The NIA-AA Research Framework: Rationale for a new point of view

Reisa Sperling, M.D.
Center for Alzheimer Research and Treatment
Brigham and Women's Hospital
Massachusetts General Hospital
Harvard Medical School

Disclosures and Funding

Consultant to:

AC Immune, Biogen, Eisai, Merck, Roche, Takeda

Research funding from:

National Institute on Aging:

P01AG036694; U24AG057437; P50AG005134

K24AG035007; U19AG010483; R01AG053798

Alzheimer's Association

Fidelity Biosciences, GHR Foundation

Eli Lilly, Janssen

Accelerating Medicines Partnership FNIH

ELSEVIER

CrossMark

Alzheimer's & Dementia 14 (2018) 535-562

Alzheimer's & Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

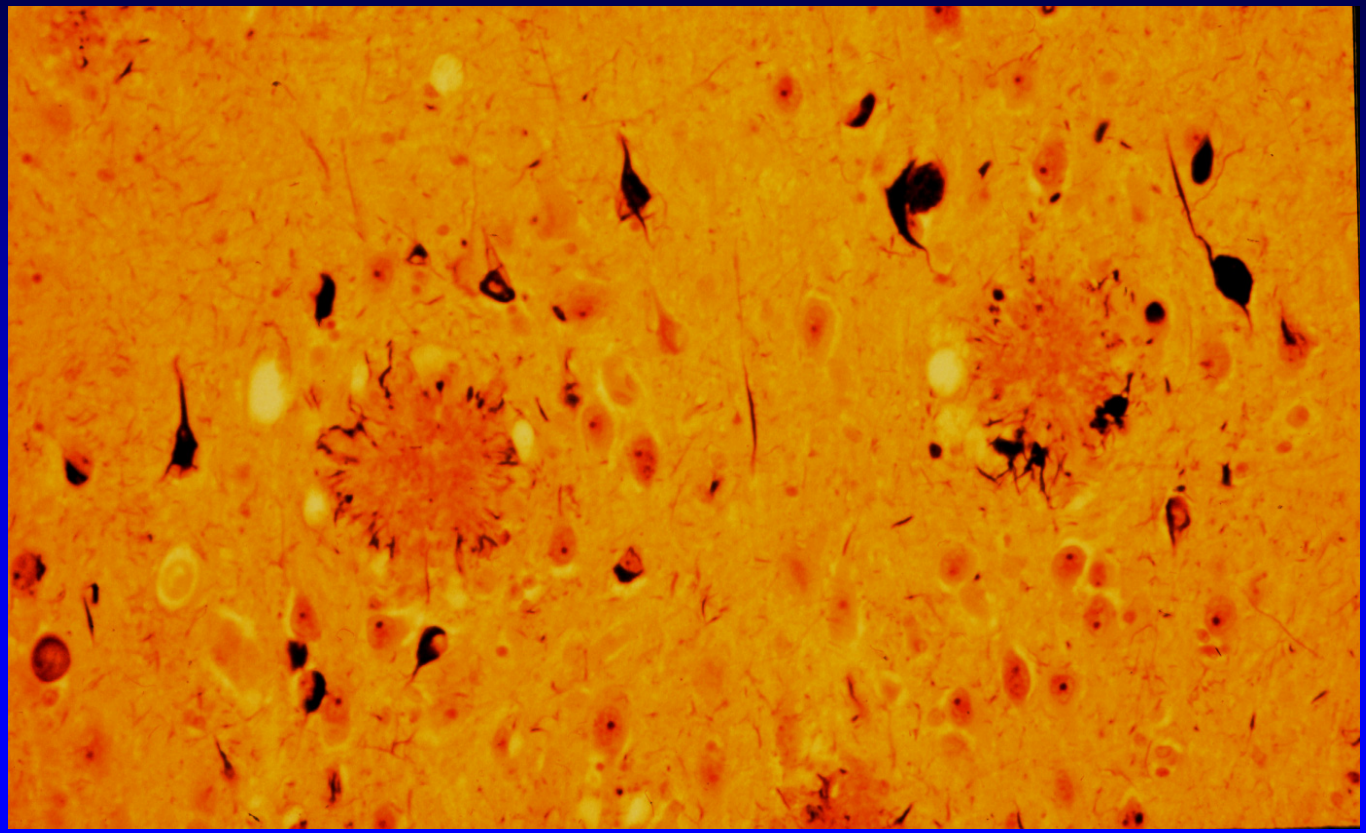
Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]

Contributors[†]**:** Cerise Elliott, Eliezer Masliah, Laurie Ryan, and Nina Silverberg

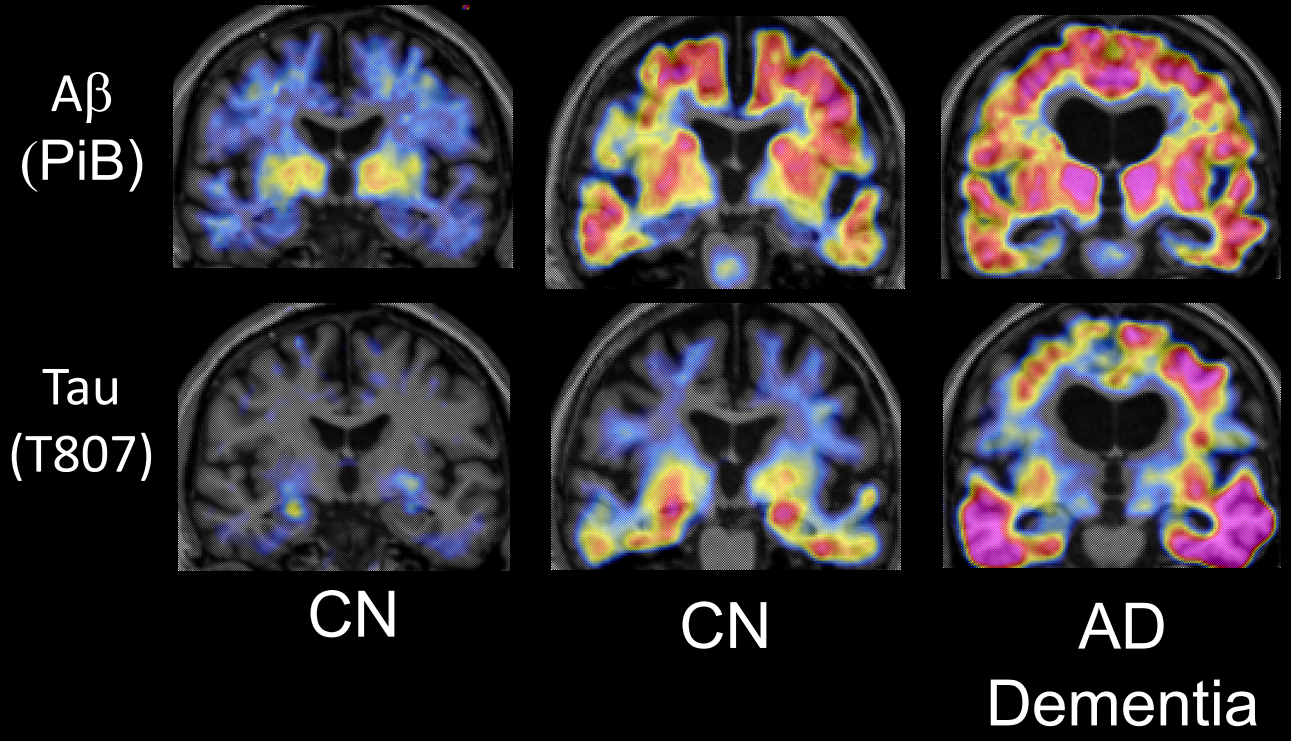
What is Alzheimer's disease?

- As defined in 1906, Alzheimer's disease is a pathophysiologic process in the brain
- AD has an associated clinical continuum that begins with a long asymptomatic or preclinical phase that typically (but not invariantly) progresses to dementia
- Dementia is a clinical syndrome that can be caused by multiple processes in the brain. Even with the prototypical amnestic progression – may not be AD

Alzheimer's Disease



Amyloid and Tau PET Imaging



Sperling, Mormino, Johnson *Neuron* 2014

NIA-AA Research Framework - Biomarkers

AT(N) biomarker grouping

A: Aggregated Aβ or associated pathologic state
- CSF $A\beta_{42}$, or $A\beta_{42}/A\beta_{40}$ ratio
- Amyloid PET

T: Aggregated tau (neurofibrillary tangles) or associated pathologic state
- CSF phosphorylated tau
- Tau PET

(N): Neurodegeneration or neuronal injury
- Anatomic MRI
- FDG PET
- CSF total tau

Abbreviations: Aβ, β amyloid; CSF, cerebrospinal fluid.
NOTE. See section 9.4 for explanation of (N) notation.

AT(N)(C) measures have different roles for definition and staging

Definition
- A: Aβ biomarkers determine whether or not an individual is in the Alzhe
- T: Pathologic tau biomarkers determine if someone who is in the Alzheir

Staging severity
- (N): Neurodegenerative/neuronal injury biomarkers
- (C): Cognitive symptoms

A and T indicate specific neuropathologic changes that define Alzheimer's dis
Alzheimer's disease and are therefore placed in parentheses.

Biomarker profiles and categories

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

NIA-AA Research Framework – Clinical

Biomarker Profile	Cognitively Unimpaired	Mild Cognitive Impairment	Dementia
$A^-T^-(N)^-$	normal AD biomarkers, cognitively unimpaired	normal AD biomarkers with MCI	normal AD bio dementia
$A^+T^-(N)^-$	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pa with dementia
$A^+T^+(N)^-$	Preclinical Alzheimer's disease	Alzheimer's disease with MCI(Prodromal AD)	Alzheimer's dis dementia
$A^+T^+(N)^+$			
$A^+T^-(N)^+$	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with MCI	Alzheimer's an suspected non A pathologic char
$A^-T^+(N)^-$	non-Alzheimer's pathologic change, cognitively unimpaired	non-Alzheimer's pathologic change with MCI	non-Alzheimer with dementia
$A^-T^-(N)^+$			
$A^-T^+(N)^+$			

Numeric clinical staging—Applicable only to individuals in the Alzheimer's continuum

Stage 1

Performance within expected range on objective cognitive tests. Cognitive test performance may be compared to normative data of the investigator's choice, with or without adjustment (the choice of the investigator) for age, sex, education, etc.*

Does not report recent decline in cognition or new onset of neurobehavioral symptoms of concern.

No evidence of recent cognitive decline or new neurobehavioral symptoms by report of an observer (e.g., study partner) or by longitudinal cognitive testing if available.

Stage 2

Normal performance within expected range on objective cognitive tests.

Transitional cognitive decline: Decline in previous level of cognitive function, which may involve any cognitive domain(s) (i.e., not exclusively memory).

May be documented through subjective report of cognitive decline that is of concern to the participant.

Represents a change from individual baseline within past 1–3 years, and persistent for at least 6 months.

May be corroborated by informant but not required.

Or may be documented by evidence of subtle decline on longitudinal cognitive testing but not required.

Or may be documented by both subjective report of decline and objective evidence on longitudinal testing.

Although cognition is the core feature, mild neurobehavioral changes—for example, changes in mood, anxiety, or motivation—may coexist. In some individuals, the primary compliant may be neurobehavioral rather than cognitive. Neurobehavioral symptoms should have a clearly defined recent onset, which persists and cannot be explained by life events.†

No functional impact on daily life activities

Stage 3

Performance in the impaired/abnormal range on objective cognitive tests.

Evidence of decline from baseline, documented by the individual's report or by observer (e.g., study partner) report or by change on longitudinal cognitive testing or neurobehavioral behavioral assessments.

May be characterized by cognitive presentations that are not primarily amnestic.†

Performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life, that is, may take more time or be less efficient but still can complete, either self-reported or corroborated by a study partner.

Stage 4

Mild dementia

Substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance. Documented by the individual's report or by observer (e.g., study partner) report or by change on longitudinal cognitive testing.

Clearly evident functional impact on daily life, affecting mainly instrumental activities. No longer fully independent/requires occasional assistance with daily life activities.

Stage 5

Moderate dementia

Progressive cognitive impairment or neurobehavioral changes. Extensive functional impact on daily life with impairment in basic activities. No longer independent and requires frequent assistance with daily life activities.

Stage 6

Severe dementia

Progressive cognitive impairment or neurobehavioral changes. Clinical interview may not be possible.

Complete dependency due to severe functional impact on daily life with impairment in basic activities, including basic self-care.

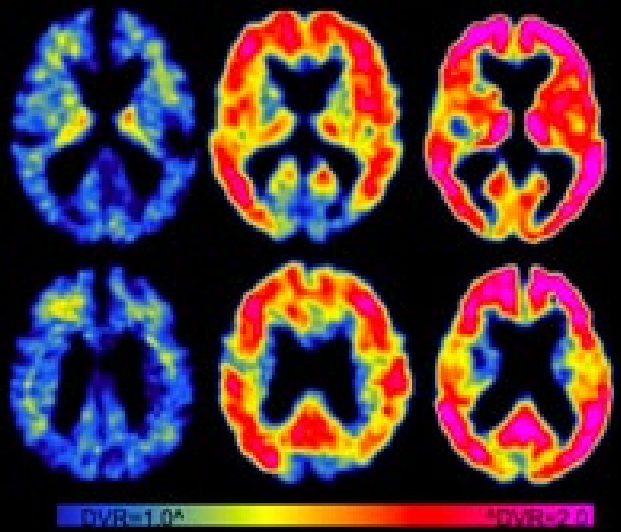
What the NIA-AA Framework IS and IS NOT

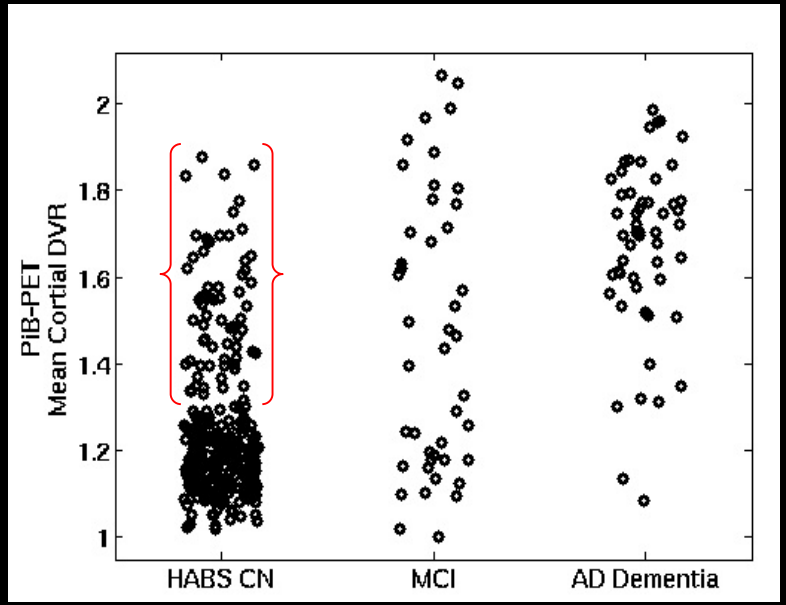
- Intended to be a research framework – explicitly stated this is NOT ready for use in the clinic
- Is applicable to both observational and clinical trials
- Is NOT a mandate for biomarker only research
- Does NOT devalue importance of clinical syndrome
- Testable hypotheses - generate alternative approaches
- Help learn “What we don’t know that we don’t know”

Why is it important to define AD as a biological entity?

- Most importantly to find an effective treatment!
- Focus on 2 specific issues:
  - We do not always get the diagnosis right clinically
  - Disease exists prior to clinically evident symptoms

PET Amyloid Imaging Across the Spectrum of AD





Harvard Aging Brain Sudy

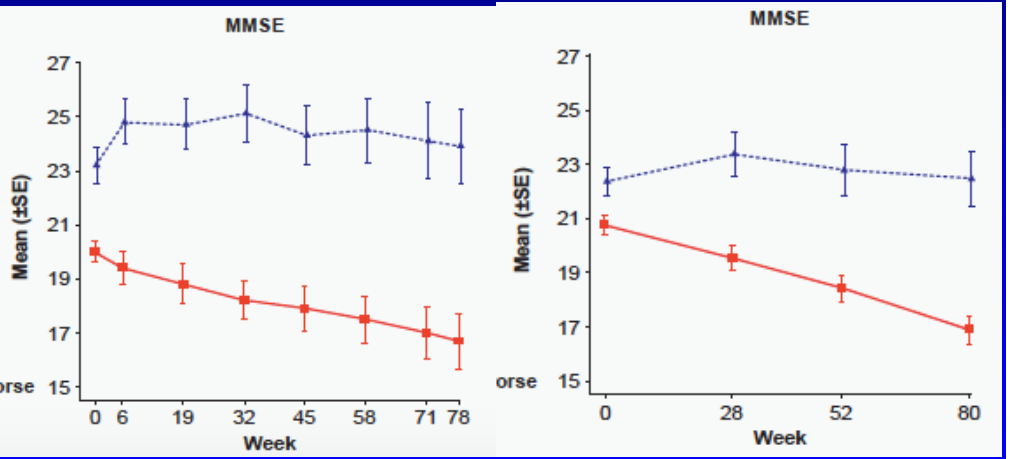
Sperling, Mormino, Johnson *Neuron* 2014

We do not always get it right clinically

- Recent clinical trials with 9-24% of clinically diagnosed mild-moderate AD dementia and up to 50% of MCI do not have evidence of Aβ pathology
- Similar results from autopsy studies of "blue ribbon" AD mild-moderate dementia patients from ADRC's - 14% did not show evidence of elevated amyloid plaque, 59% of those were Braak stage 0-II (Serrano-Pozo et al. *Annals of Neurology* 2014)

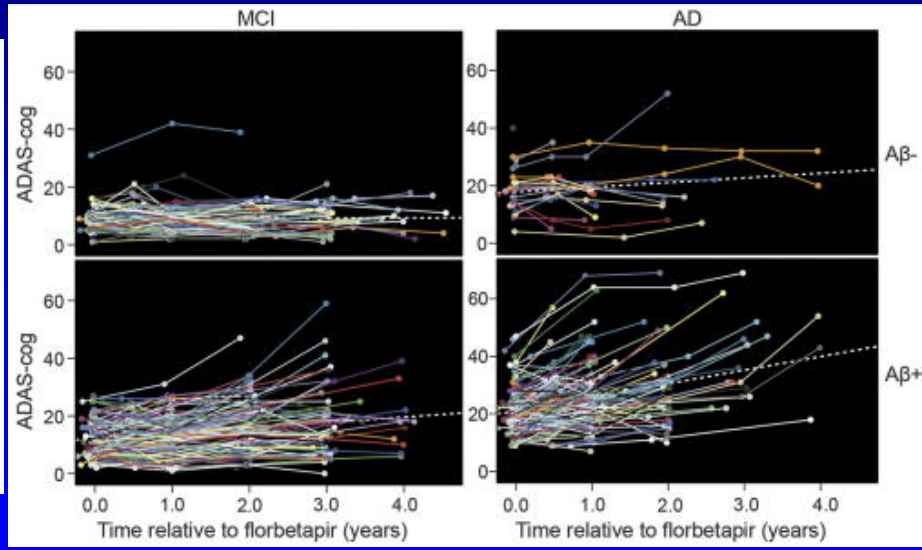
Does misdiagnosis matter?

- Amyloid negative dementia patients do not decline at the same rate



Bapi Sola

Salloway, Sperling et al. AAIC 2014



ADNI

Landau et al *Neurology* 2016

Does misdiagnosis matter in large epi studies?

- If 10-20% of "AD dementia" do not have AD pathology and 30% of "normal controls" do have AD pathology - may contribute noise to even large studies
- Attempts to replicate GWAS hits from clinical cohorts confirmed only 12 out of 21 loci in autopsy cohort (Beecham et al. *PLoS Genet* 2014)
- Misattribute risk factors – Example diabetes contributes to cerebrovascular pathology rather than AD (Abner E et al. *Alz & Dem* 2016)

Need for biomarkers in large studies!

- Need to validate less expensive biomarkers (blood, eye, etc) and sensitive computerized cognitive tests using "Gold Standard" biomarker confirmed samples
- Diversity is critical – both for race/ethnicity and for range of socio-economic status
  - Relatively little biomarker data in non-white or non-highly educated individuals -Data in African-Americans thus far suggest that multiple pathologies may play greater role
- Consider biomarkers in representative subsets

Biologic definition should enhance understanding of clinical syndrome

- Of course the clinical syndrome associated with AD is important – this is what matters to patients and families
- Many complex contributing factors to cognitive decline and dementia beyond AD pathology, we must define what we can and investigate the unexplained variance
- Important to elucidate all contributing factors to cognitive impairment and target appropriate treatments

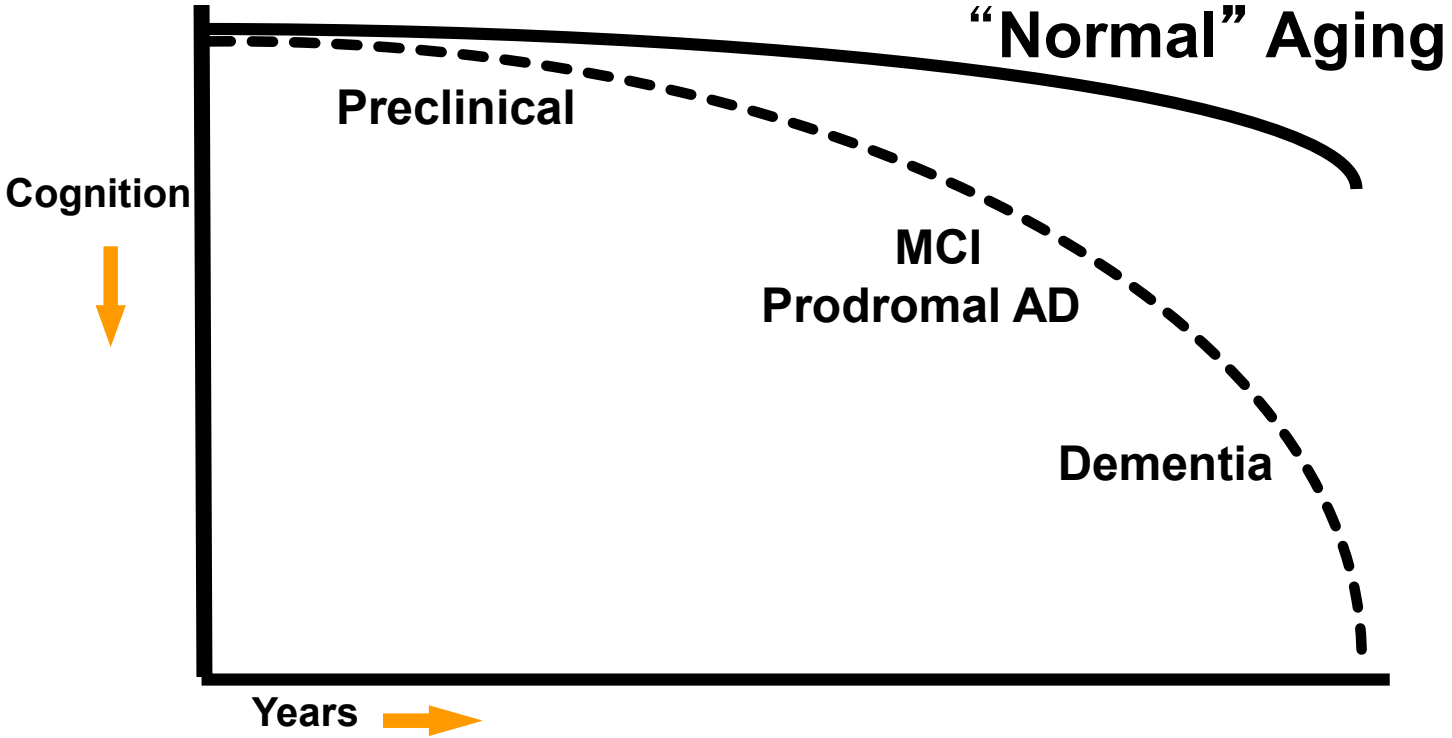
Hypothetical Scenario 1

- A 78 year old woman has been followed for 1 year with progressive amnestic cognitive impairment
- She has a follow-up clinic visit - diagnosed with dementia due to Alzheimer's disease
- She is hit by a bus on the way home from clinic. The autopsy reveals minimal evidence of amyloid plaque and neurofibrillary tangles,(A1 B1 C1), with hippocampal sclerosis
- **Did this patient have Alzheimer's disease?**

Alzheimer's disease begins prior to clinically evident impairment

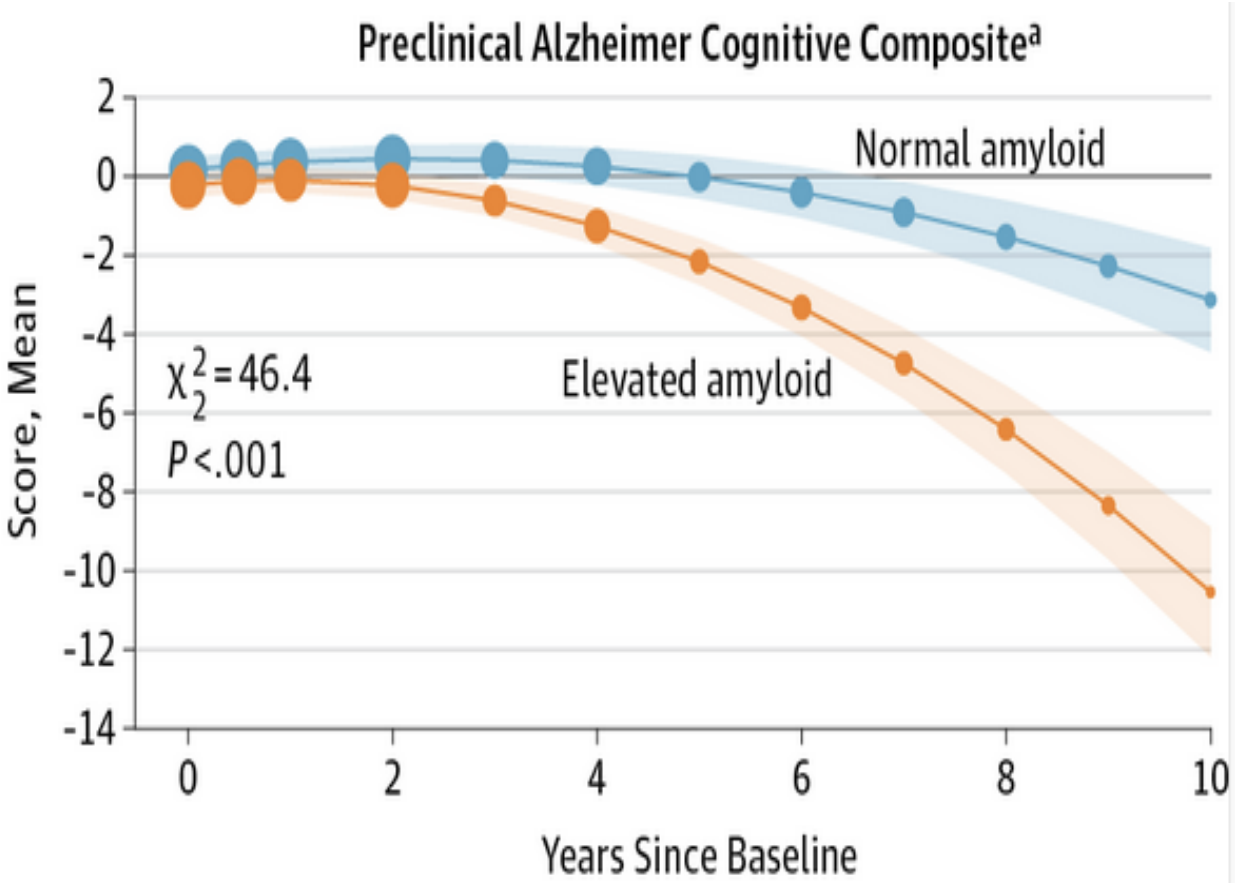
- Very consistent evidence from imaging, biomarker, and autopsy studies in both genetic-at-risk and age-at-risk cohorts that Aβ and NFTs accumulate more than a decade prior to symptoms
- Cognitively unimpaired older individuals who are Ab+, and especially those who are T+ are at very high risk for cognitive decline

The continuum of Alzheimer's disease



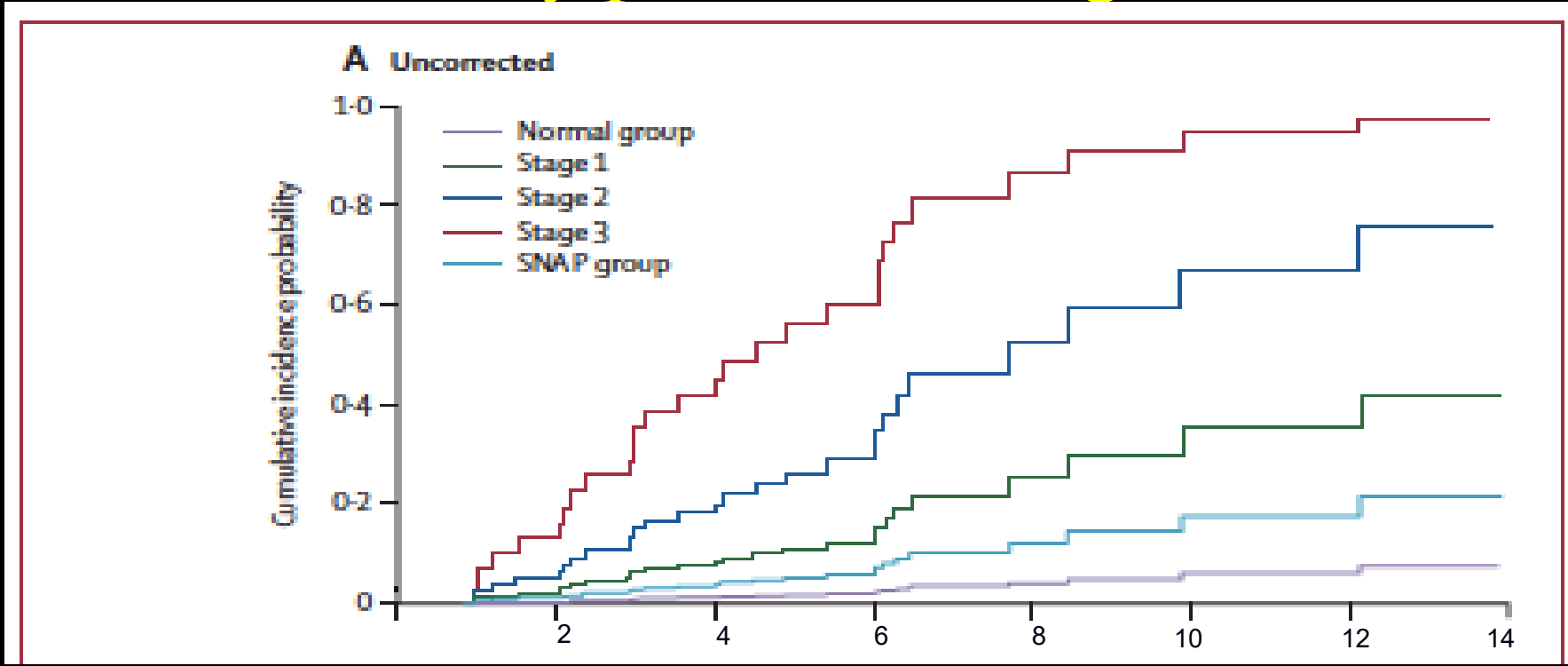
Sperling R et al 2011
NIA-AA Preclinical Workgroup

Cognitive Decline in Amyloid Positive “Normals”



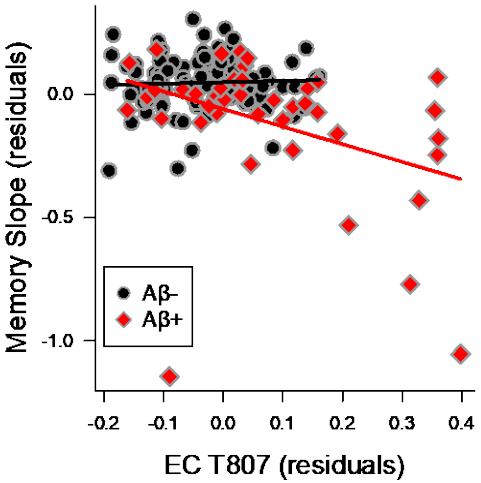
Donohue M et al. *JAMA* 2017

Prediction of progression to symptomatic AD by preclinical stages

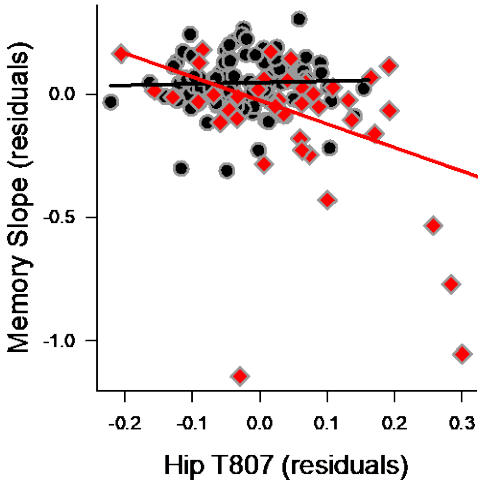


Washington University CSF - Vos et al *Lancet Neurology* 2013

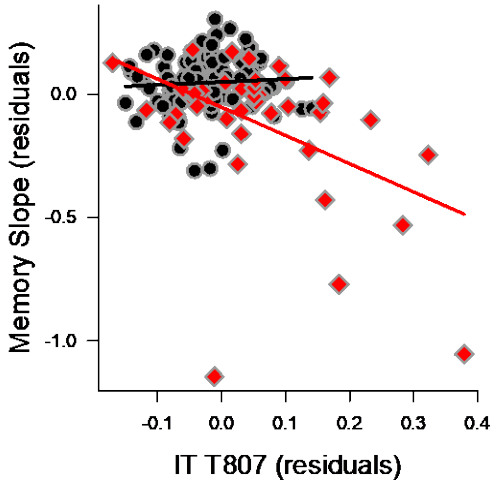
Prospective Longitudinal Memory Decline Associated with Higher Tau PET in Ab+ Normals



Entorhinal Cortex



Hippocampus



Inferior Temporal

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

Sperling, Mormino et al *Under Review*

Lifetime Risk of Dementia stratified by AD biomarkers

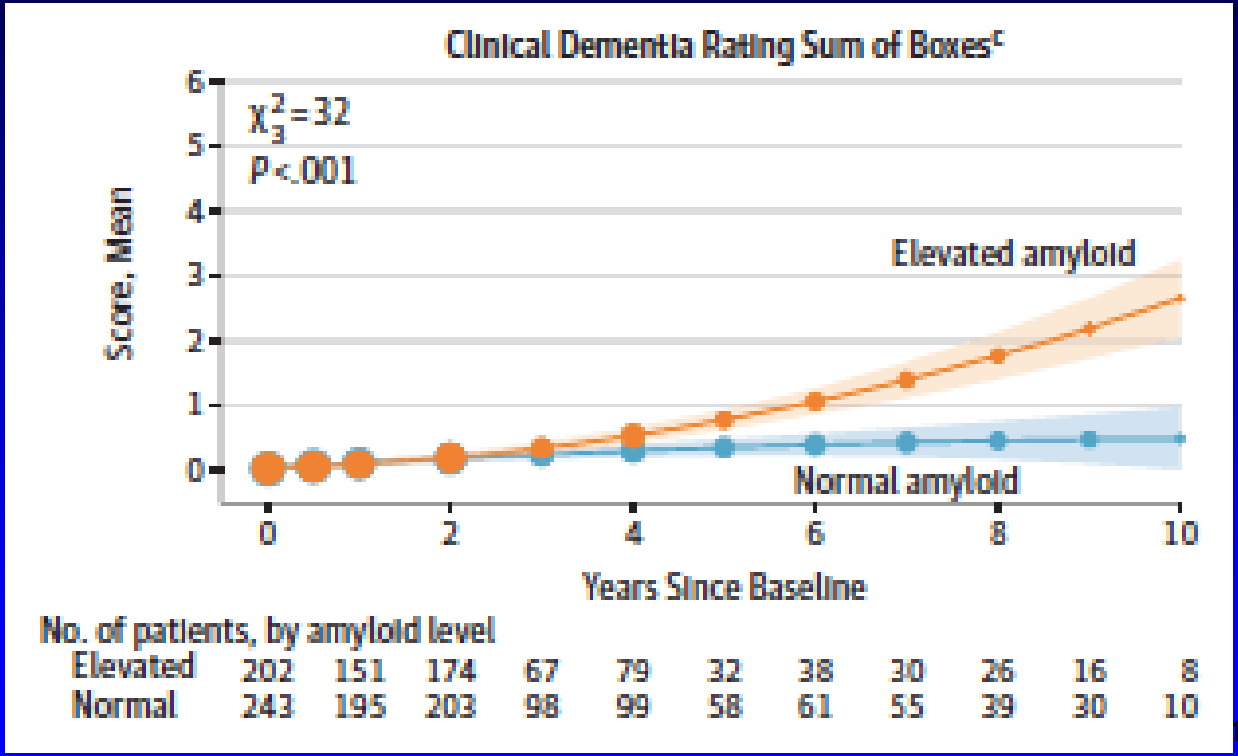
Table 3
Lifetime risks (%) of AD dementia for males based on screening for amyloidosis (A), neurodegeneration (N), and mild cognitive impairment (MCI) by age

Age	Normal state 1	A state 2	N state 3	A & N state 4	MCI & A & N state 5	MCI & N state 6
60	13.9 (6.9–25.1)	23.1 (14.9–33.0)	23.1 (11.4–44.3)	33.6 (24.4–43.5)	92.9 (91.7–93.9)	71.7 (64.3–79.2)
65	12.9 (6.3–23.6)	21.9 (13.9–31.4)	20.8 (10.3–39.4)	32.9 (23.8–42.7)	90.4 (88.6–91.7)	64.9 (57.1–73.2)
70	11.3 (5.4–21.2)	19.9 (12.5–29.0)	18.2 (9.0–34.0)	31.3 (22.5–40.7)	86.0 (83.6–87.8)	56.3 (48.6–65.0)
75	9.3 (4.3–17.8)	17.2 (10.6–25.4)	15.2 (7.5–28.2)	28.6 (20.3–37.5)	79.5 (76.5–82.0)	46.6 (39.4–55.2)
80	6.8 (3.0–13.5)	13.6 (8.2–20.6)	11.7 (5.7–21.9)	24.5 (17.1–32.5)	69.9 (66.1–73.0)	36.0 (29.8–43.8)
85	4.4 (1.9–9.2)	9.5 (5.6–14.8)	8.1 (3.9–15.5)	18.9 (13.0–25.5)	56.7 (52.6–60.2)	25.3 (20.6–31.7)
90	2.4 (1.0–5.2)	5.4 (3.1–8.8)	4.7 (2.2–9.2)	12.4 (8.3–17.0)	40.2 (36.4–43.5)	15.6 (12.5–20.0)

Abbreviation: AD, Alzheimer's disease.
NOTE. Lower and upper bounds are given in brackets.

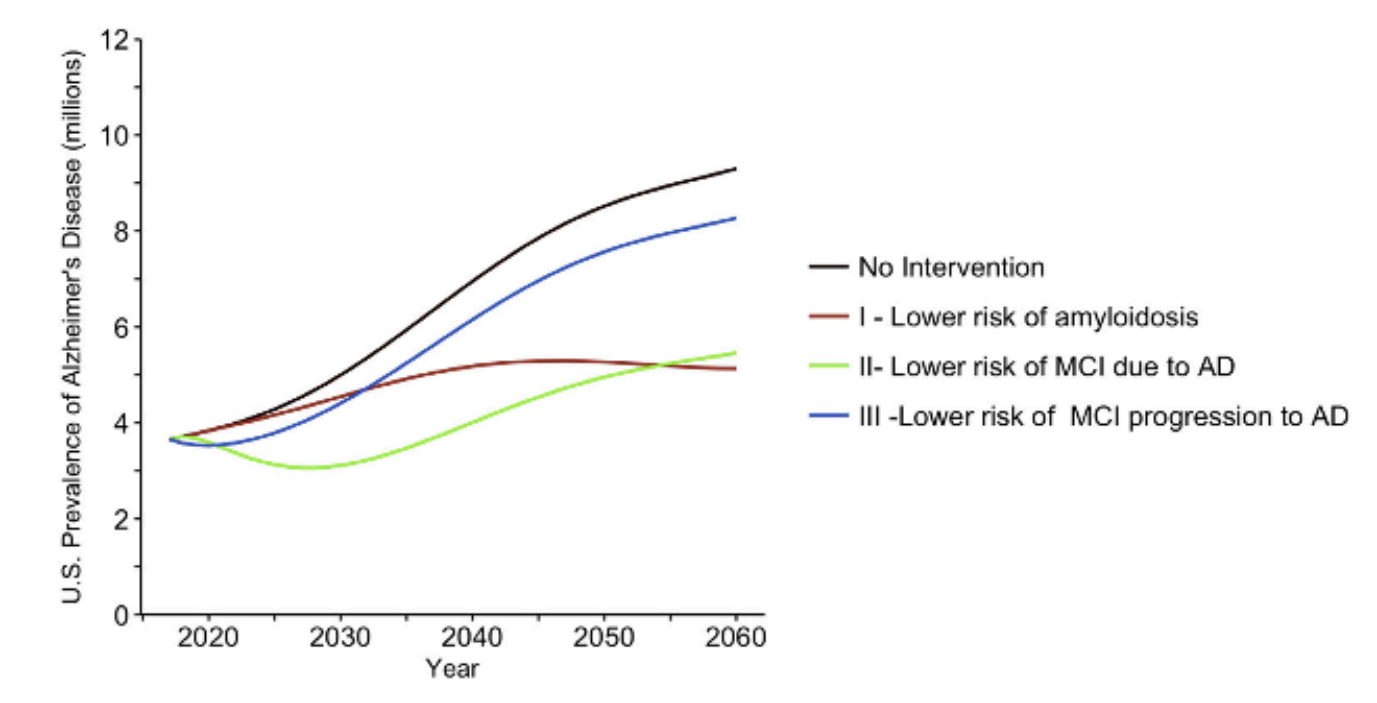
Brookmeyer R et al *Alz & Dem* 2018

Amyloid biomarkers associated with increased risk of clinical progression



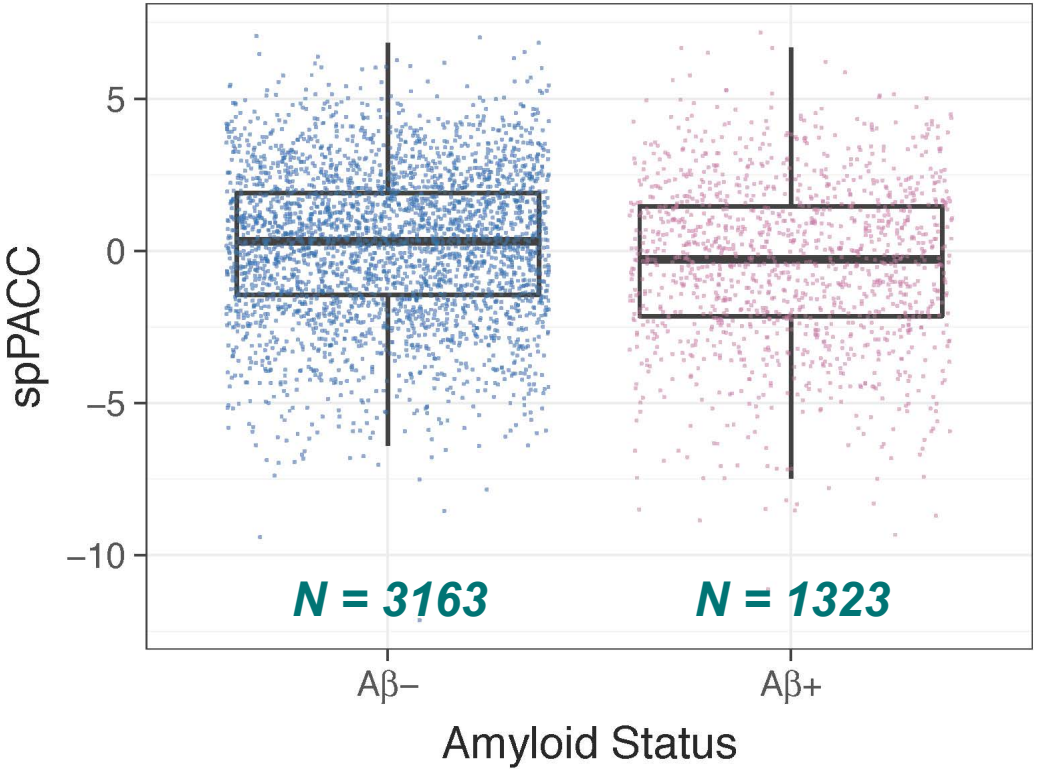
Donohue M et al *JAMA* 2017

Impact of Secondary Prevention in Preclinical AD



Brookmeyer R et al *Alz & Dem* 2018A

Results: A4 Study Screening Preclinical Alzheimer Cognitive Composite



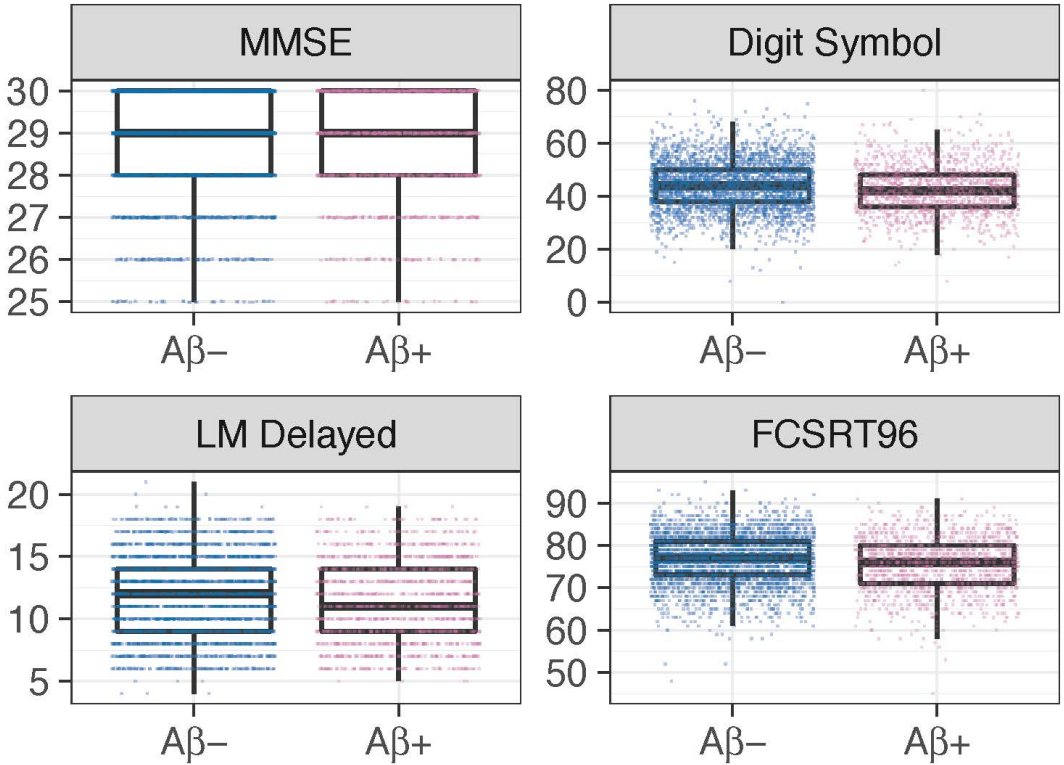
D=.32
p<0.0001
Adj* p<0.0001

*p value adjusted for age, gender, and education

Sperling R et al
AAIC 2018

A4 Screening Results: PACC Components

D= .11
p=0.013
Adj p=0.097 (ns)

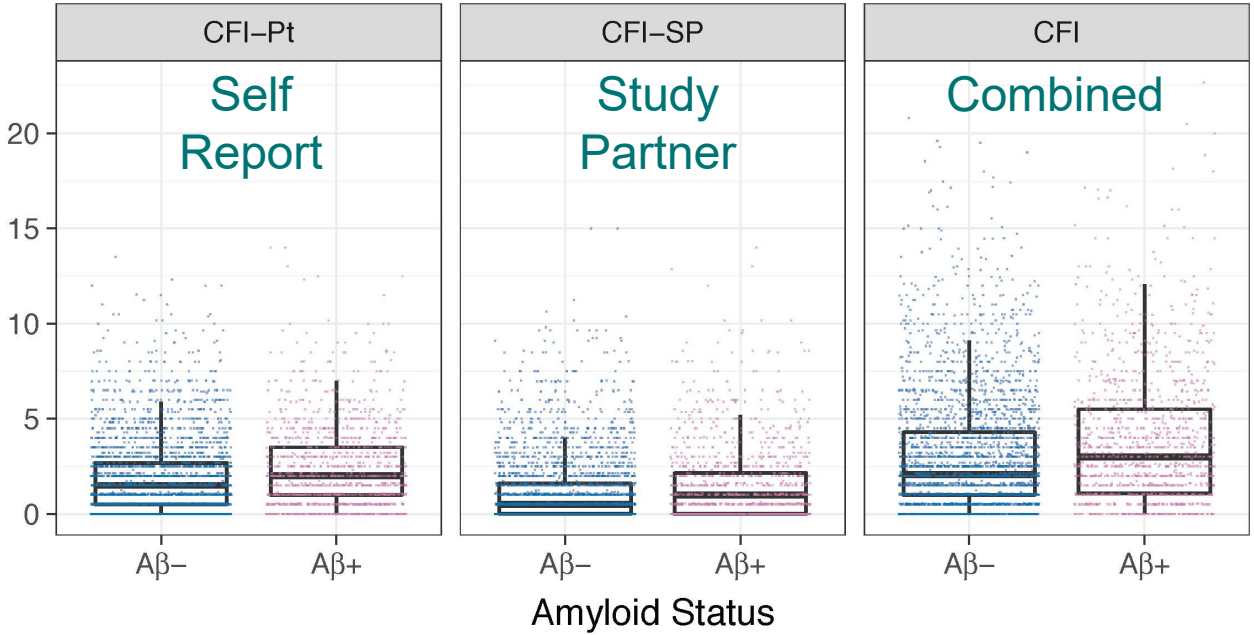


D= .26
p<0.0001
Adj p<0.0001

D= .17
p=0.0002
Adj p=0.0028

D= .27
p<0.0001
Adj p<0.0001

Results: A4 Screening Cognitive Function Index



D= .31
p<0.0001
Adj p<0.0001

D= .23
p<0.0001
Adj p<0.0001

D= .33
p<0.0001
Adj p<0.0001

Disease does not require clinical symptoms
Which of the below is NOT considered disease?

- Asymptomatic 80% stenosis of the left main coronary artery detected on cardiac catheterization
- Asymptomatic HIV infection with CD4 count <200
- Asymptomatic invasive ductal carcinoma detected on mammogram

Cannot simultaneously be at risk for a disease and have the disease, instead "at risk for symptoms"

Caveats

- Amyloid is necessary but not sufficient to predict imminent cognitive decline in preclinical AD
- Not everyone with preclinical AD will progress to clinical dementia – Need to study **resilience**, and develop predictive models for individuals
- Current biomarkers may not fully capture the toxic forms of Aβ and tau proteinopathies
- Need biomarkers for other contributing pathologies, especially TDP-43, α-synuclein, and more vascular

Hypothesis Testing -NIA-AA Framework

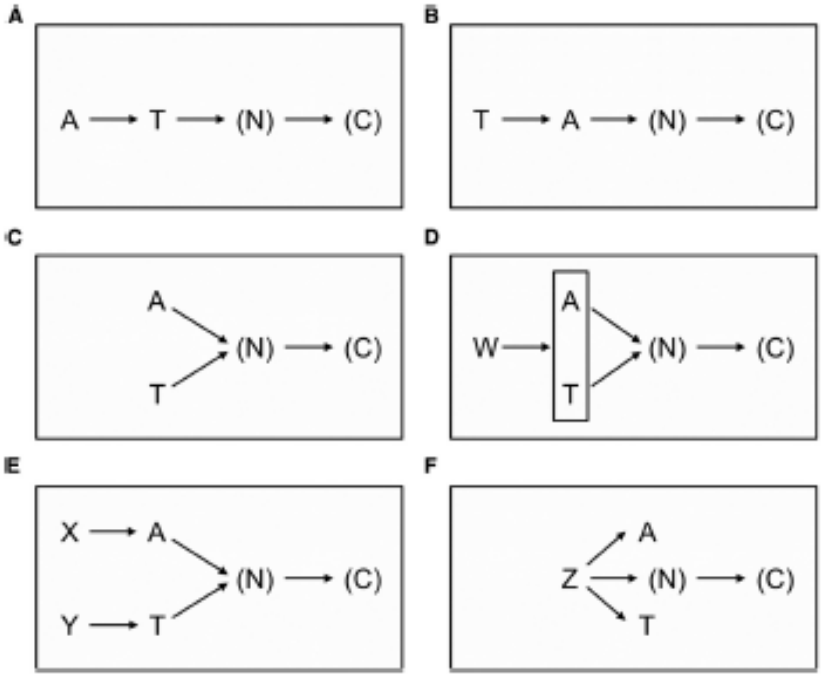


Fig. 6. Hypothesis testing using the research framework. In this figure, we outline various possible mechanistic pathways that involve A, T, (N), and (C). We believe current evidence most strongly supports the "modified amyloid cascade hypothesis" pathway denoted in (A), and this is reflected in the terminology in Table 2. However, we illustrate several alternatives that could be tested using the research framework. These are discussed in the text. This is not intended to represent an exhaustive list of all possible pathways but rather an illustration of some possible mechanistic pathways where A and T are and are not causal in AD pathogenesis. In each of these models, the final common pathway is (N) → (C), which is based on the assumption that in neurodegenerative diseases, neuronal/synaptic damage is the histopathologic feature that is most proximate to cognitive impairment. Abbreviation: AD, Alzheimer disease.

Jack C et al
Alz & Dem 2018

Why defining AD as a biologic entity for research is critically important

- We must move into the 21st century in defining AD as a biologic entity rather than a clinical syndrome
- We would never run clinical trials or observational risk studies for cancer without confirmation of pathology
- The optimal time for intervention (at least with anti-amyloid and perhaps even anti-tau therapeutics) may be prior to clinical symptoms!

Hypothetical Scenario 2

- A 72 year old woman enrolls in an observational study
- She has no memory complaints and performs in the normal cognitive range
- She is found to have abnormal Aβ and Tau on CSF
- After 2 years, she reports she has noticed a slight decline in her memory. At Year 4, she progresses to MCI. At 7 years, she has progressed to dementia.
- **At what point did she "get" Alzheimer's disease?**

Gratitude

- Keith Johnson, Dorene Rentz, Beth Mormino, Aaron Schultz from the Harvard Aging Brain Study
- Paul Aisen, ACTC and A4 Teams at Lilly, Avid, MNI, ATRI, ADCS, Mayo, CogState
- Collaboration for Alzheimer Prevention
- Alzheimer's Association, GHR Foundation, Gates Ventures, and Fidelity Biosciences, AMP FNIH
- **National Institute on Aging**

Rebuttal

Figure 4. Leading causes of death for persons ages 65 years and older by sex, 2002

Cause of death	All		Male		Female	
	Percent all deaths	Rank	Percent all deaths	Rank	Percent all deaths	Rank
Heart disease	31.8	1	31.8	1	31.8	1
Cancer	21.6	2	25.0	2	18.8	2
Stroke	7.9	3	6.5	4	9.1	3
Chronic lower respiratory diseases	6.0	4	6.5	3	5.6	4
Influenza and Pneumonia	3.2	5	3.1	5	3.4	6
Alzheimer's disease	3.2	6	2.1	7	4.1	5
Diabetes	3.0	7	2.9	6	3.1	7
Nephritis, nephrotic syndrome, and nephrosis	1.9	8	2.0	9	1.8	8
Accidents	1.9	9	2.1	8	1.7	9
Septicemia	1.5	10	1.4	10	1.5	10

CDC Report 2005

Survival rates for prostate cancer

According to the most recent data, when including *all* stages of prostate cancer:

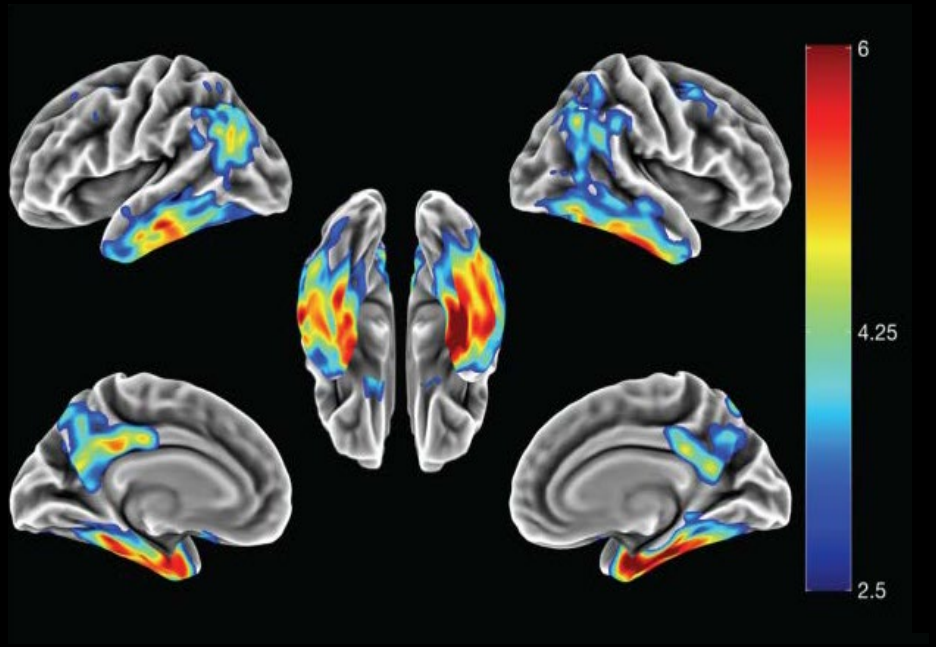
- The 5-year relative survival rate is 99%
- The 10-year relative survival rate is 98%
- The 15-year relative survival rate is 96%

American Cancer Society

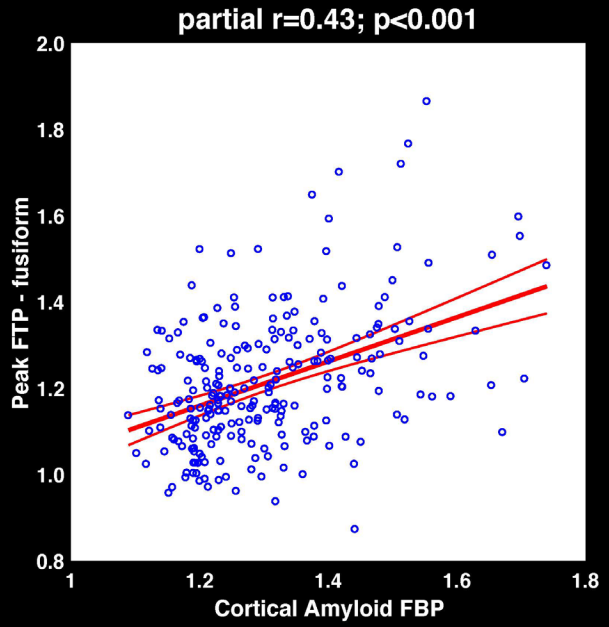
Encouraging history from other fields

- Cholesterol Wars in Cardiology in the 70's
  - Secondary prevention trials in familial hypercholesterolemia and in post-MI with intact cardiac function
  - 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 be impacted at the optimal time

Greater Amyloid Associated with Greater Tau Burden (A4 Study Baseline Data)



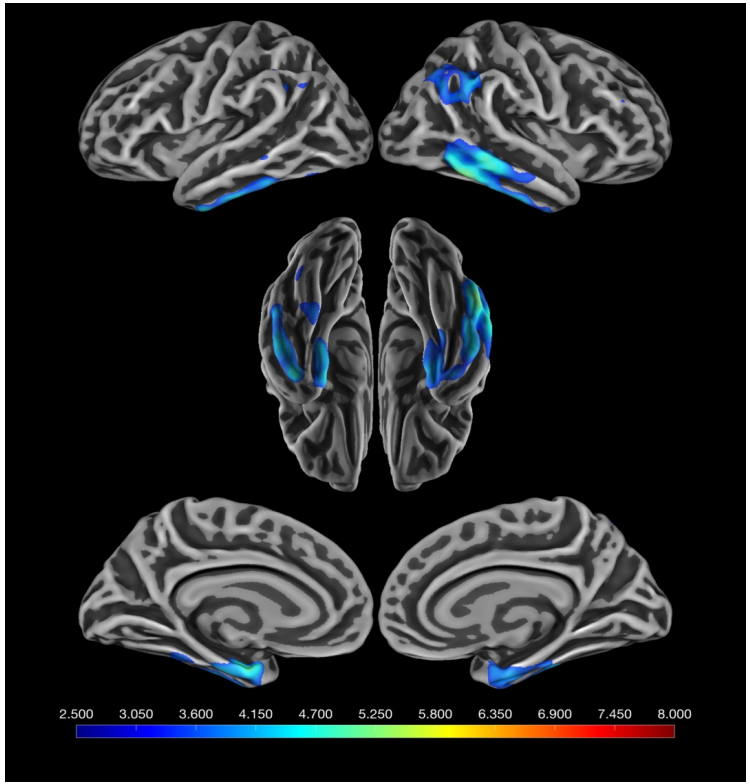
FTP PET Vertex correlations with cortical FBP SUVR (n=239)



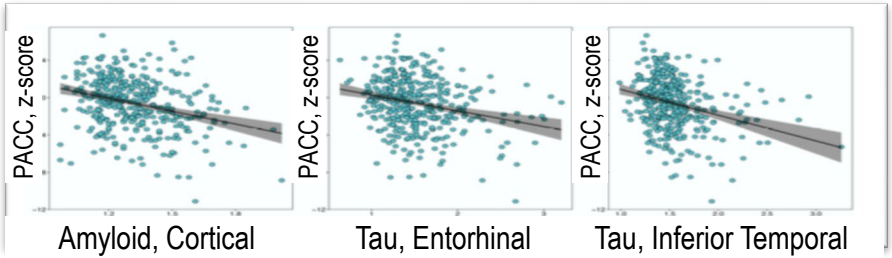
Left Fusiform

Sperling R et al HAI 20

A4 Tau PET and Cognitive Performance



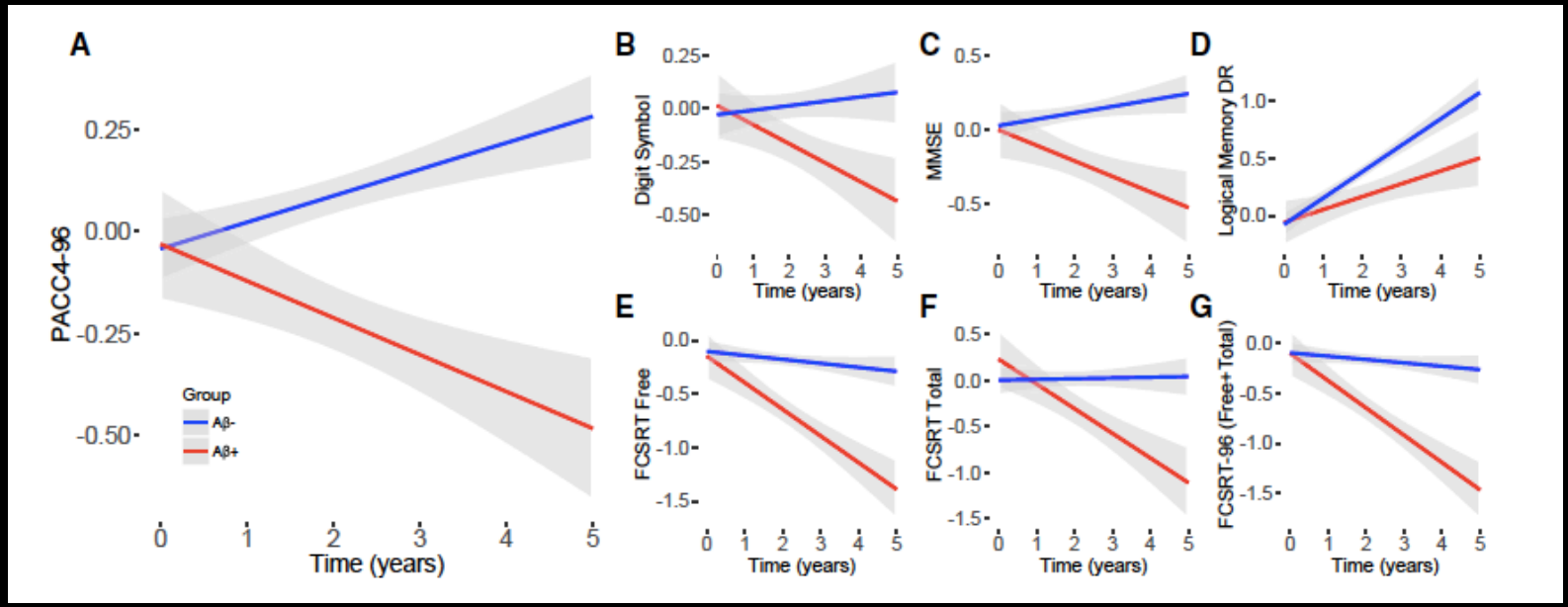
		Amyloid	Tau
PACC	EC	β = -0.18 [-0.27, -0.09] p<0.001	β = -0.17 [-0.26, -0.08] p<0.001
	IT	β = -0.17 [-0.26, -0.07] p<0.001	β = -0.19 [-0.28, -0.09] p<0.001



Johnson K et al AAIC 2018

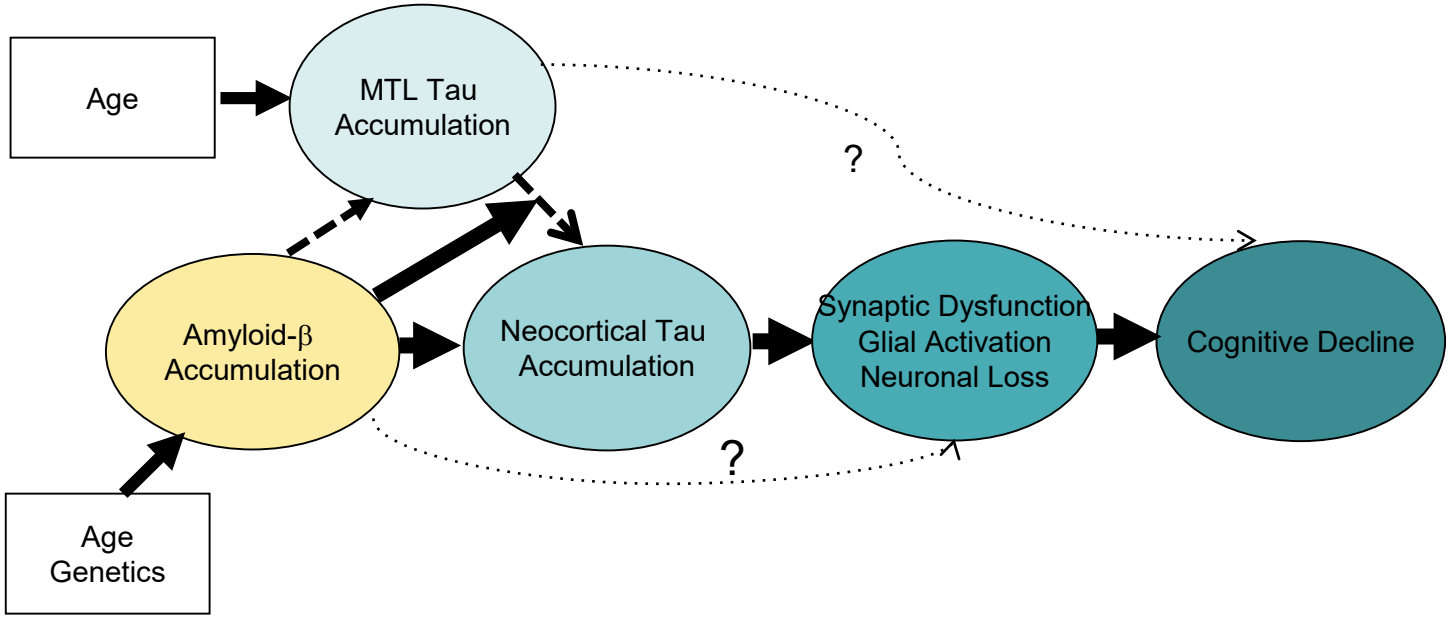
Preclinical Alzheimer Cognitive Composite

Harvard Aging Brain Study (n=277)



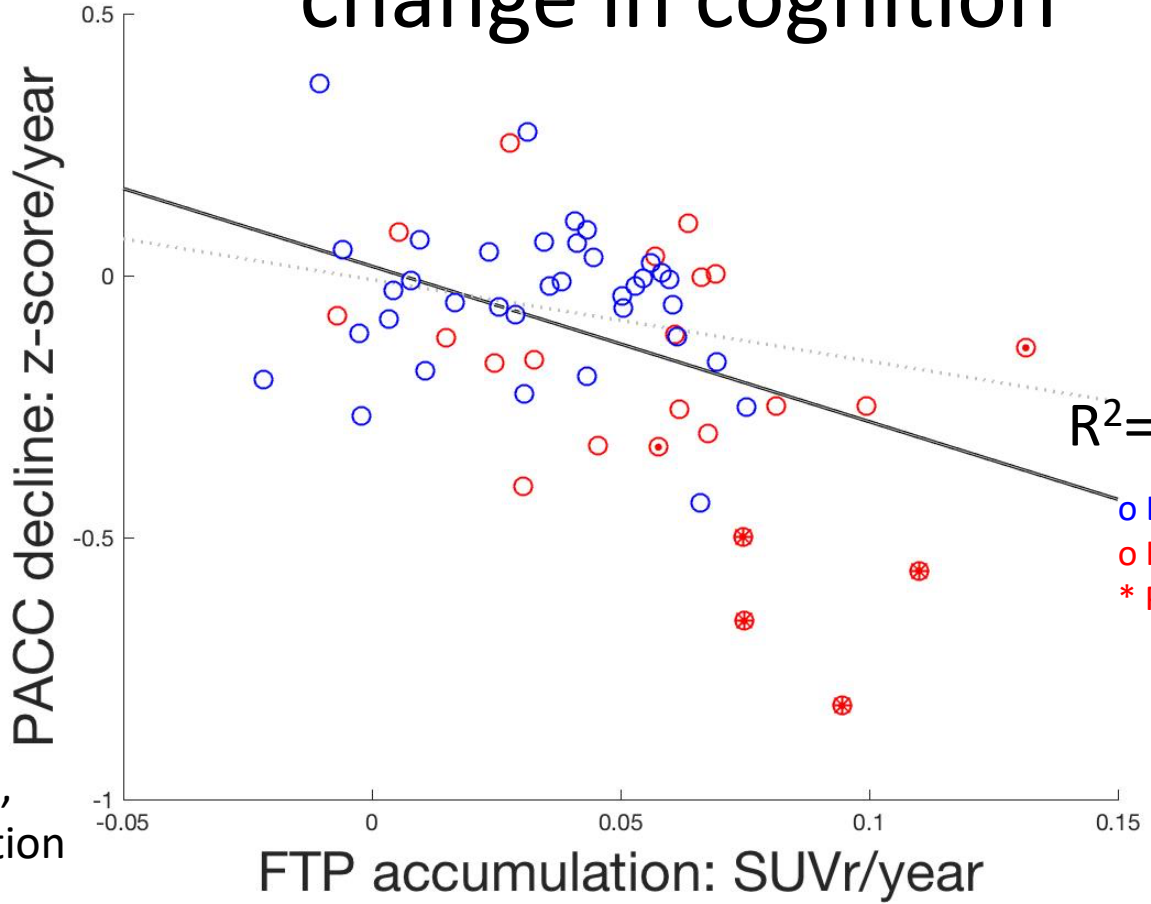
Mormino E et al. *Alz & Dementia* 2017

Hypothetical Interaction of Amyloid and Tau in Preclinical AD



Sperling, Mormino, Johnson *Neuron* 201

Change in Tau PET associated with change in cognition



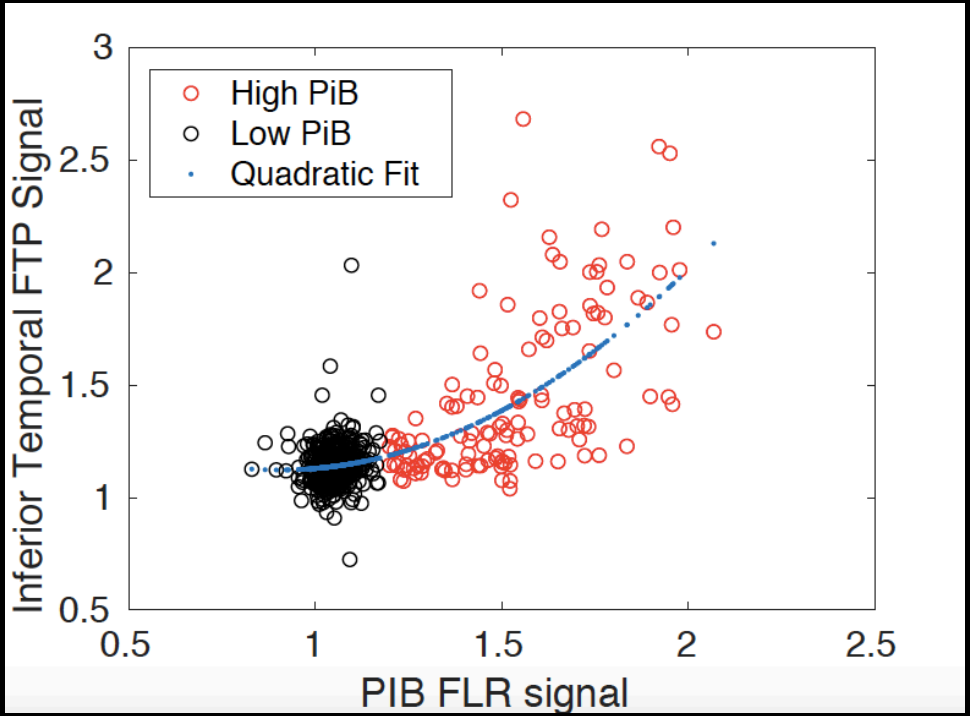
R^2=0.23, p=0.0001

o Low Amyloid
o High Amyloid
* Progression to MCI

Covariates: Age, Sex, and Education

Hanseeuw B et al
Under Review

The relationship between A and T



Harvard Aging Brain Study Data

Aaron Schultz and Keith Johnson