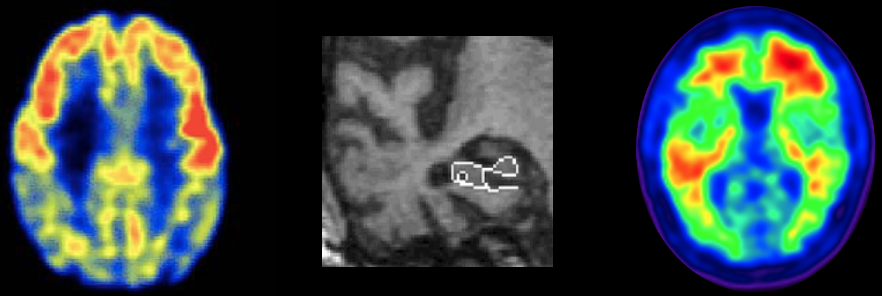
The Relationship between Biomarkers for Measuring and Predicting Progression in Aging, MCI and AD

Susan Landau



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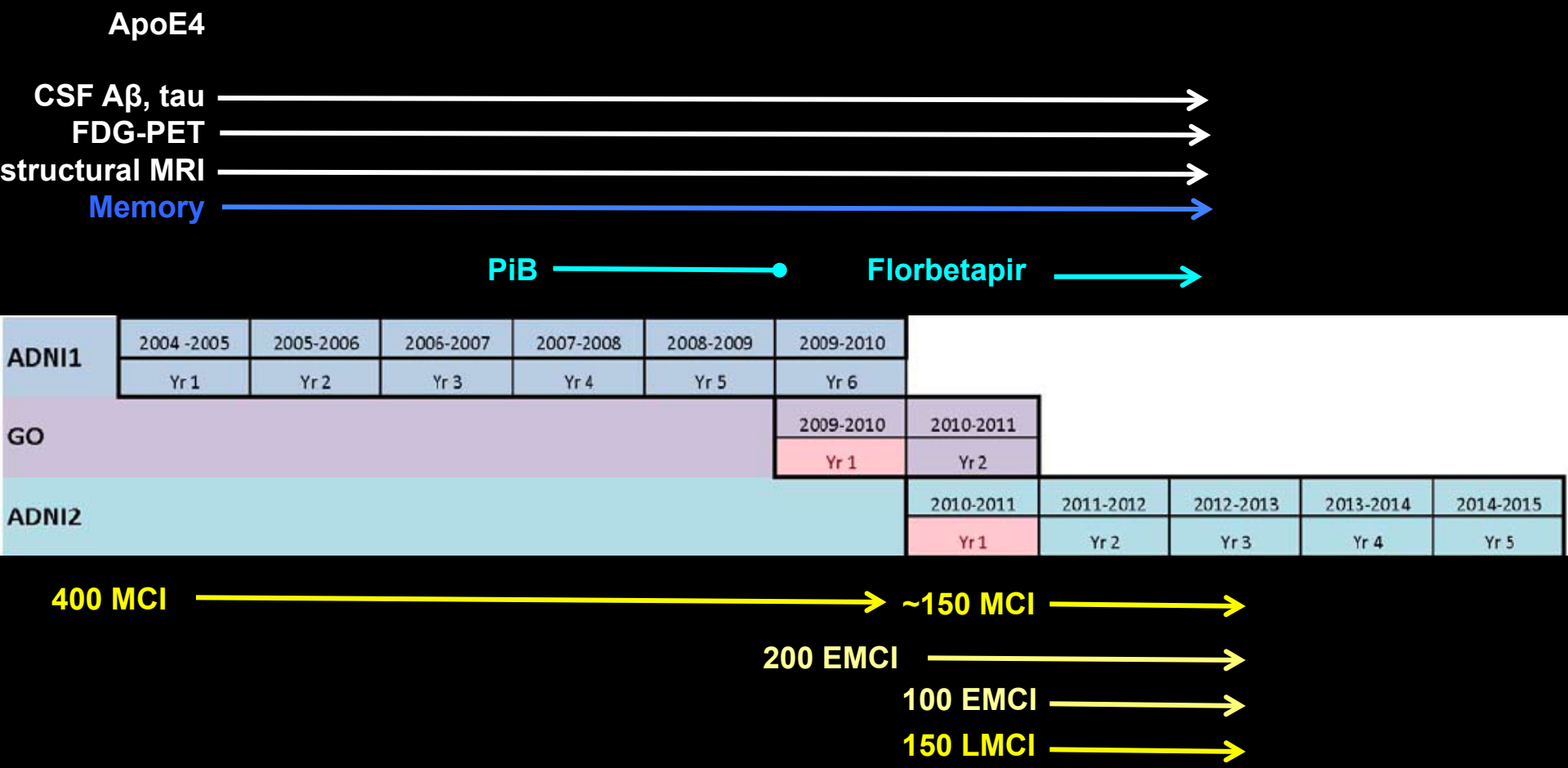
Challenges in MCI

Heterogeneous population

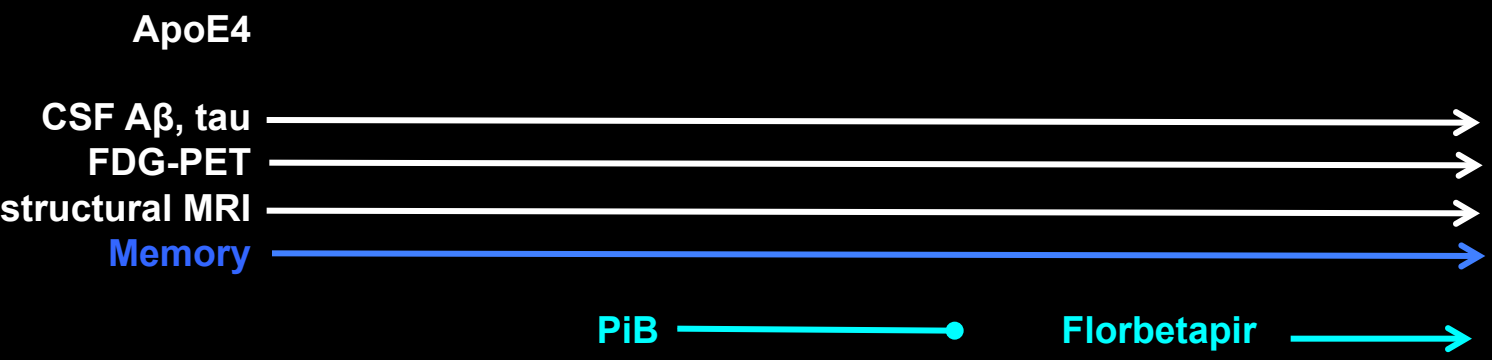
Clinical evaluation of conversion to AD involves subjectivity

Biomarkers and clinical measurements actively changing and likely to be in grey/borderline area

ADNI timeline



ADNI timeline



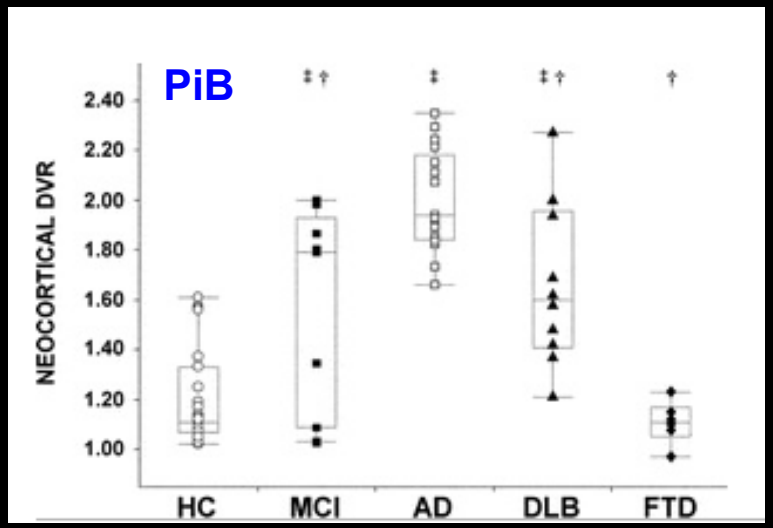
Biomarkers predict conversion

A variety of biomarkers are useful for predicting conversion, both independently and in multivariate models

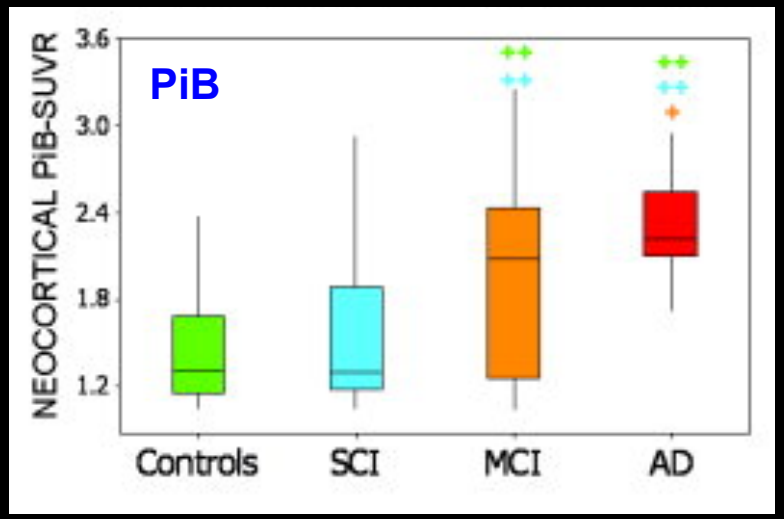
Ewers et al. Neurobiol Aging 2010
Gomar et al. Arch Gen Psych 2011
Cui et al. PLOSone 2011
Davatzikos et al. Neurobiol Aging 2011
Zhang et al. Neuroimage 2011
Westman et al. Neuroimage 2012

Findings vary as a result of different combinations of markers, statistical models, cutoffs

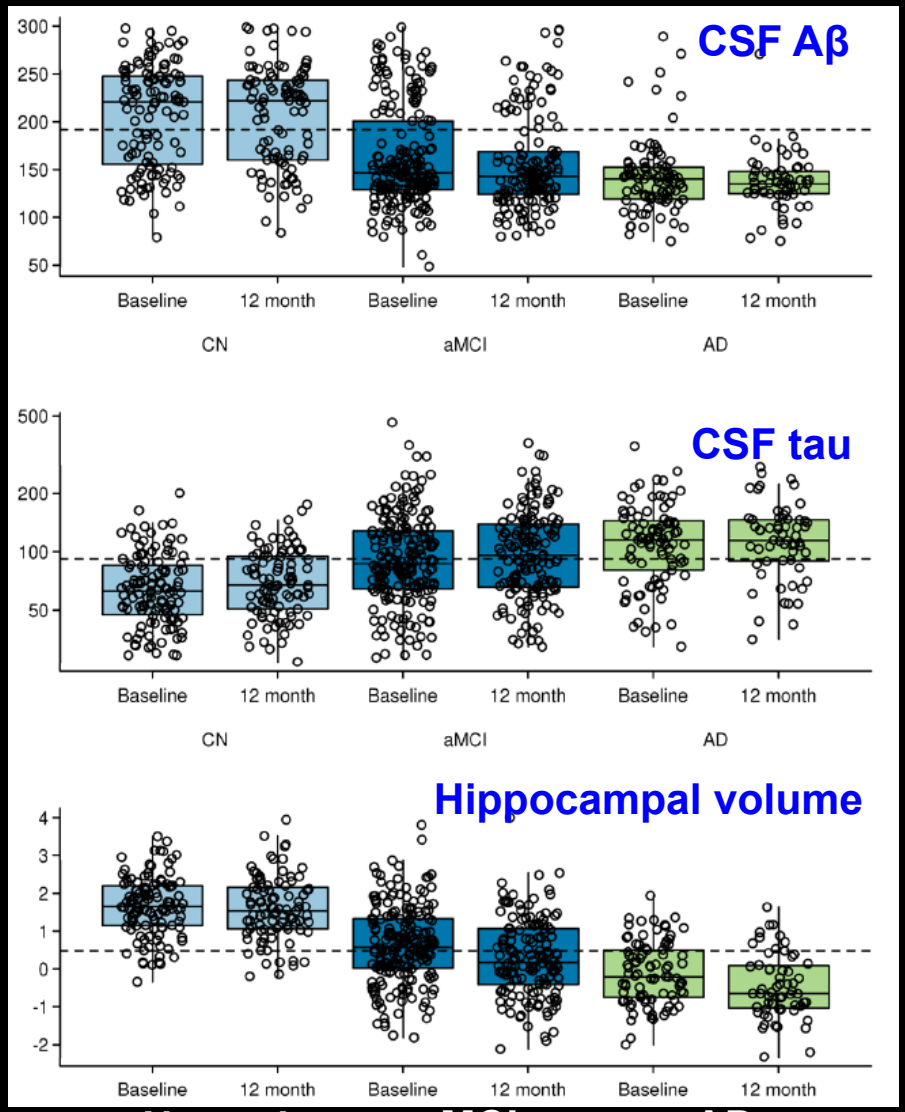
Biomarkers are intermediate & variable in MCI



Rowe et al. Neurology 2007



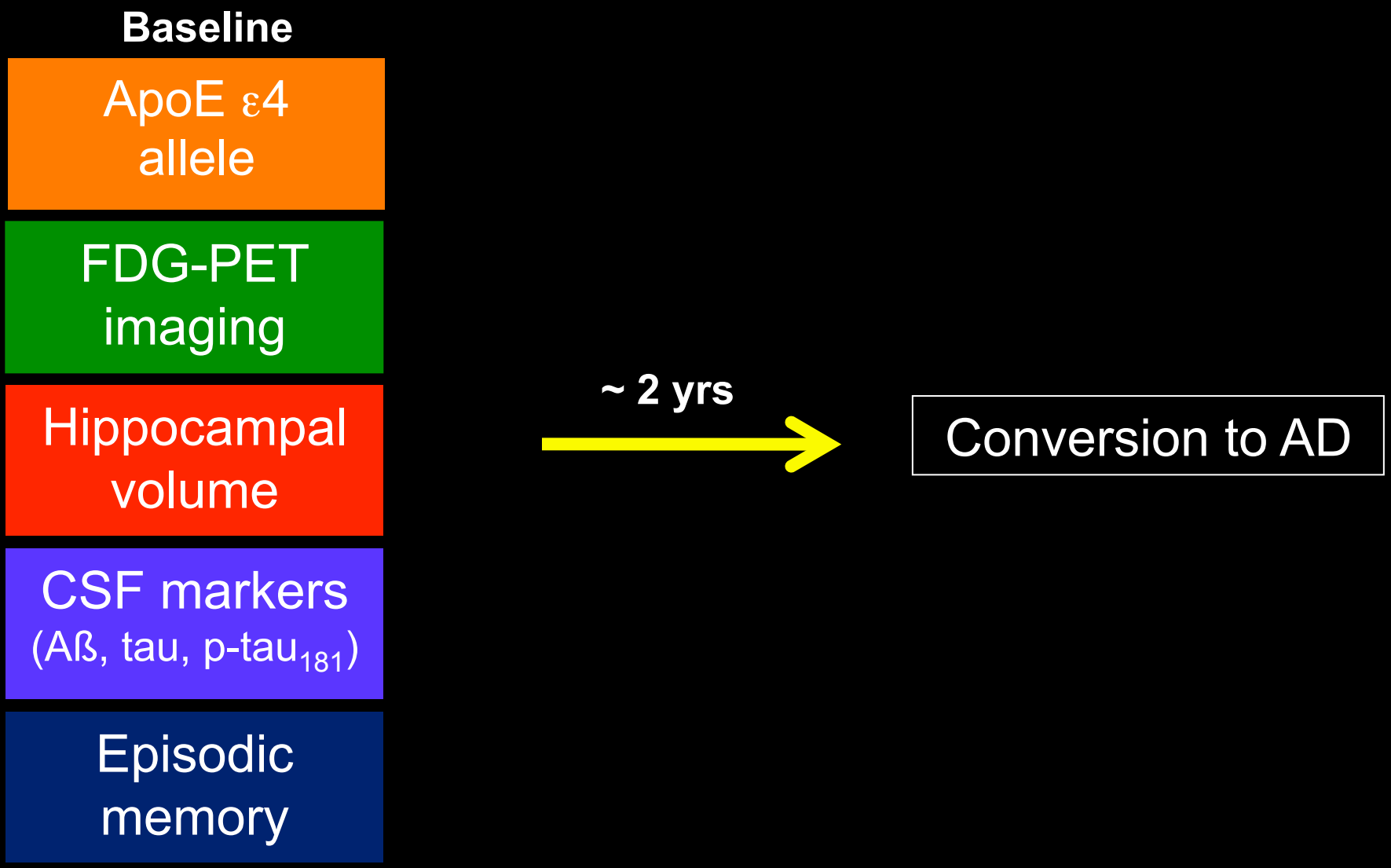
Chetelat et al. Ann Neurol 2010



Normal **MCI** **AD**

Jack et al. Arch Neurol 2011

Multiple biomarkers predict conversion



Multiple biomarkers predict conversion

Baseline	Hazard ratio	p-value
ApoE ε4 allele	1.94	p = 0.10
FDG-PET imaging	2.94	p = 0.02
Hippocampal volume	2.49	p = 0.04
CSF markers ($p\text{-}tau_{181}$/Aß)	3.99	p = 0.03
Episodic memory	4.68	p = 0.01

→ Conversion to AD

Landau et al. Neurology 2010

Multiple biomarkers predict conversion

Baseline	Hazard ratio	p-value
FDG-PET imaging	2.95	p = 0.02
Episodic memory	5.08	p = 0.01

→ Conversion to AD

Landau et al. Neurology 2010

Multiple biomarkers predict decline

Baseline p-value

FDG-PET imaging

p = 0.09

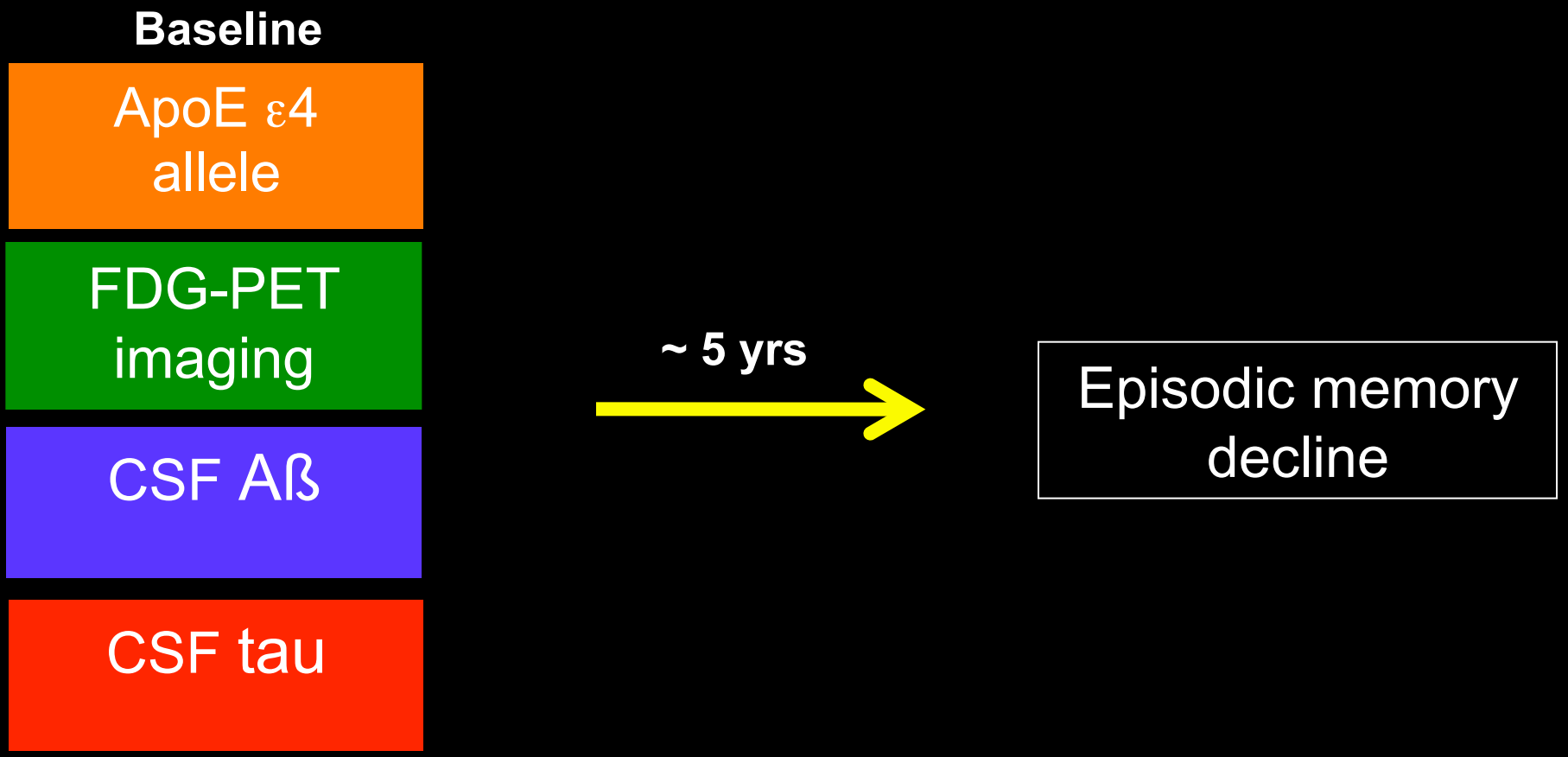
CSF markers ($p\text{-}tau_{181}$/Aß)

p = 0.04

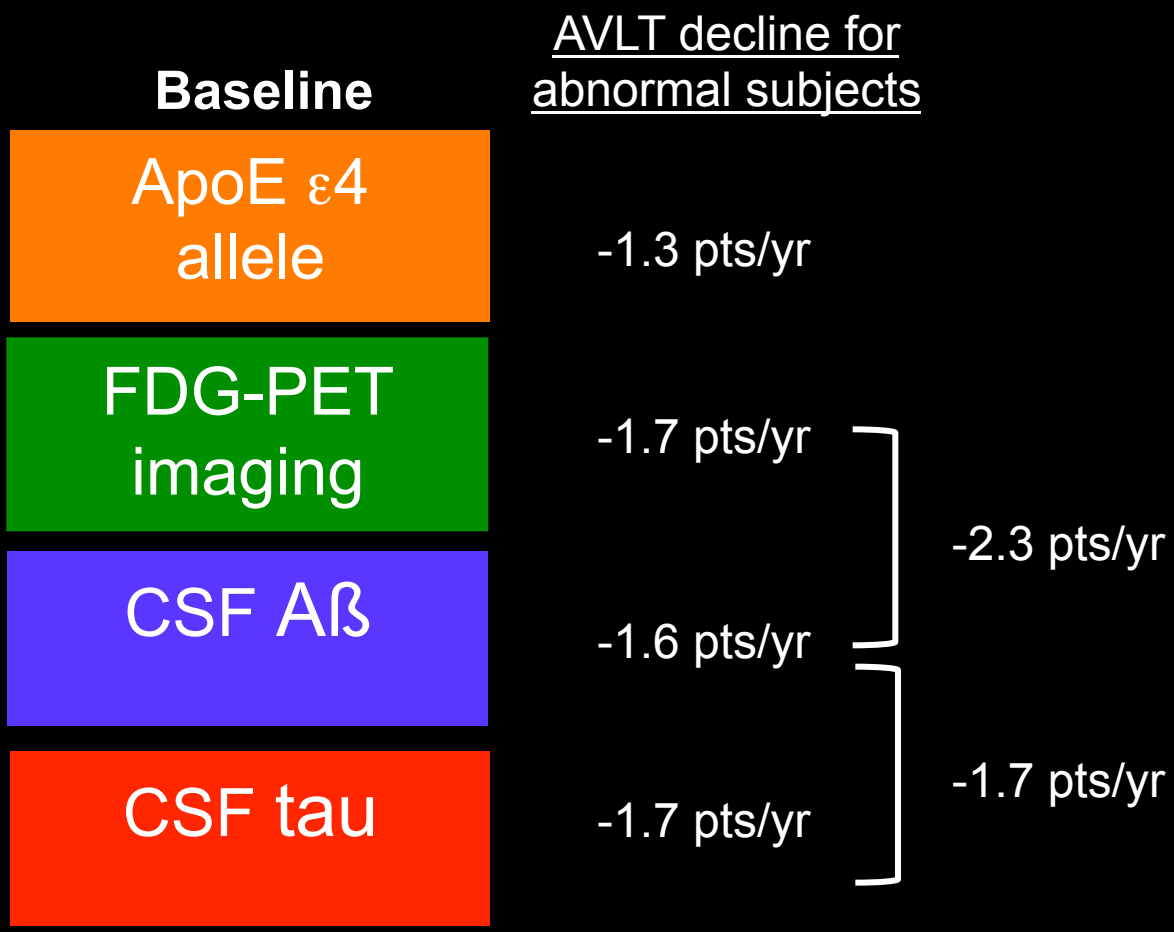
→ Episodic memory decline

Landau et al. Neurology 2010

Updated longitudinal data



Updated longitudinal data



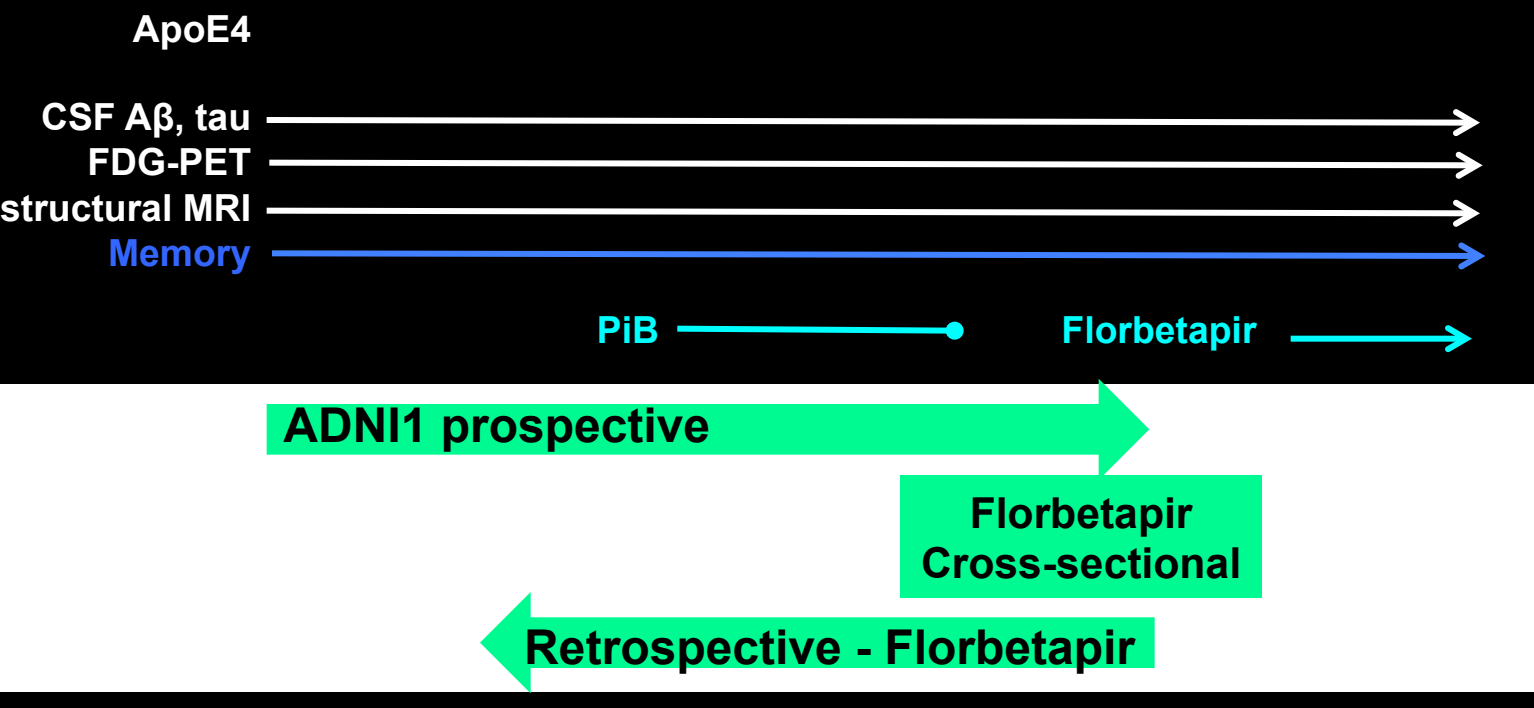
So far

Cognitive, amyloid, and neuronal injury measurements predict decline and progression

Neuronal injury markers (linked to later stages of disease) are especially useful for prediction

Unclear yet whether abnormal status on both amyloid & neuronal injury markers results in greater decline

ADNI timeline



ADNI1 prospective

Florbetapir Cross-sectional

Retrospective - Florbetapir

Disagreement between biomarkers

NIA/AA criteria: MCI due to AD

MCI criteria incorporating biomarkers

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (tau, FDG, sMRI)
MCI–core clinical criteria	Uninformative	Conflicting/indeterminant/untested	Conflicting/indeterminant/untested
MCI due to AD—intermediate likelihood	Intermediate	Positive Untested	Untested Positive
MCI due to AD—high likelihood	Highest	Positive	Positive
MCI—unlikely due to AD	Lowest	Negative	Negative

Albert et al. Alz & Dementia 2011

Conflicts occur between

Amyloid markers: CSF-Aβ & florbetapir

Amyloid & neuronal injury markers

CSF-Aβ & CSF-tau

Florbetapir & FDG-PET

Prodromal AD and MCI IWG criteria

Aß-PET, CSF, FDG-PET, structural MRI

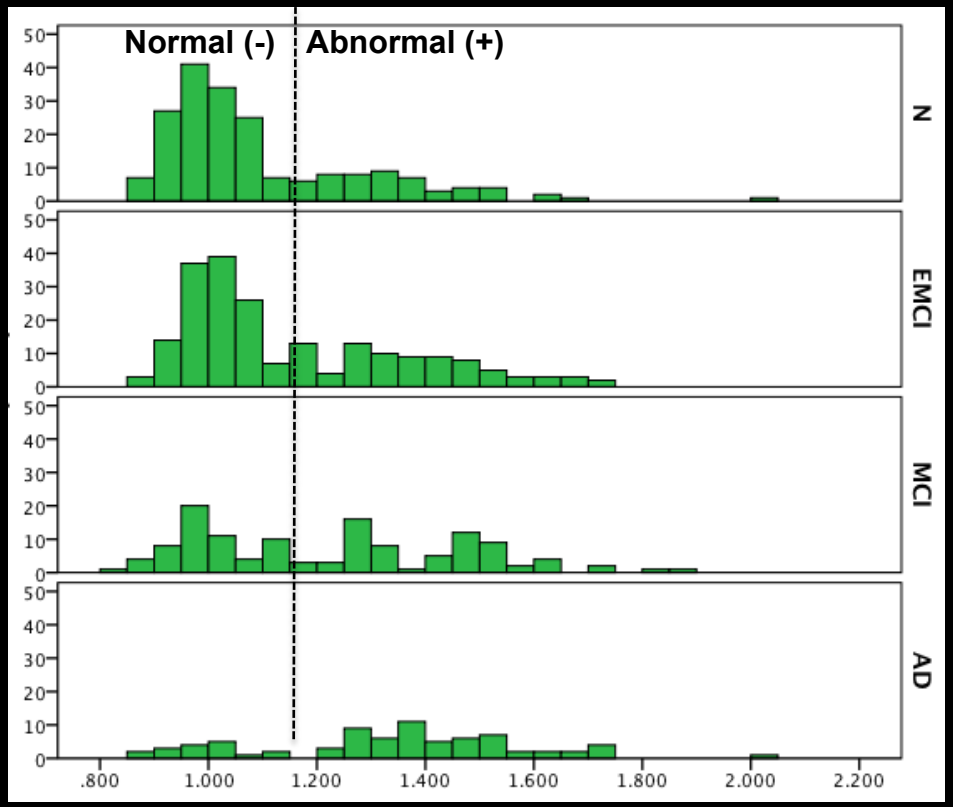
	AD diagnosis	Presence of impairment on specified memory tests	Evidence of biomarkers in vivo	Additional requirements
Typical AD	Yes	Required	Required	None
Atypical AD	Yes	Not required	Required	Specific clinical presentation
Prodromal AD	Yes	Required	Required	Absence of dementia
AD dementia	Yes	Required	Required	Presence of dementia
Mixed AD	Yes	Required	Required	Evidence of comorbid disorders
Preclinical AD				
Asymptomatic at risk for AD	No	Not present	Required	Absence of symptoms of AD
Presymptomatic AD	No	Not present	Not required	Absence of symptoms of AD and presence of monogenic AD mutation
Mild cognitive impairment	No	Not required	Not required	Absence of symptoms or biomarkers specific for AD

AD=Alzheimer's disease.

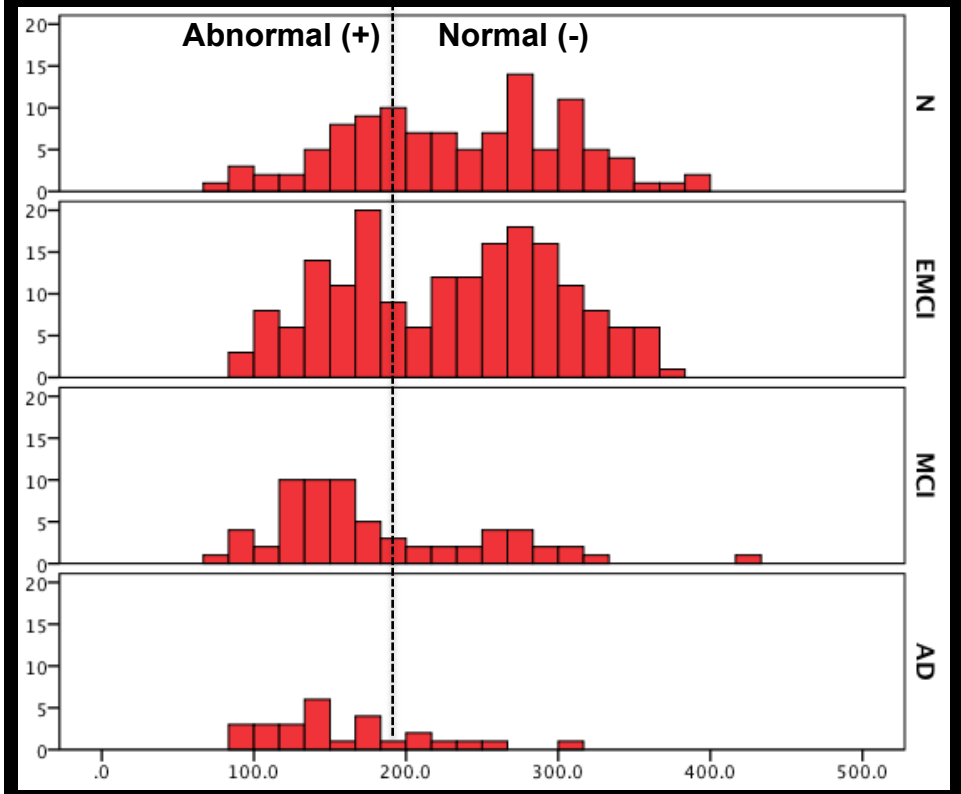
Dubois et al. Lancet Neurol 2010

Amyloid biomarkers

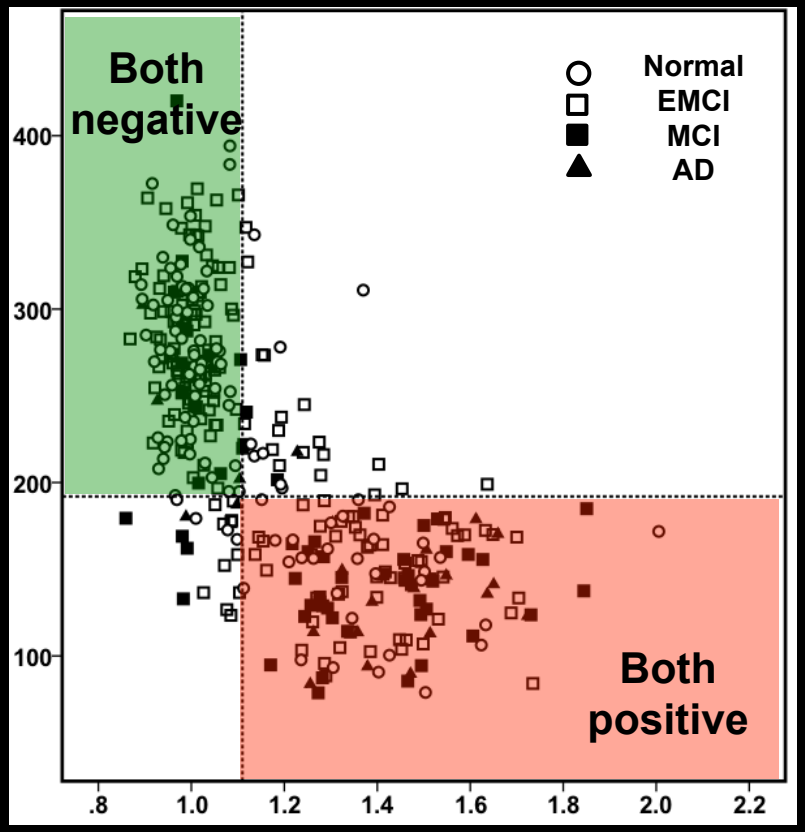
Florbetapir-PET

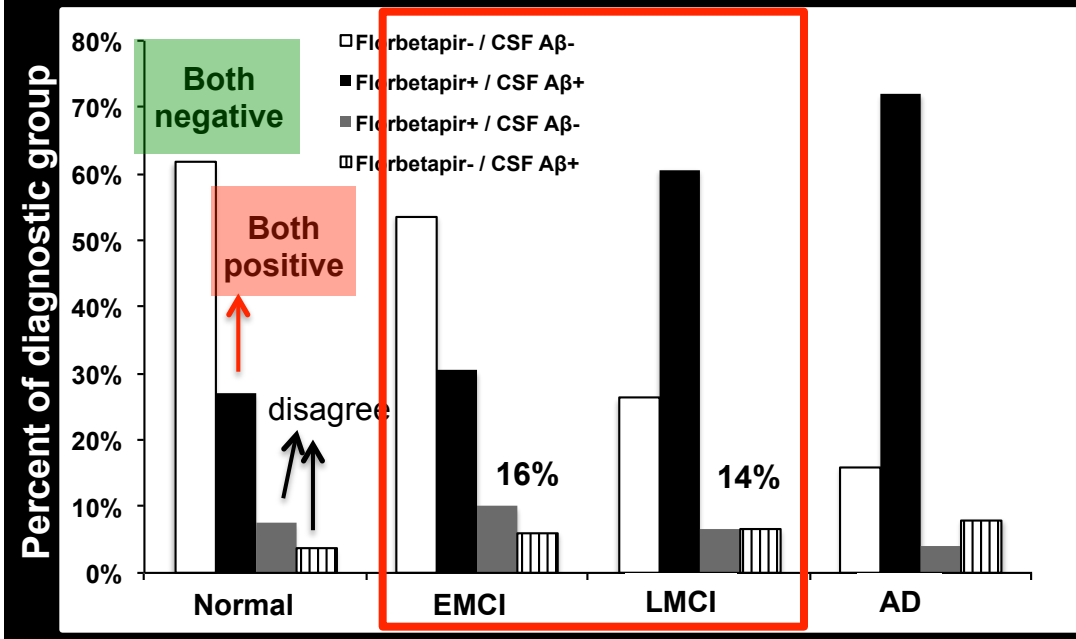


CSF Aβ



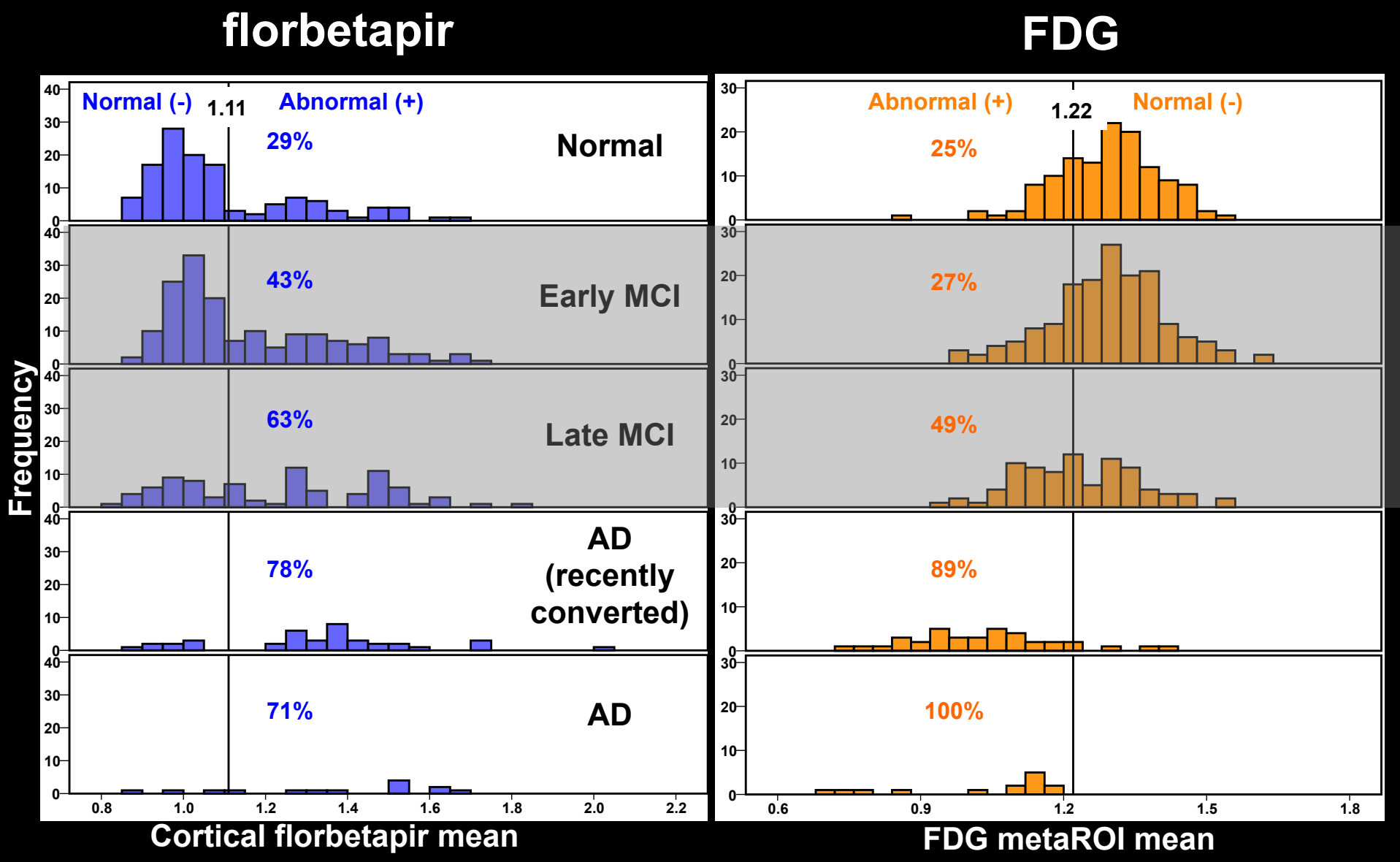
Agreement between Aβ markers: CSF Aβ and florbetapir





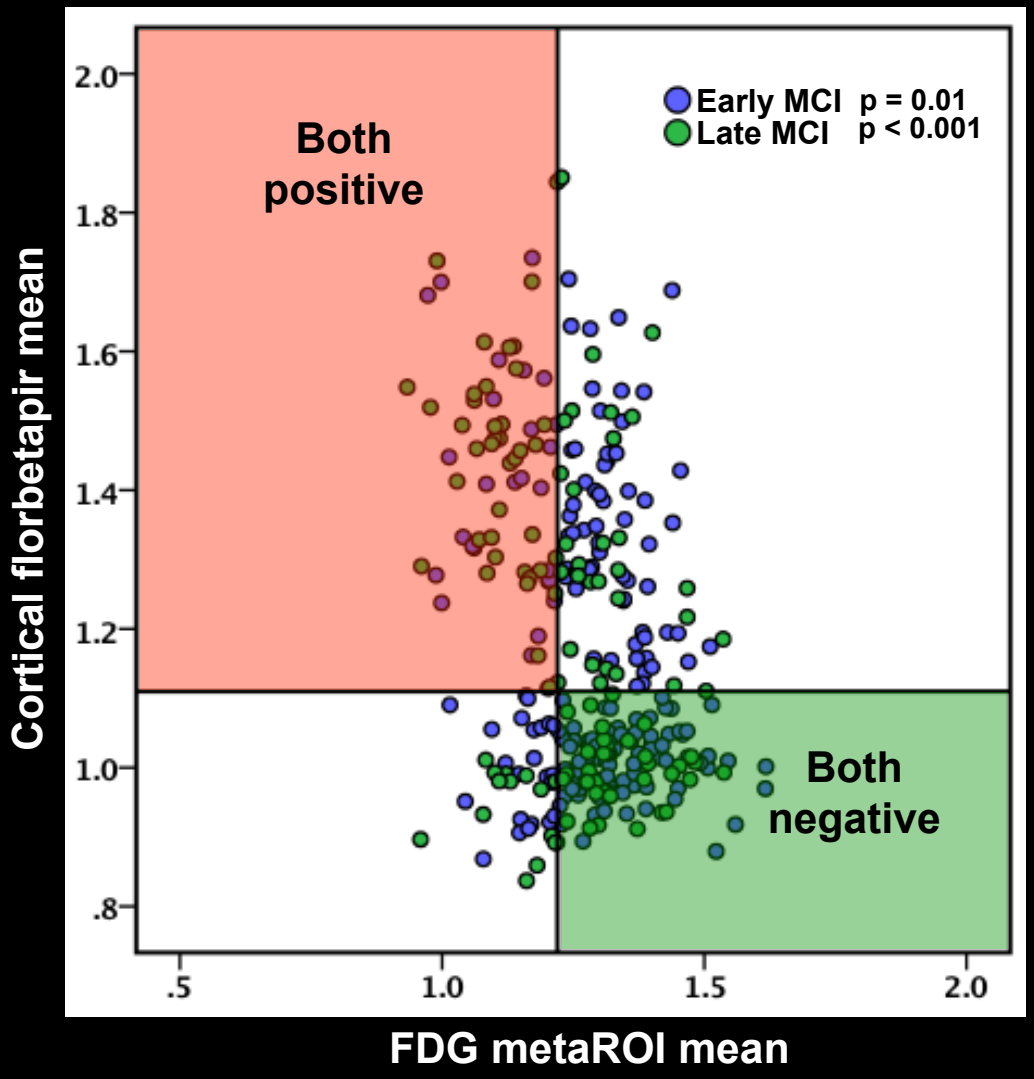
Aβ markers conflict for about 15% MCIs

Amyloid and hypometabolism in ADNI

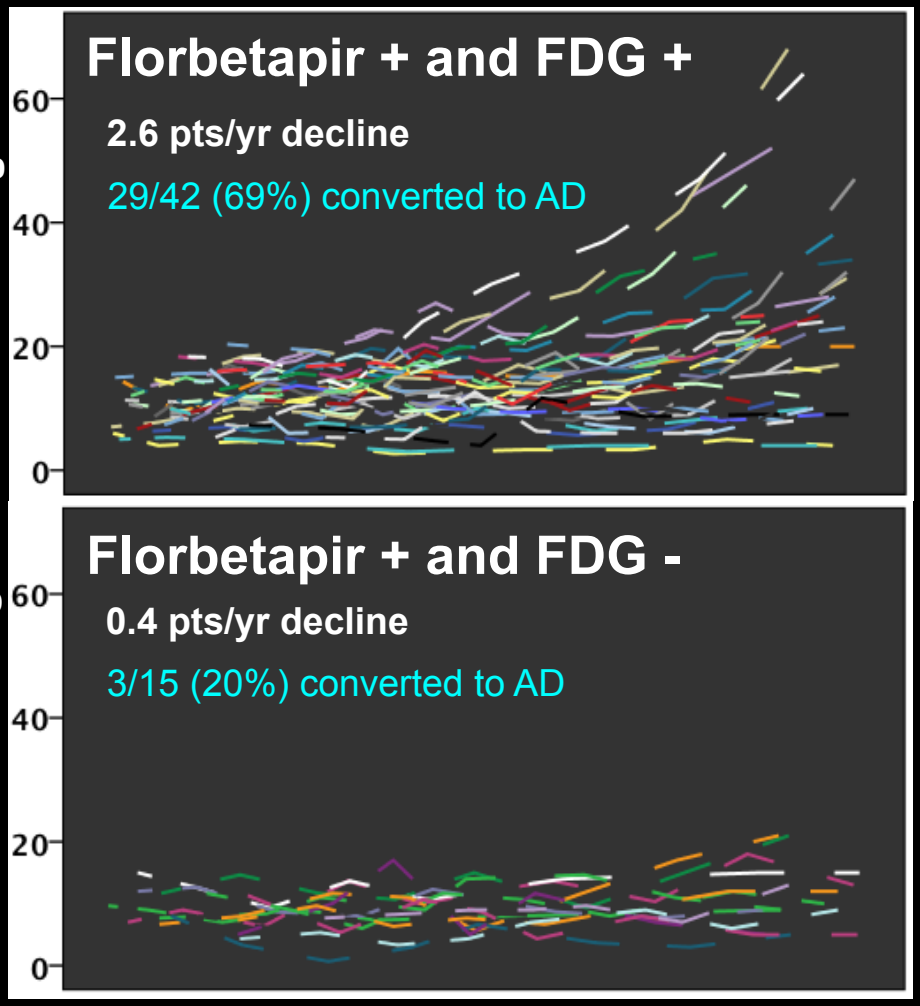


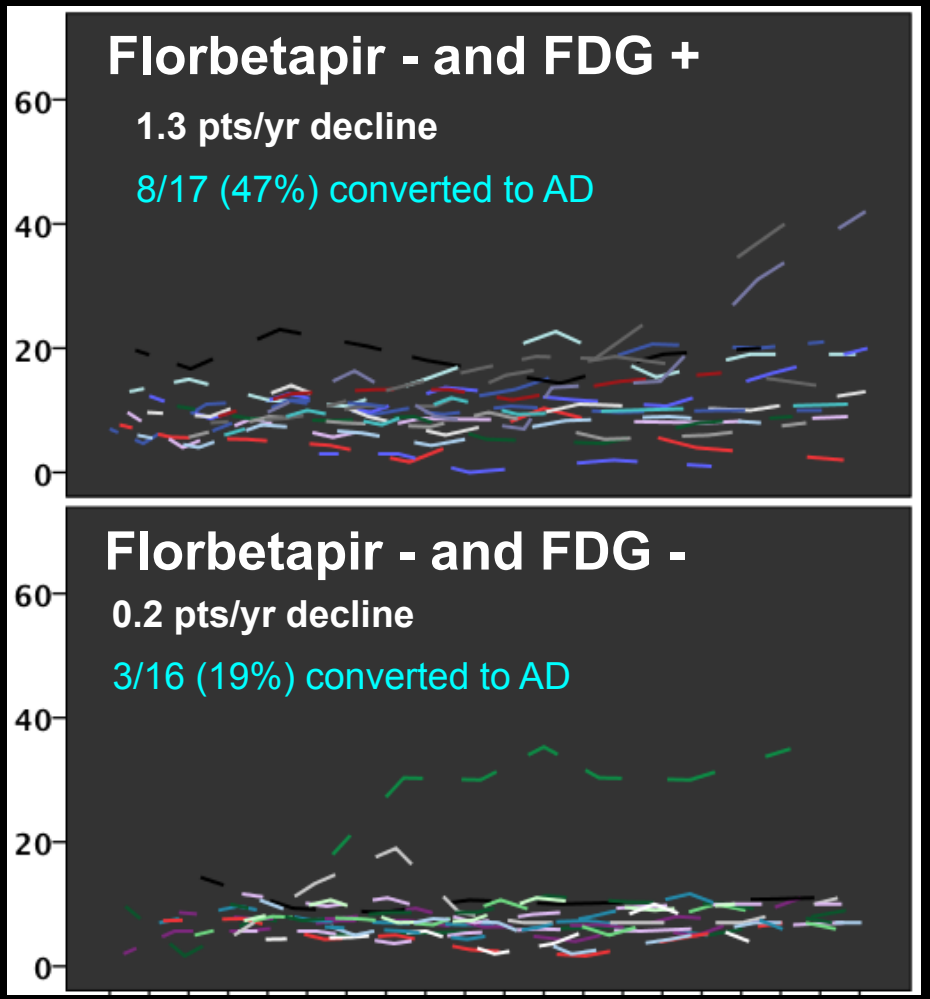
Landau et al. Annals Neurol in press

Agreement between florbetapir and FDG



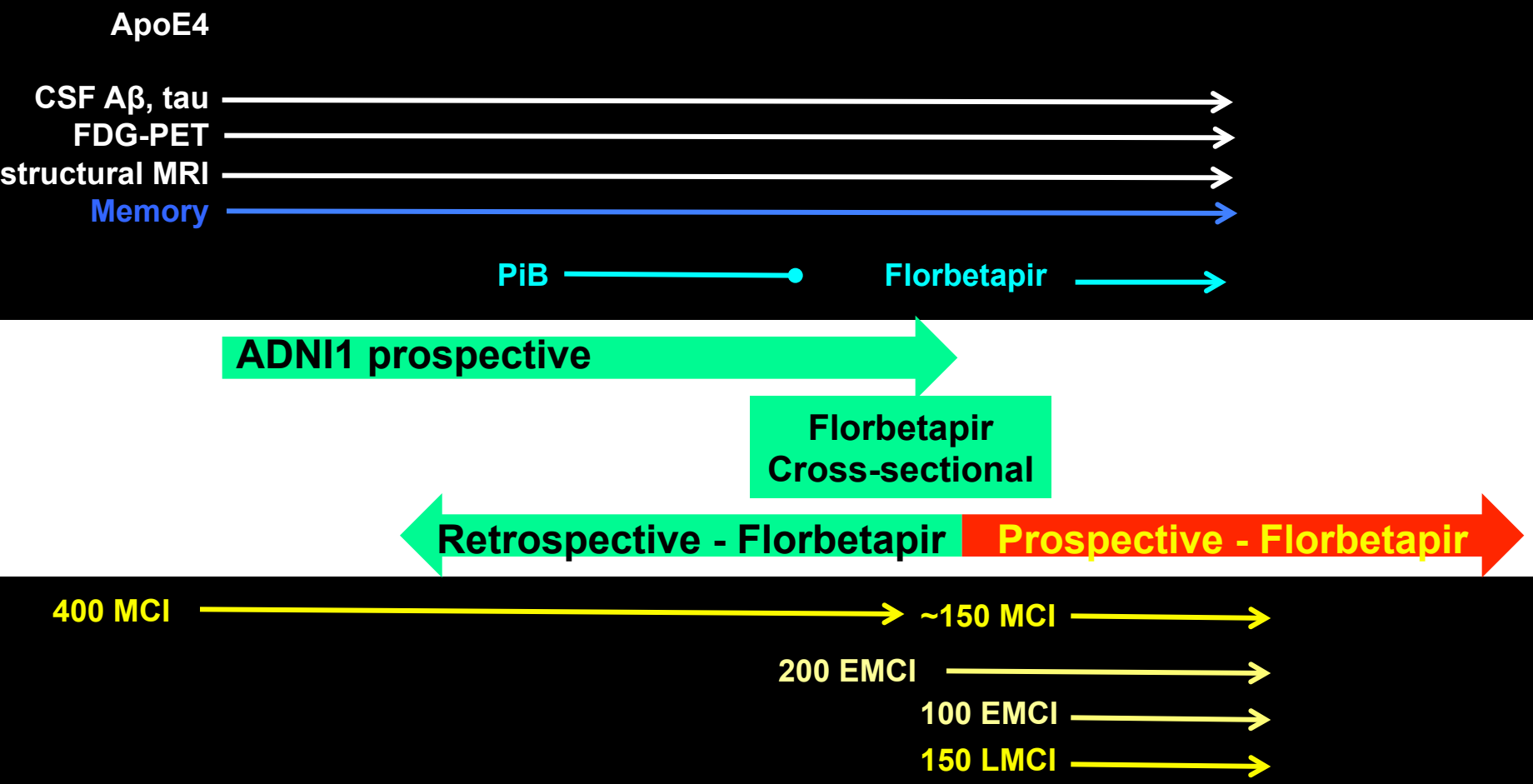
MCI: Retrospective cognitive change



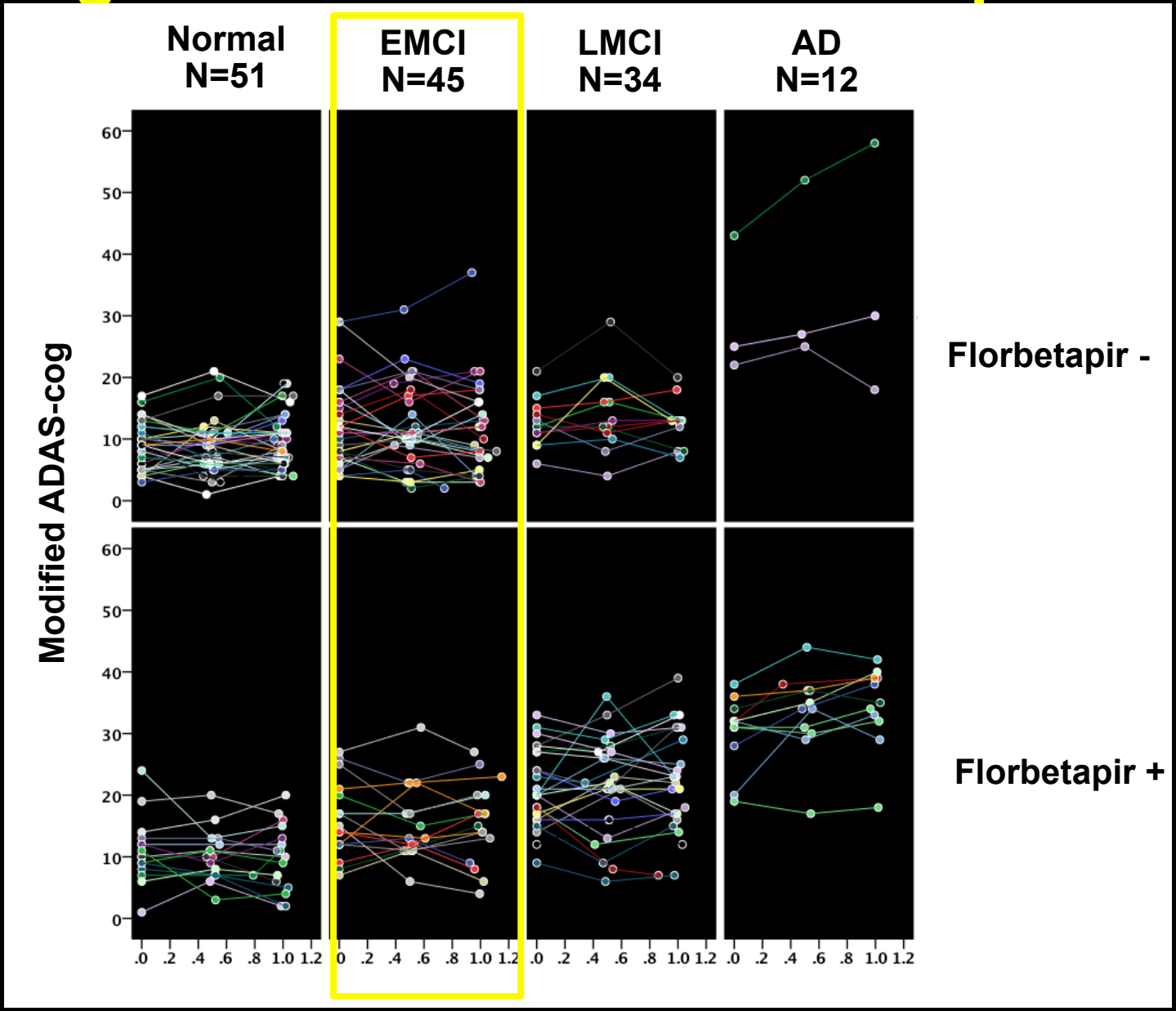


Landau et al. Ann Neurol 2012

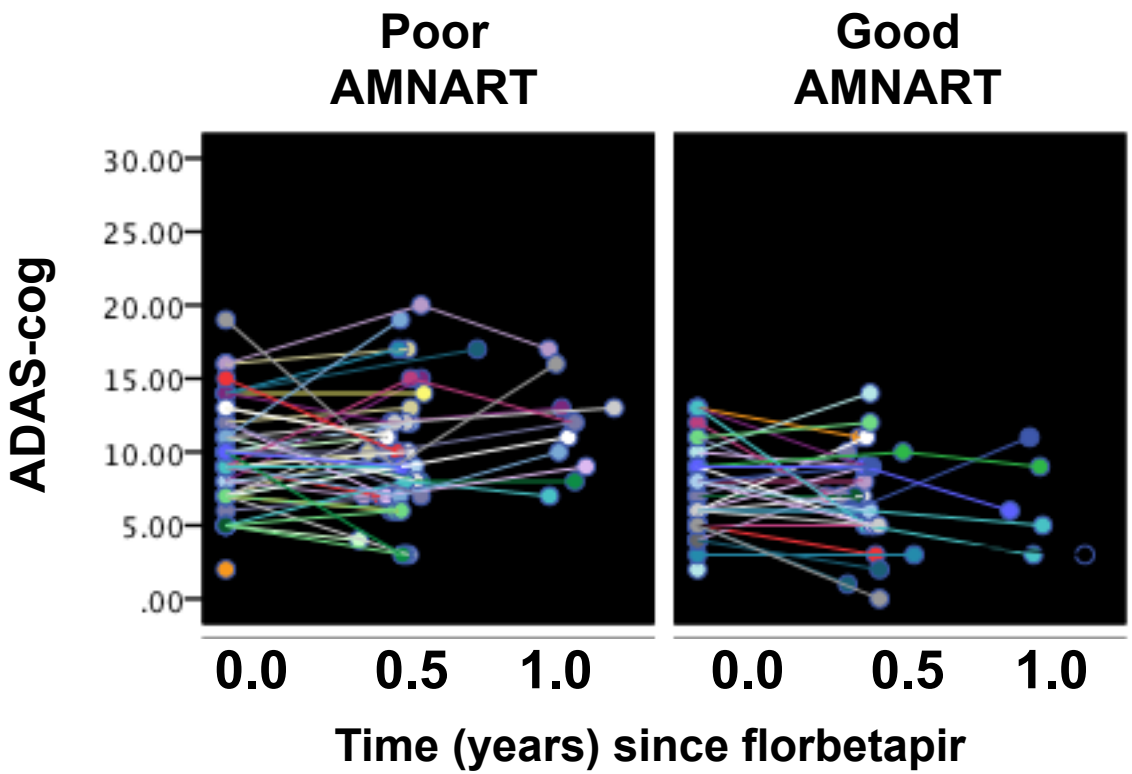
ADNI timeline



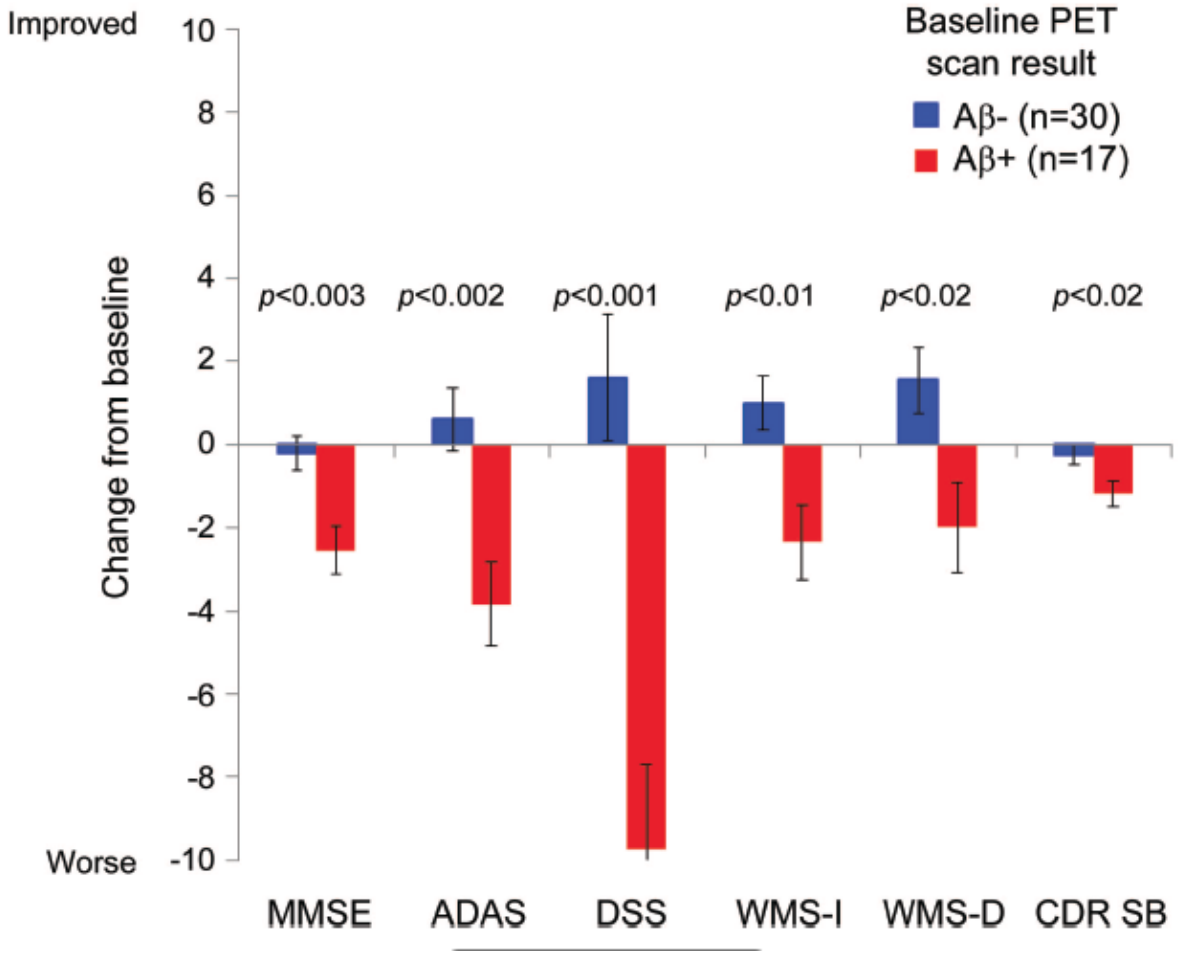
12m follow up not sufficient to see cognitive change associated with florbetapir status



Florbetapir+ EMCIs



Florbetapir status predicts subsequent cognitive change in MCI



Doraiswamy et al. Neurology 2012

Integrating biomarker information

10-15% MCIs have conflicting Aß & neuronal injury status

Longitudinal consequences of conflicting markers unclear (prospective data important)

Combining biomarker info

- Abnormal florbetapir *and* FDG-PET status was associated with the greatest retrospective decline
- FDG-PET was the strongest individual marker

Determining which amyloid+ individuals decline and which do not is next key step

Thank you

ADNI

Bill Jagust

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John Trojanowski
Cliff Jack
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