Molecular Imaging Heterogeneity of Clinically Defined AD

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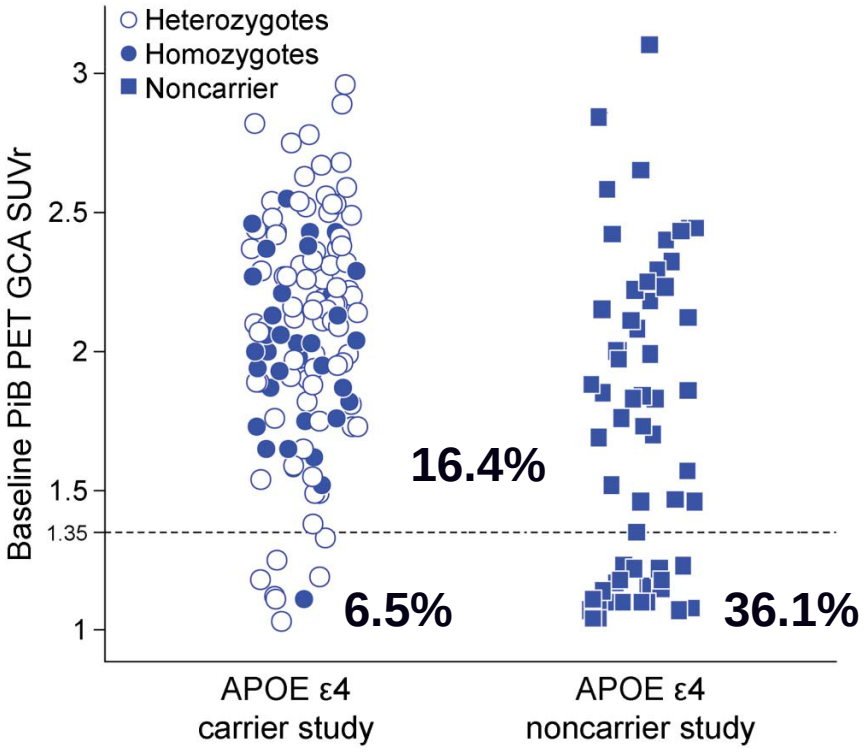
  - Eisai, Genentech, Lundbeck, Merck, Putnam, Roche

Outline

- Heterogeneity in causes of clinical AD dementia
  - Amyloid-negative MCI/AD
    - Prevalence
    - Demographics, clinical features
    - Biomarker signatures, relationship to SNAP
- Heterogeneity in clinical presentations of AD neuropathology
  - Molecular correlates of non-amnestic AD
  - Early age-of-onset AD (sporadic)

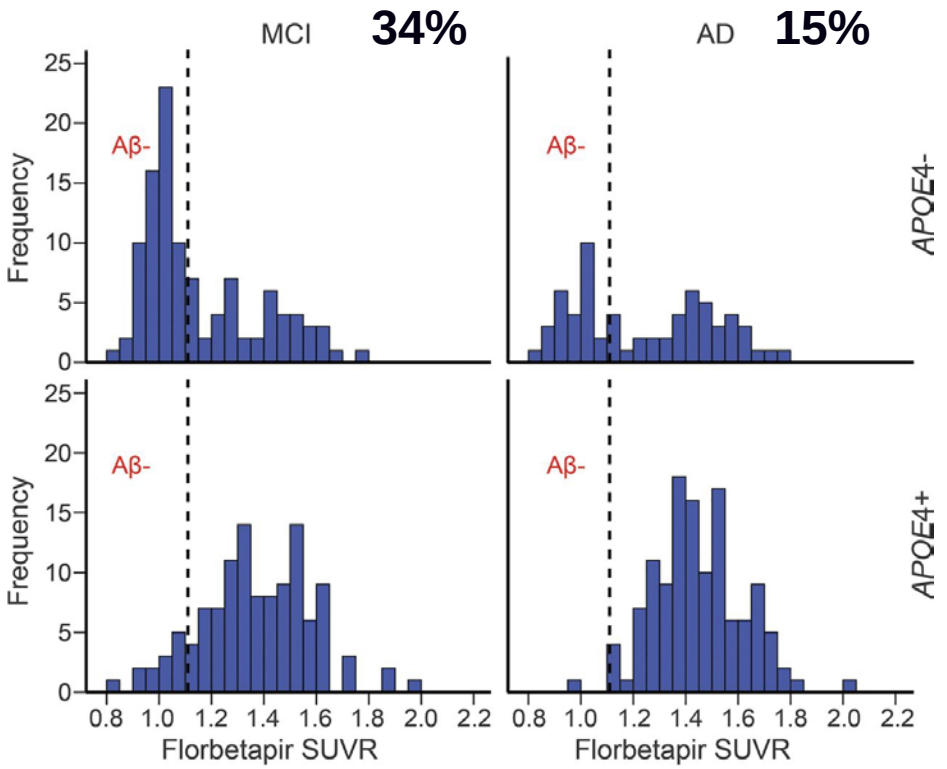
Rates of Aβ Biomarker Negativity in Clinical AD

Bapineuzumab: Mild-Mod AD



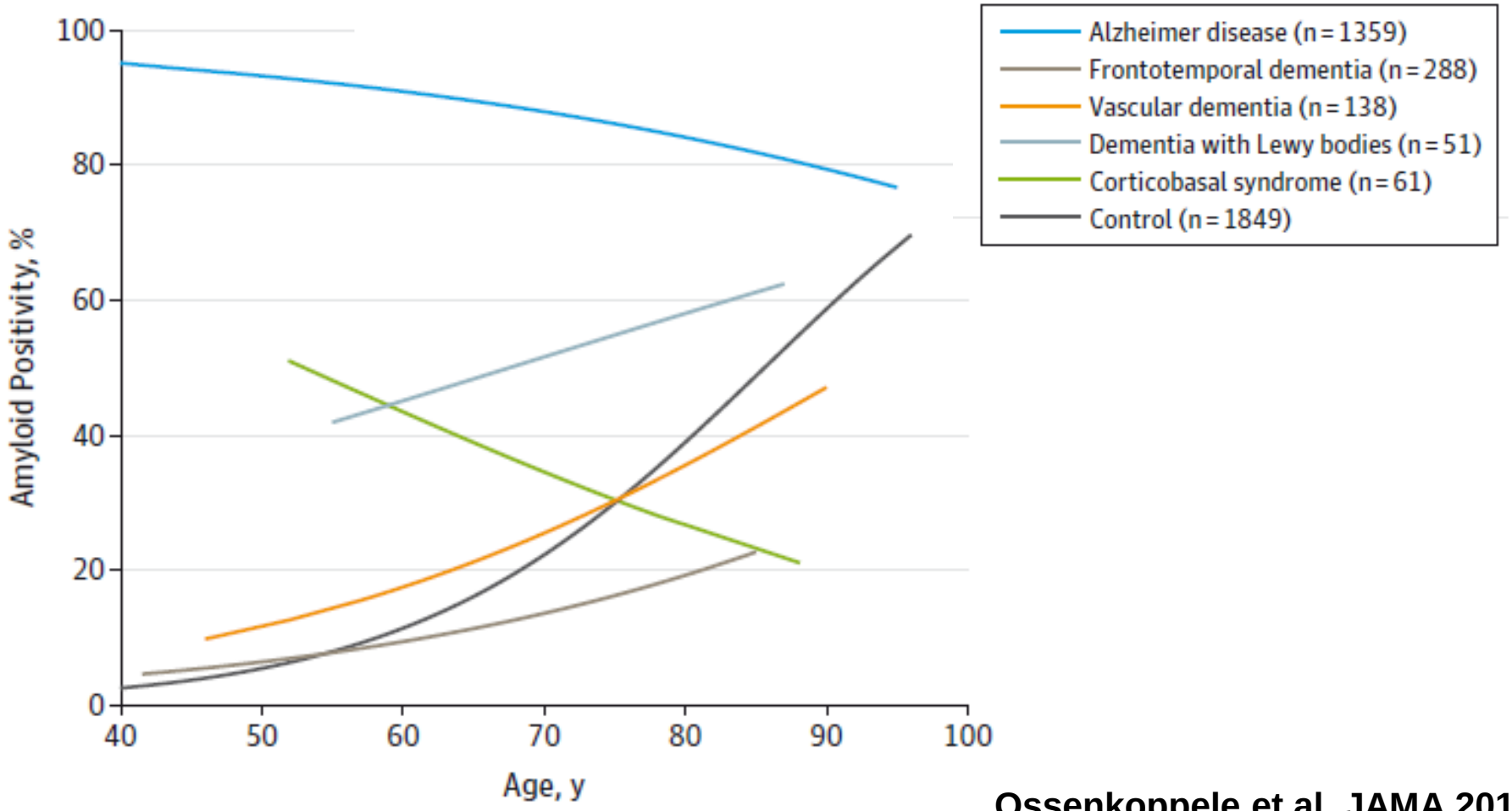
Liu et al. Neurology 2015

ADNI: Late MCI and AD



Landau et al. Neurology 2016

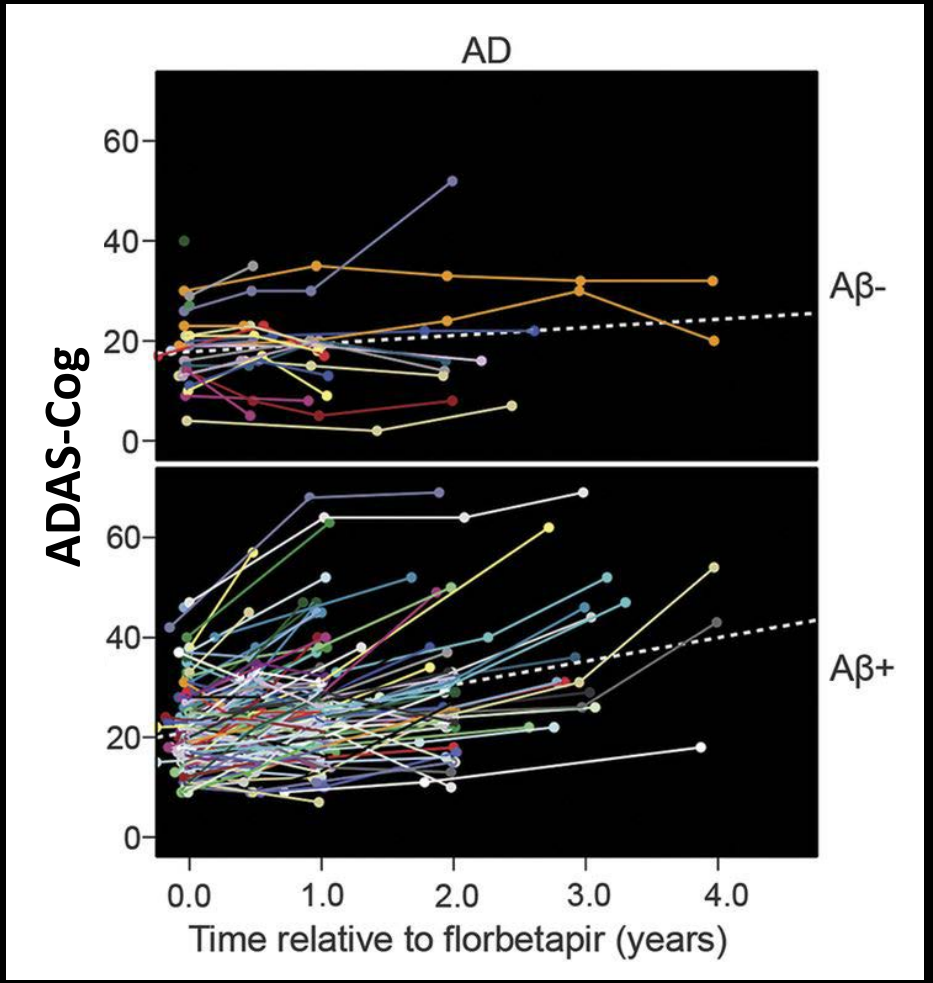
Prevalence of Aβ+ in Clinical AD Decreases with Age



Ossenkoppele et al. JAMA 2015

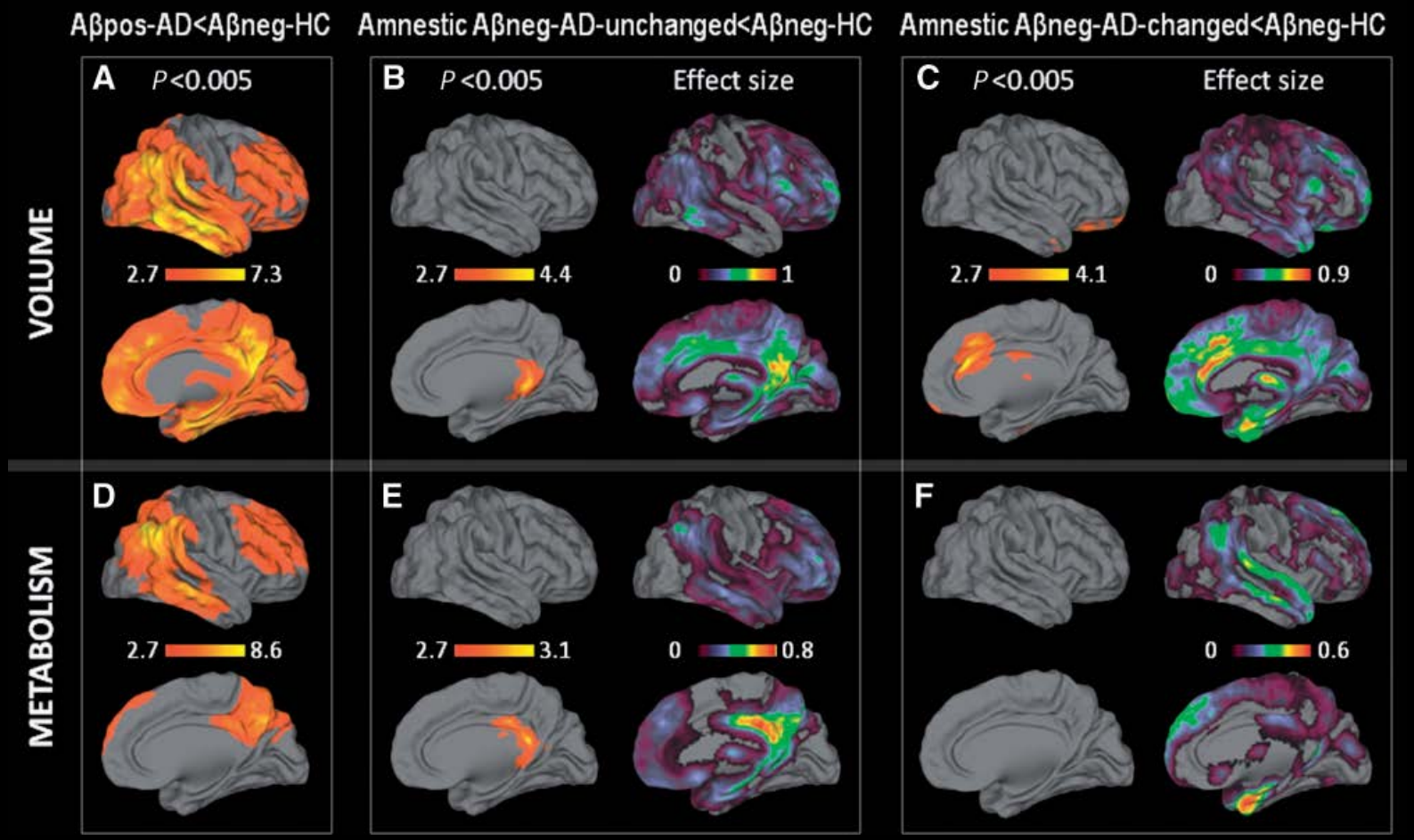
Characterization of Aβ- MCI/AD in ADNI

- Demographics
  - Older than Aβ+
  - M > F
- Cognition and function
  - Better at baseline (MCI)
  - Slower decline (MCI and AD)
- Lower prevalence ApoE4
  - MCI: Aβ- 16% vs. Aβ+ 71%
  - AD: Aβ- 4% vs. Aβ+ 75%
- Less abnormal neurodegeneration biomarkers
  - CSF t-tau, p-tau
  - Baseline MRI and FDG
  - Longitudinal MRI



Landau et al. Neurology 2016

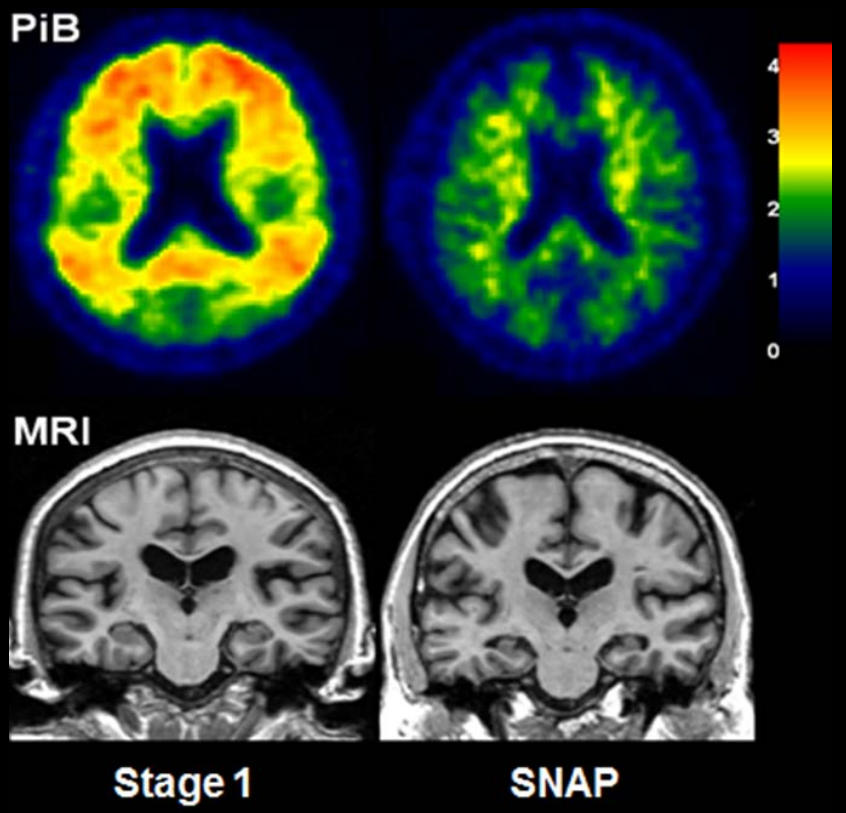
Neurodegeneration in Aβ-negative Amnestic AD (N=21)



Chételat et al. Brain 2016

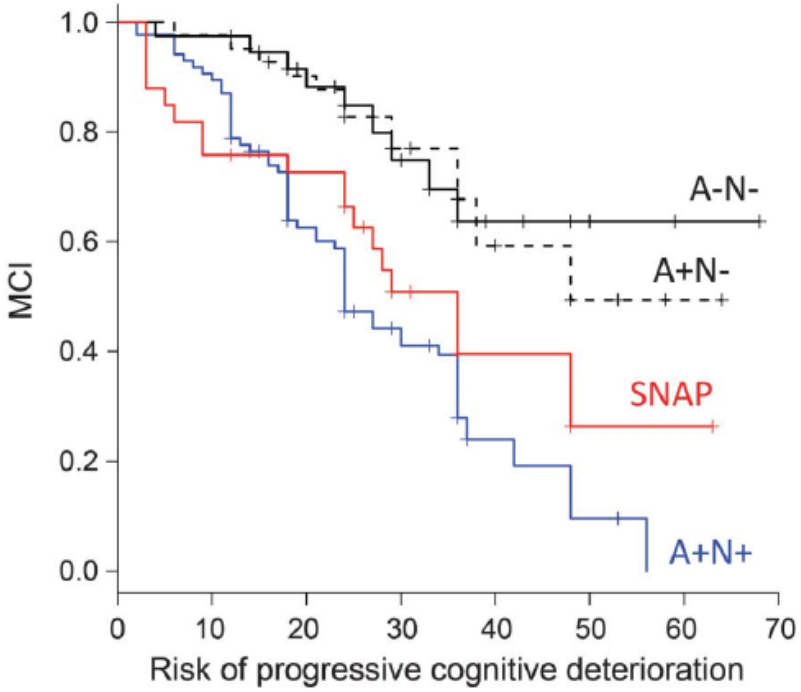
Suspected Non-Alzheimer Disease Pathology (SNAP)

- SNAP in MCI and AD dementia
  - 17%-35% of MCI
  - ~6%-15% of AD dementia
  - Older age-of-onset
  - Male > female
  - ApoE4 rates 11%-32%
- Rate of decline intermediate between A-/N- and A+/N+
- No clinical fingerprint of a single underlying disease
  - Increased WMH in some studies
  - No features of DLB
  - No increases (yet) in tau PET



Jack et al. Nature Rev Neurol 2016

Intermediate Risk of Cognitive Decline in MCI-SNAP



201 MCI from ADNI/EU
Followed up to 5 yrs (mean 2.5)
Decline:

Conversion to AD
MMSE decline ≥ 3 pts/yr
MMSE ≤ 24

	Crude		Adjusted	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***
MCI A+N-	1.13 (0.49 – 2.62)	0.771	0.83 (0.34 – 2.09)	0.689
MCI SNAP	2.66 (1.20 – 5.93)	0.016	2.38 (1.00 – 5.62)	0.049
MCI A+N+	3.85 (1.91 – 7.78)	<0.001	3.36 (1.55 – 7.27)	0.002

Caroli et al. Neurology 2015

Neuropathological Diagnoses in Low Amyloid Clinical AD (N=50)

Table 4. Primary NP Diagnosis for No to Sparse CERAD Neuritic Plaque Density in *APOE4* Carriers and Noncarriers[a]

	Braak Stages 0-II		Braak Stages III-IV	
Primary NP Diagnosis	*APOE4* Noncarriers	*APOE4* Carriers	*APOE4* Noncarriers	*APOE4* Carriers
Normal brain	3 (15.0)[b]	0	1 (7.7)	1 (20.0)
AD	0	2 (28.6)	1 (8.3)	1 (20.0)
AD abnormality present but insufficient for diagnosis	2 (10.0)	1 (14.3)	1 (8.3)	0
Lewy body disease	3 (15.0)	0	2 (15.4)	1 (20.0)
Vascular disease	5 (25.0)	0	2 (15.4)	1 (20.0)
FTLD	2 (10.0)	1 (14.3)	1 (8.3)	0
Hippocampal sclerosis	3 (15.0)	1 (14.3)	1 (8.3)	0
Rosenthal fiber encephalopathy	1 (5.0)	0	0	0
Nigral degeneration with focal tauopathy	1 (5.0)	0	0	0
Tauopathy NOS	0	1 (14.3)	0	0
Progressive supranuclear palsy	0	1 (14.3)	1 (8.3)	0
Senile dementia with tangles (tangle-only dementia)	0	0	1 (8.3)	1 (20.0)
FTD-NFT	0	0	1 (8.3)	0
Tauopathy/diffuse grain disease	0	0	1 (8.3)	0

Dementia onset late 70s, death mid 80s

ApoE4 – 26%

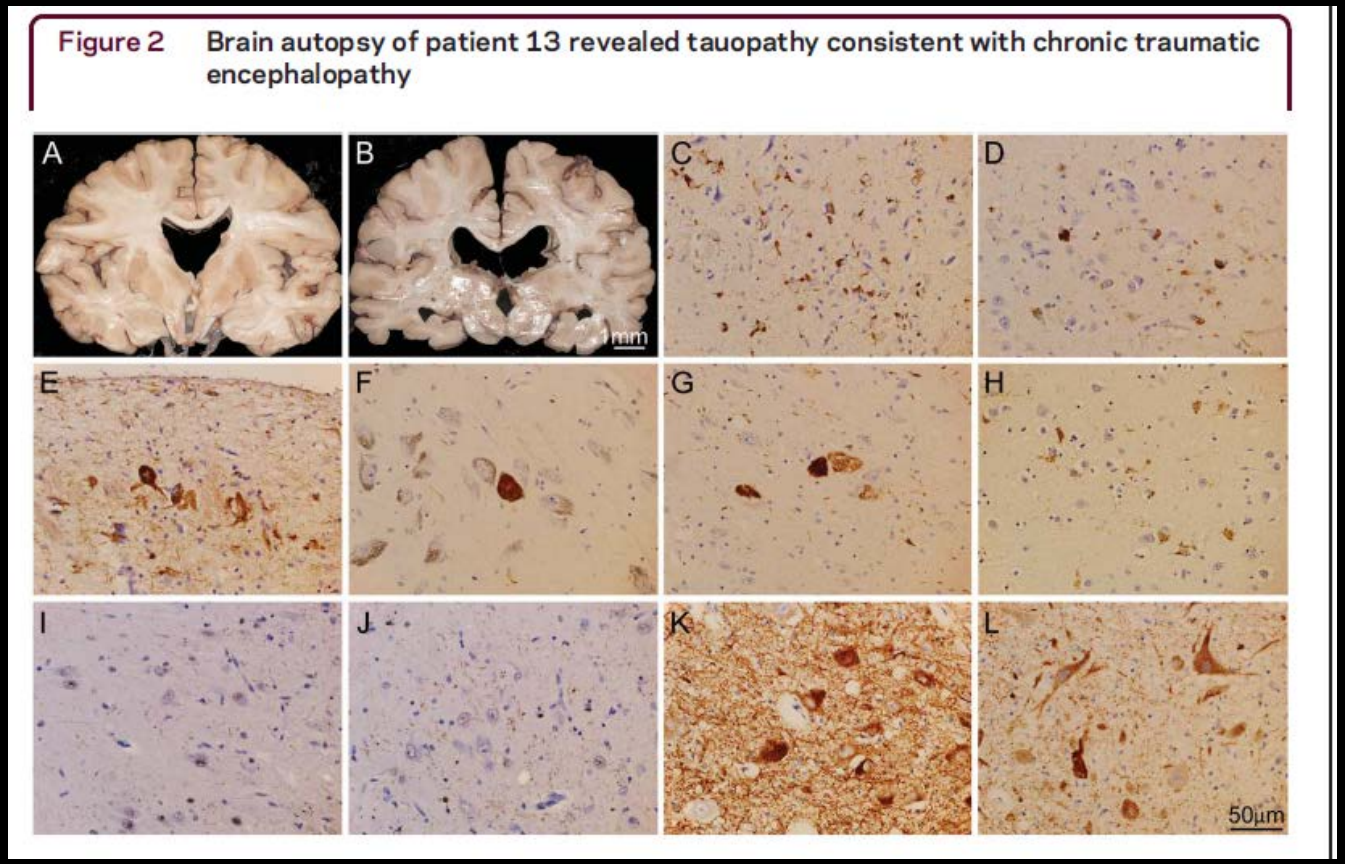
Most common diagnoses: AD (8), VaD (8), DLB (5), HS (5), normal brain (5) FTLD (4)

PART not diagnosed but 44% had Braak III/IV

Monsell et al. JAMA Neurol 2015

CTE at Autopsy in Aβ-PET Negative AD

79 year-old retired NFL player with progressive memory loss

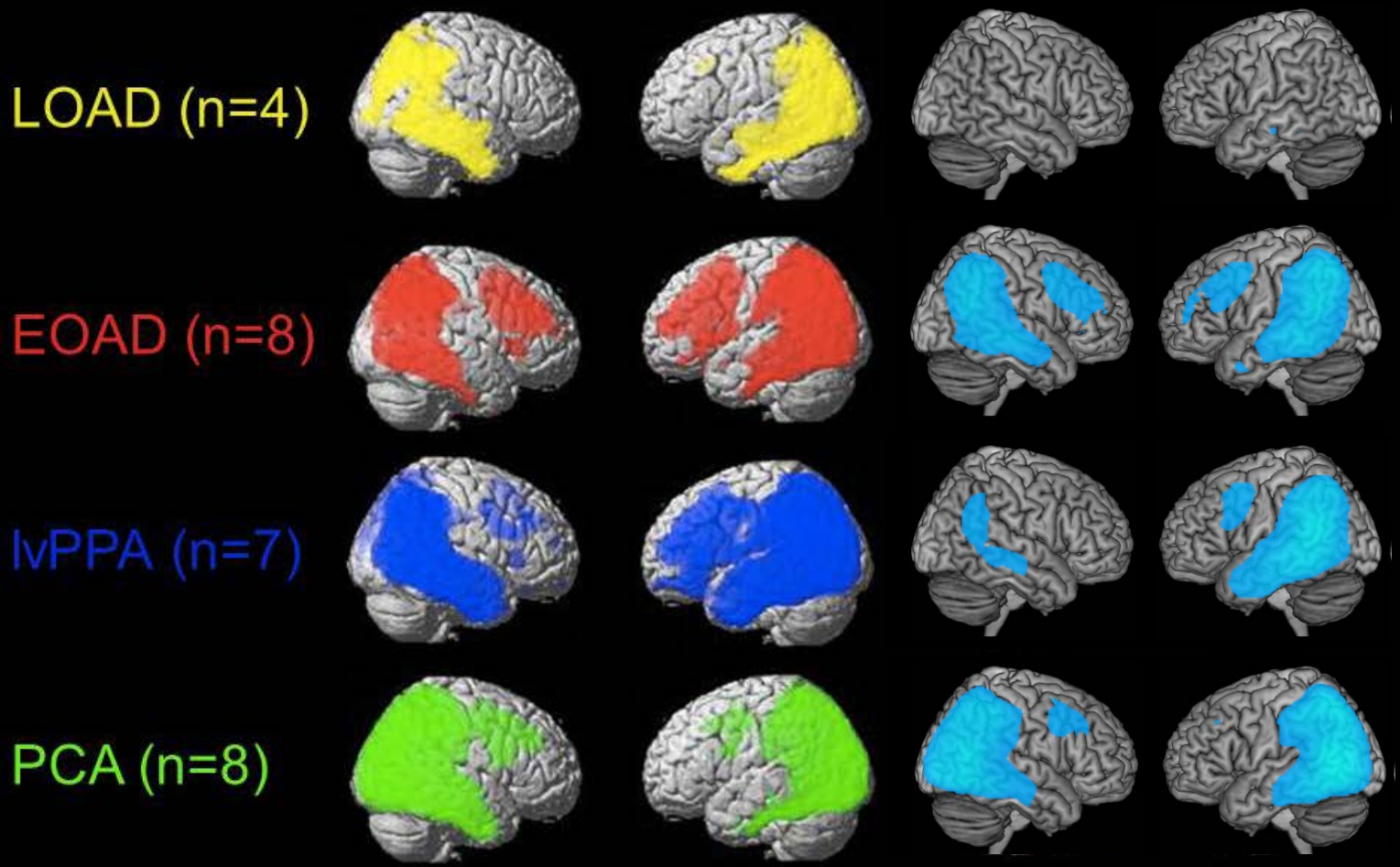


Gardner et al. Neurol Clin Pract 2015

Heterogeneity of Aβ+ AD

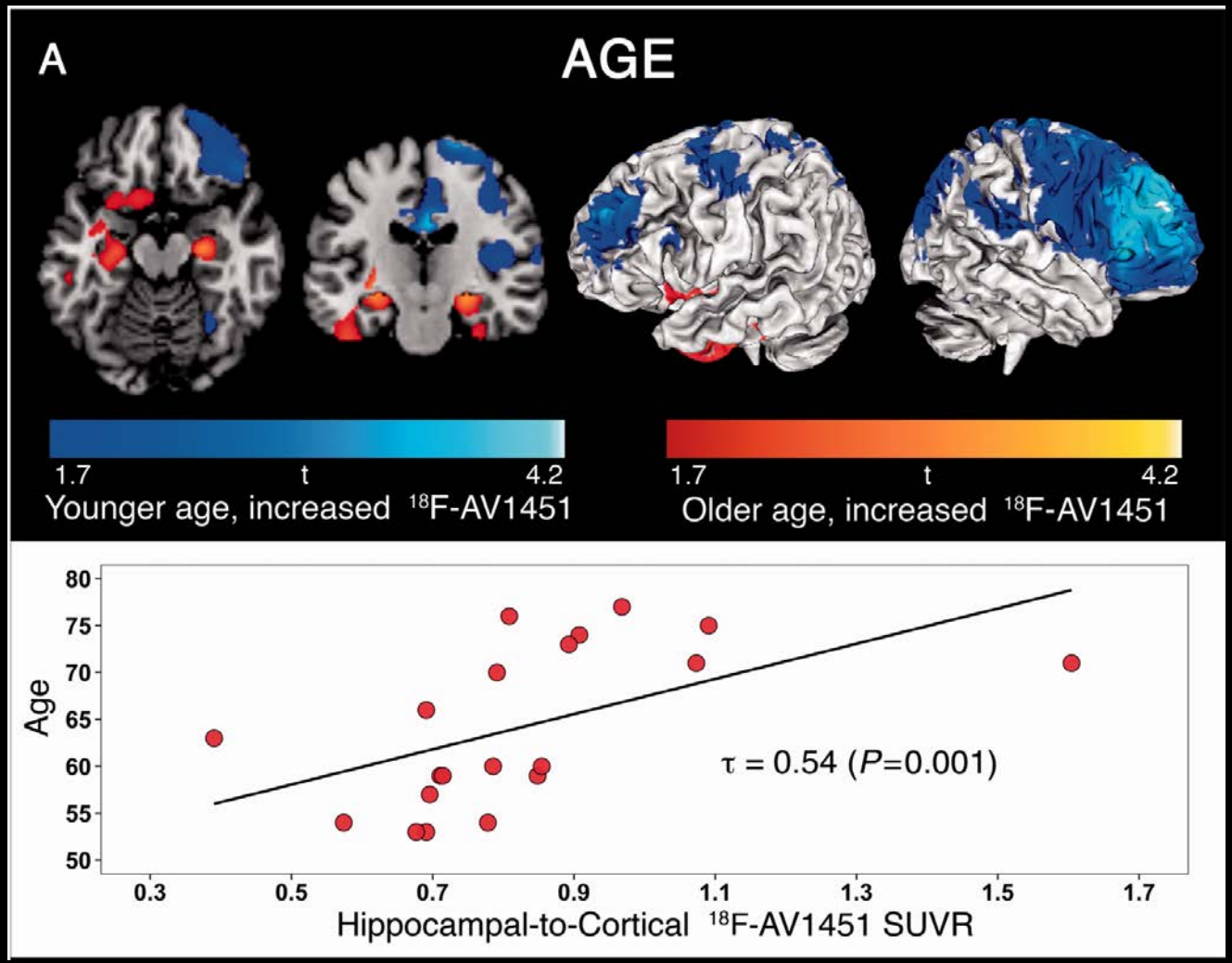
Lehmann et al. Brain 2013

Tau PET Patterns Correlate with AD Phenotype



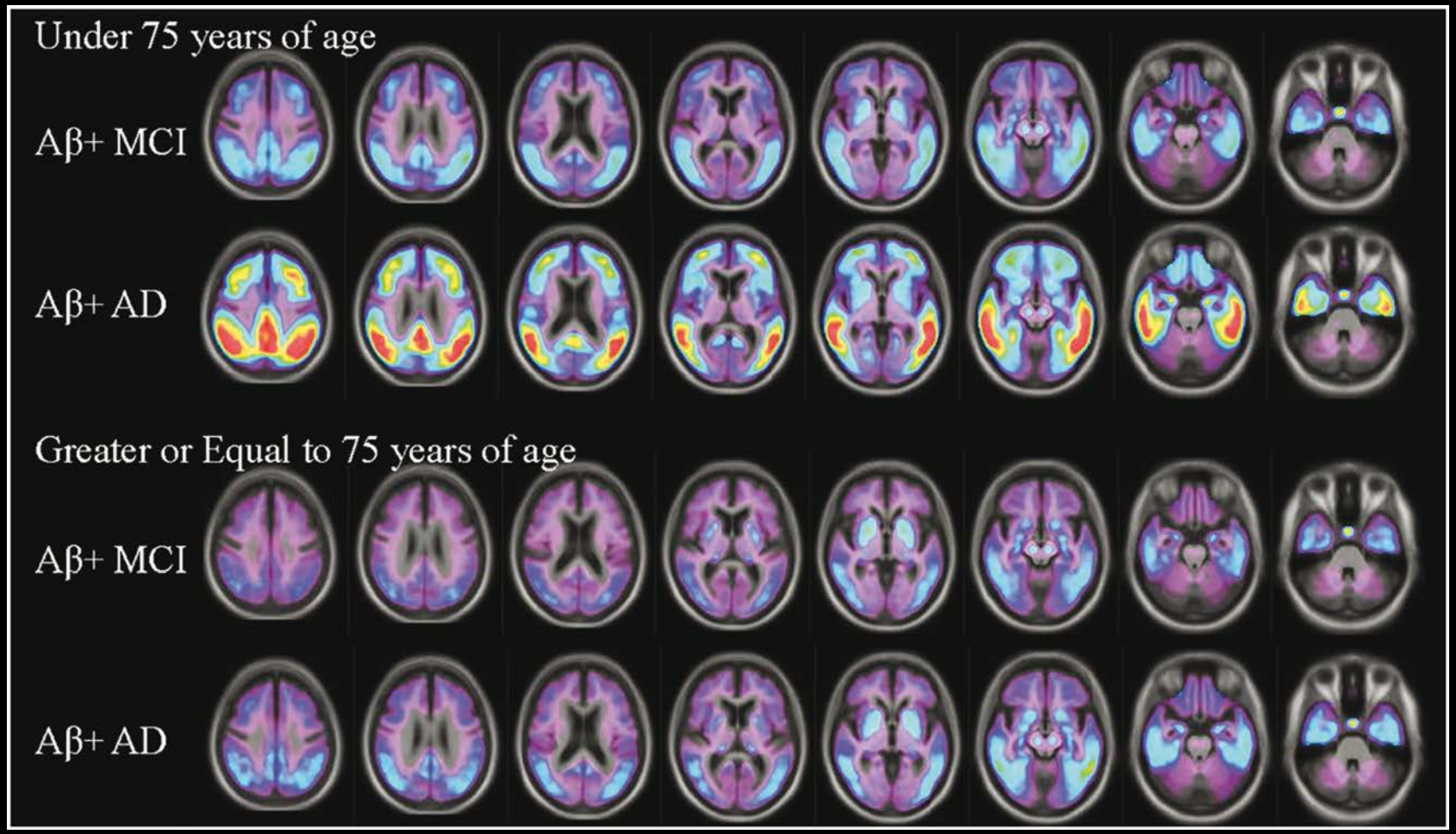
Ossenkoppele et al. Brain 2016
Xia et al. JAMA Neurol 2017
Day et al. Alz Dis Assoc Disord 2017

Age Moderates Tau Pattern in AD



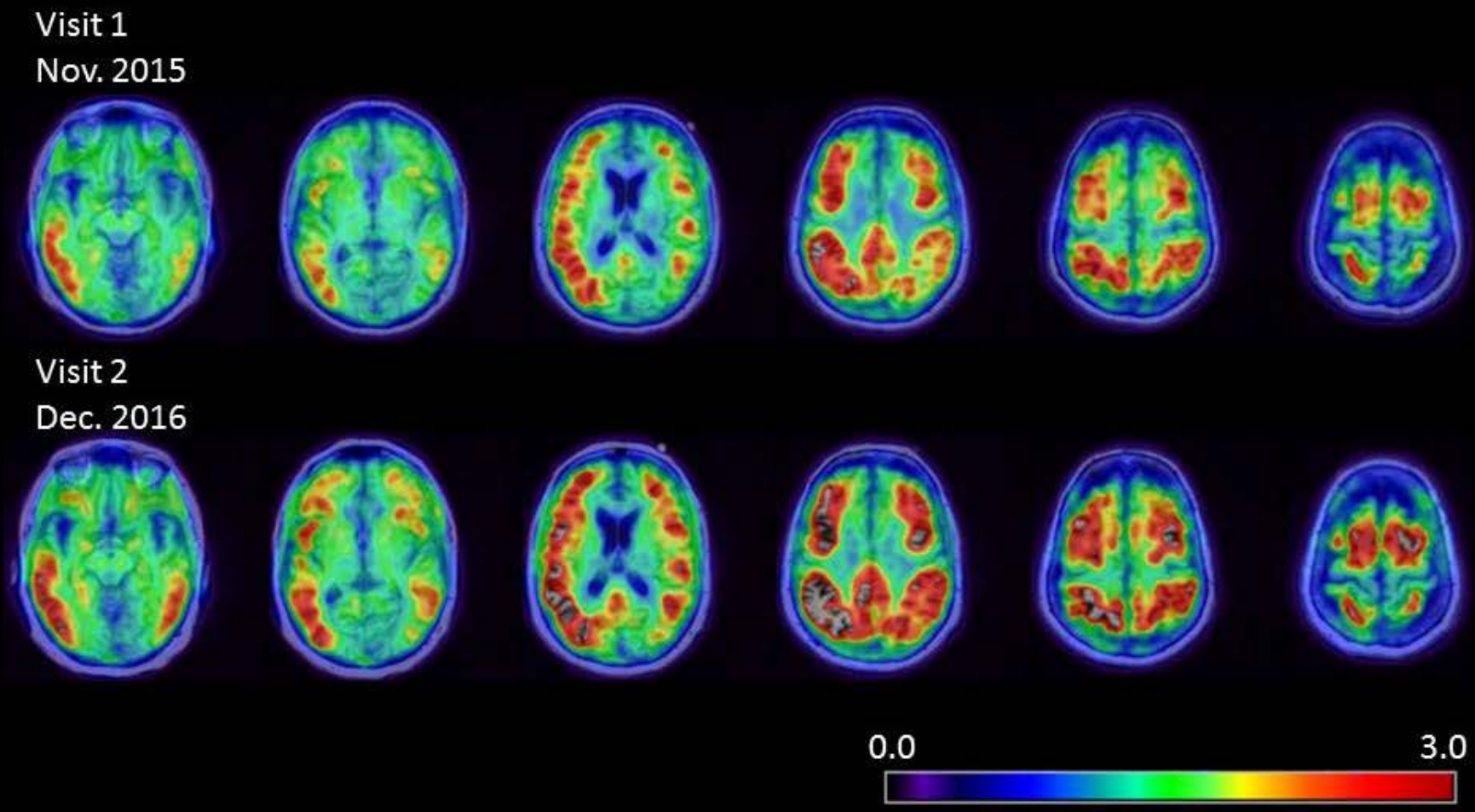
Ossenkoppele et al. Brain 2016

Tau Burden in AD is Negatively Correlated with Age



Pontecorvo et al. Brain 2017

Longitudinal Tau PET in EOAD



Conclusions

- Biomarkers identify patients with non-Aβ pathologies mimicking clinical AD
  - Consistently ~15% of AD dementia
  - Associated with ApoE4 neg, older age, male
  - Better prognosis than Aβ+ (but not benign)
  - Likely represents a mix of neuropathologies
    - PART, CARTS, AGD, vascular, DLB
- Biomarkers can identify AD pathology as cause of heterogeneous syndromes
  - Early-onset AD critical and under-studied cohort in which to investigate mechanisms that drive heterogeneity
  - Dedicated study will require multi-site collaborations

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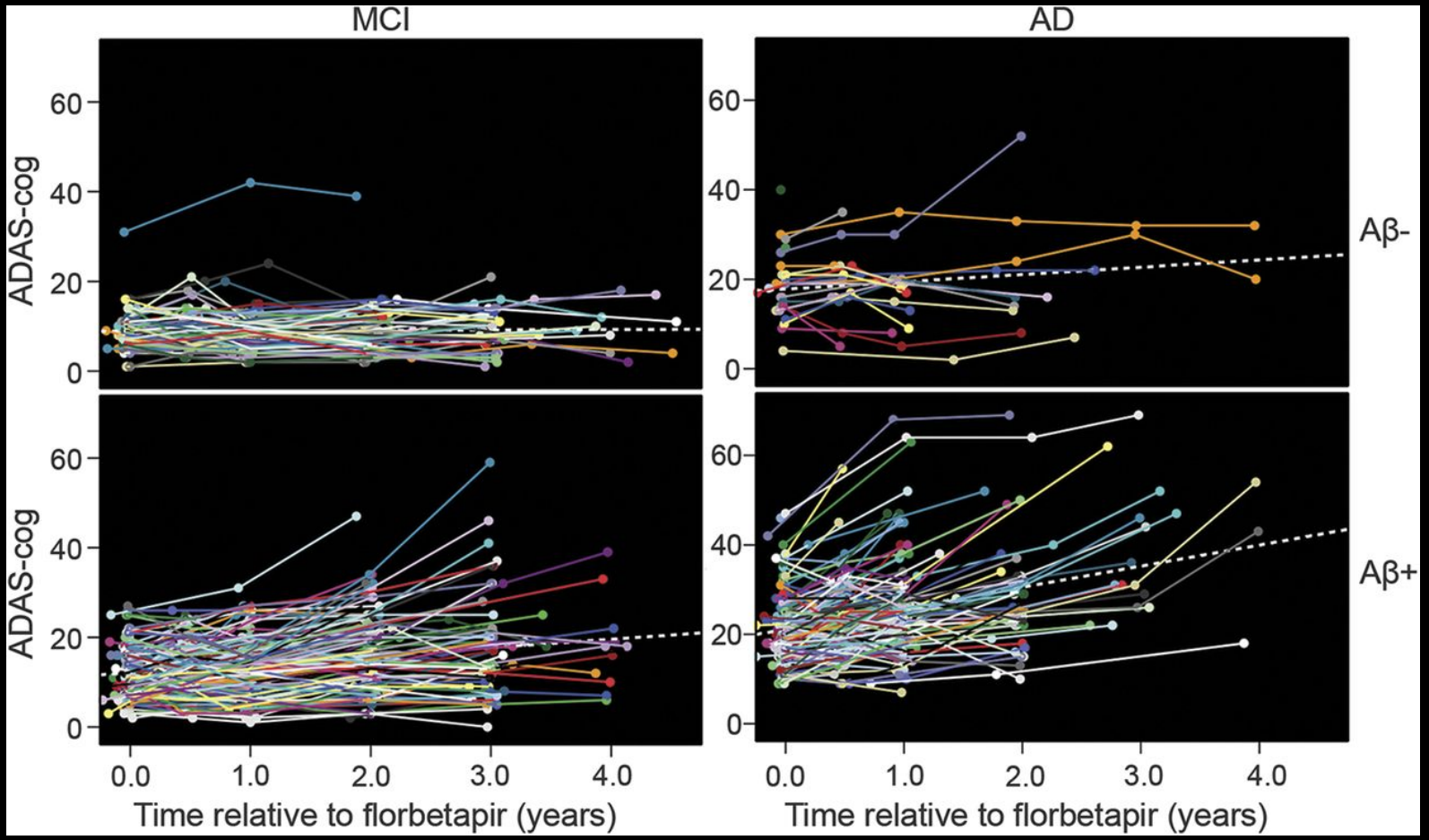
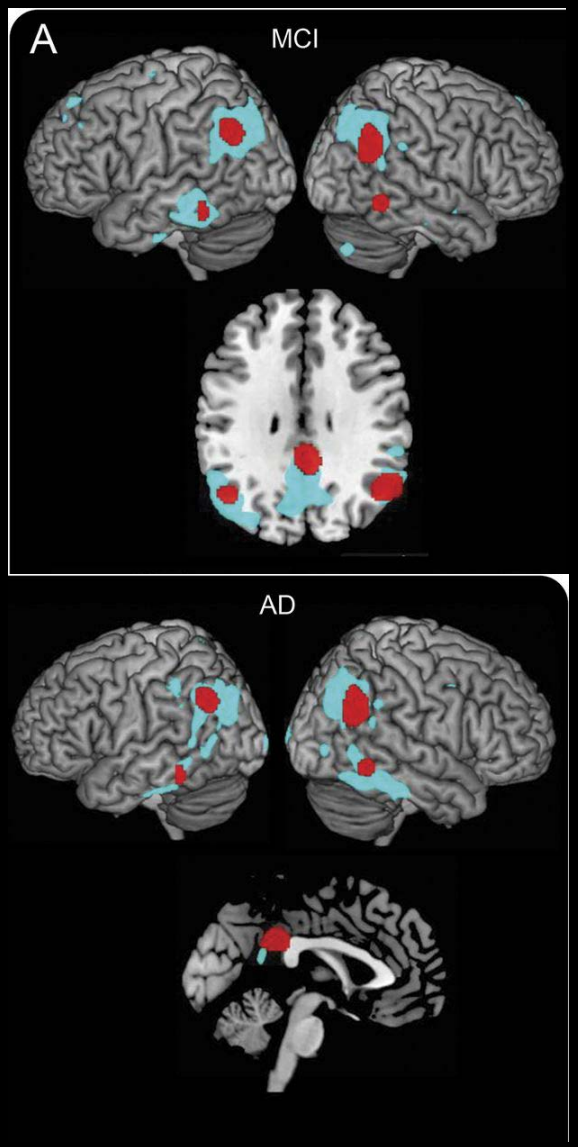
Cognitive Trajectories By Aβ Status



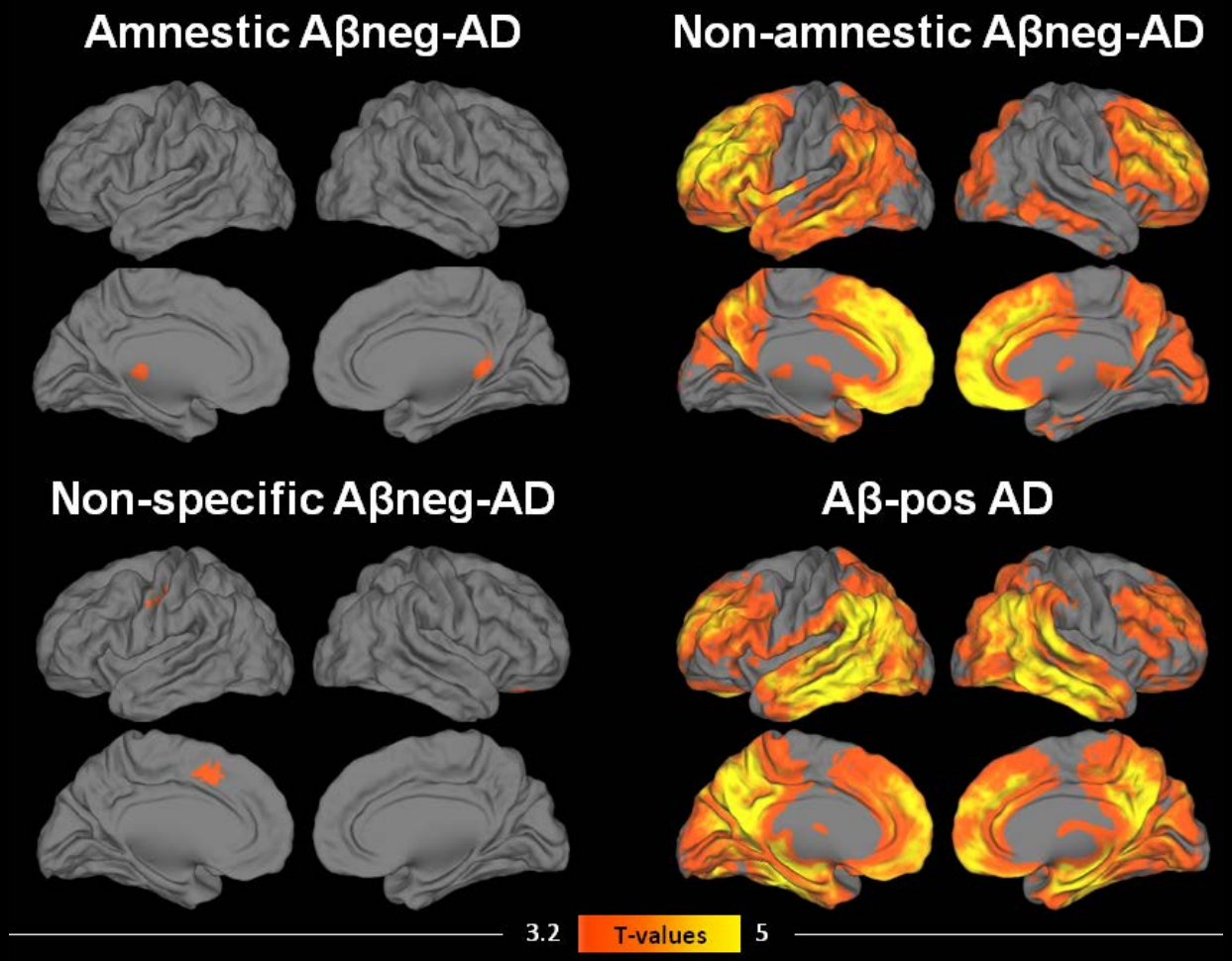
Landau et al., Neurology 2016

Characterization of Aβ- MCI/AD in ADNI

- Slightly older than Aβ+ (AD only)
  - Mean age 78 vs. 74
- Lower ApoE4
  - MCI: Aβ- 16% vs. Aβ+ 71%
  - AD: Aβ- 4% vs. Aβ+ 75%
- Better baseline cognition and function (MCI only)
- Slower cognitive decline (both groups)
- Higher prevalence of depression and hypertension
- Lower neurodegeneration biomarkers
  - CSF t-tau; p-tau, baseline MRI and FDG, longitudinal MRI



Atrophy in Aβ-Neg AD Dementia



Chételat **et al,** ***in revision***

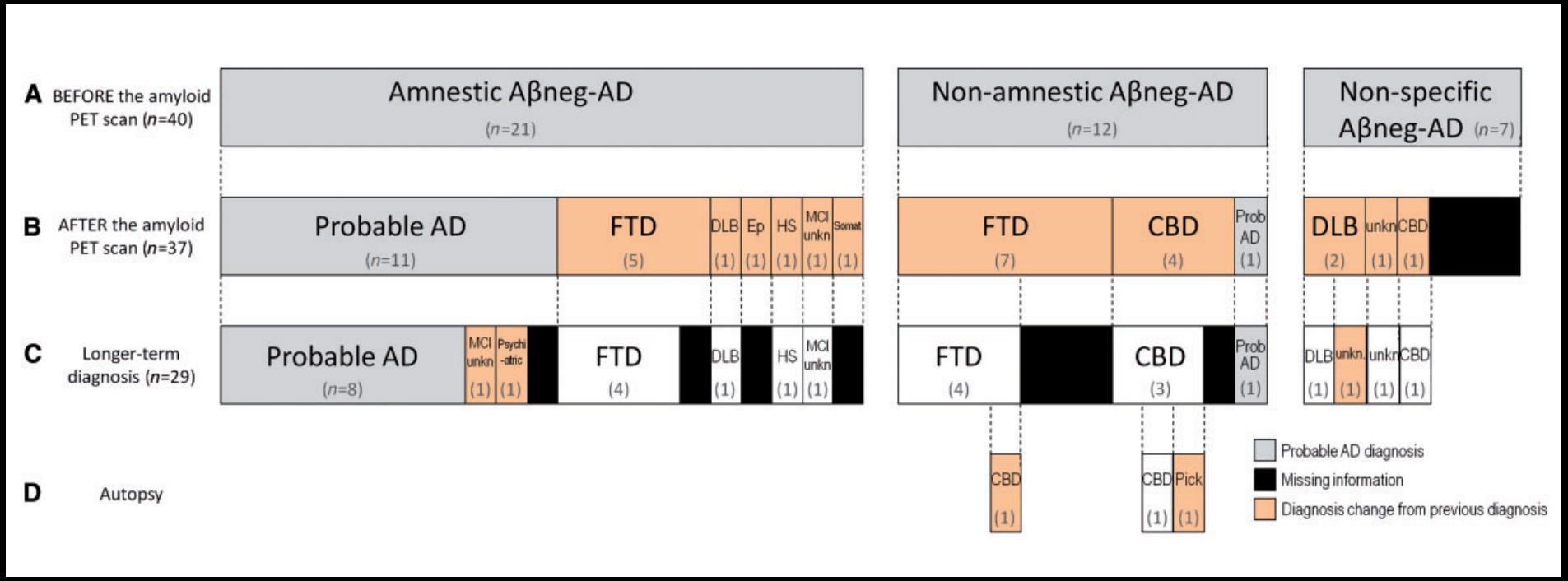
Conclusions

- SNAP is a biomarker-derived construct
  - Subject to limitations of biomarker distributions, thresholds and classifications
  - Current definition of “neurodegeneration” is cross-sectional, not longitudinal
- The biological substrate of SNAP is likely diverse
  - Non-degenerative: developmental differences, age, depression, hormonal (estrogen, cortisol), sleep, diabetes, genetics, etc.
  - Degenerative: vascular, DLB, PART, AGD, HS±TDP-43, FTLD

Conclusions

- The prognosis of SNAP differs by baseline cognitive status
  - Healthy elderly: relatively benign (simailar to A-N-)
  - MCI: intermediate between A-N- and A+N+
  - Dementia: majority show continued decline
- The substrate of SNAP likely differs by baseline cognitive status
  - Healthy elderly: greater contribution of non-degenerative factors (or very slow pathologies)
  - Dementia: primarily non-AD cortical/subcortical (non-amnestic) or limbic (amnestic) pathologies
  - MCI: mix of degenerative vs. non-degenerative

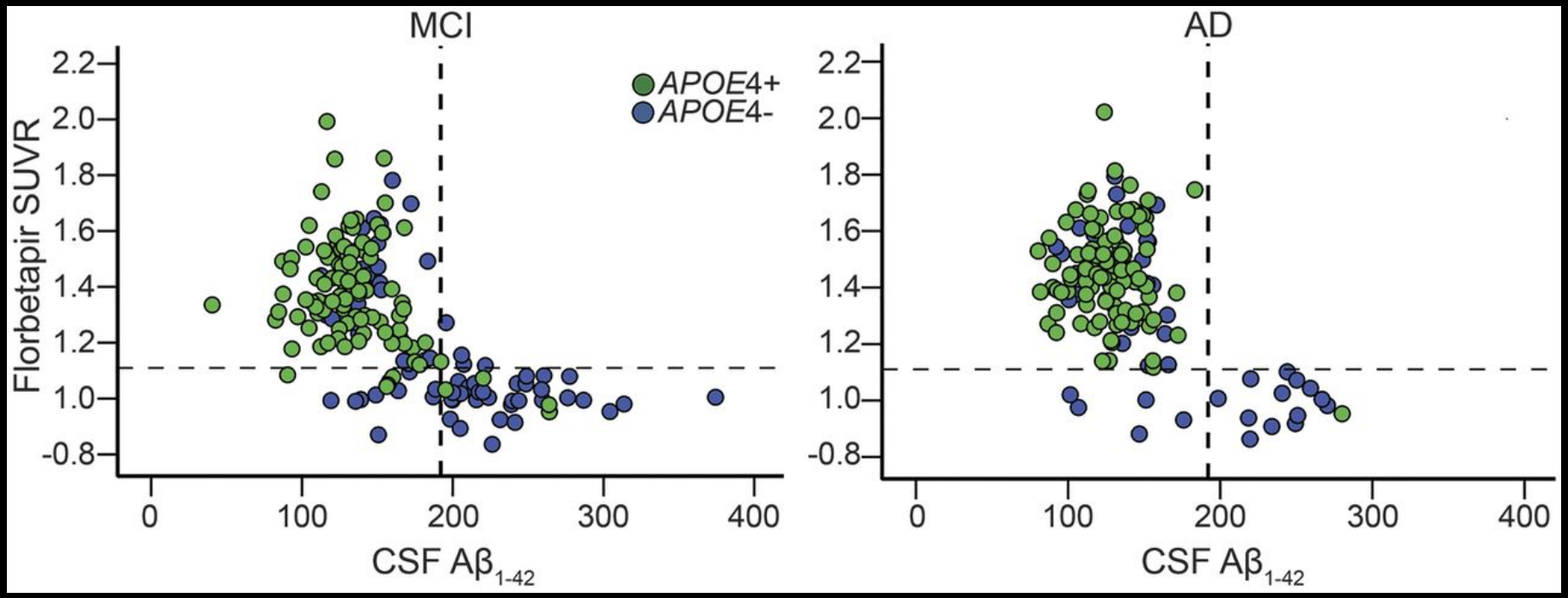
Outcomes in Clinical AD Dementia with Negative Amyloid PET



Amnestic: primary and predominant deficit in episodic memory
Non-amnestic: primary and predominant deficit in language, visuospatial, or executive functions
Non-specific: diffuse pattern of cognitive deficits

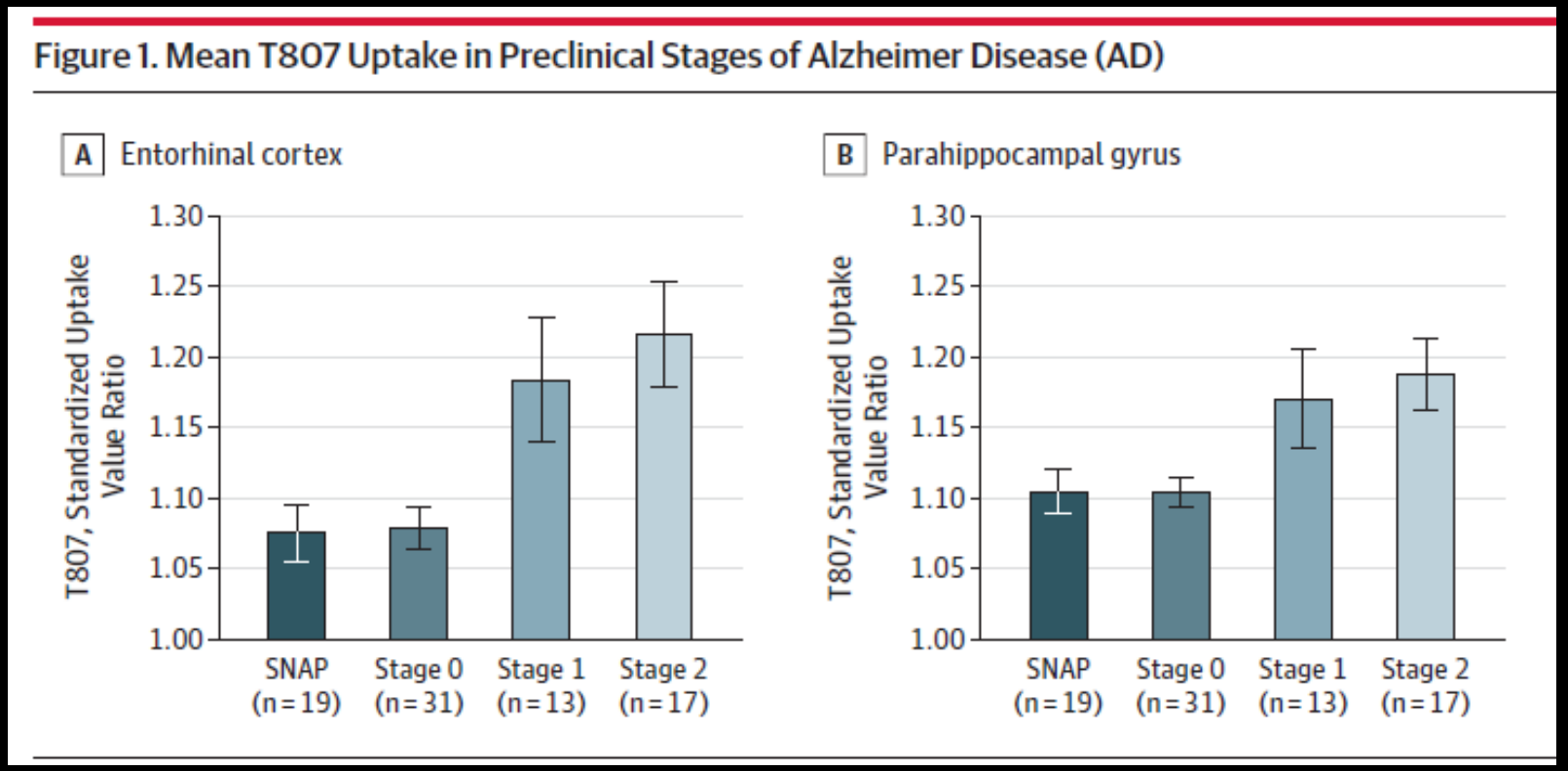
Chételat et al., Brain 2016

Agreement Between CSF $A\beta_{42}$ and Florbetapir PET



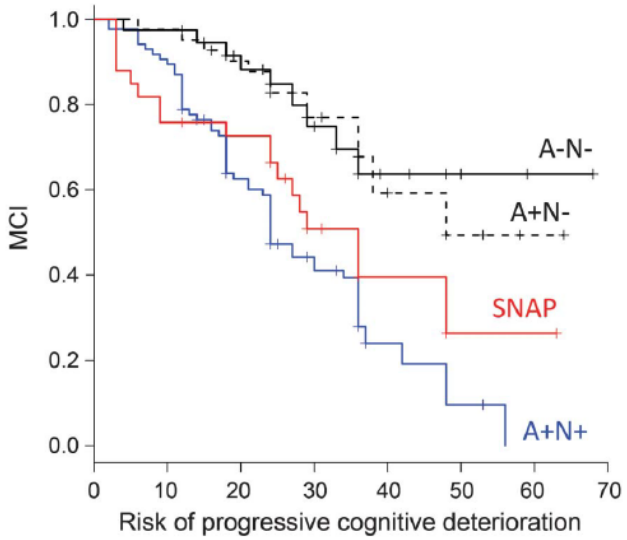
Landau et al., Neurology 2016

Early Tau PET Data Suggest SNAP ≠ PART



Mormino et al, JAMA Neurol 2016

Intermediate Risk of Cognitive Decline in MCI-SNAP



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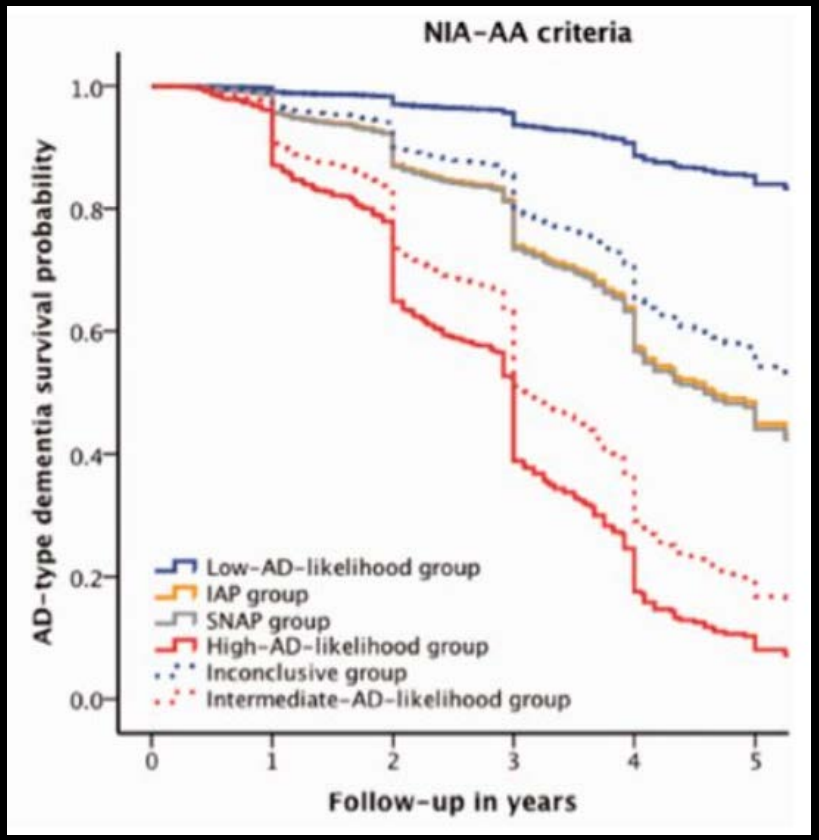
Caroli et al, Neurology 2015



Vos et al, Brain 2015

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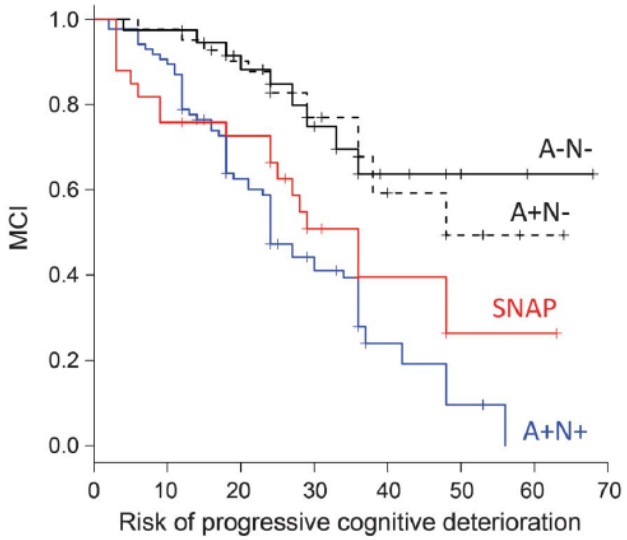

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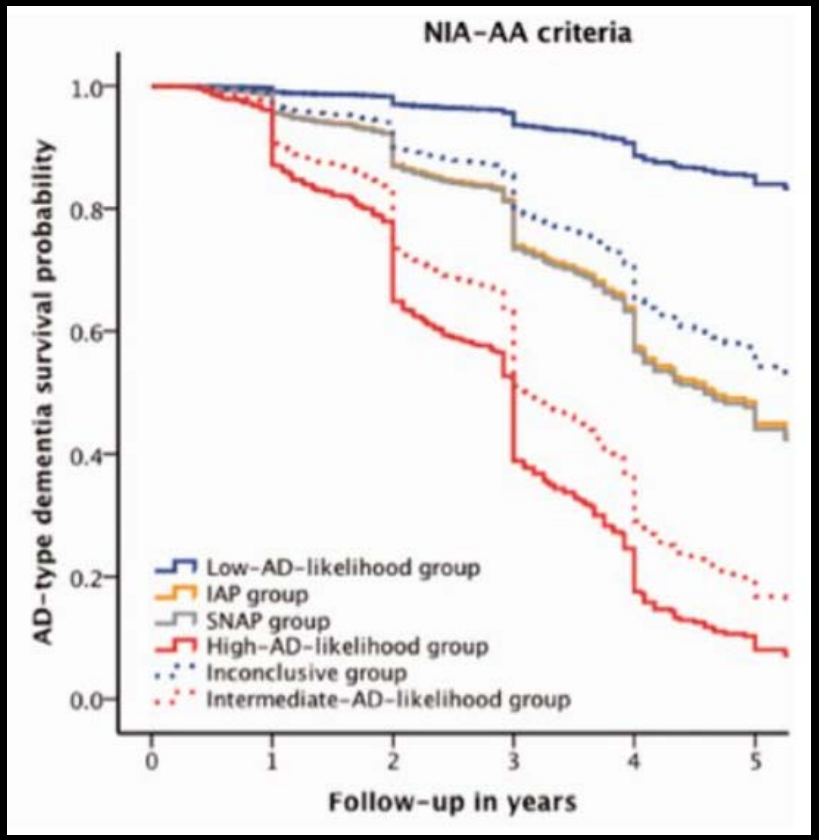
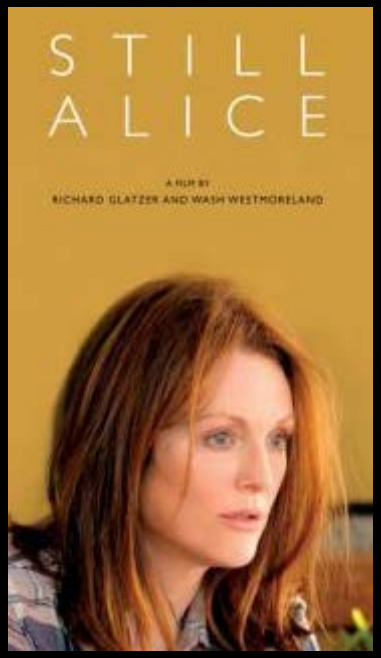


Vos et al, Brain 2015

Early-Onset AD (Age ≤ 65)



- 5% of all AD patients = ~250,000 in U.S.
  - Only ~5%-10% harbor APP/PSEN mutations
- Study mechanisms of heterogeneity and selective vulnerability in AD
  - Non-amnestic clinical presentations; focal cortical syndromes (lvPPA, PCA, fvAD)
- Identify novel genetic risk factors
  - Only ~50% carry ApoE4
  - Not represented in GWAS; will require targeted effort
- Employ biomarkers
  - Improve clinical diagnosis
  - Study mechanisms of “pure” AD: fewer co-pathologies
  - Under-represented in ADNI, not included in DIAN