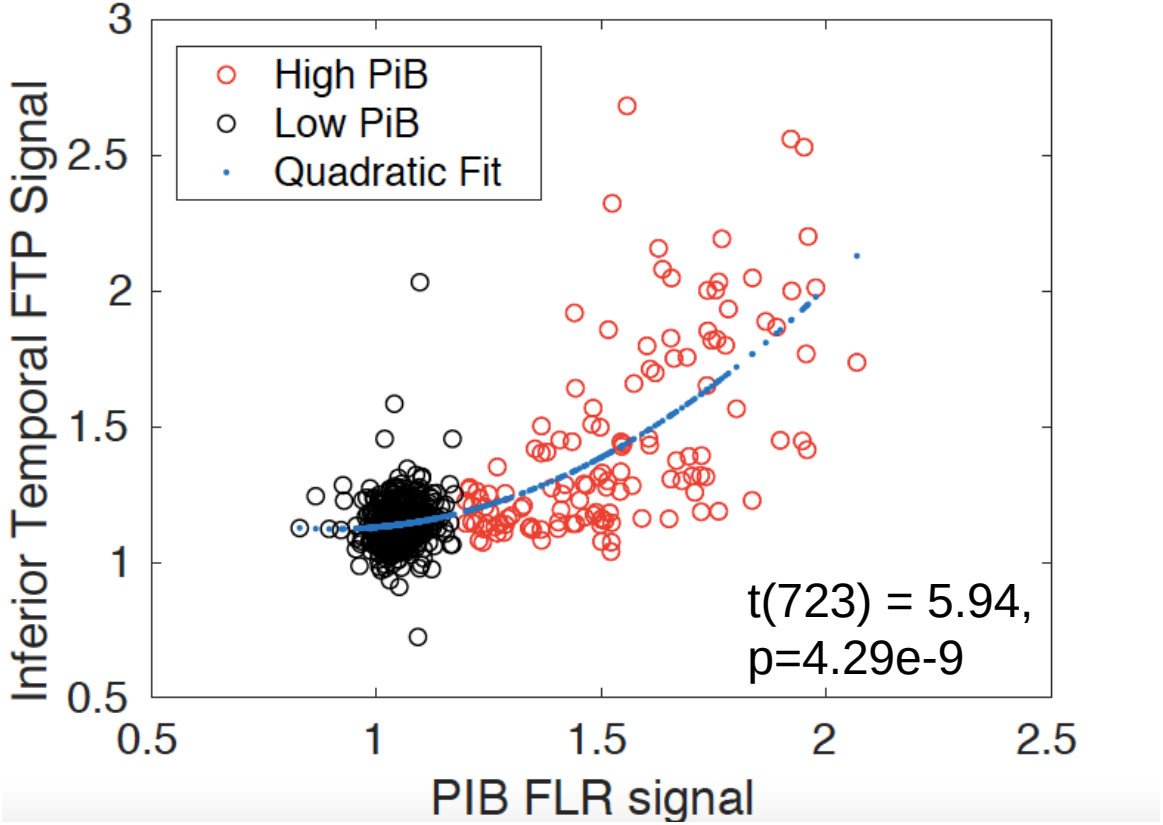


Harvard Aging Brain Study n=140
Mean prospective follow-up post-tau PET 2.01+/- .77 years

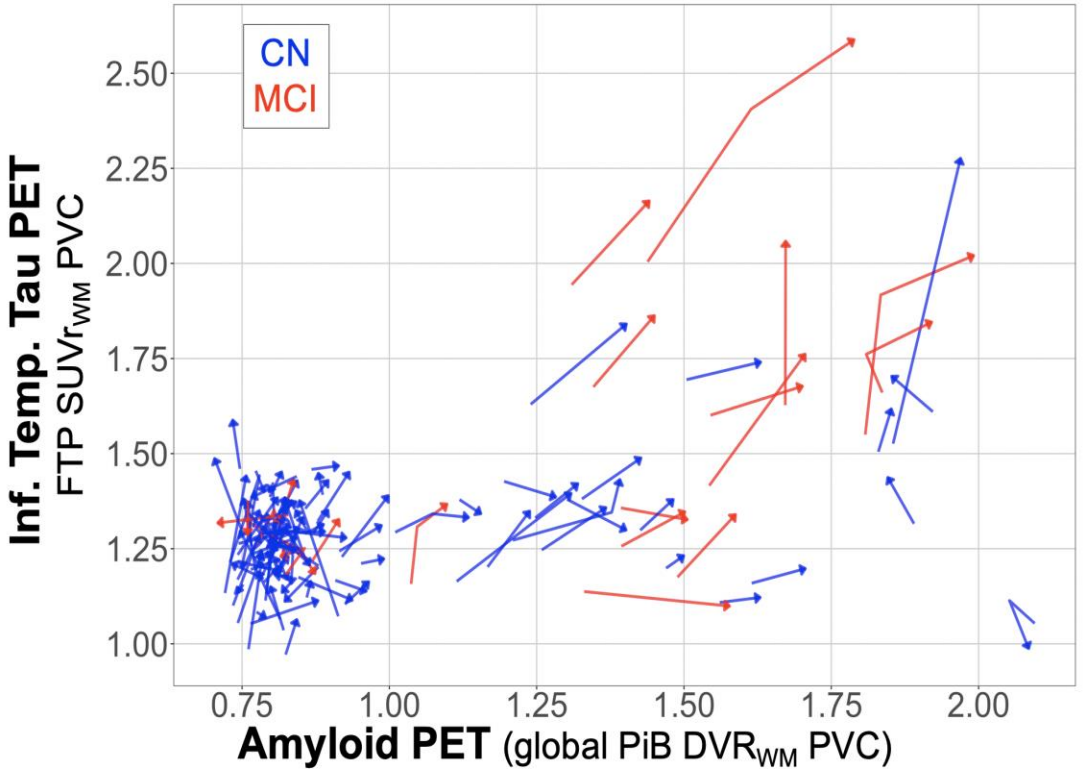
Sperling et al *Annals of Neurology* 2019

Is there a critical level of Amyloidosis associated with rapid Tau accumulation (“ca-tau-strophe”)?

Cross-Sectional HABS data



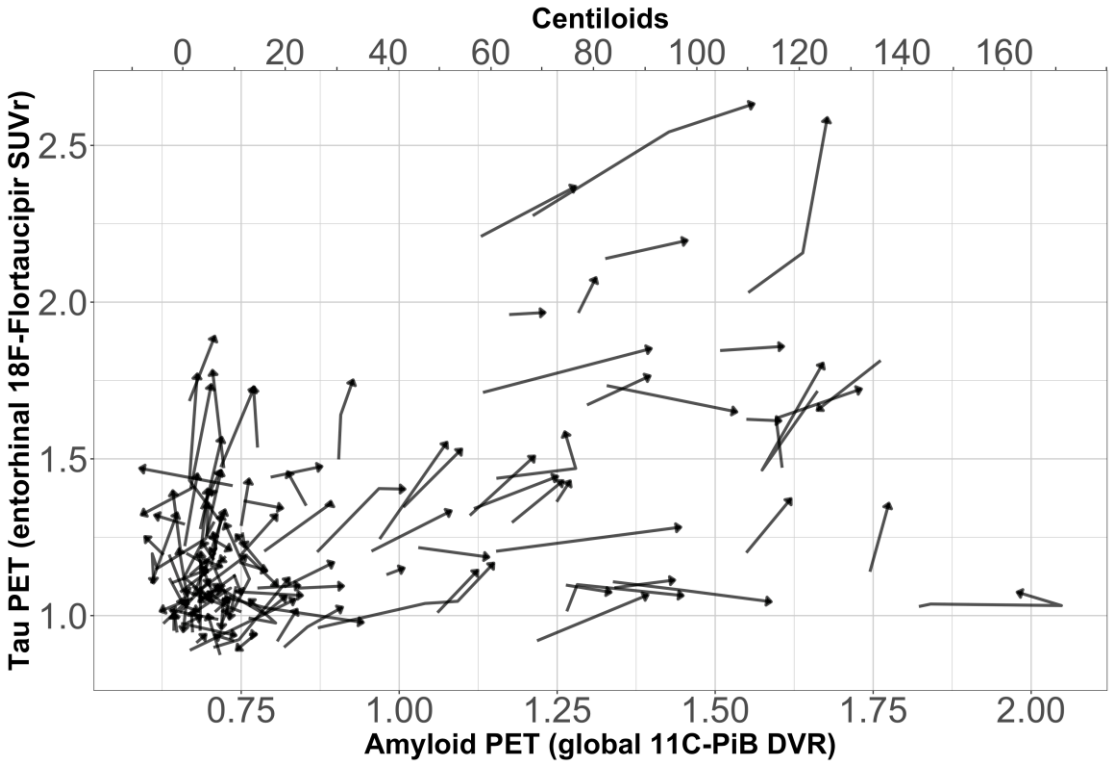
Longitudinal HABS data



Keith Johnson - Harvard Aging Brain Study

Does change and location of ”T” matter in early stages?

Entorhinal (allocortex)



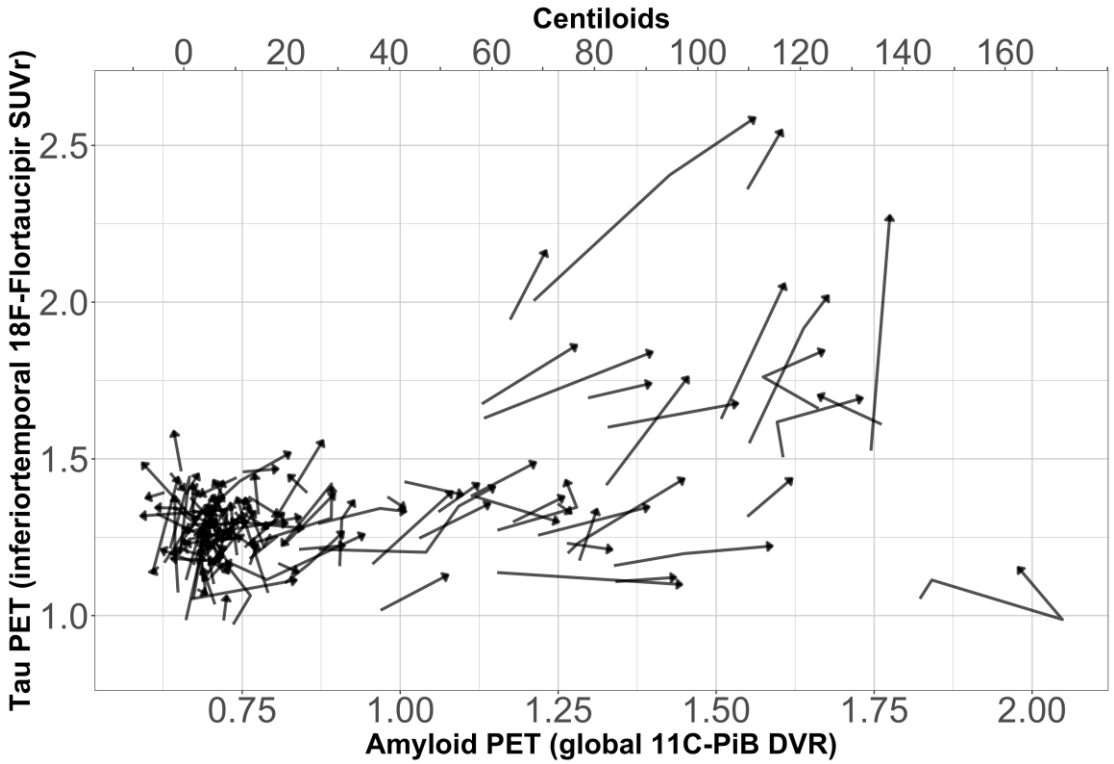
Low PiB | High PiB

Tau change, mean (SD) SUVr/yr

0.04 (0.05) | 0.06 (0.06)

(All p<0.001)

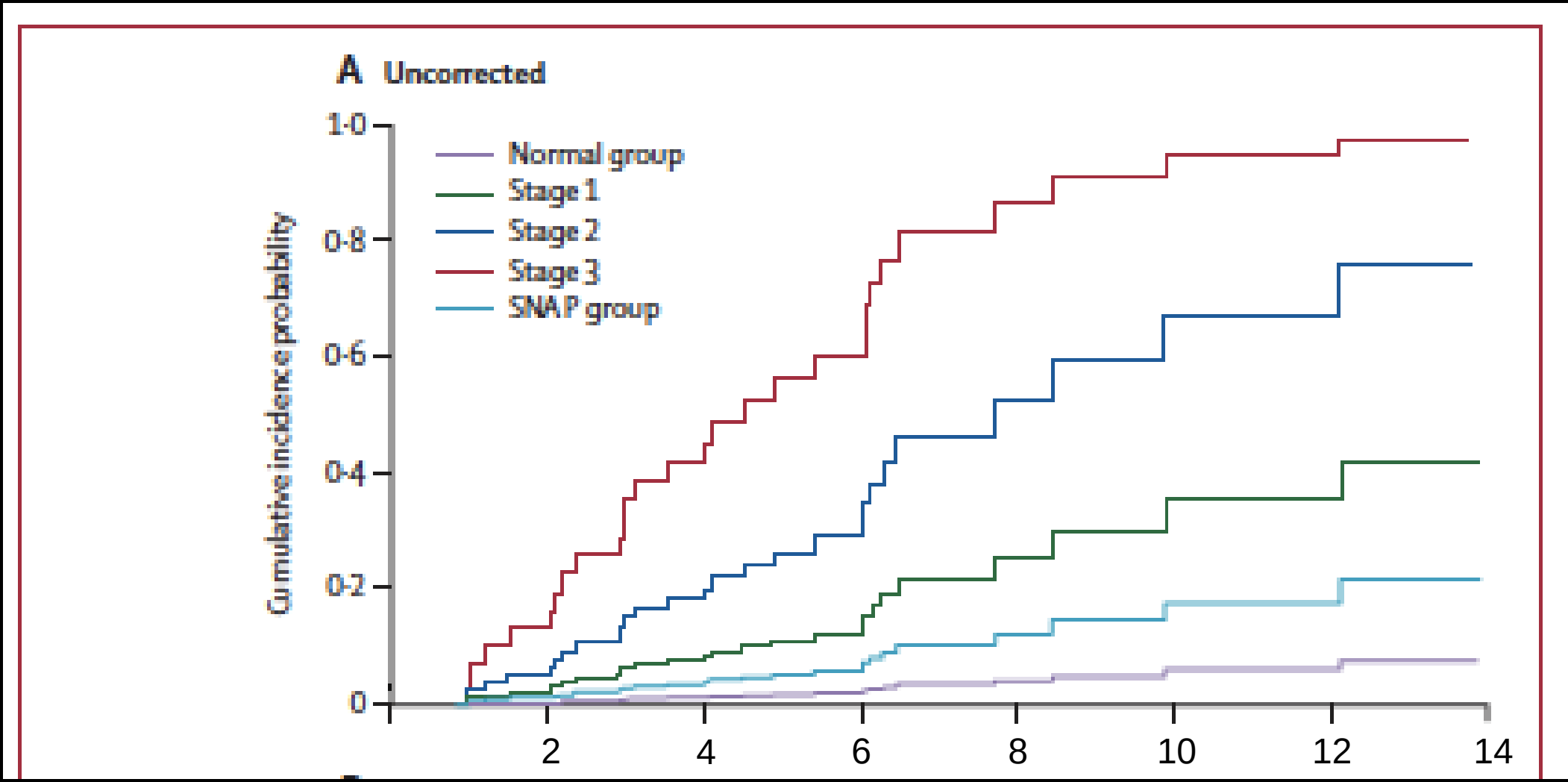
Inferior temporal (neocortex)



Low PiB | High PiB

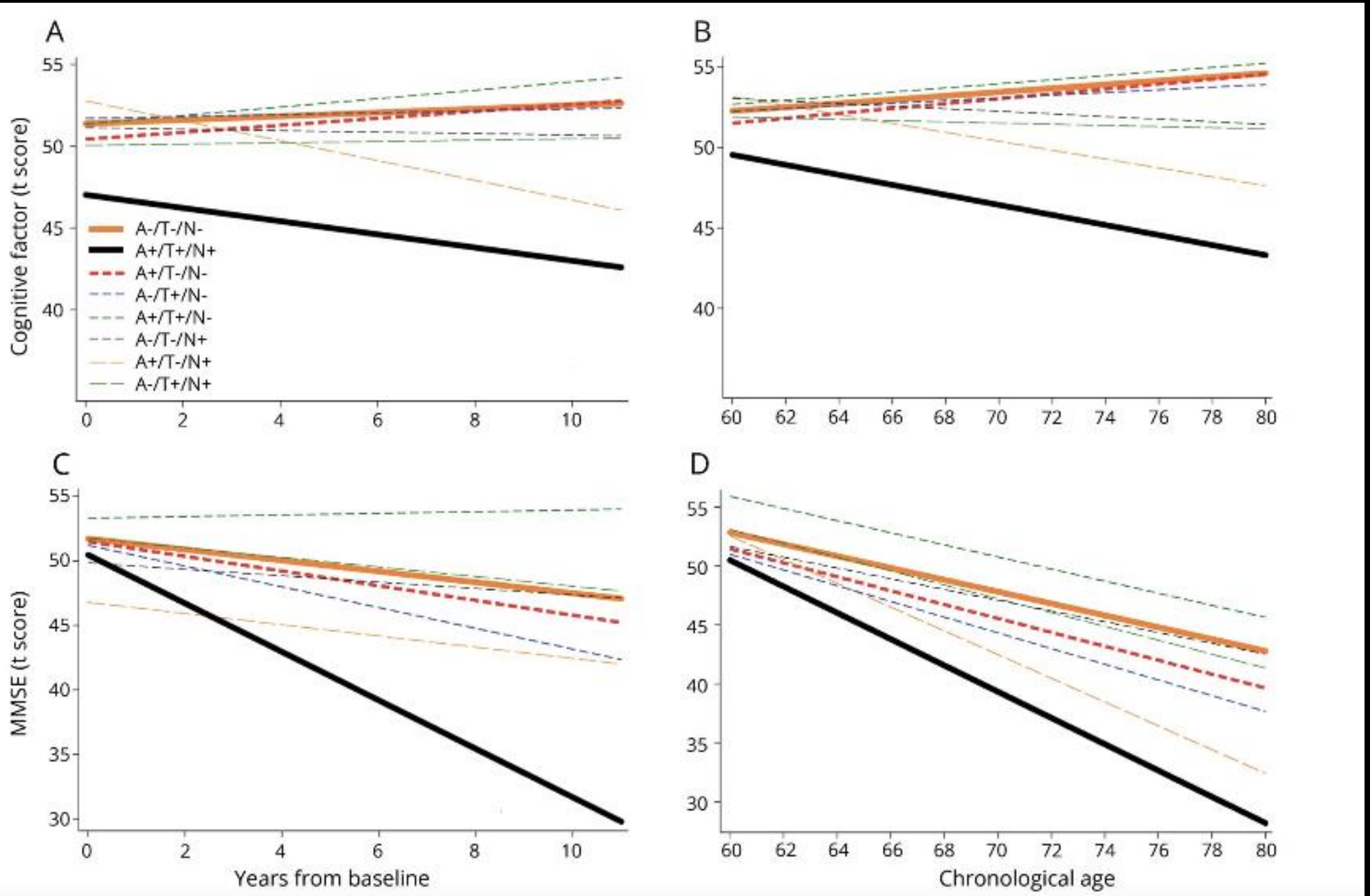
0.02 (0.04) | 0.06 (0.06)

Clinical Progression related to Stages of Preclinical AD



Vos et al *Lancet Neurology* 2013

Decline related to ATN (using CSF) in Cognitively Unimpaired

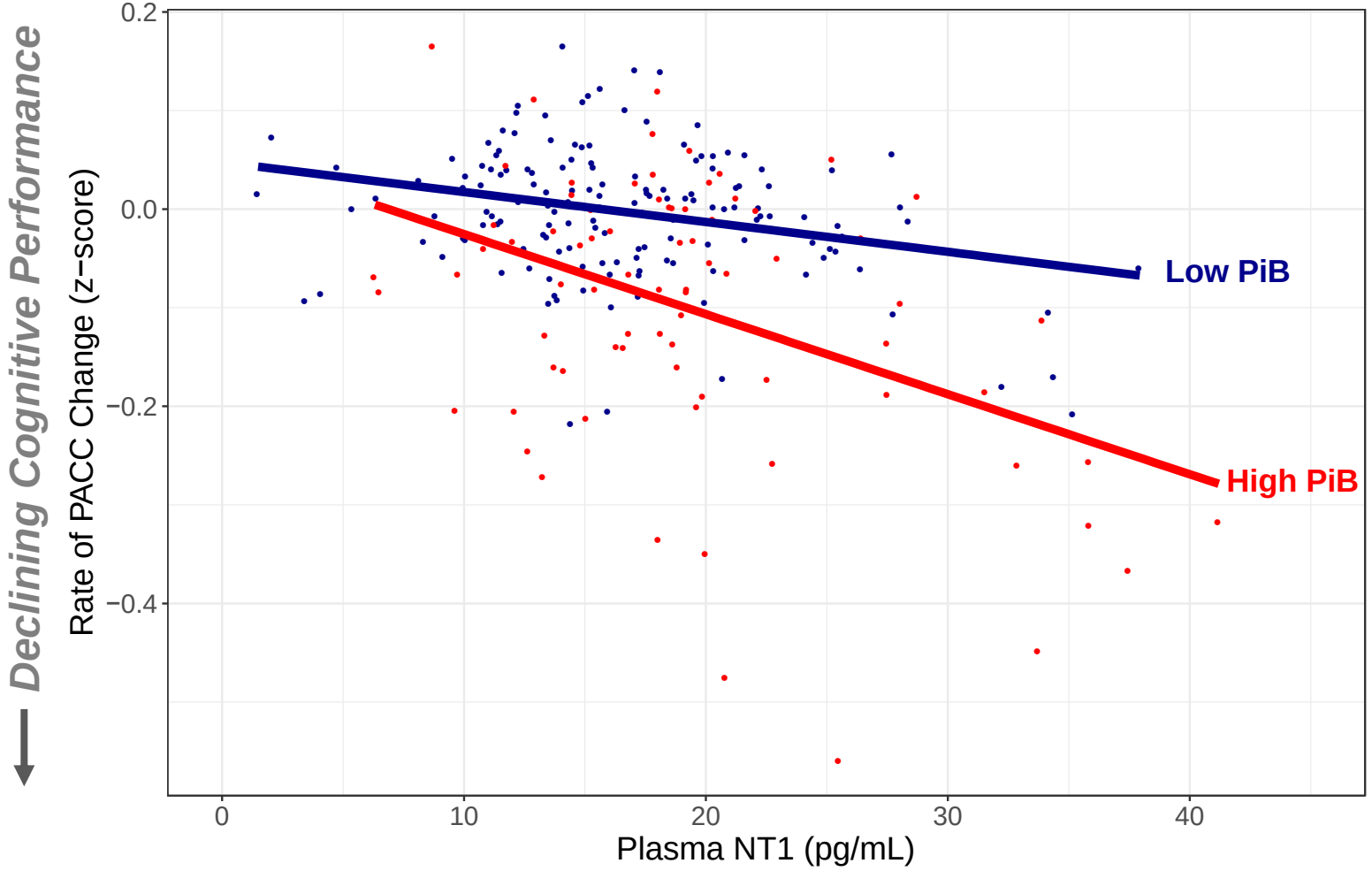


Soldan A et al
Neurology
2019

Why is the “N” in parentheses - AT(N)

- Although neurodegeneration is commonly seen in AD, not required for the neuropath diagnosis
- Multiple measures of N – ranging from hippocampal volume, FDG-PET, neurofilament light (NfL), total tau
- N not specific to AD - measures may reflect co-pathologies: TDP-43, vascular, FTLD, injury (NfL up in head trauma)
- N measures very age-related (NfL performs much better in autosomal AD than in sporadic AD)
- N measures may reflect neurodevelopment processes and brain reserve – particularly hippocampal volume and FDG

"N" vs. "T"- Greater baseline plasma levels of N-terminus tau (NT-1) are predictive of greater cognitive decline, alone and interactively with Aβ



All Participants:
$t(230) = -5.04, p = 1.93 \times 10^{-7}$

High PiB: t(74) = -3.09, p = 0.003, cohen's d = 0.72

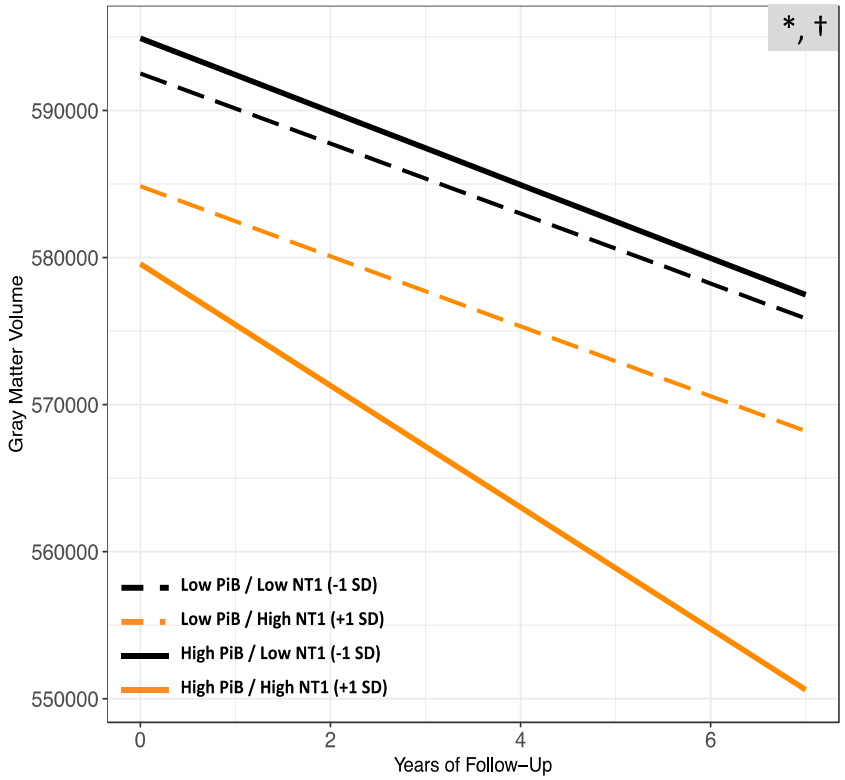
Low PiB: t(151) = -3.00, p = 0.003, cohen's d = 0.49

N = 236, 5.04 +/-0.99y

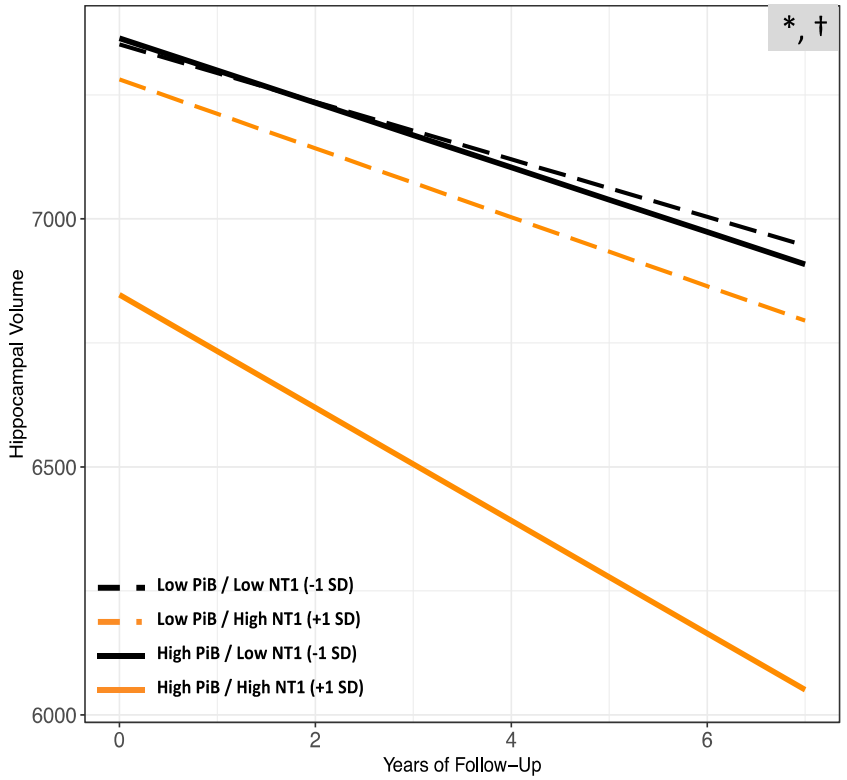
Chhatwal J et al. HAI 2020

*Greater baseline plasma levels of NT1 are associated with greater Neurodegeneration (**longitudinal MRI**)*

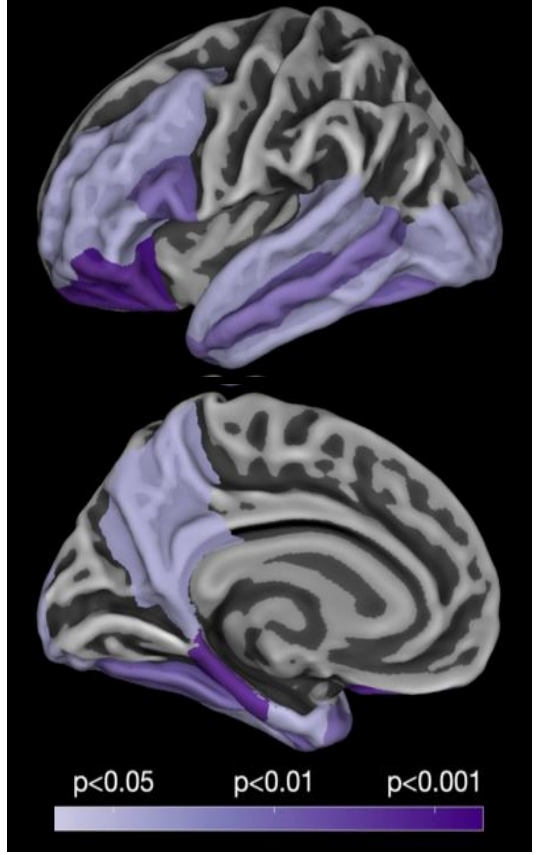
Longitudinal Gray Matter Volume



Longitudinal Hippocampal Volume



*PiB*NT1 Interactions Longitudinal Cortical Thickness*



*, † corresponds to p ≤ 0.05, respectively for the main effect of NT1 and the interaction of NT1*PiB, respectively

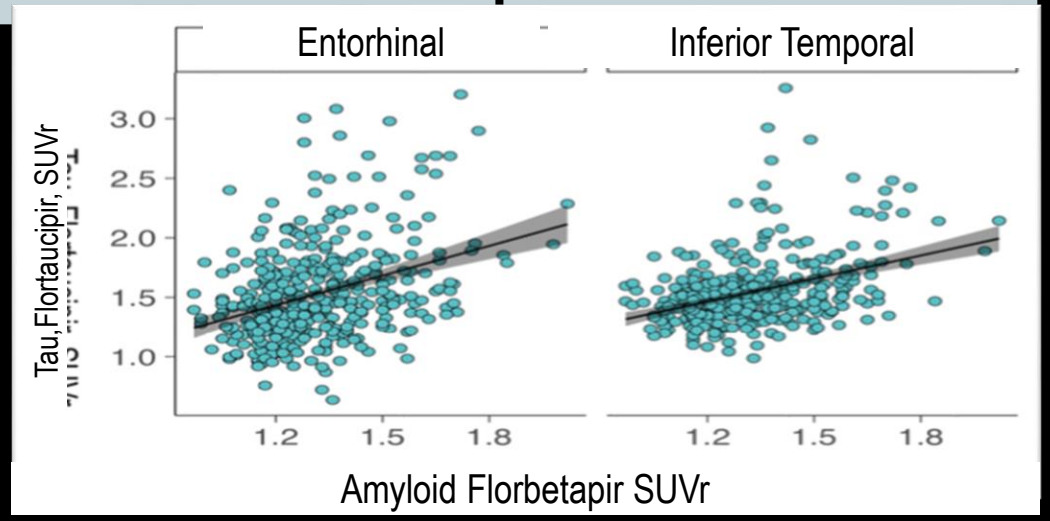
Chhatwal J et al HAI 2020

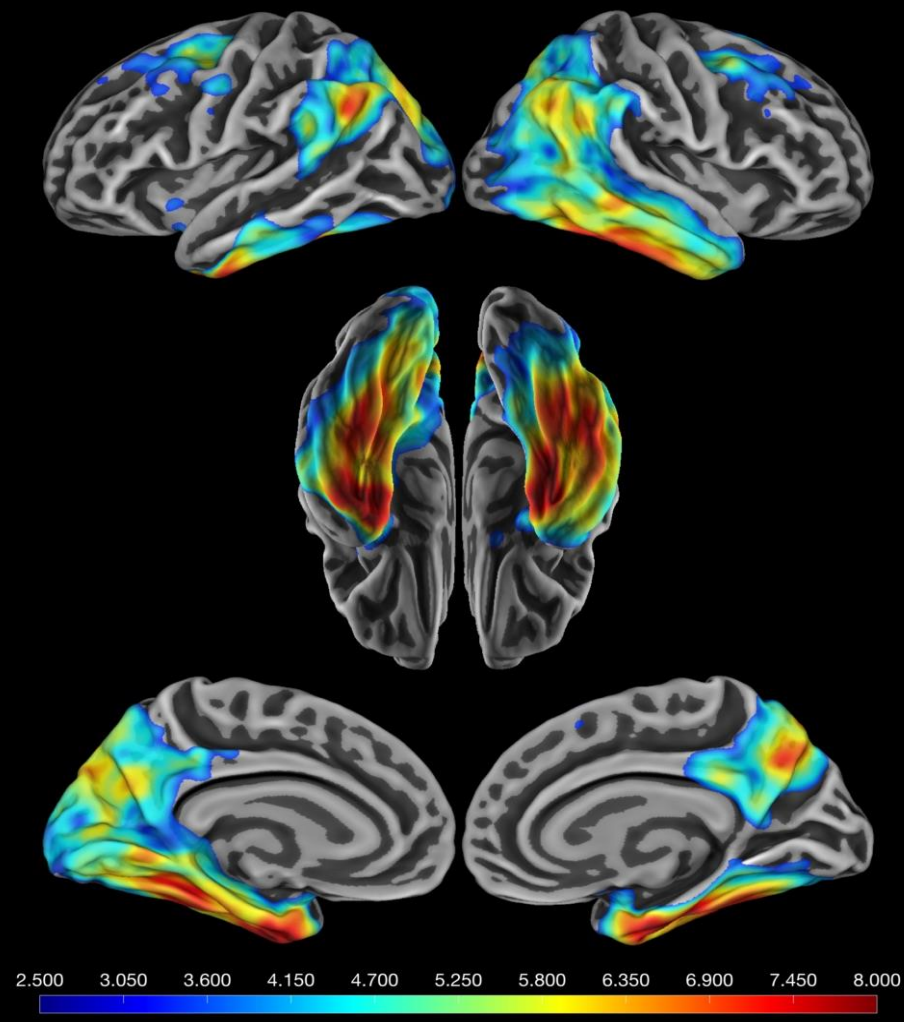
Anti-Amyloid Treatment of Asymptomatic Alzheimer's disease (A4) Study

- Secondary prevention trial in clinically normal older individuals (age 65-85y) elevated Aβ screening PET
- Phase 3 randomized, double-blind, placebo-controlled trial of solanezumab vs. placebo – 240 weeks (4.5 years)
- 67 sites in U.S., Canada, Australia, Japan
- Enrollment goal N=1150; 575 per treatment arm, stratified by APOE
- LEARN companion study of Aβ–
- Amyloid Disclosure Ethics Substudy

A4 Study Baseline Tau PET

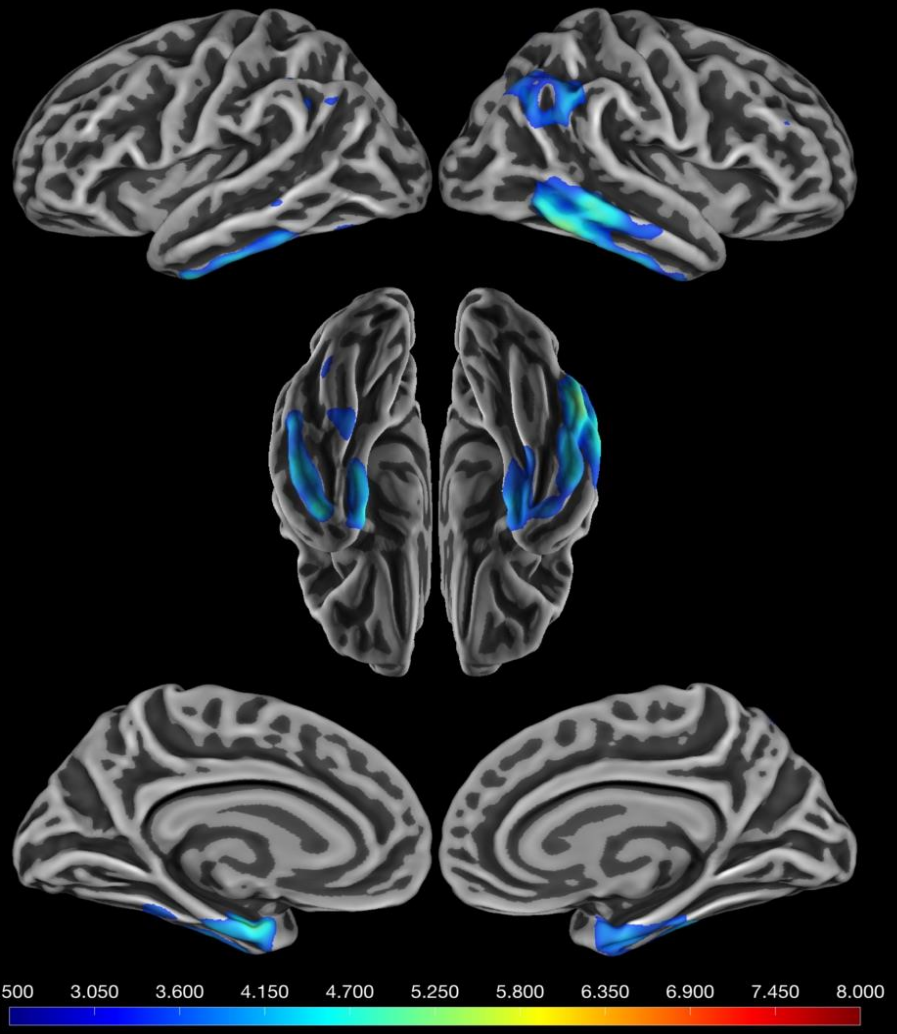
Demographics	Total (N = 390)
Age, y	72.1 (4.8)* Range: [65.0, 85.5)
Sex (n females. %)	224 F (57.4%)
Education, y	16.16 (2.8) Range: [8, 30]
PACC Score	-0.60 (2.76) Range: [-11.11, 6.67]
Amyloid PET Global Burden, SUVr	1.317 (0.18) Range: [.97, 2.02]
Tau PET Entorhinal (EC), SUVr	1.531 (0.41) Range: [0.63, 3.20]
Tau PET Inferior Temporal (IT), SUVr	1.540 (0.29) Range: [0.99, 3.26]



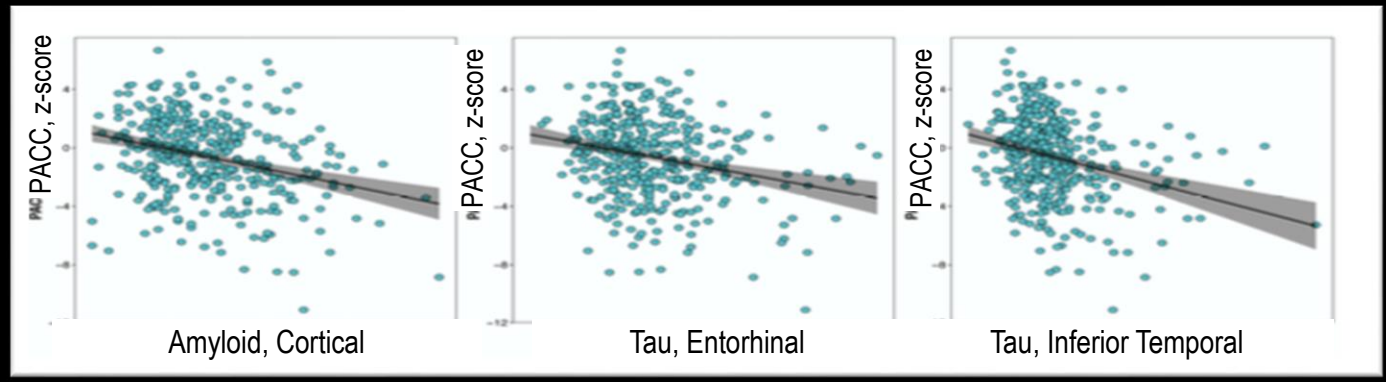


Johnson K et al AAIC 2018

Baseline A4 Tau PET and Cognitive Performance



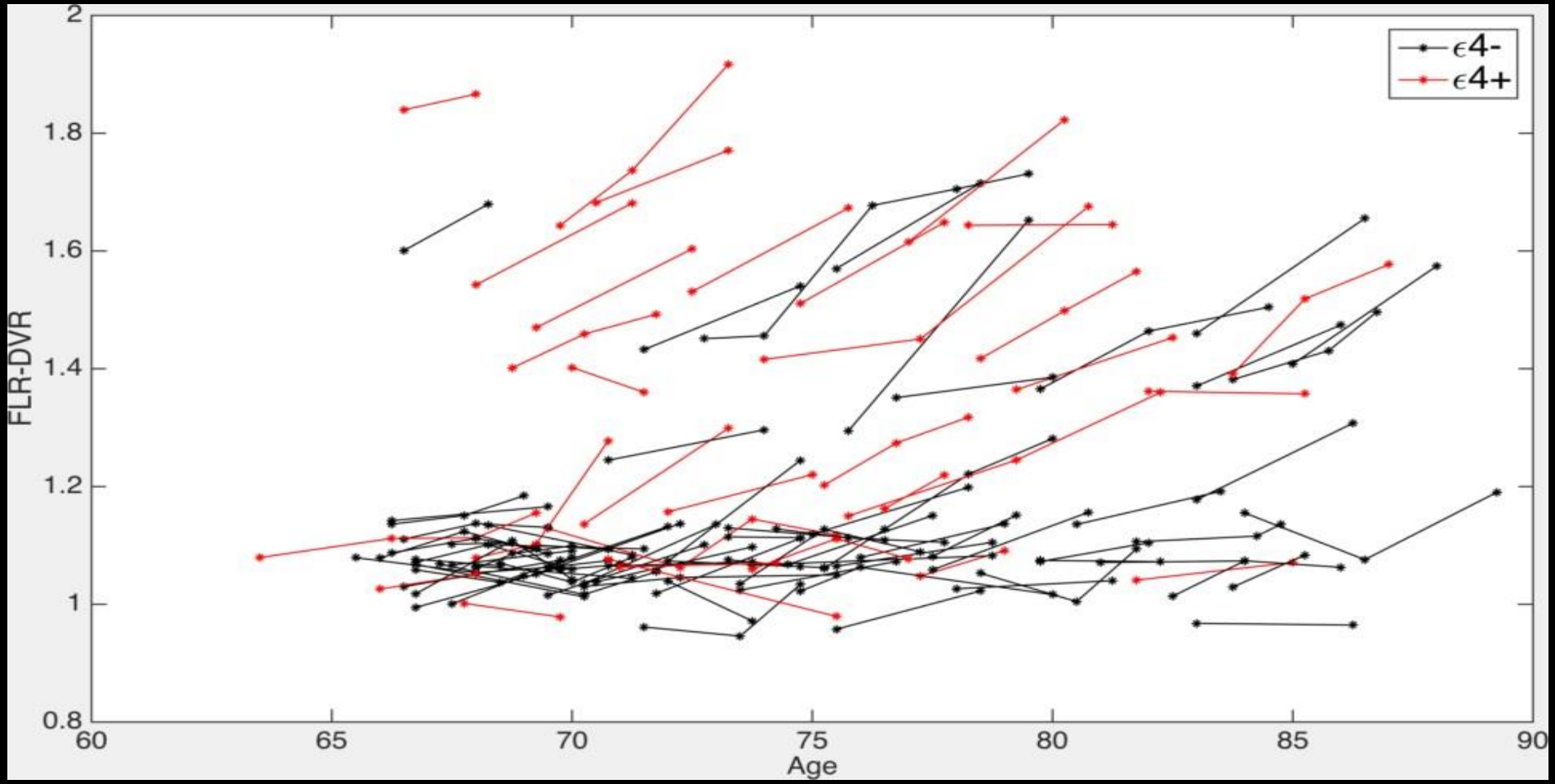
		Amyloid	Tau
PACC	EC	β = -0.18 [-0.27, -0.09] p<0.001	β = -0.17 [-0.26, -0.08] p<0.001
	IT	β = -0.17 [-0.26, -0.07] p<0.001	β = -0.19 [-0.28, -0.09] p<0.001



Johnson K et al AAIC 2018

Longitudinal Amyloid-β Accumulation in Clinically Normal Elders

Harvard Aging Brain Study

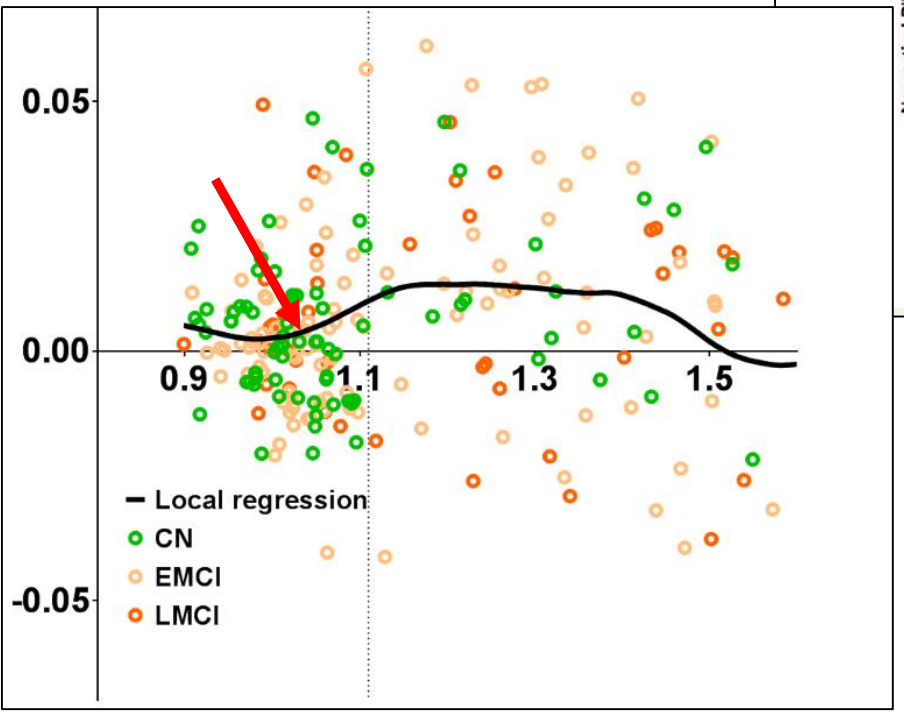


Aaron Schultz and Keith Johnson HAI 2015

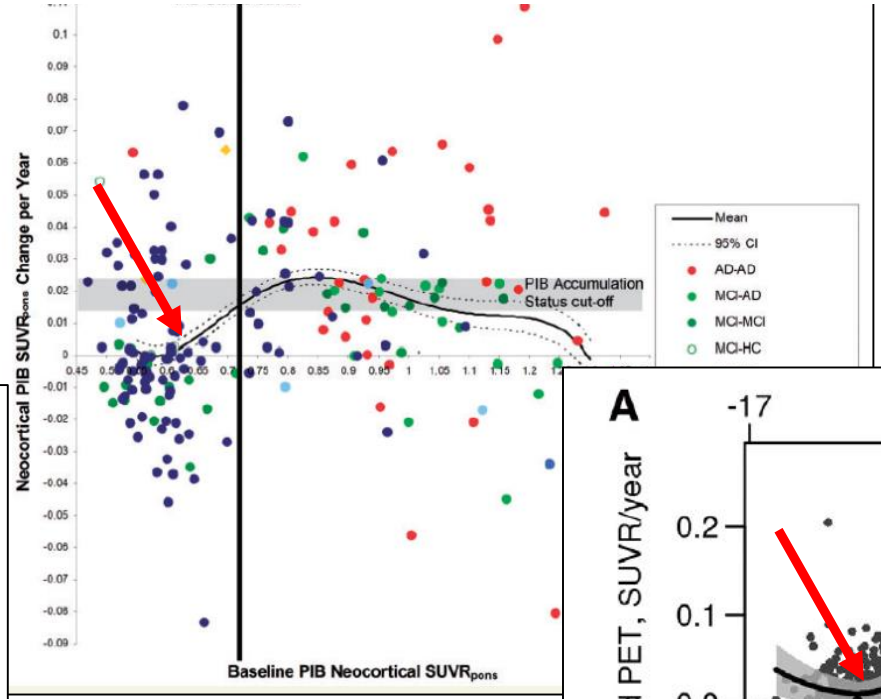
Optimal Time to Intervene to Prevent Aβ Accumulation

Targeting Interval of Rapid Acceleration

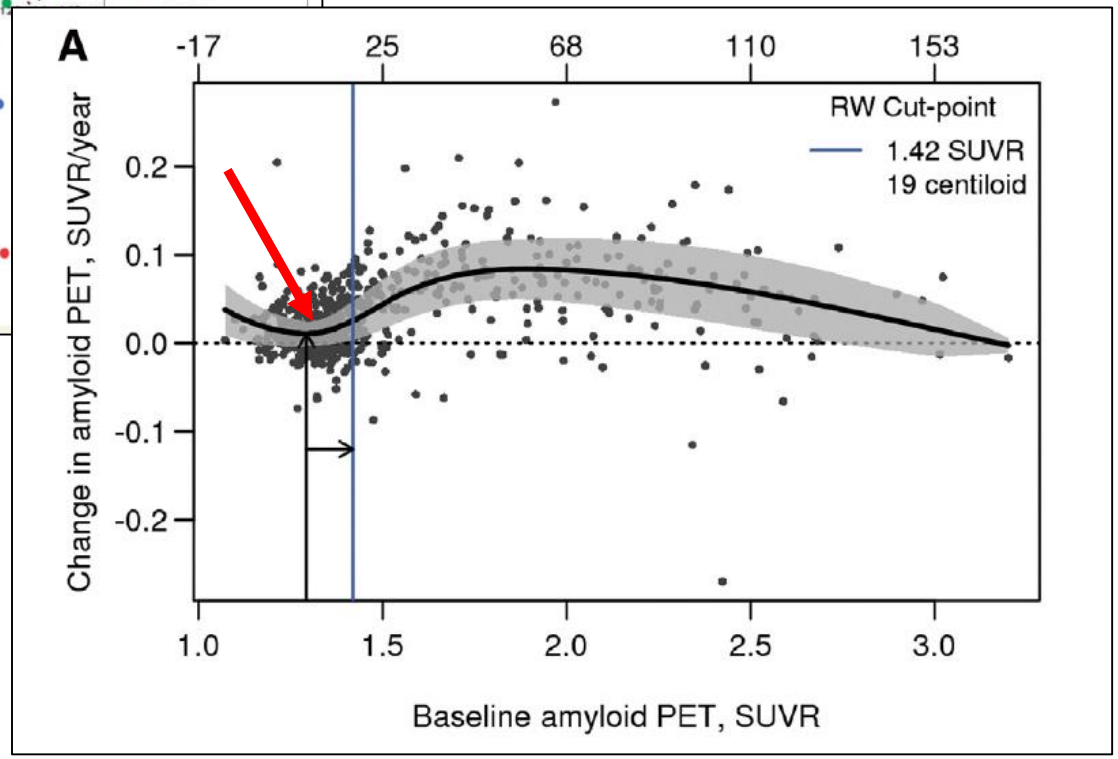
A3: FBP 1.07-1.17
A45: FBP ≥1.17



ADNI data
Courtesy of John Sims



AIBL data
Villain et al *Brain* 2012

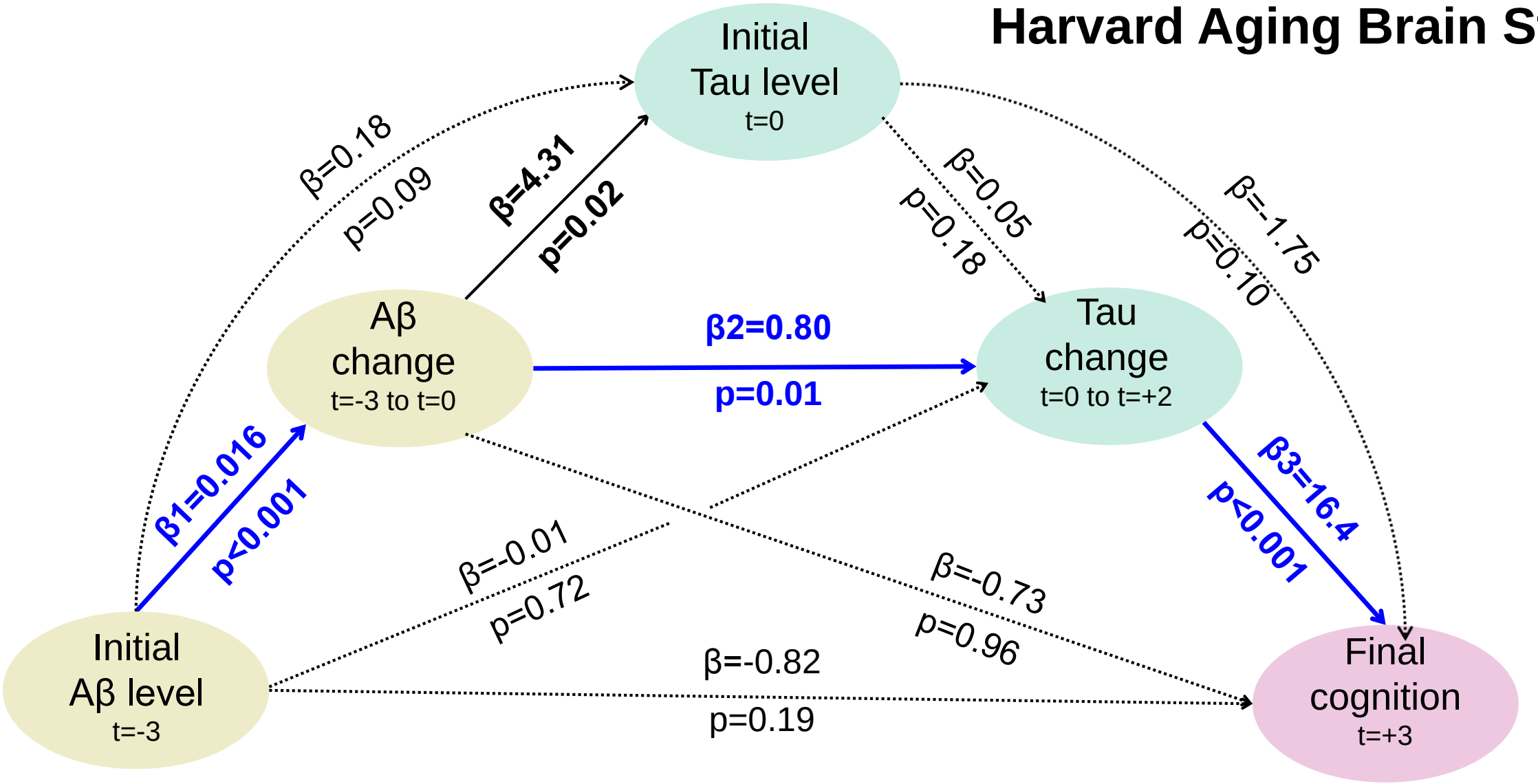


Mayo Clinic data
Jack C et al *Alz & Dem* 2016

Serial mediation model from initial Aβ to final cognition:

Indirect effect via Aβ change and Tau change

Harvard Aging Brain Study

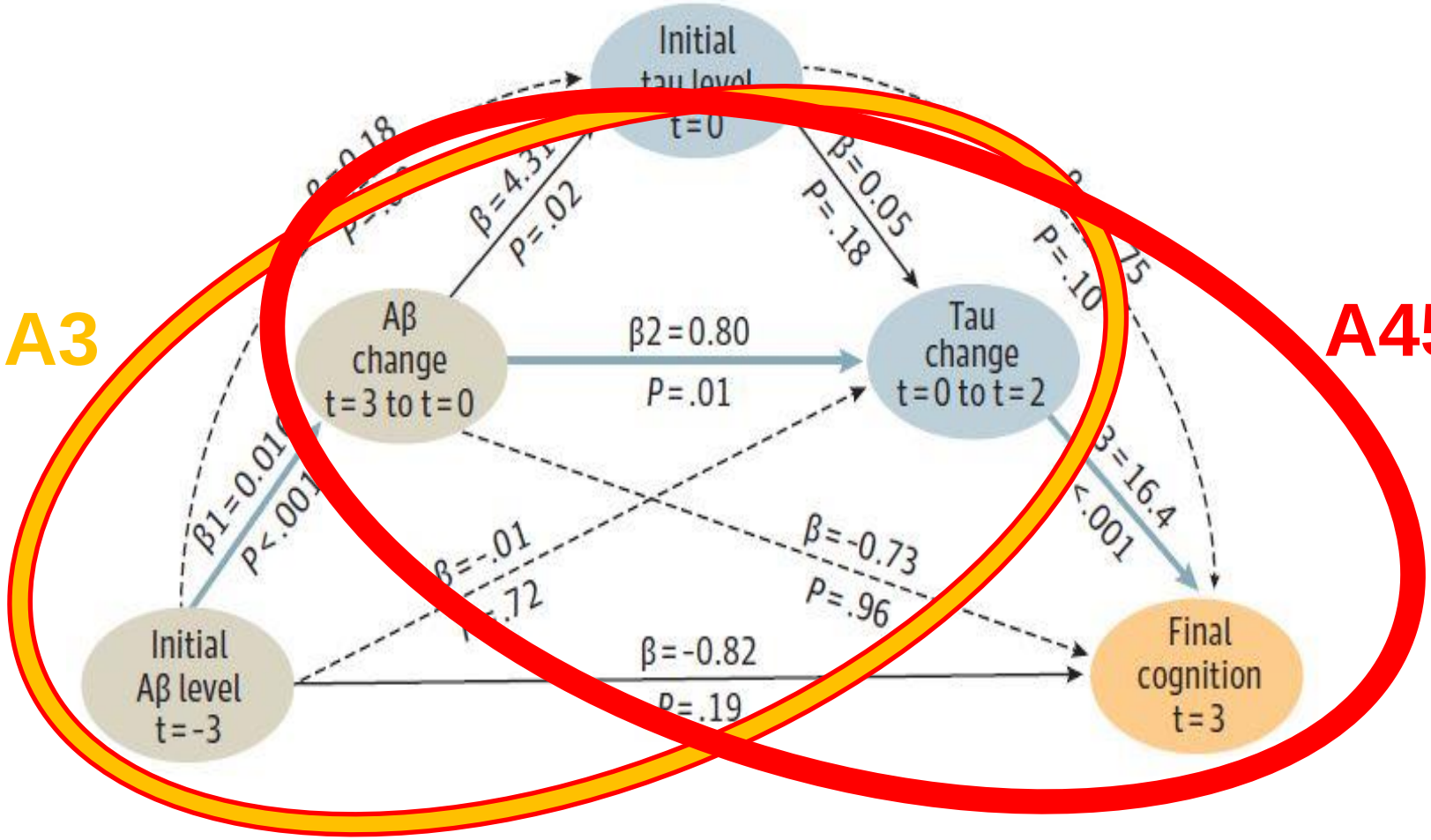


Hanseeuw B et al *JAMA Neurology* 2019

Targeted dosing regiment of anti-Aβ antibody to prevent Tau spreading and cognitive decline – AHEAD Study

A3

Amyloid Intermediate



A45

High Amyloid

Differential dosing of BAN2401 as appropriate for initial amyloid level

AT(N) Summary

- Accumulating and consistent evidence that high A associated with increased risk of cognitive decline
- High levels of both A and T required for rapid progression
- (N) not specific to AD – may reflect co-pathologies as well as AD neurodegeneration (and perhaps reserve or neurodevelopmental factors) but may be marker of risk for rapid decline
- No biological dichotomous cut point on any of these (ATN) and threshold will depend on question being asked

Acknowledgments

- Keith Johnson, Dorene Rentz, Beth Mormino, Rebecca Amariglio, Kate Papp, Jas Chhatwal, Aaron Schultz, Dennis Selkoe- Harvard Aging Brain Study
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- A4/LEARN site personnel
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