Anti-amyloid treatment in Asymptomatic* AD
A4 Trial

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Disclosures

Consultant to:

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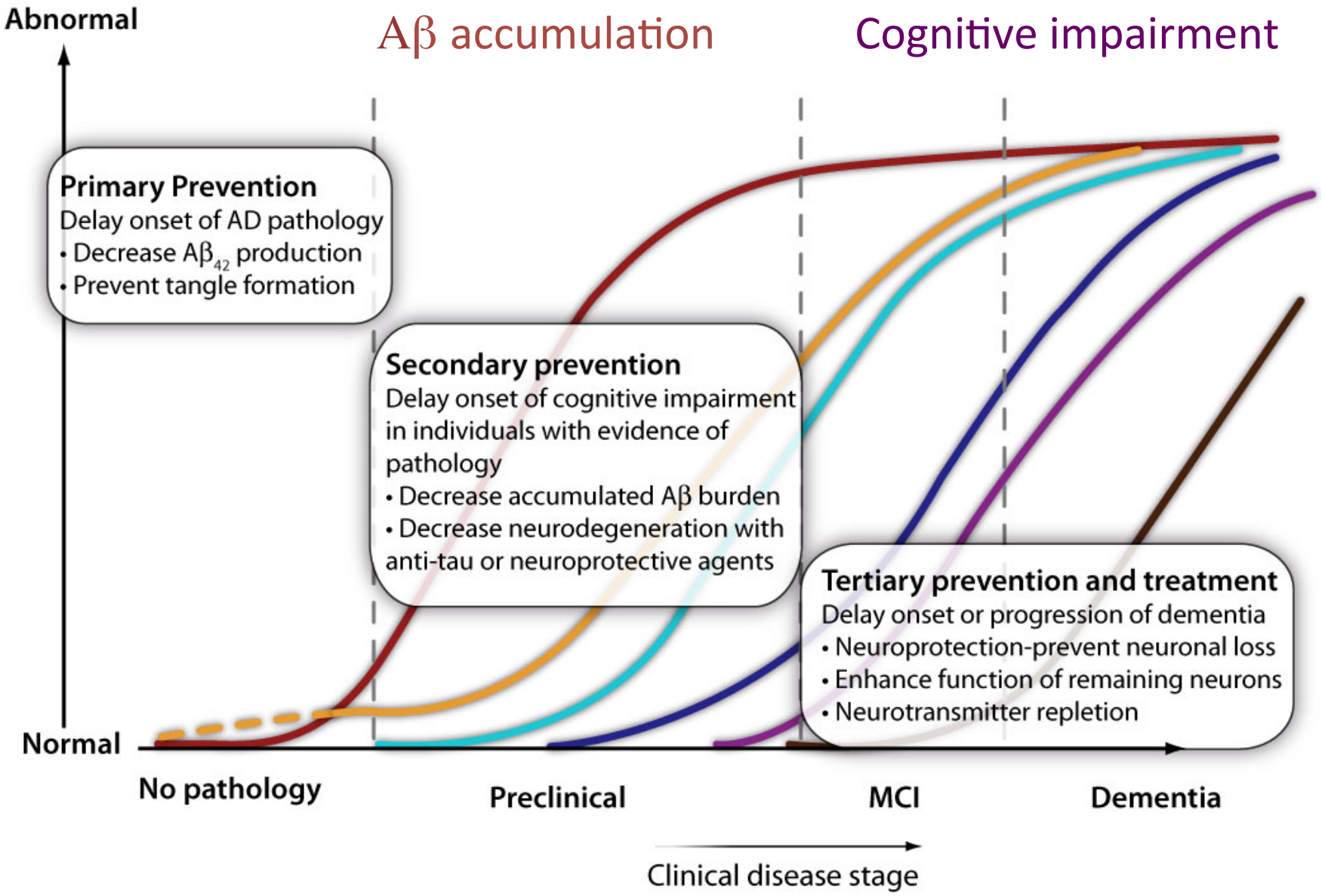
R01AG027435; K24AG035007

Alzheimer's Association, American Federation of Aging Research, American Health Assistance Foundation

A4 Trial Rationale

- Multiple trial failures at the stage of mild to moderate dementia with anti-Aβ therapies, despite evidence of biological activity
- Converging data from both genetic at-risk and age at-risk cohorts suggest that the pathophysiological process of AD begins > decade prior to dementia
- Need to actually test the amyloid hypothesis at a stage of AD when Aβ may drive the cascade and before widespread irreversible neuronal damage
- The therapeutic success of the study does not require that Aβ is the cause of AD, merely that it is a critical early factor in the pathogenesis of AD

Testing the Right Target and Right Drug at the Right Stage of AD



Sperling, Jack, Aisen *Science Trans Med* 2011

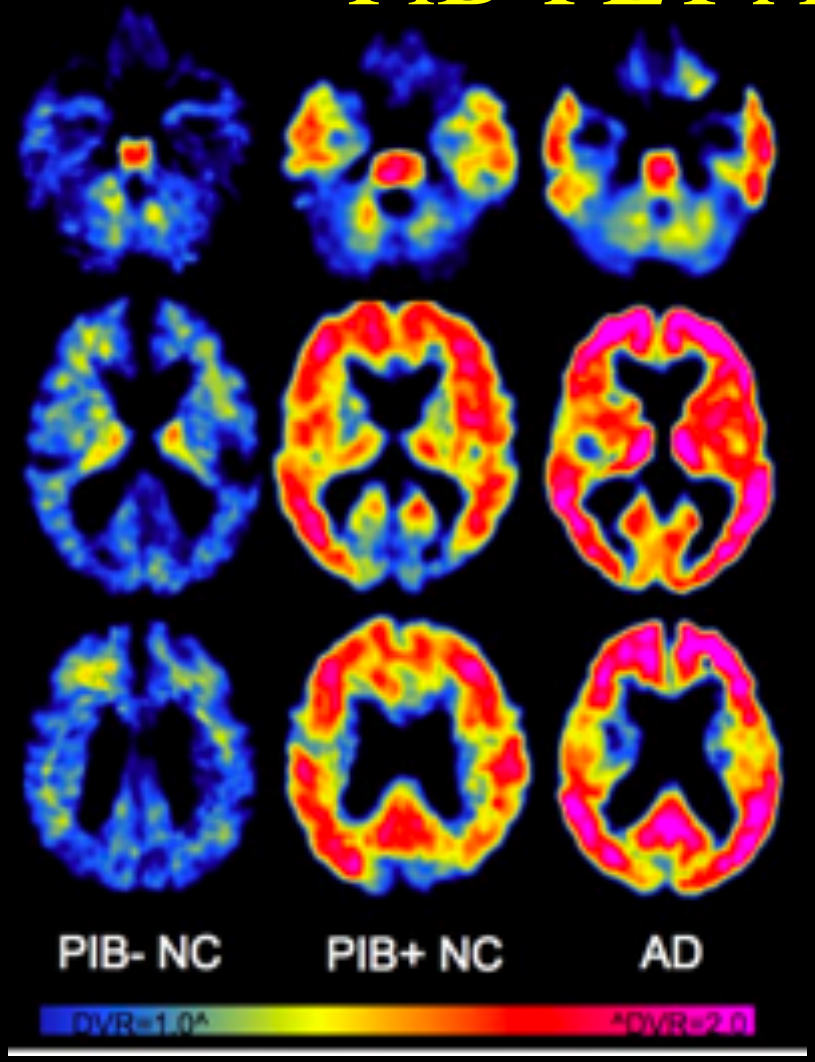
A4 Trial Synopsis

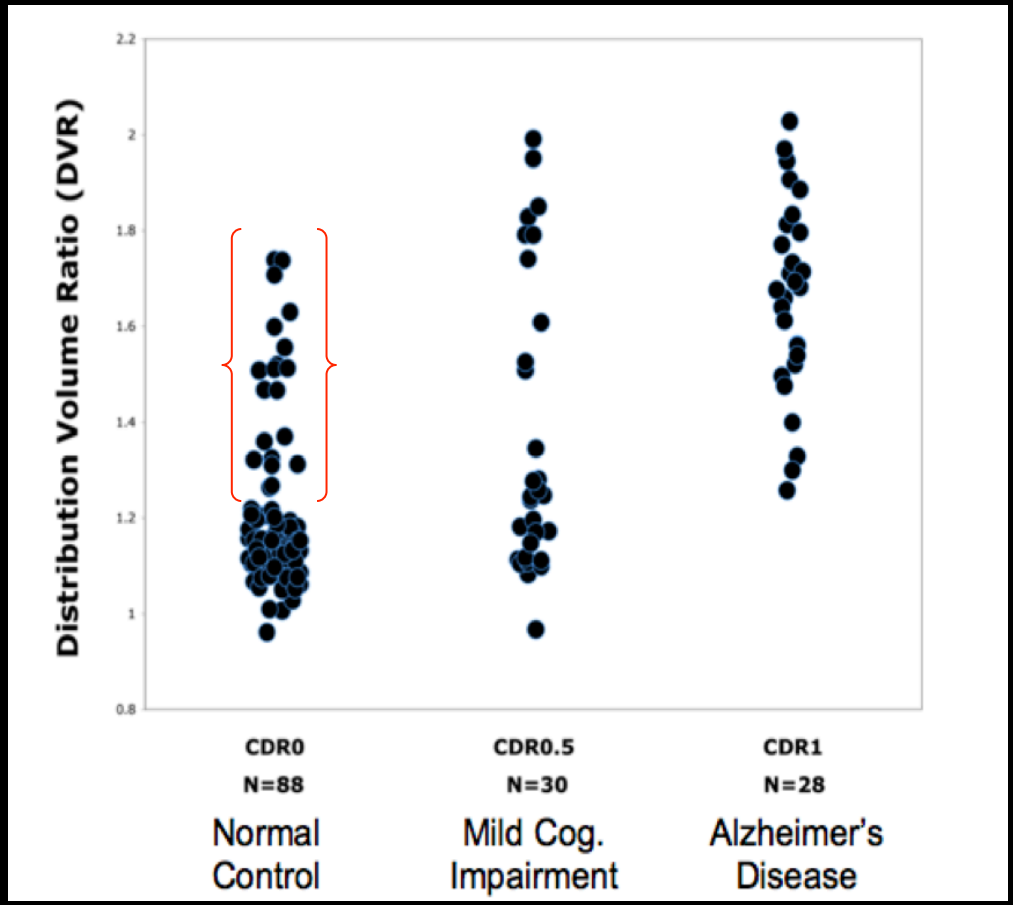
- Secondary prevention trial in clinically normal older individuals (> age 70) Aβ+ on PET imaging
- Treat with biologically active compound for 3 years randomized, double-blind, placebo-controlled trial
  - Total N=1000 (N=500 per treatment arm)
  - At least 2 year additional clinical follow-up
- Include Aβ- arm (N = 500) for natural history study
- Ethics substudy: Disclosure of Aβ (J. Karlawish)
- Novel outcome development substudies: computerized cognitive test battery and task-free functional connectivity MRI

A4 Rationale: Older Aβ+

- More than 1/3 of clinically "normal" individuals over age 65 harbor amyloid plaque pathology
- Clinically normal older individuals with biomarker evidence of Aβ accumulation demonstrate functional and structural neuroimaging abnormalities, subtle cognitive deficits, and increased likelihood of cognitive decline similar to MCI and AD dementia
- Unlike autosomal dominant AD, there is a nearly unlimited pool of potential older subjects, but much less certainty about progression to dementia

Harvard Aging Brain Study
PiB-PET Amyloid Imaging

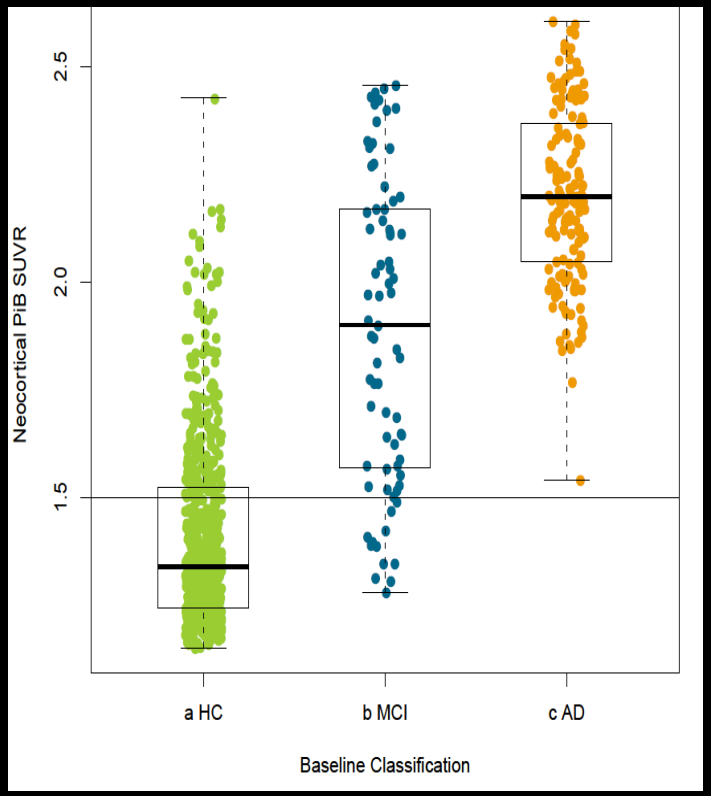




Sperling R et al *NeuroMolecular Medicine* 2010

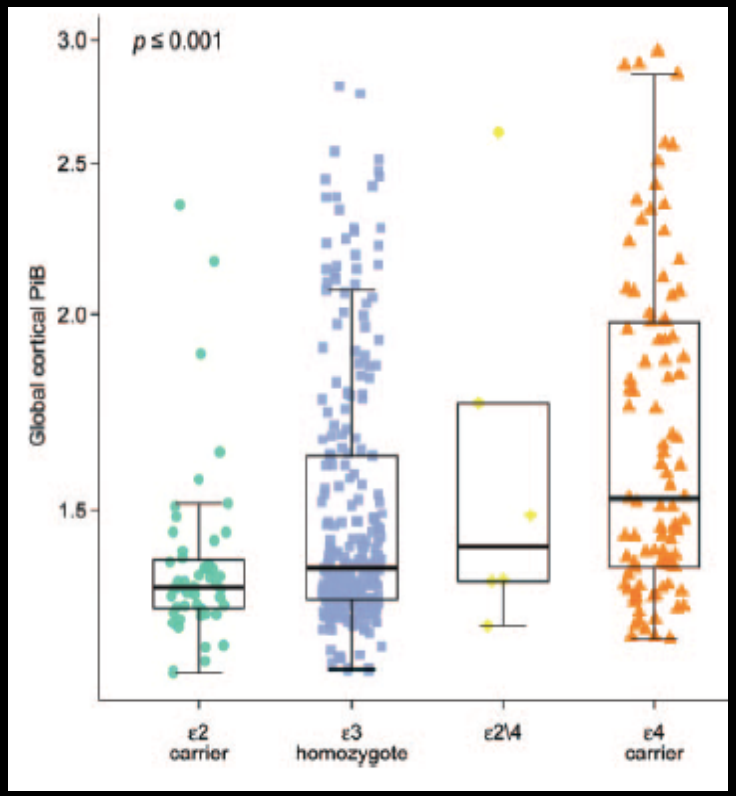
Amyloid Imaging in Normal Older Cohorts

AIBL Study



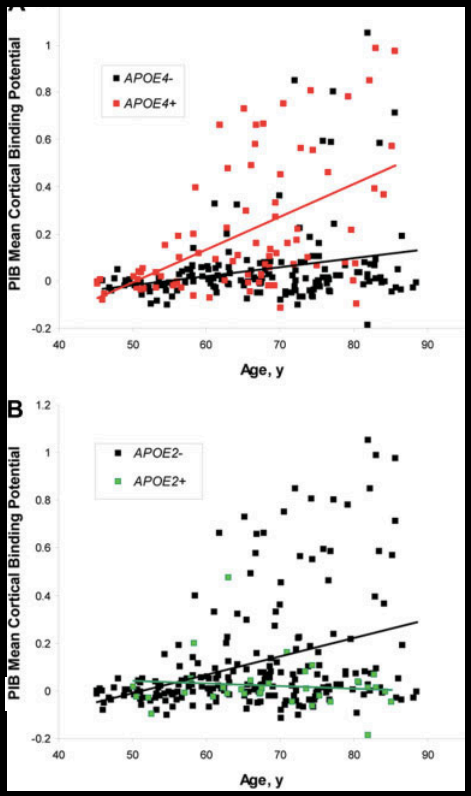
Villemagne and Rowe

Mayo Clinic



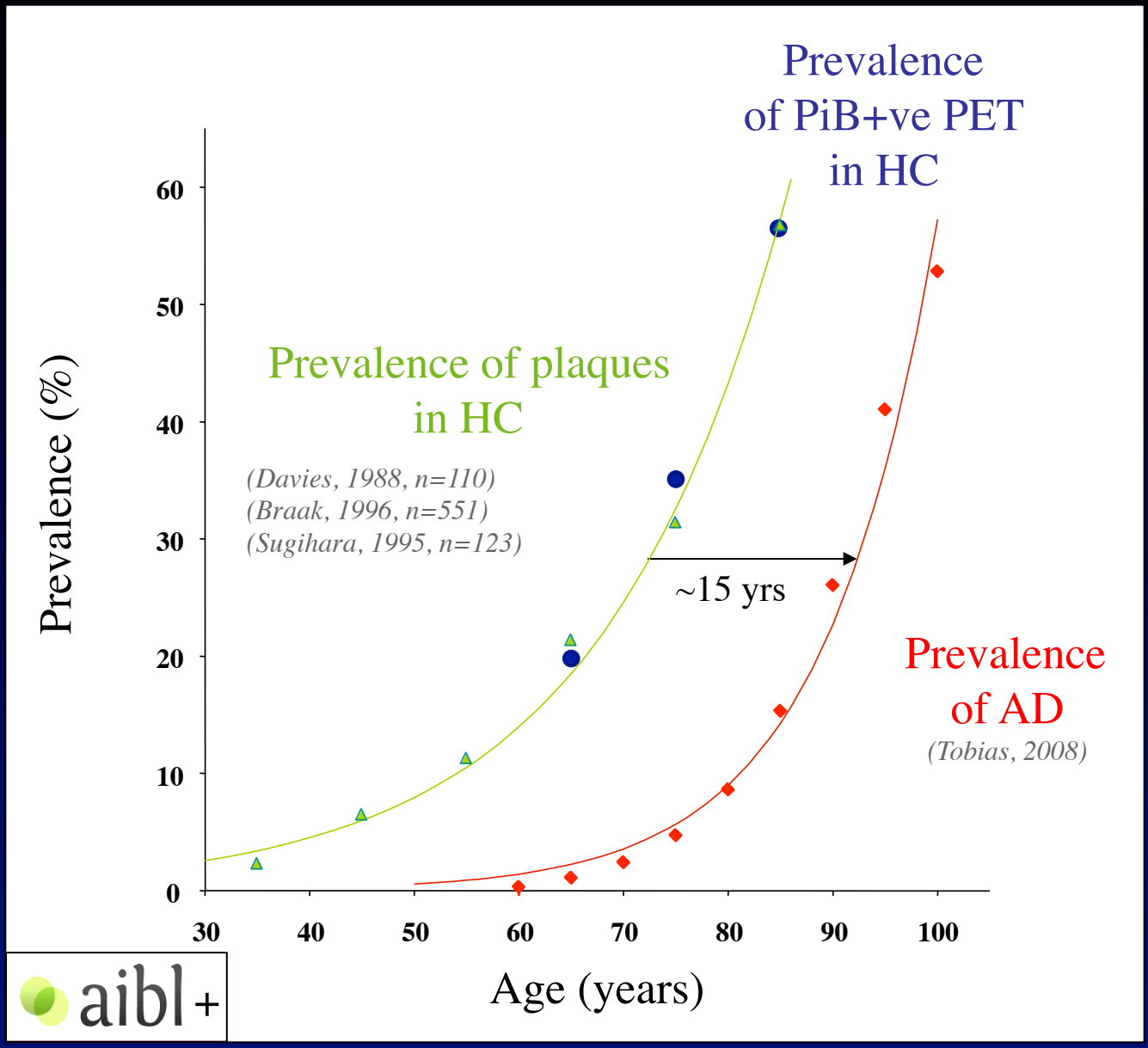
Kantarci and Jack

Wash U



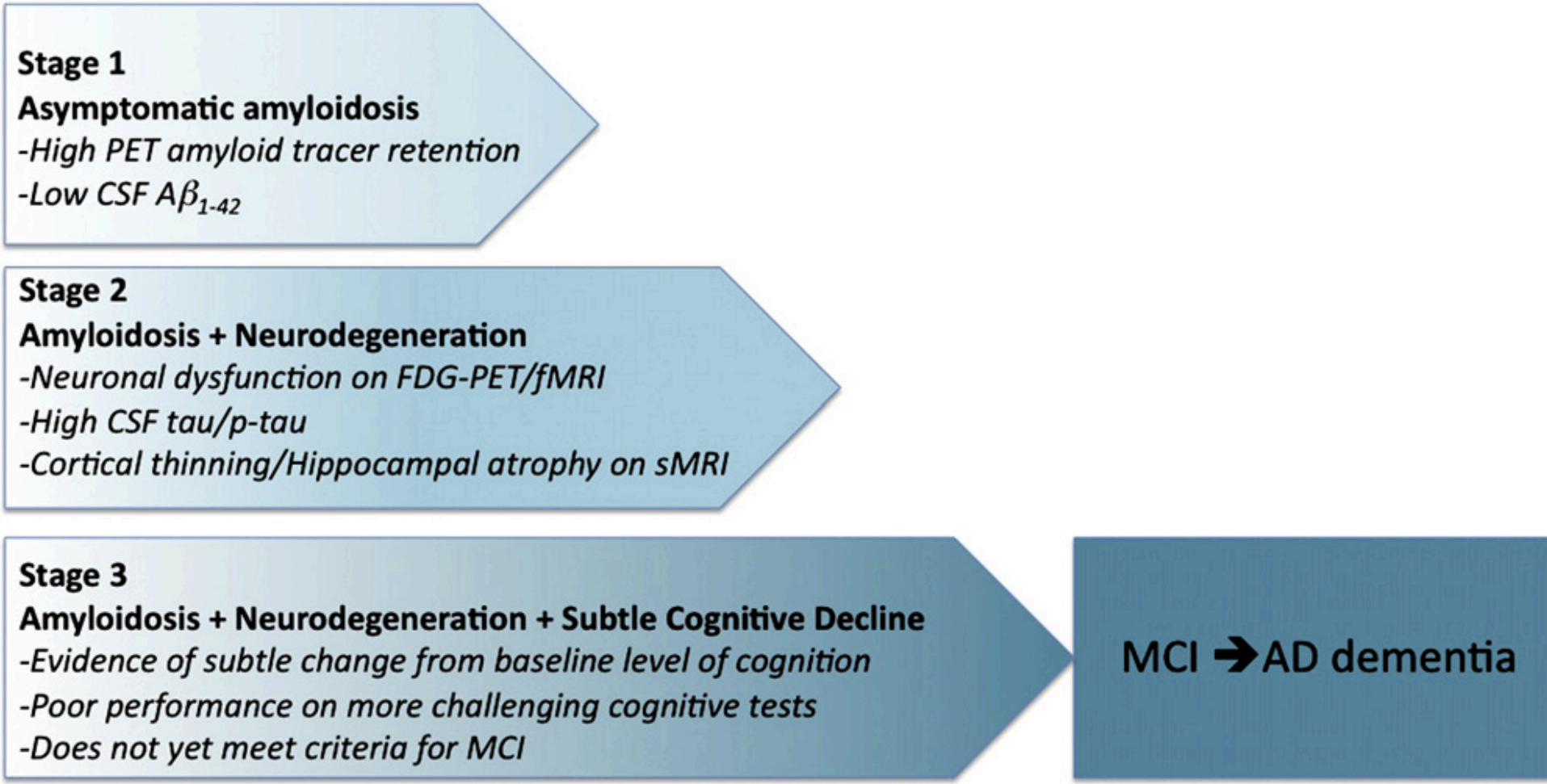
Mintun and Morris

Preclinical Alzheimer's Disease?



Rowe C et al *Neurobiology of Aging* 2010

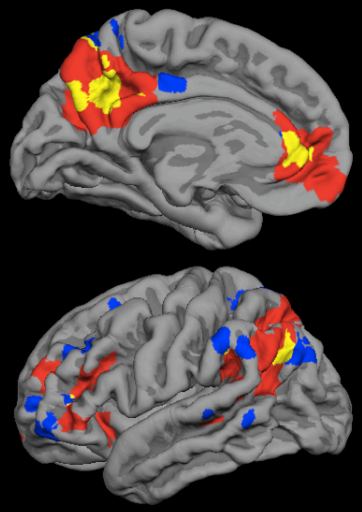
Staging Framework for Preclinical AD

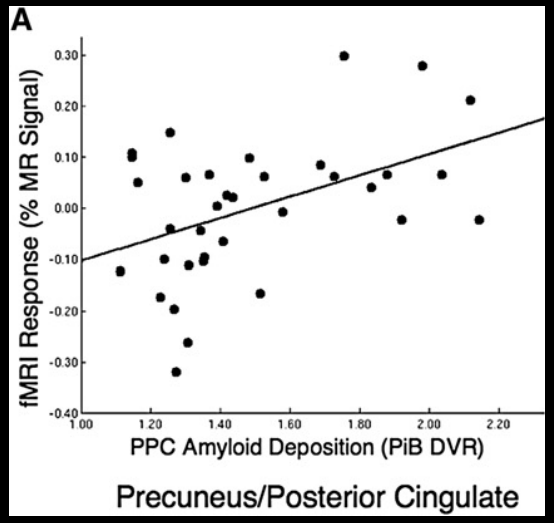


Sperling R et al *Alzheimer's & Dementia* 2011

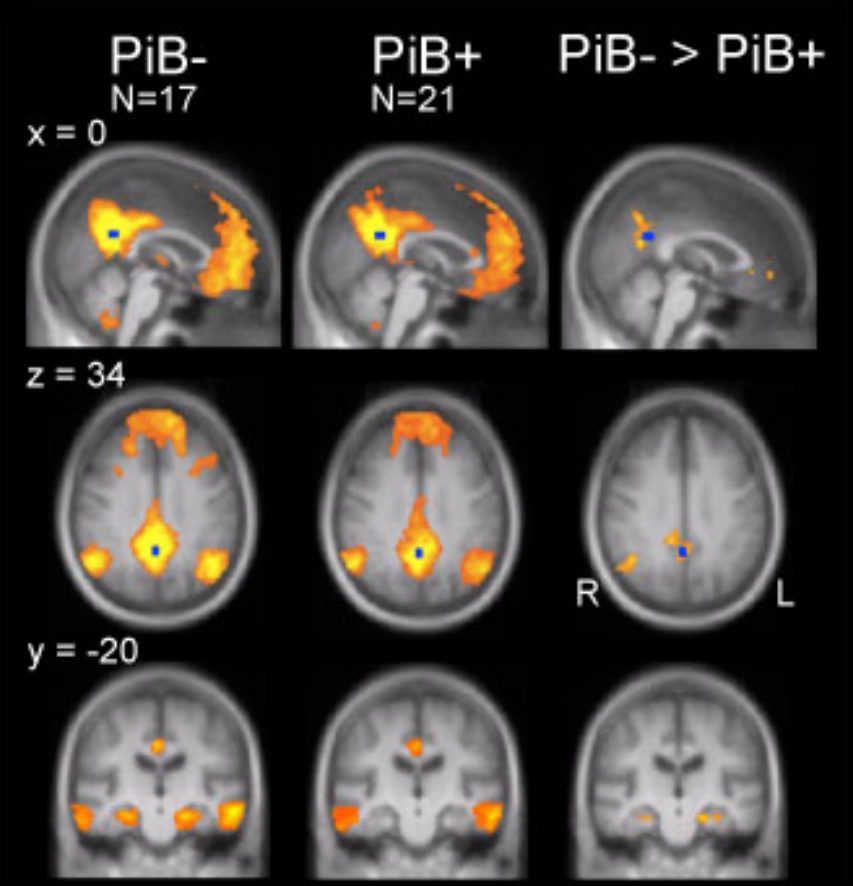
Fagan *Annals* 2009; Jack *Annals* 2012; Desikan *Archives* 2012; Knopman *Neurology* 2012

Aβ burden in normal elderly associated with default network dysfunction in task and task-free fMRI



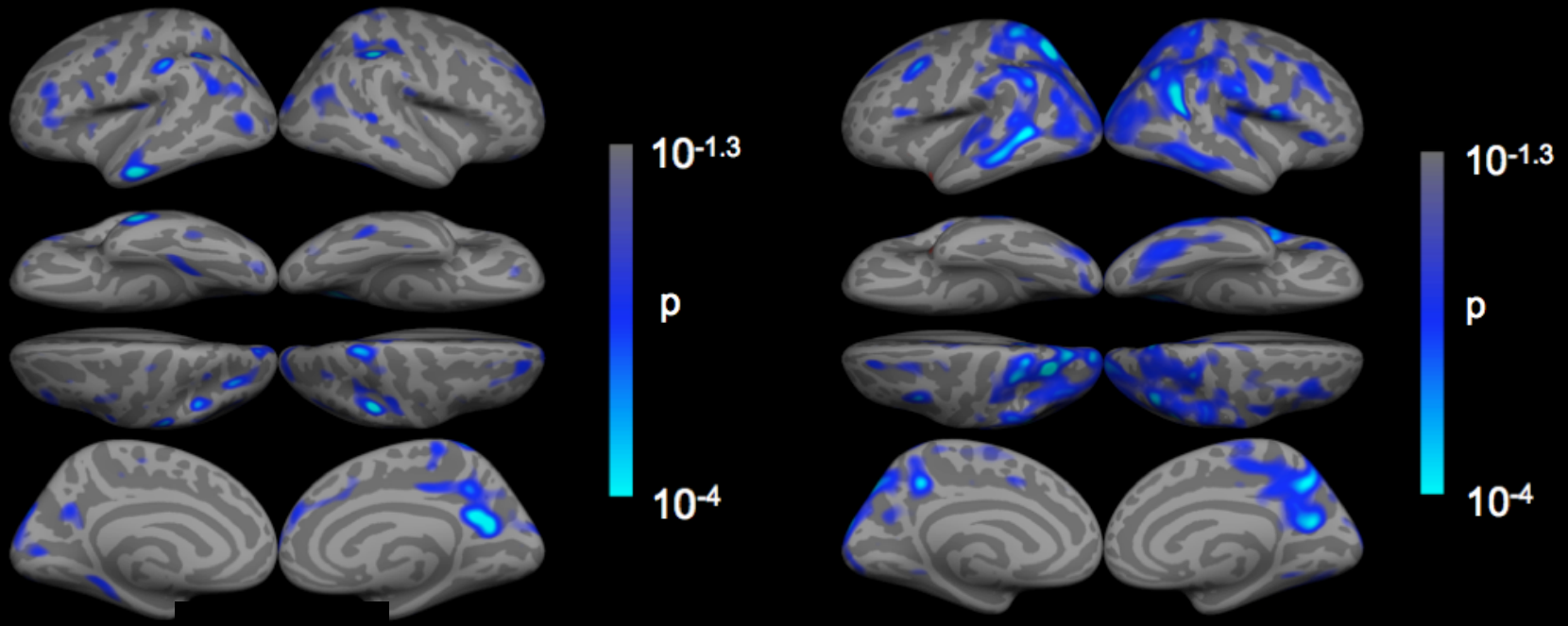


Sperling et al. *Neuron* 2009
(Also see Vannini *Neurobio of Aging* 2011; Vannini *Cerebral Cortex* 2012; Kennedy *NeuroImage* 2012)



Hedden et al. *J Neurosci* 2009
(Also see Sheline *Bio Psych* 2010; Mormino *Cerebral Cortex* 2011; Drzezga *Brain* 2011)

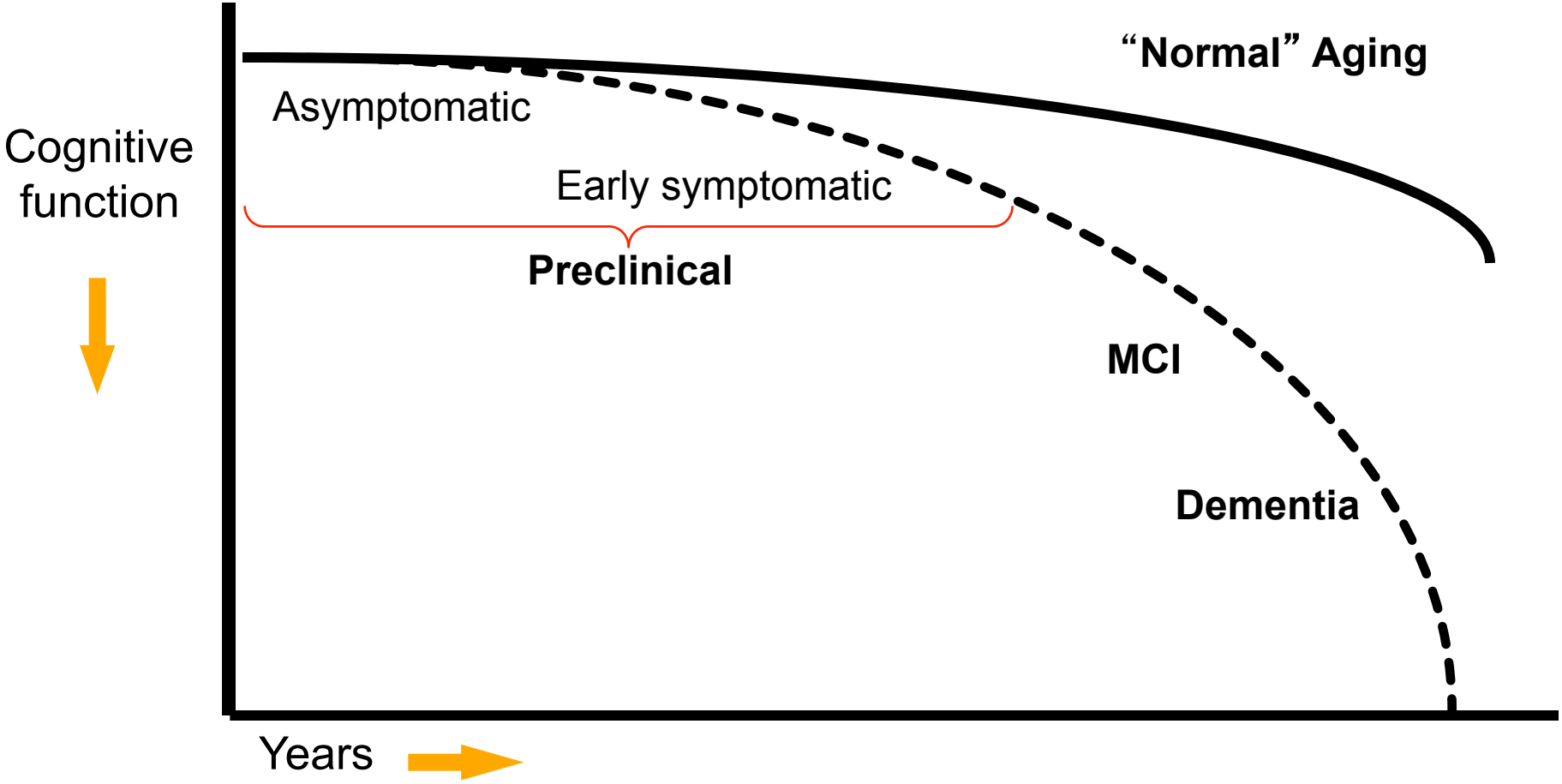
Aβ-associated reduction in cortical thickness in clinically normal elderly



Becker JA et al. *Annals of Neurology* 2011

(Also Schott *Annals* 2010; Dickerson *Cerebral Cortex* 2009;*Neurology* 2011; Sabuncu *Arch Neurology* 2011;Chetalat *Neurology* 2012)

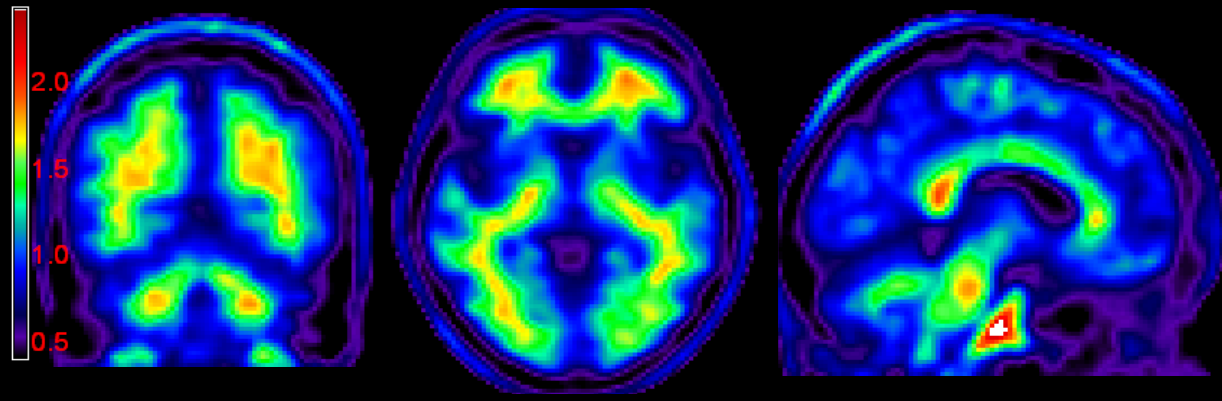
The continuum of Alzheimer's disease



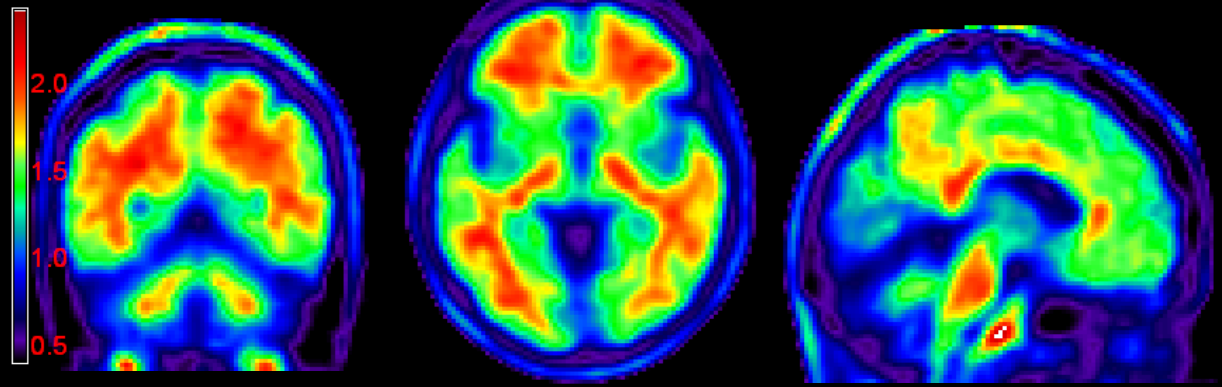
Sperling R et al *Alz & Dementia* 2011

^{18}F-AV-45 Representative Images: Healthy Controls

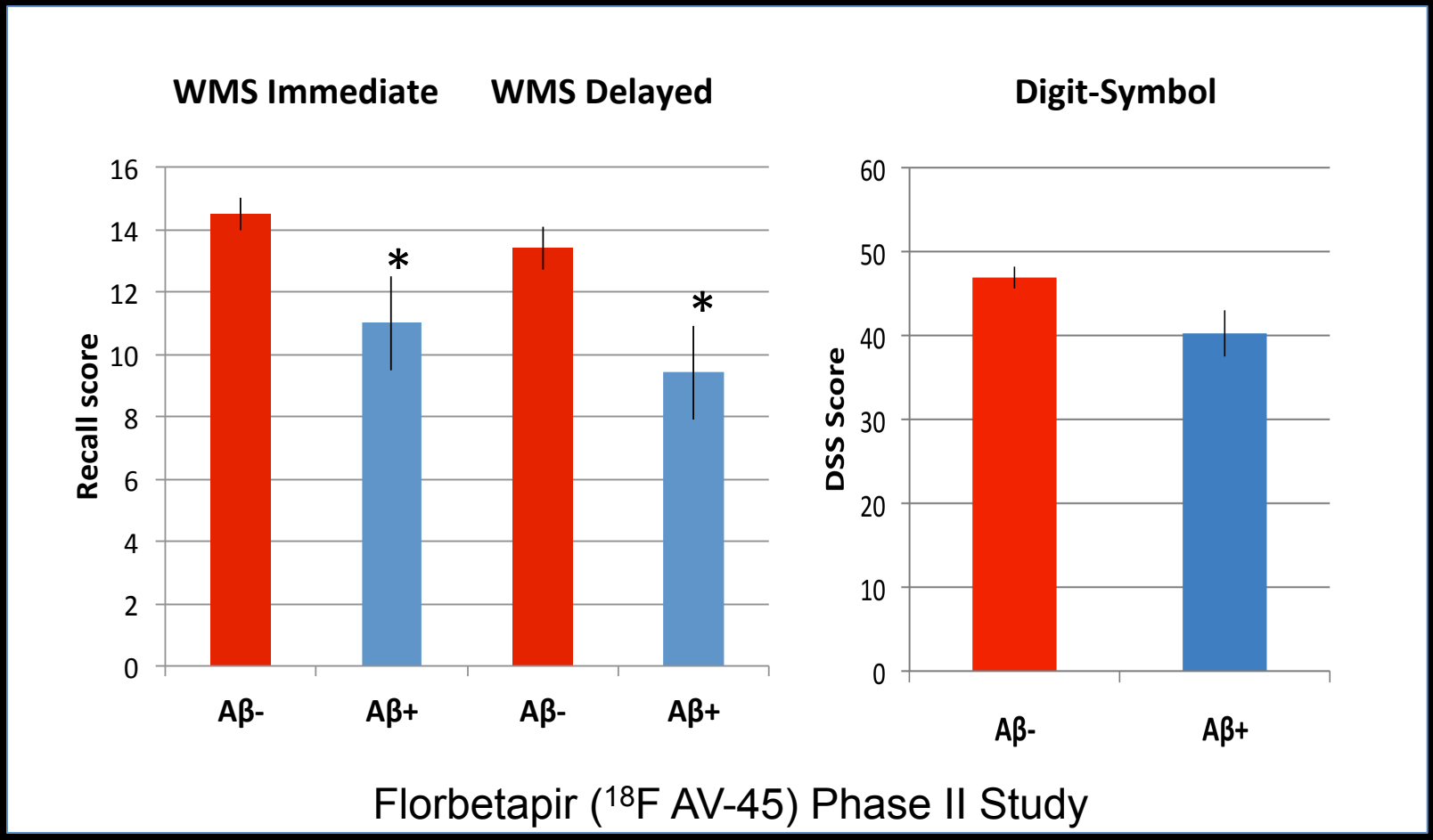
Amyloid Negative HC



Amyloid Positive HC

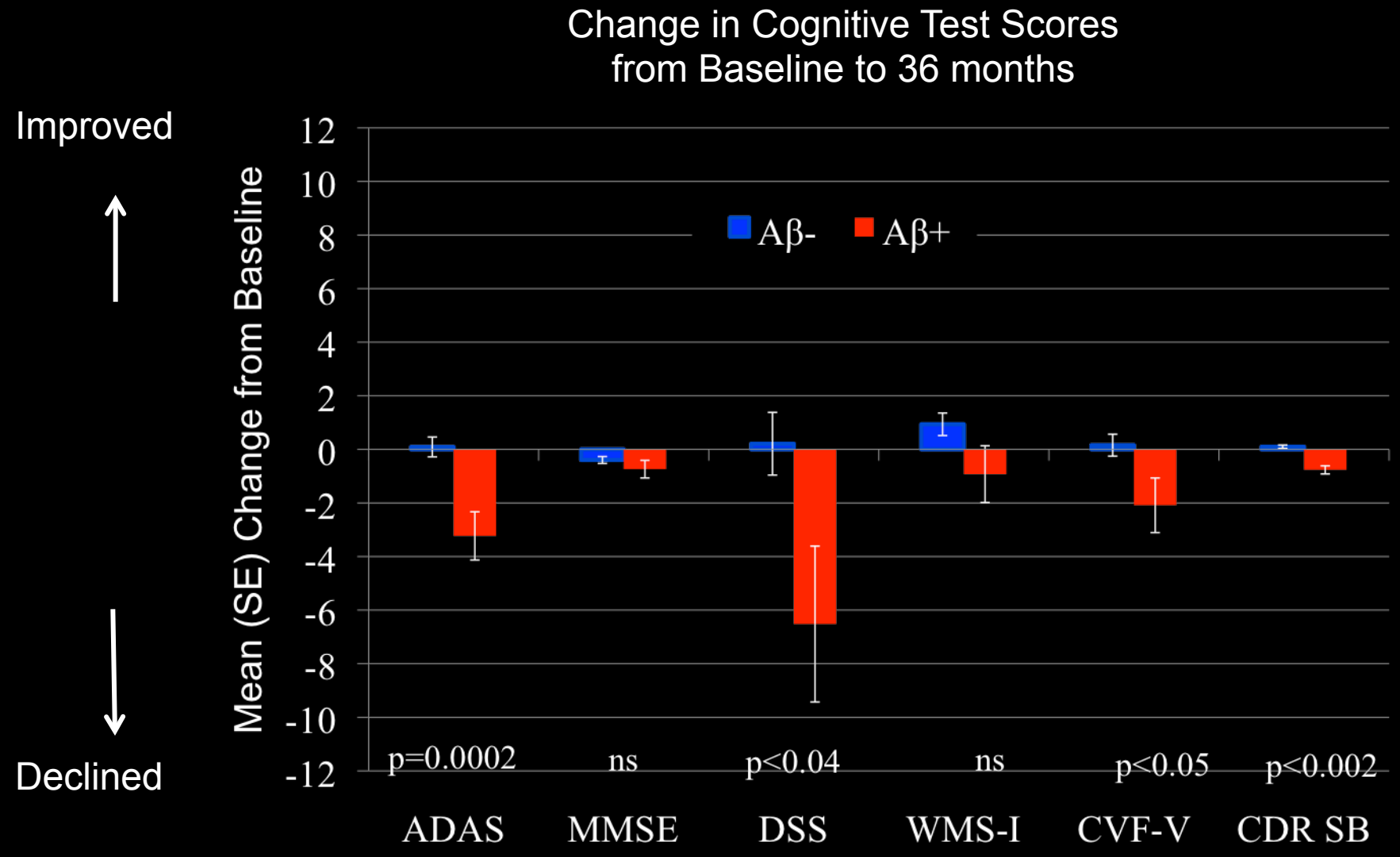


Cognition in Aβ Pos vs. Neg in HC > 70 years old



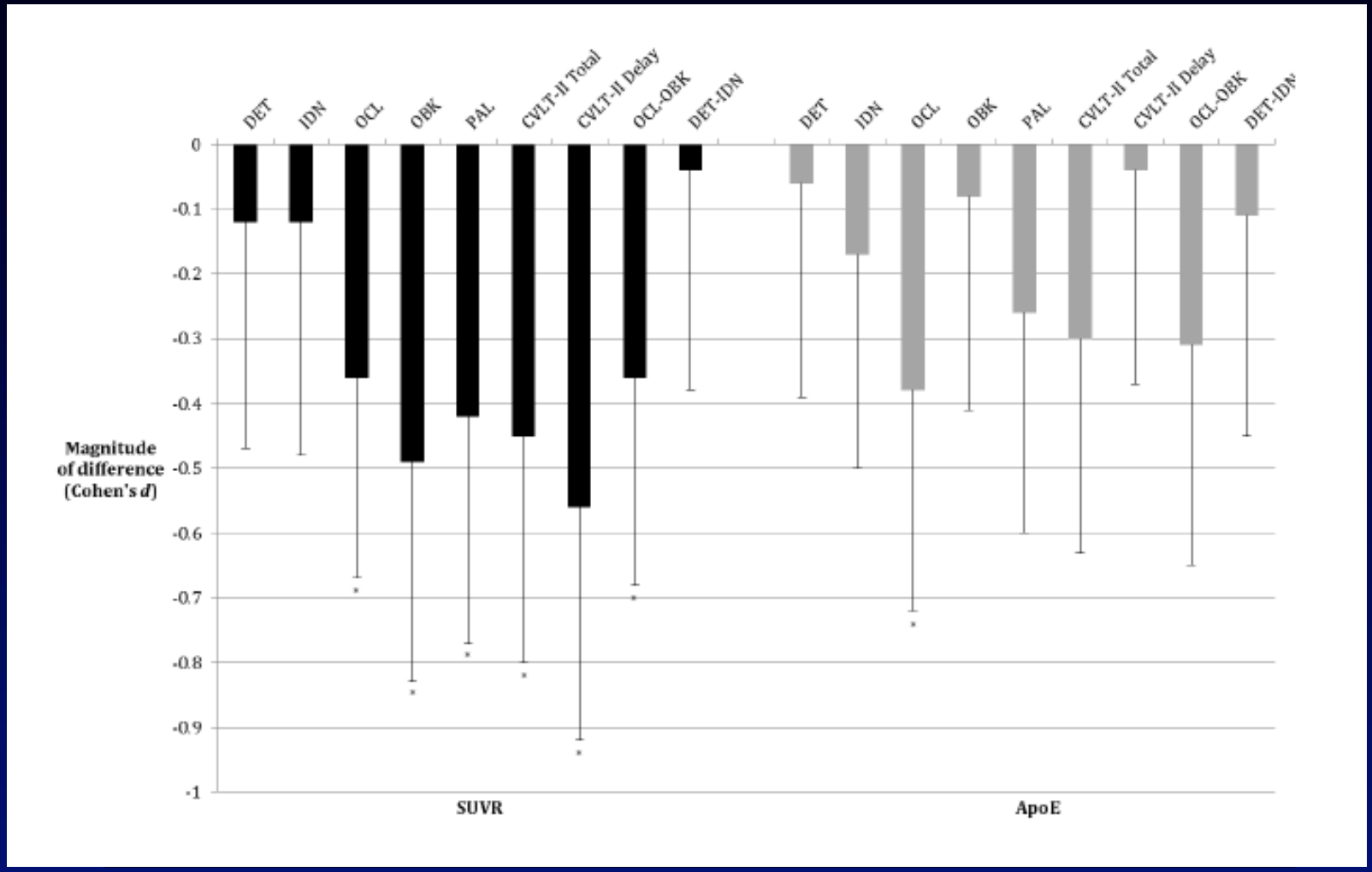
Sperling R et al *Neurobiology of Aging* 2012

Aβ related cognitive decline - Prospective Florbetapir Phase 2 Follow-up Study



Doraiswamy M, Sperling R, Coleman E et al. AAIC 2012

Faster rate of cognitive decline in HC with high Aβ burden – AIBL data



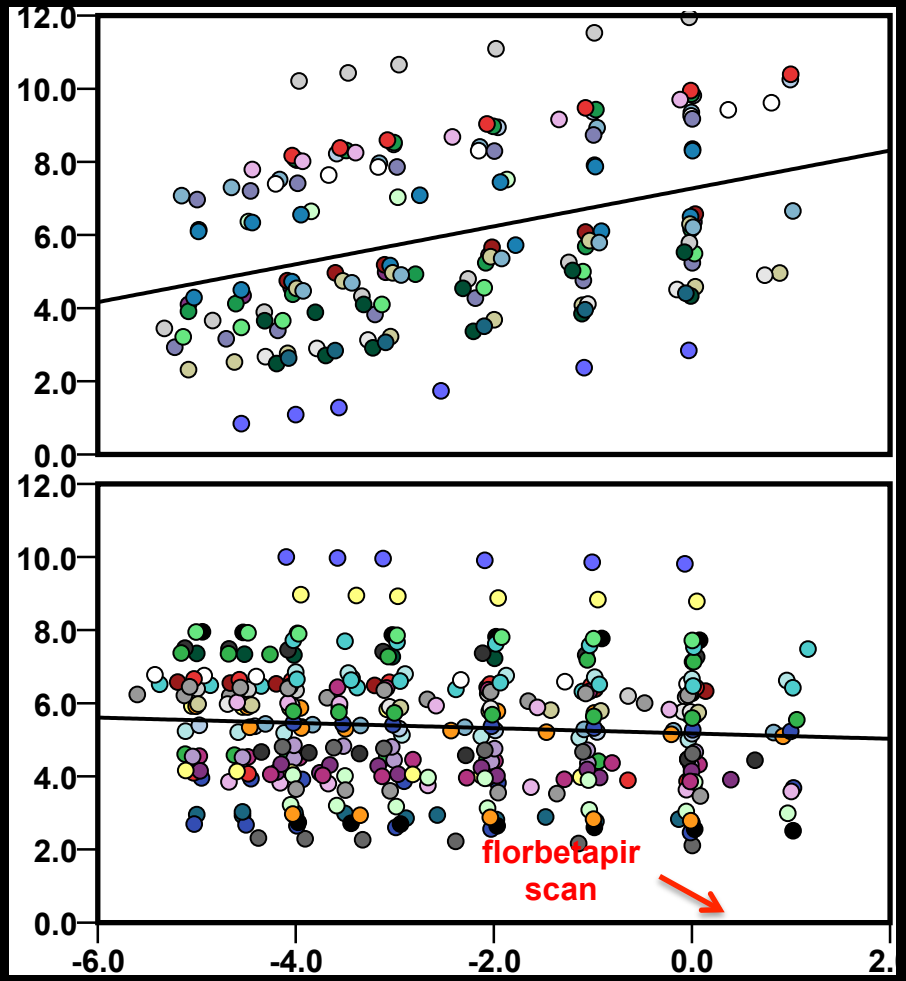
Lim et al. *Neurology* 2012

Aβ related cognitive decline - Retrospective
ADNI Normal Subjects (N=72)

Longitudinal ADAS-Cog Scores

Florbetapir +
N=23

Florbetapir –
N=49



Aβ+ 0.5 pt/year greater decline compared to Aβ- normals (p<0.001)

Landau S et al, *Annals of Neurology* In press

Testing the Criteria in the Community
Mayo Clinic

Table 3 Proportion of participants who progressed to MCI/AD within 15 months by stage

Comparison	Proportion progressed to MCI/ dementia within 15 mo, n (%)	p Value
Trend test stage 0–3	6 (5), 5 (11), 8 (21), 3 (43)	<0.001
Stage 0 vs 1–3	6 (5) vs 16 (18)	0.002
Stage 1 vs 2	5 (11) vs 8 (21)	0.26
Stage 2 vs 3	8 (21) vs 3 (43)	0.21
Stage 1–3 vs SNAP group	16 (18) vs 7 (10)	0.18
Stage 2 + 3 vs SNAP group	11 (24) vs 7 (10)	0.05
Stage 0 vs SNAP	6 (5) vs 7 (10)	0.15

Knopman et al. *Neurology* 2012

A4 Specific Aims

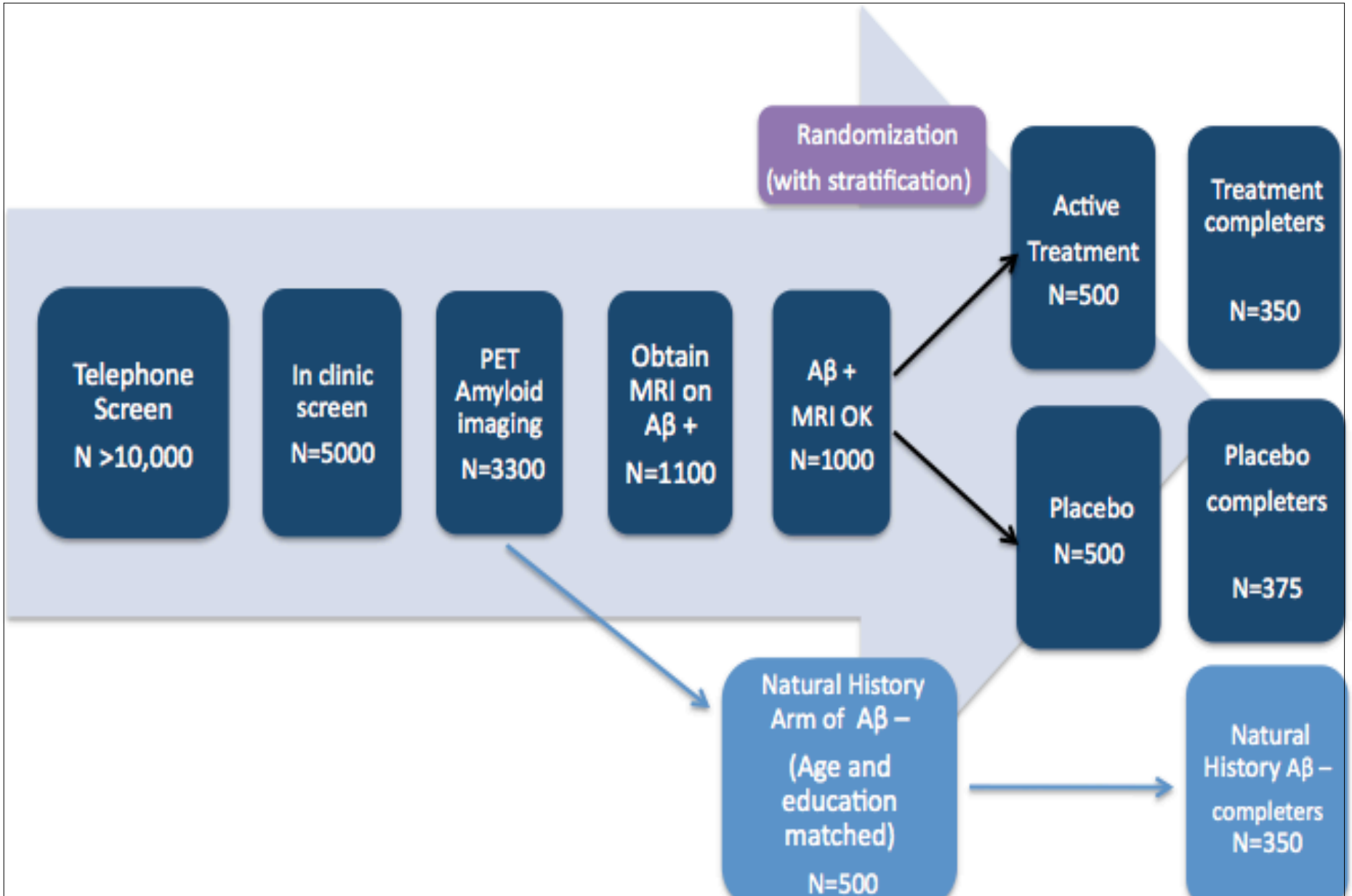
- To determine whether treatment with an anti-amyloid agent will slow the rate of cognitive decline in clinically normal older Aβ+ individuals at risk for progression to MCI and AD dementia
- To investigate the impact of anti-Aβ treatment on "downstream" markers of neurodegeneration, and explore whether there is a "critical window" for anti-Aβ therapy within the preclinical stages of AD
- To develop more sensitive outcome measures to improve the efficiency of future secondary prevention trials

Subjects Inclusion Criteria

- Ages 70 – 85; Positive on PET amyloid imaging
- 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 – 9 for high education

Education	<12	13-15	16	17+
Mean (sd) of normative group	10.5 (4.3)	12.3 (4.0)	12.8 (4.1)	13.7 (4.2)
0.5	13	14	15	16
-0.5	8	10	11	12
-1	6	8	9	10
-1.5	4	6	7	8
-2	2	4	5	7

A4 Screening and Randomization



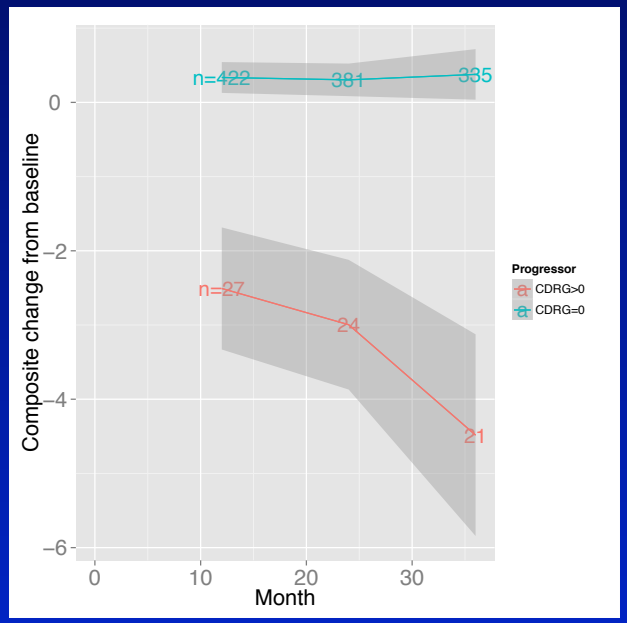
Natural History Arm

- Will screen fail 60-70% of A4 subjects for randomization to treatment arms
- Important group to capture baseline cognitive measures and blood samples – gold standard Aβ−
- Plan to follow at least 500 Aβ− matched for age, education in natural history arm. Current plan is clinical and cognitive assessments only
- Work to find funding to obtain biomarkers and follow-up imaging, potentially enlarge sample and study as natural history aging cohort

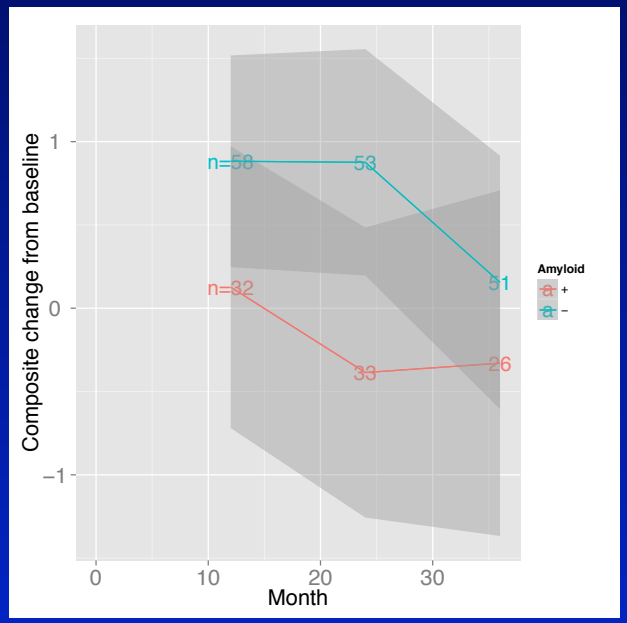
A4 – Power Calculations

- Primary outcome – Cognitive Composite
- Utilized longitudinal data sets from ADCS, AIBL, ADNI, Wash U comparing Aβ+ vs. Aβ- decline
- Ran large number of analyses assuming:
  - Power=.80 to detect 30% difference in rate of decline
  - 30% attrition, MMRM model, alpha 0.05 two-sided
  - Total N =1000 (500 per treatment arm) yields power to detect 28% difference in rate of cognitive decline over 3 years
  - Well-powered to detect change on biomarkers

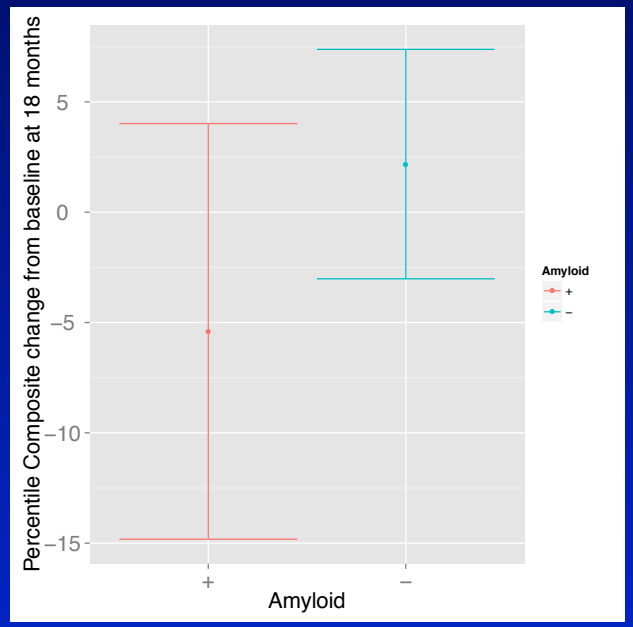
Decline estimates in clinically normal older populations divided by Aβ positivity (also APOE or Progression to MCI)



ADCS PI
Total N =238



ADNI
Total N = 1078



AIBL
Total N = 610

- Power with N =1000 (500 per arm) to detect 30% difference
  But just in case, built in Sample Size re-estimation algorithm based on decline in the placebo group

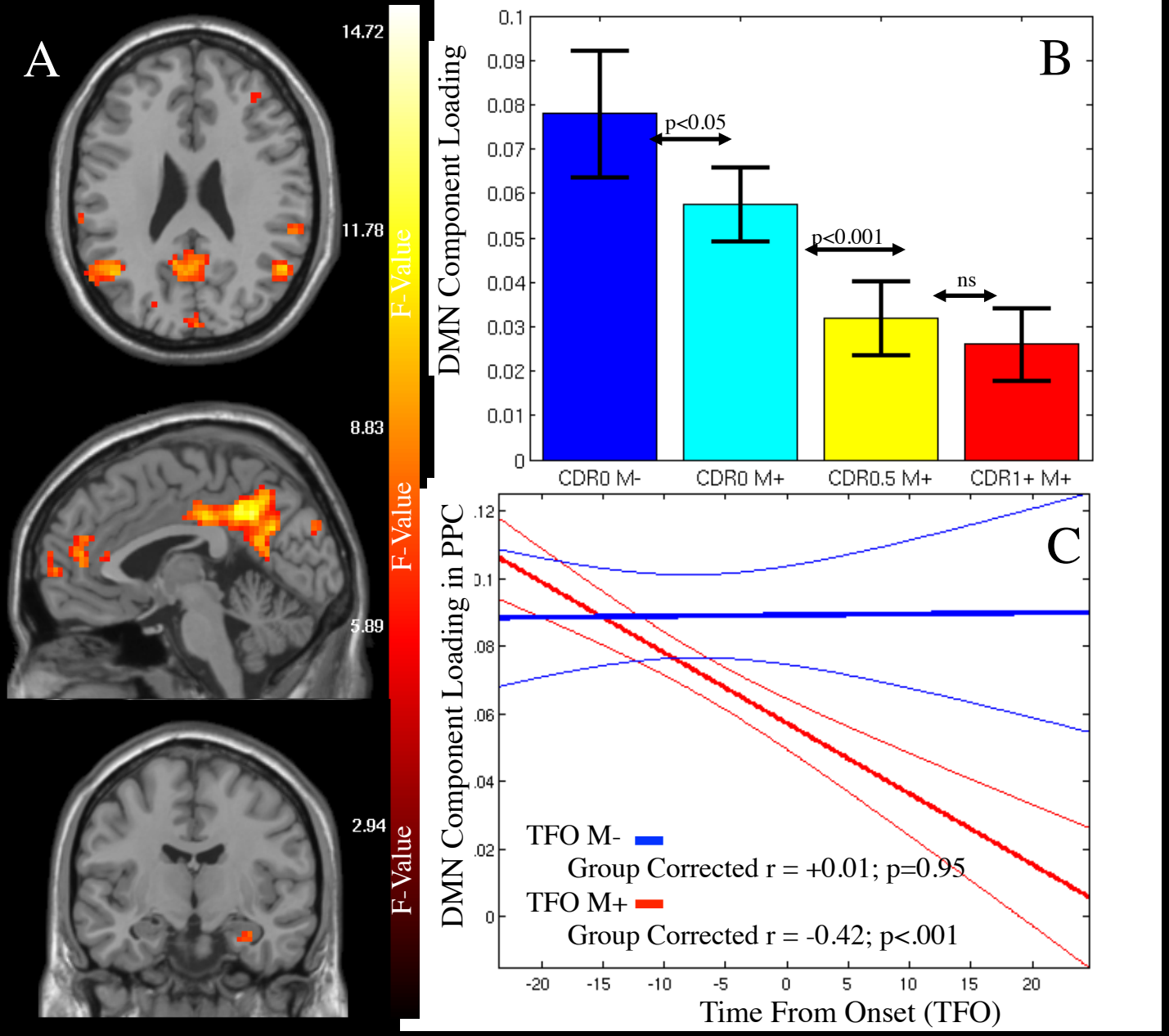
A4 Clinical Outcome Measures

- Primary outcome – Rate of decline on Cognitive Composite
  - Episodic memory – Free and Cued Selective Reminding delayed recall and LM paragraph recall
  - Timed executive function test – Digit Symbol
  - MMSE
- Secondary clinical outcomes
  - Novel computerized battery – face-name memory, object pattern separation, attentional measures CogState
  - Patient reported outcomes – e-COG, others
  - CDR Sum of Boxes

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
  - Default network connectivity
- Consider FDG in subset if can obtain additional funding

Multi-center Task-free Functional Connectivity:DIAN



Chhatwal et al. AAIC 2012

A4 Decisions–Therapeutic Agent

- Must have evidence of biological activity/target engagement and adequate safety data to support a 3 year trial in clinically normal older subjects
- Company willing to partner with ADCS
- Process for selection: partnership with DIAN treatment selection committee, final approval by the ADCS steering committee
- Current plan for decision late 2012/early 2013
- Considering future addition of second arm via prevention RFA or combination (2 x 2 factorial)

A4 Ethical Considerations

- Will be revealing amyloid status to normal subjects
- Unknown risk at individual subject level of progression to MCI and AD dementia
- Risks of biologically active anti-amyloid agents
- A4 Ethics substudy
  - Pilot work on language for consent form and factors that impact likelihood of participation
  - Substudy project within A4 to assess impact of consent process and of revealing amyloid status to both amyloid positive and negative individuals

Collaboration for Alzheimer's Prevention

- A4, API, DIAN, other international prevention efforts, Alzheimer's Association, NIA, Fidelity
- Harmonize the primary outcome measures
  - If not identical then at least overlapping tests
  - Cross validation computerized cognitive composite
- Harmonize biomarker and imaging data acquisition for comparability
- Joint meetings with regulatory authorities
- Working together on selection of therapeutic agents

Urgency

- We are running trials at the end stages of a disease process that begins decade(s) before dementia
- Think about what happens when we wait to treat until after symptoms are clearly evident in cancer, HIV, stroke, osteoporosis, cardiac disease, diabetes… and the success with preventative Tx
- We have 10,000 baby-boomers turning age 65 every day in the US entering the age of risk
- We have many challenges but we must make the best decisions possible based on currently available data and move forward

Acknowledgments

- Paul Aisen, Mike Donohue, Ron Thomas and Alzheimer's Disease Cooperative Study
- Keith Johnson, Dorene Rentz, and Randy Buckner from the Harvard Aging Brain Study
- Colleagues from DIAN and API and the Collaboration for Alzheimer's Prevention
- National Institute on Aging