Sex Differences in AD biomarker progression: the role of APOE

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Disclosures

- Funding: NIH and Alzheimer’s Association
- Paid consultant to Eli Lilly, Roche, Neurotrack

Objectives

- Classify the major biomarkers for assessing dementia etiology.
- Identify the relationship between APOE genotypes and AD biomarkers.
- Describe findings of differential biomarker progression among men and women at risk for dementia.

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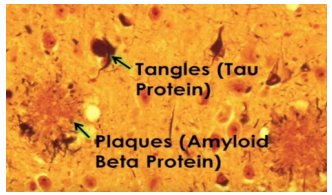
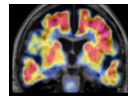
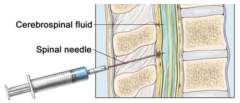
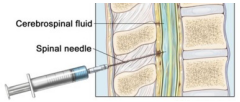
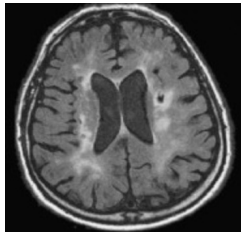
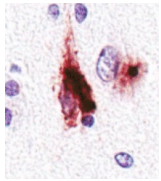
Biomarkers for common etiologies associated with dementia

Clinical Diagnosis	Etiology	Biomarkers
Alzheimer's disease	Amyloid plaques & Tau tangles 	PET, CSF, Plasma   
Dementia with Lewy bodies (& Parkinson's with dementia)	Alpha-synuclein/Lewy bodies 	CSF (Seed Amplification Assay) 
Vascular dementia	Vascular Injury 	MRI
LATE	TDP-43 	In development; need validation

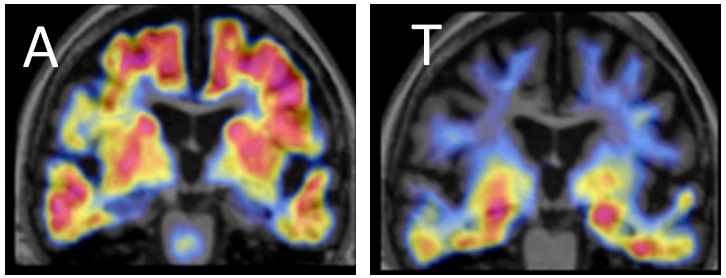
Alzheimer's Disease Amyloid/Tau/Neurodegeneration Research Framework

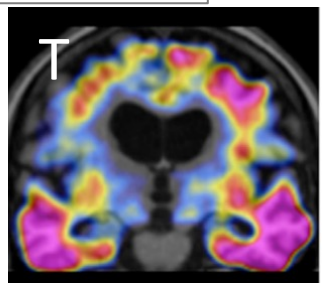
Dementia

Mild Cognitive Impairment (MCI)

Clinically Unimpaired (CU)

Amyloid → Tau → Neuronal Dysfunction → Neuronal Degeneration





In Vivo Biomarkers

→ Can measure with cerebrospinal fluid (CSF) via lumbar puncture

→ Can measure with plasma via blood draw

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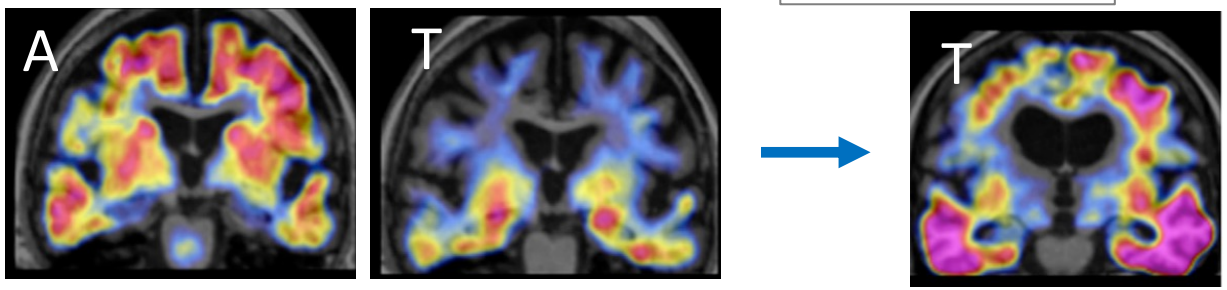


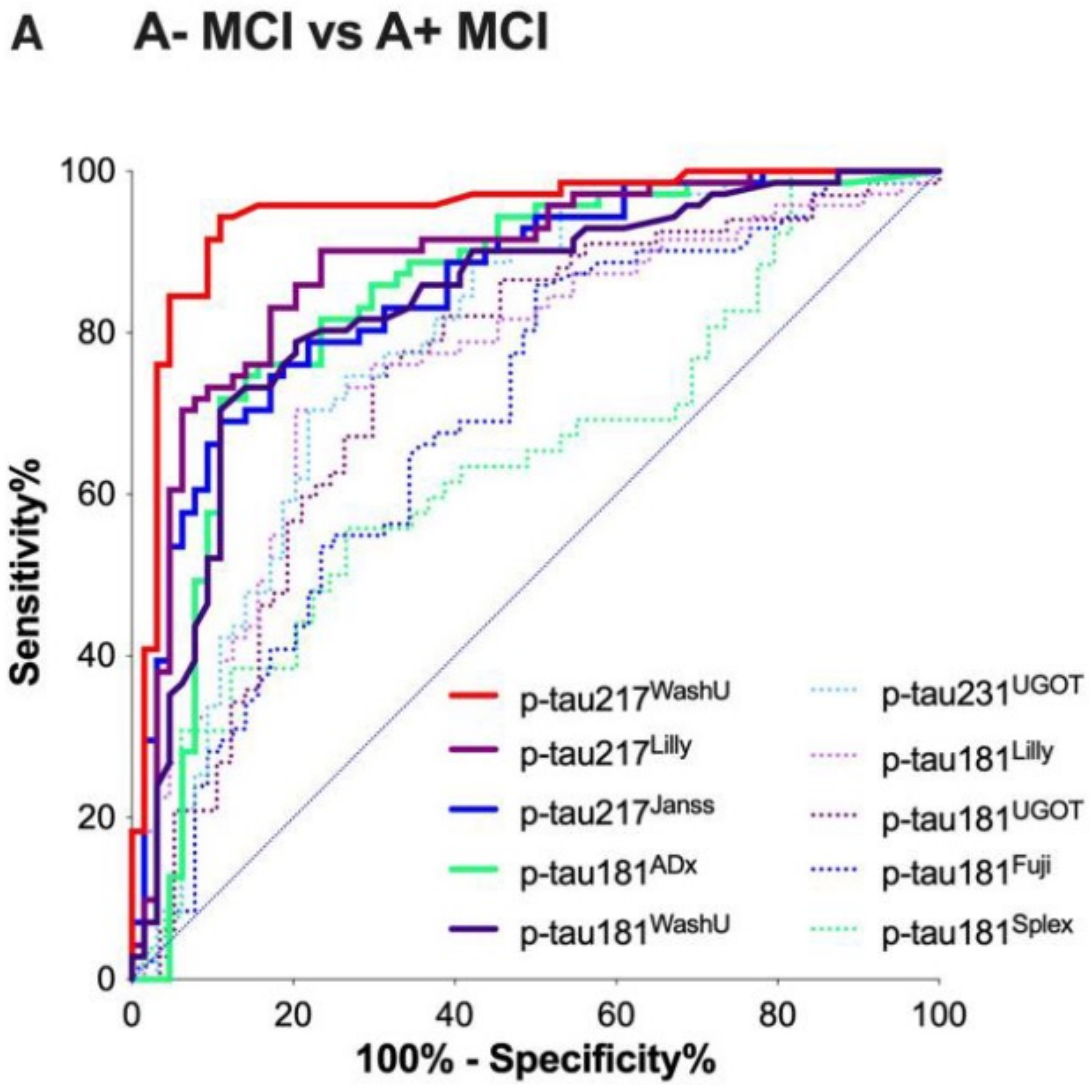
FDA Approved Amyloid PET

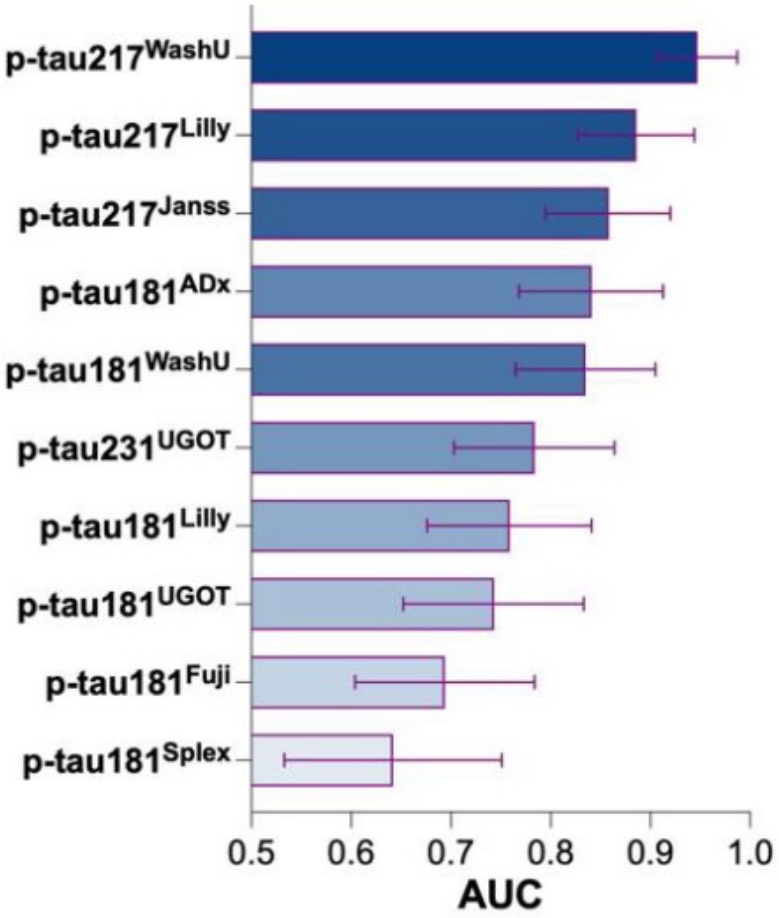
2012: Florbetapir (Amyvid)
2013: Flutemetamol (Vizamyl)
2014: Florbetaben (Neuroceq)

FDA Approved Tau PET

2020: Flortaucipir FDA approved (Tauvid)

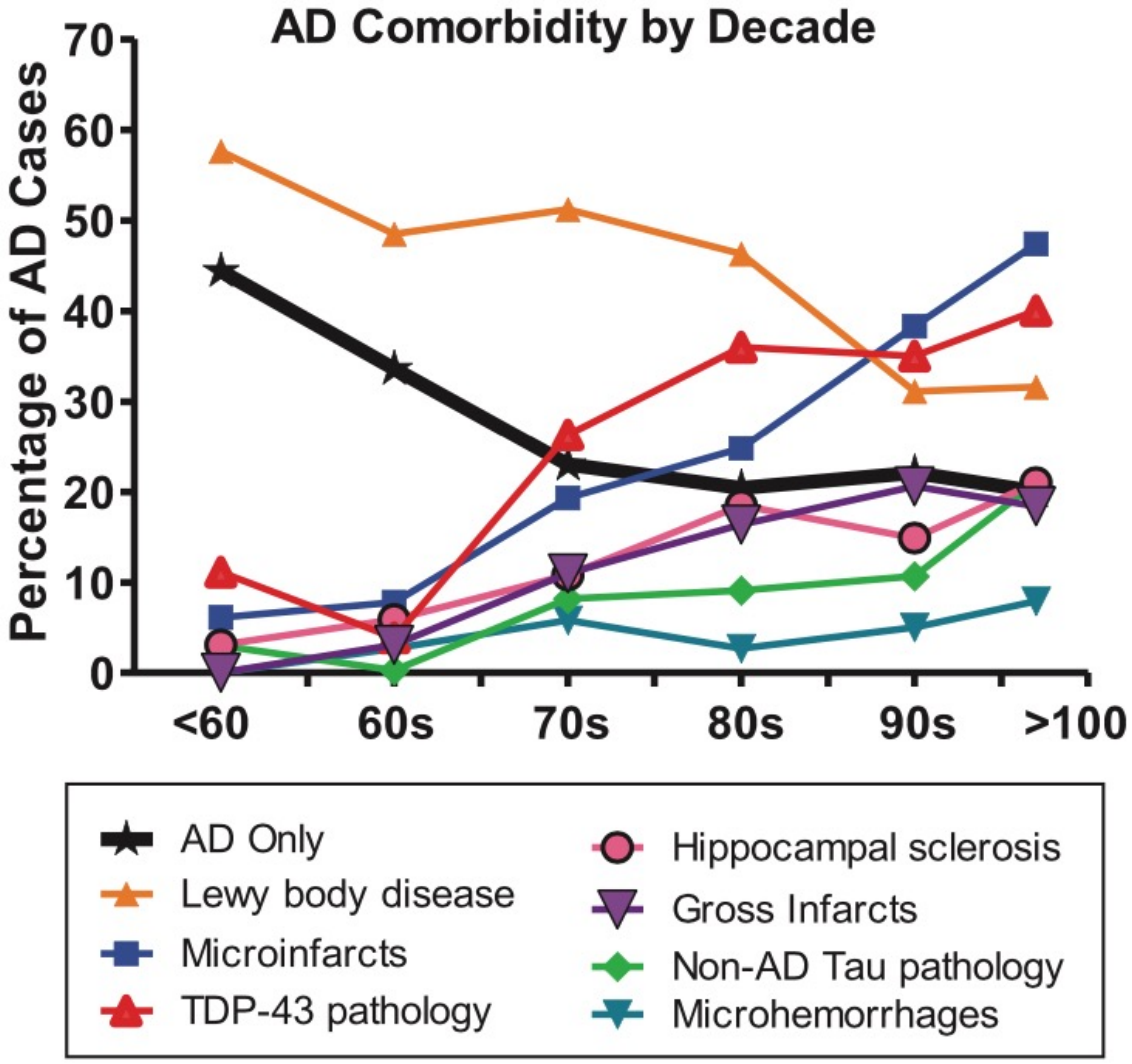
AD Plasma Biomarkers





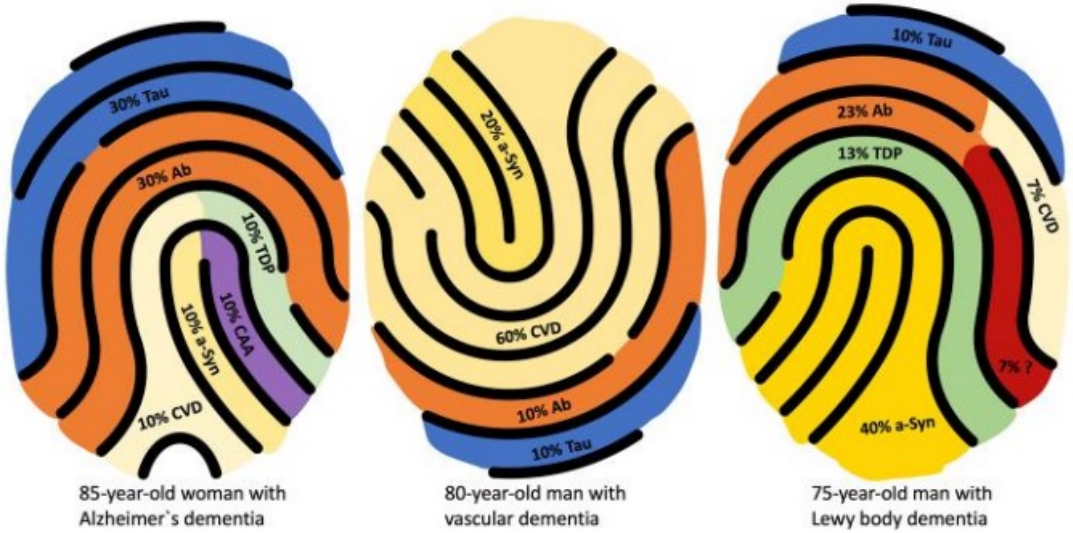
Janelidze 2022

Co-Etiology is Common



Beach 2021

Person-specific profiles



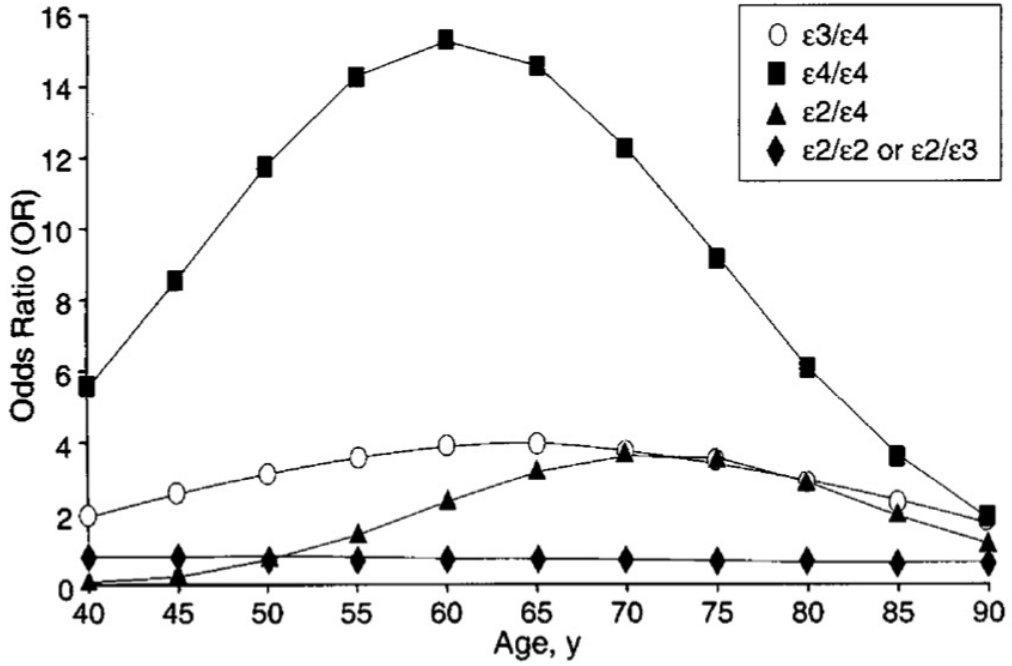
Younes & Mormino 2023

→ **Capturing AD etiologies in isolation is a limitation of current biomarker research and interpretation of biomarkers in clinic**

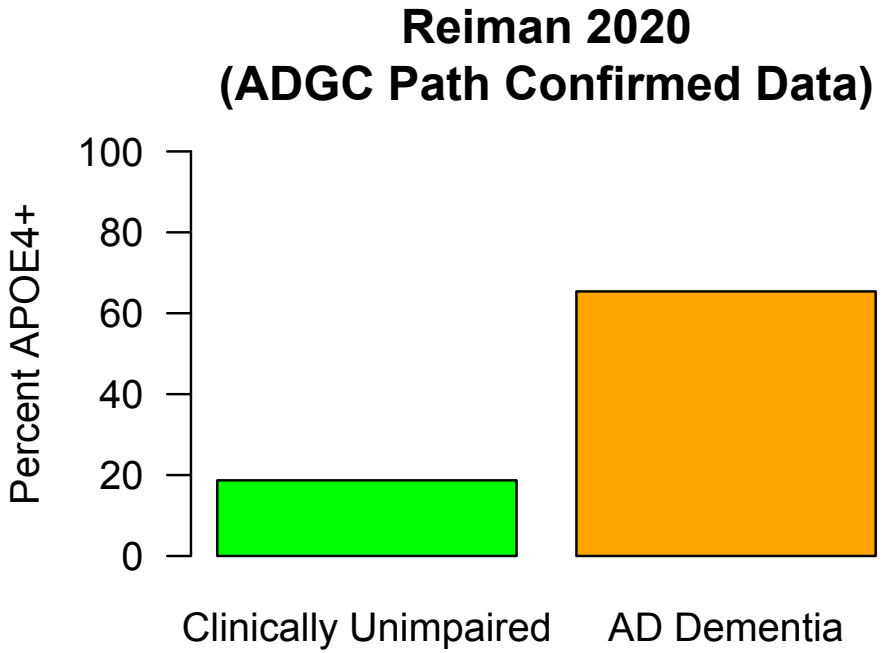
Objectives

- Classify the major biomarkers for assessing dementia etiology.
- Identify the relationship between APOE genotypes and AD biomarkers.
- Describe findings of differential biomarker progression among men and women at risk for dementia.

APOE genotype is a strong predictor of AD dementia risk

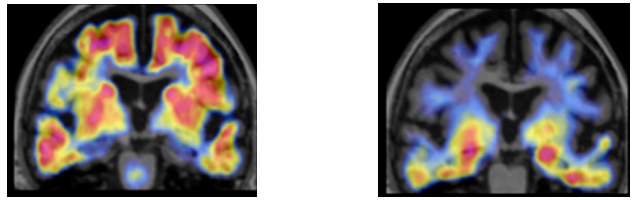


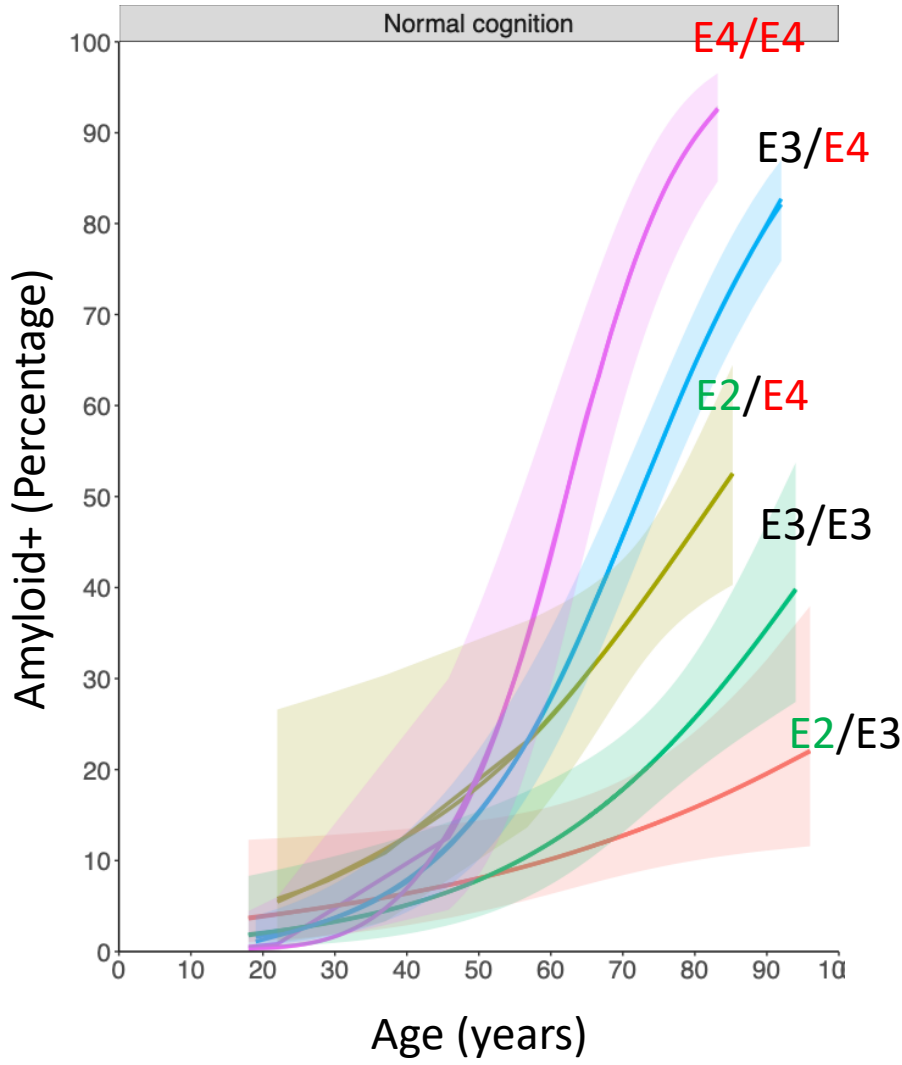
Farrer 1998



APOE is strong predictor of amyloid-positivity

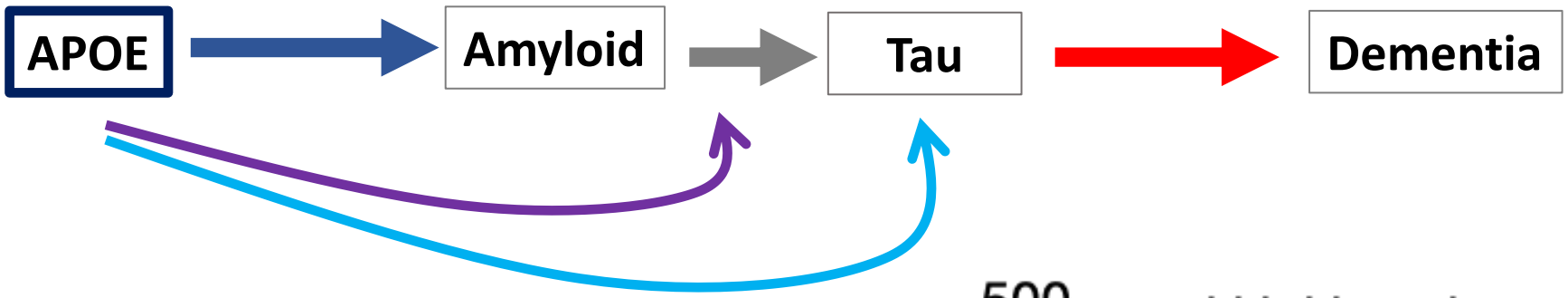
APOE 4>3>2 → Amyloid → Tau → Dementia

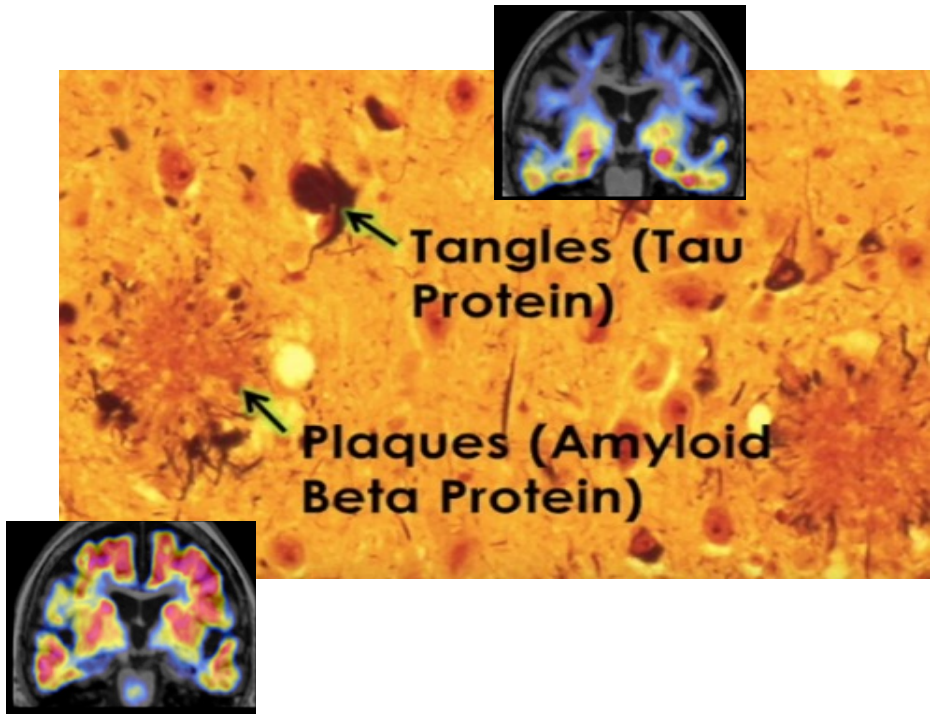


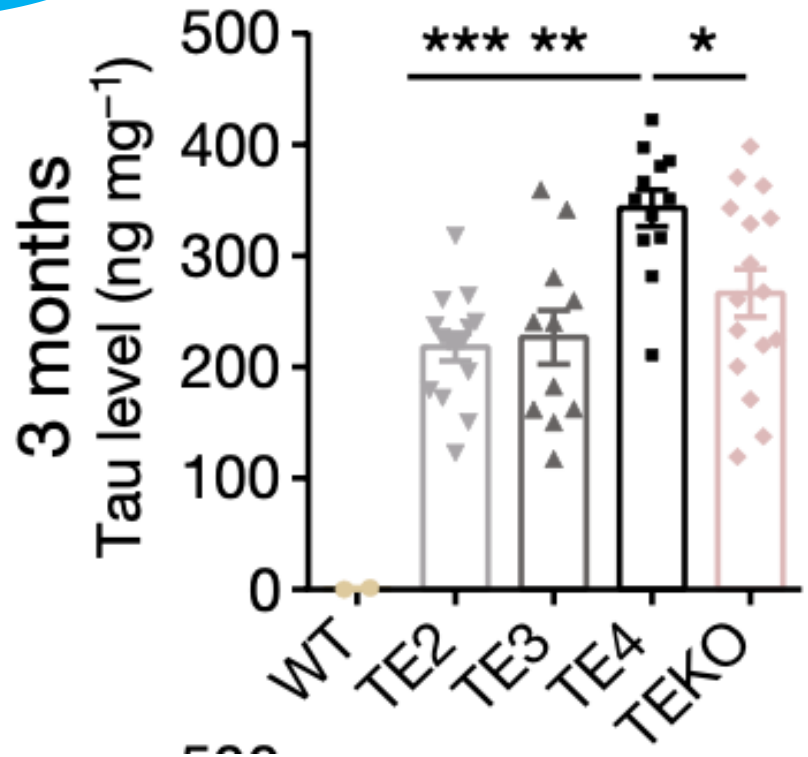


Jansen 2022

APOE Effects on Tau

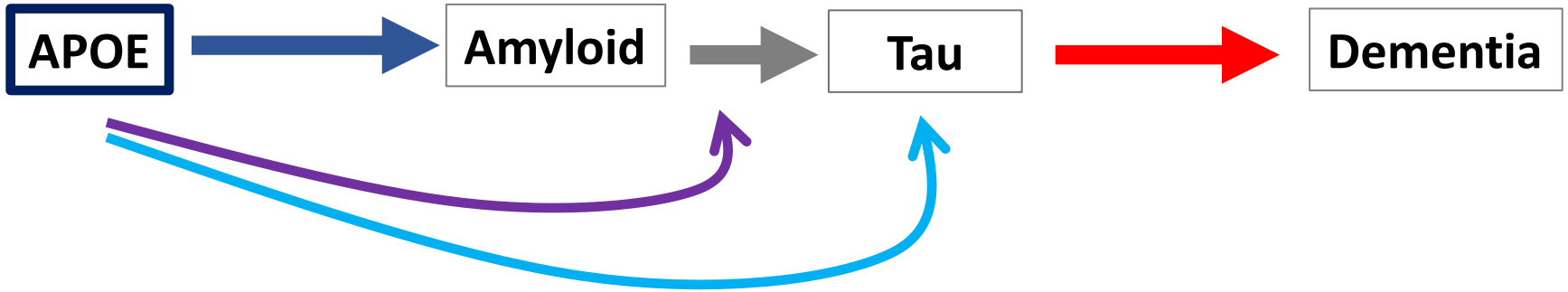




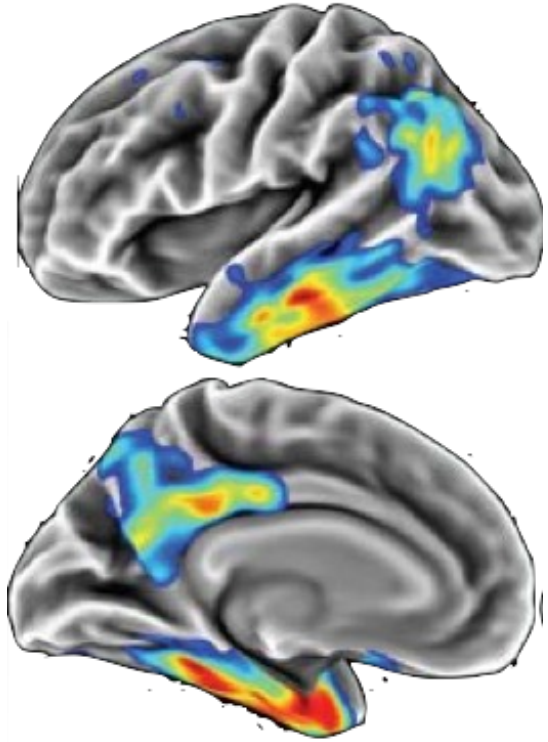


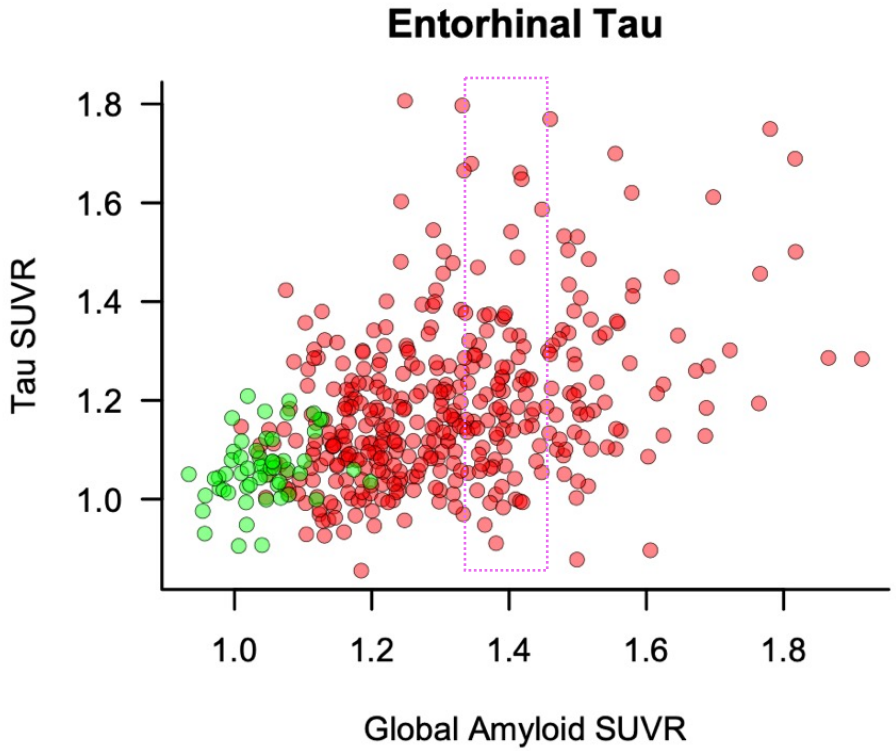
Reduced Tau Clearance in APOE4+ > APOE4-

Shi 2017



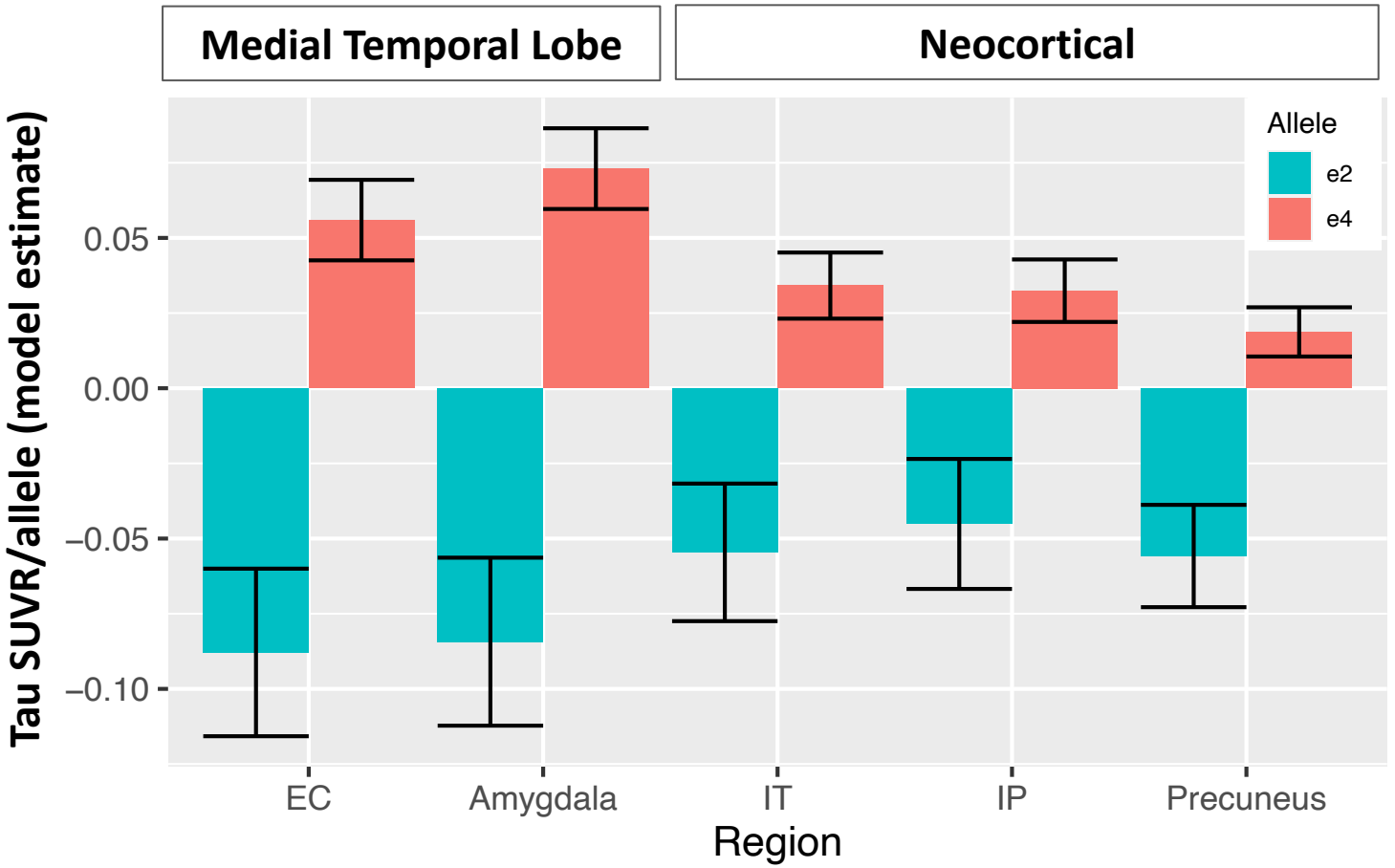
Global Amyloid~Voxelwise Tau





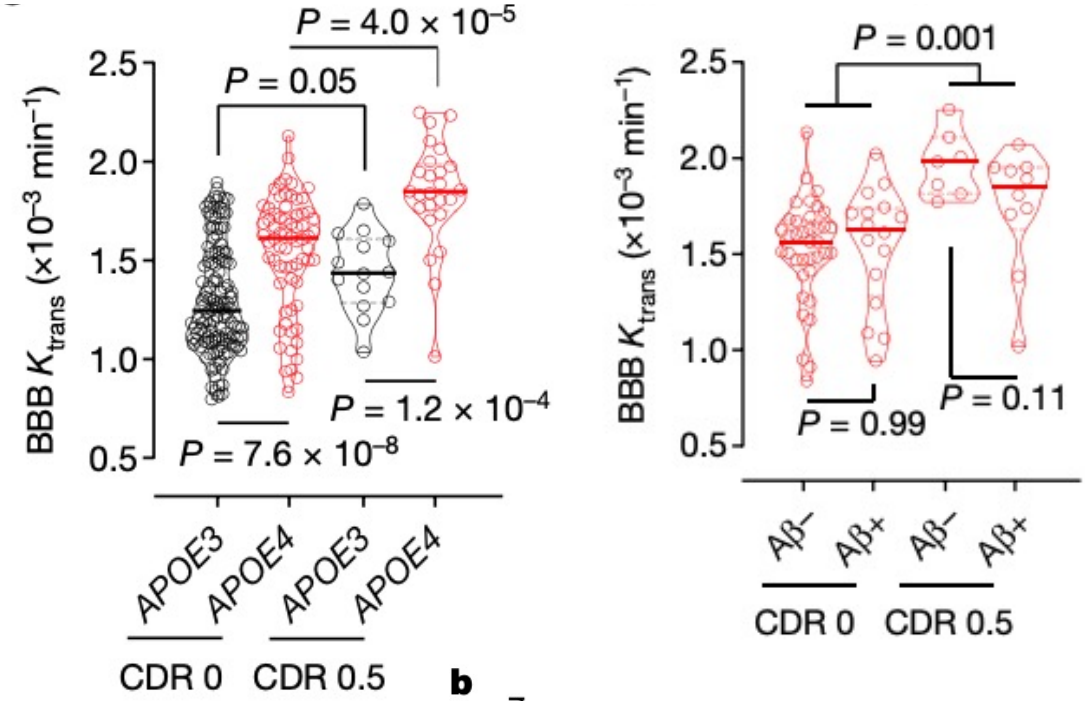
→*Does APOE contribute to this variability?*

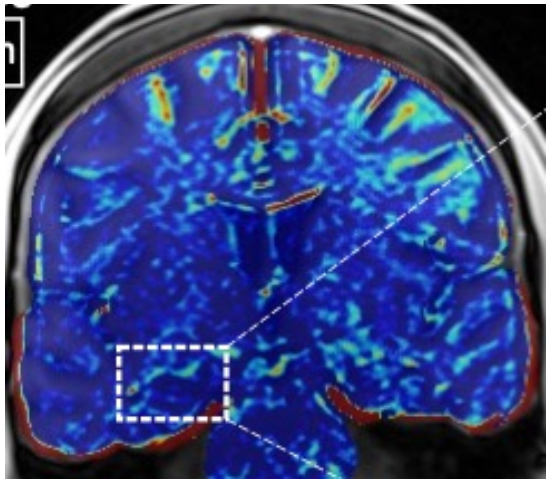
APOE effects on regional tau PET among Amyloid+ individuals



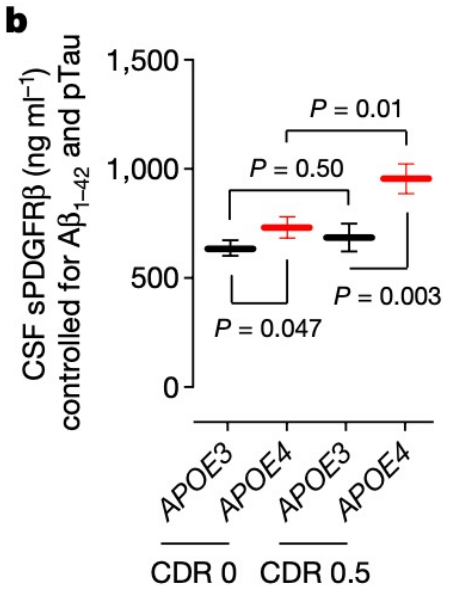
Young 2023

Additional APOE Effects among Amyloid- : Blood Brain Barrier





Montagne 2020



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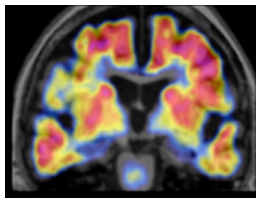

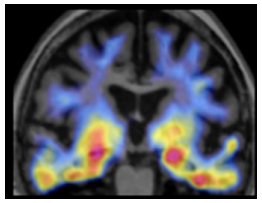

Microglial Pathways

Blood Brain Integrity

APOE Effects

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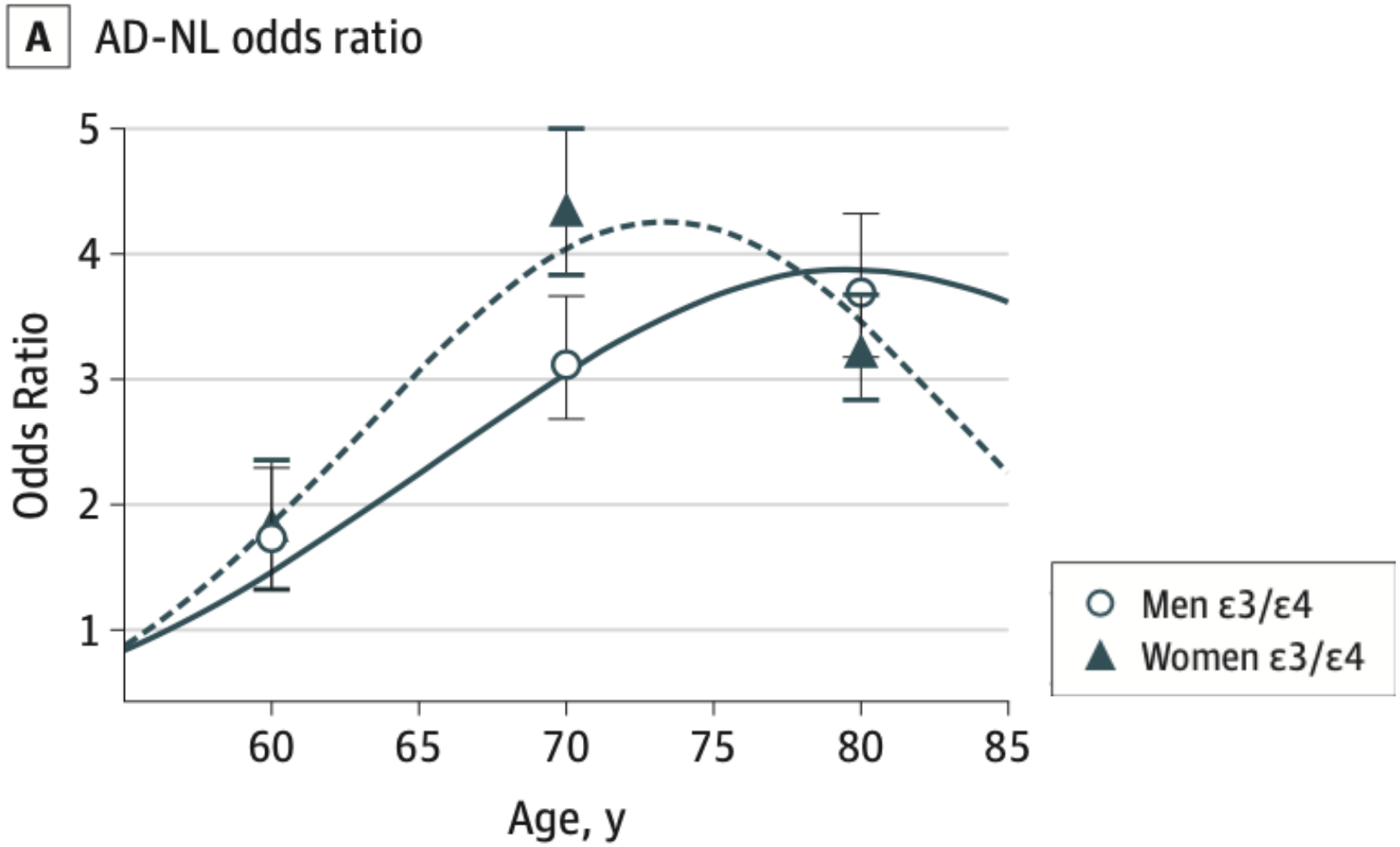
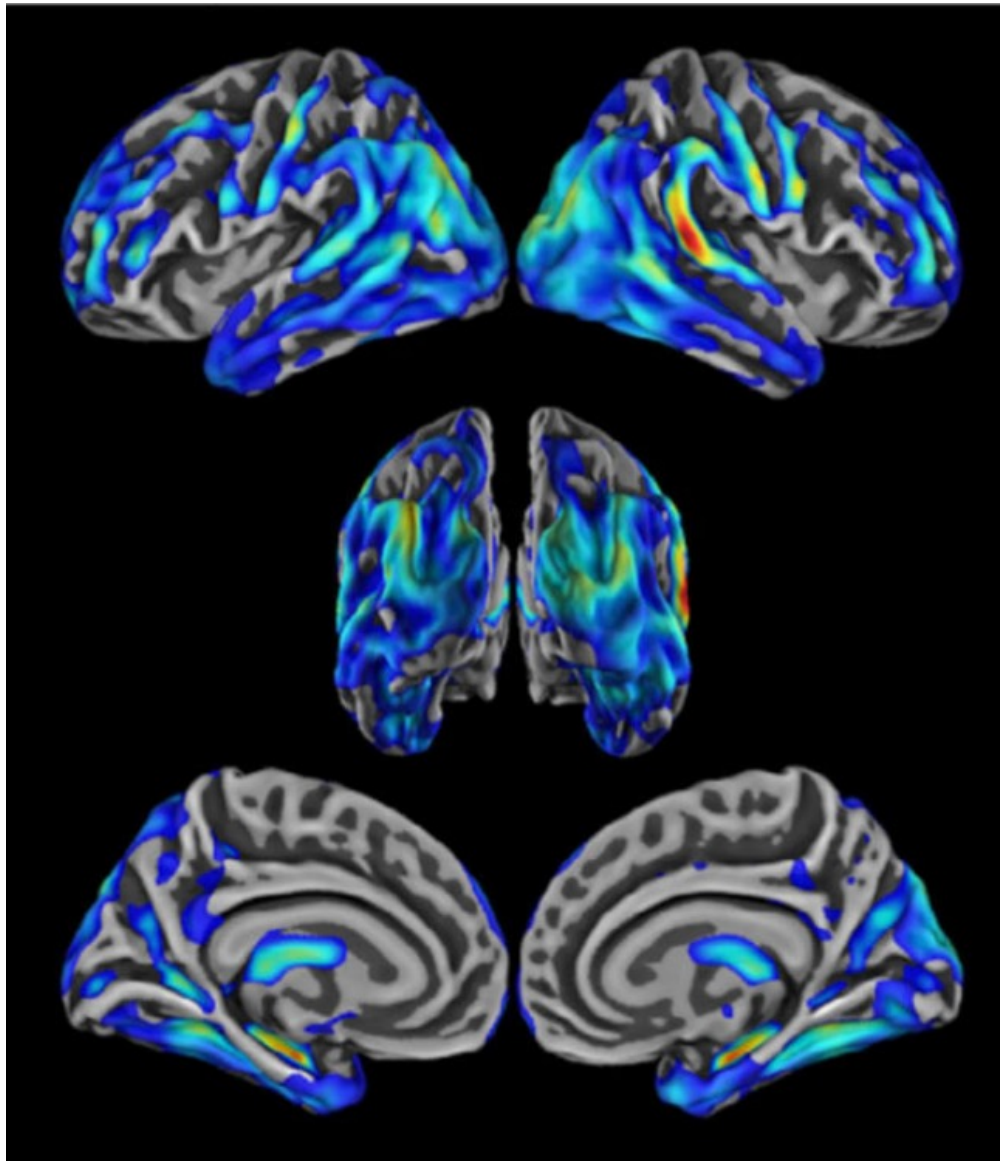
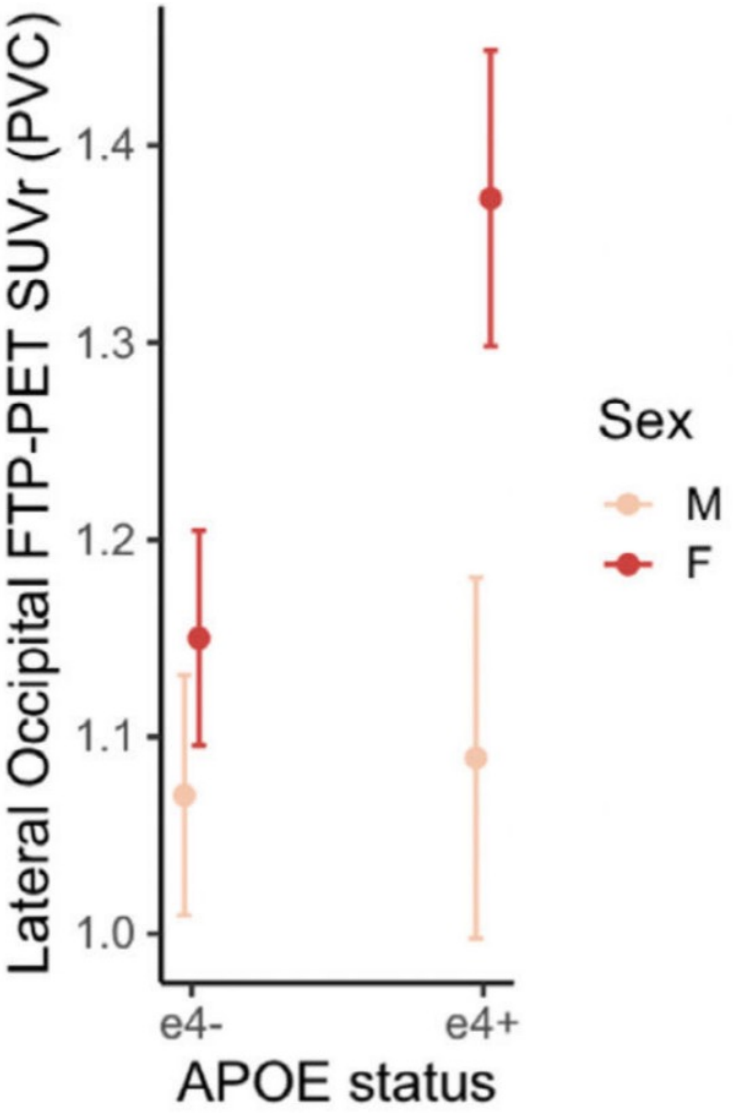
Greater risk of AD in women with APOE4+ women



Neu 2017 JAMA Neurology

Greater tau pathology in women

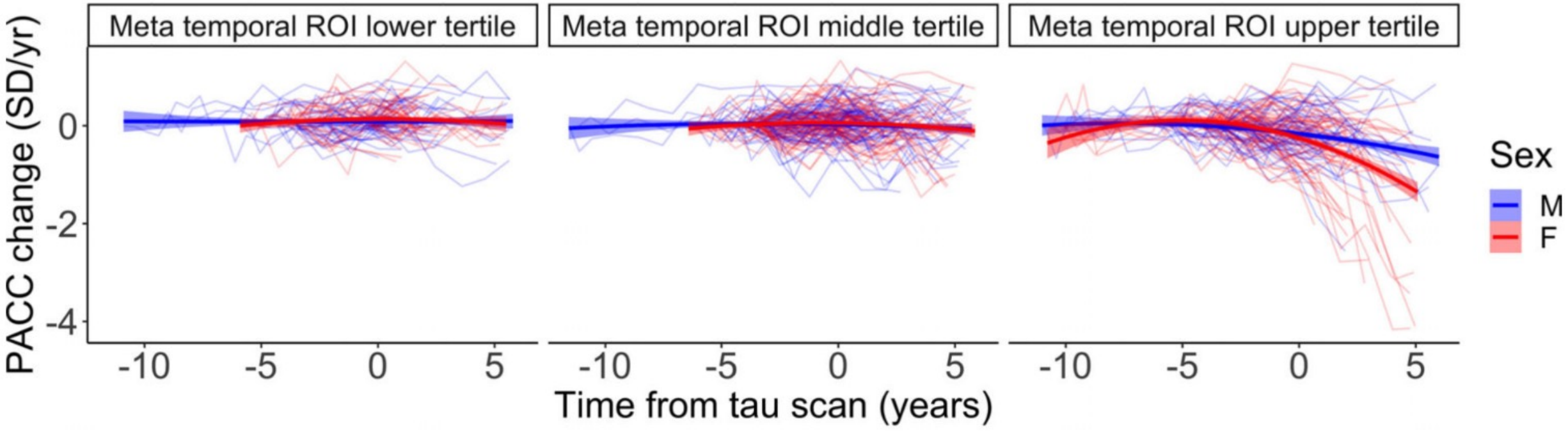




Buckley 2020

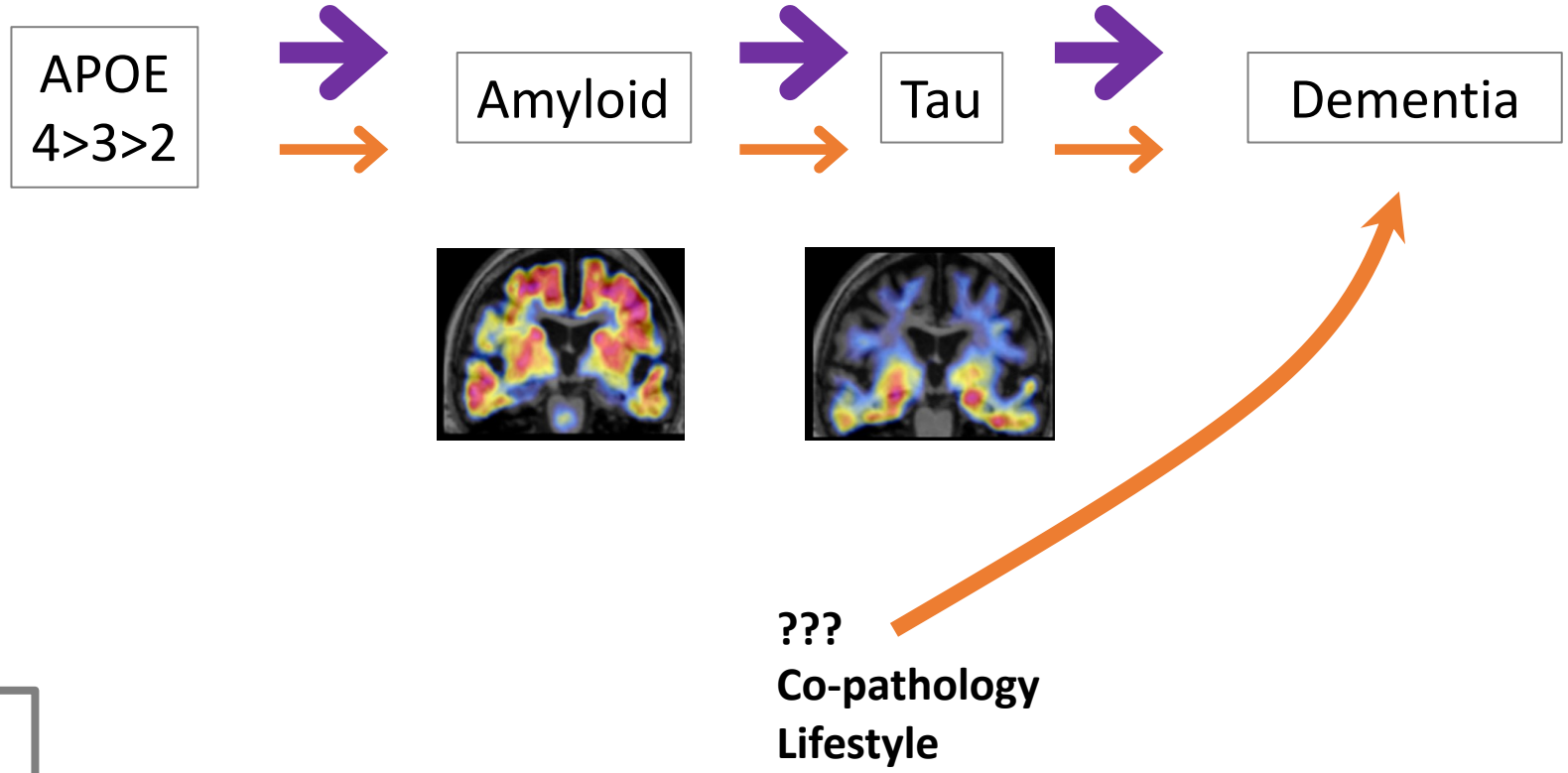
Greater decline in women with risk factor

Higher Tau PET levels



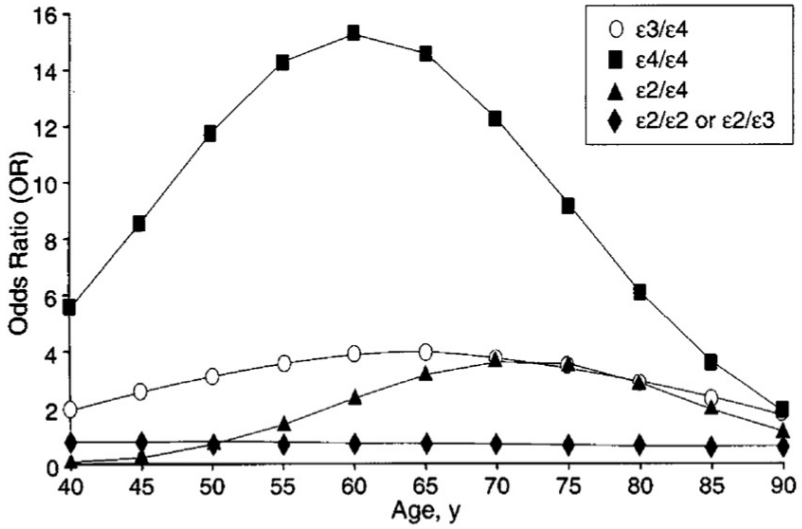
Buckley 2020

Differential progression in women and men?



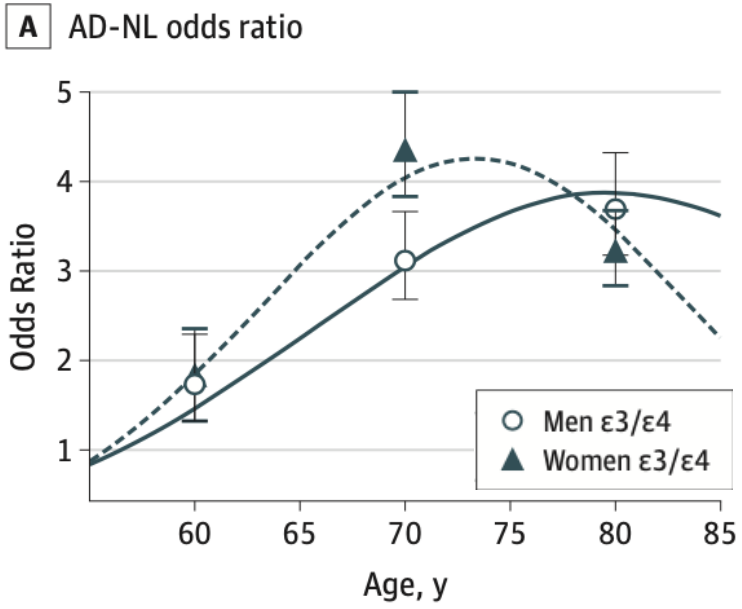
Risk profiles change at older ages

APOE



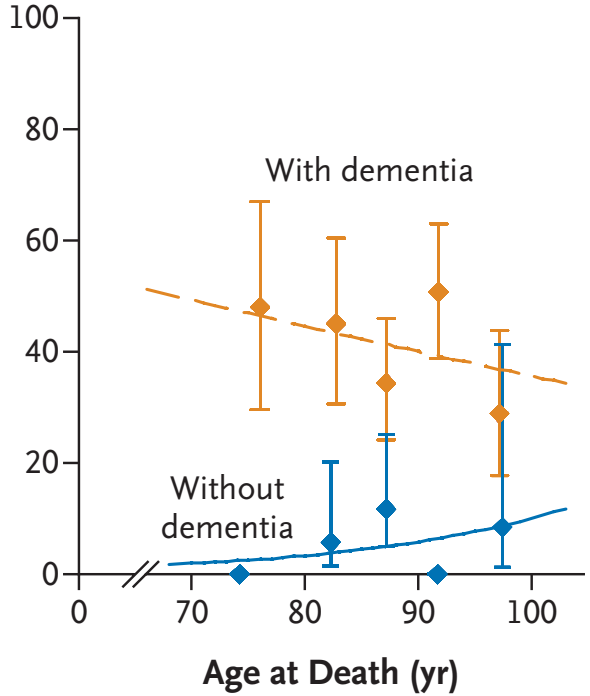
Farrer 1998

APOE risk in Women



Neu 2017

Tau Tangles



Savva 2009

Summary

- **Robust PET and biofluid biomarkers for assessing Alzheimer's disease etiology.**
- **Current missing biomarkers to capture other common age-related etiologies.**
- **APOE genotype influences multiple components of the Alzheimer's disease cascade.**
- **Increased risk of AD dementia in women may be mediated by APOE genotype and/or elevated tau burden.**
- **Need to integrate multiple factors to understand disease progression and underlying mechanisms in humans (sex, age, co-pathologies).**

Thank you

STANFORD AGING & MEMORY STUDY

A·D·R·C for healthy brain aging

adsp Alzheimer's Disease Sequencing Project

PHC PHENOTYPE HARMONIZATION CONSORTIUM

NIH
R01AG074339, P30AG06615,
U24AG067418, U24AG074855

Internal
Stanford Wu Tsai Neuroscience Institute (Complete),
Stanford PHIND Institute (Complete),
Good Planet Foundation

Fellowships
AARFD-21-852597 (T. Tran)
NIH F32-AG074625 (J. Winer)
AARFD-21-849349 (C. Young)

Career Development
NIH K99-AG071837 (C. Young)
NIH K99-AG075184 (A. Trelle)

EXTRA

Limitations with generalizability

Caucasians: Population-based Studies			
ε3/ε3	2683	1.0 (Referent)	. . .
ε2/ε2	36	0.9 (0.3-2.8)	.94
ε2/ε3	568	0.6 (0.5-0.9)	.93
ε2/ε4	152	1.2 (0.8-2.0)	<.01
ε3/ε4	1226	2.7 (2.2-3.2)	.15
ε4/ε4	193	12.5 (8.8-17.7)	.03
African Americans			
ε3/ε3	206	1.0 (Referent)	. . .
ε2/ε2	6	2.4 (0.3-22.7)	.35
ε2/ε3	54	0.6 (0.4-1.7)	.09
ε2/ε4	10	1.8 (0.4-8.1)	.27
ε3/ε4	164	1.1 (0.7-1.8)	.03
ε4/ε4	34	5.7 (2.3-14.1)	.01

Farrer 1998

FDA approved F18 Amyloid PET tracers

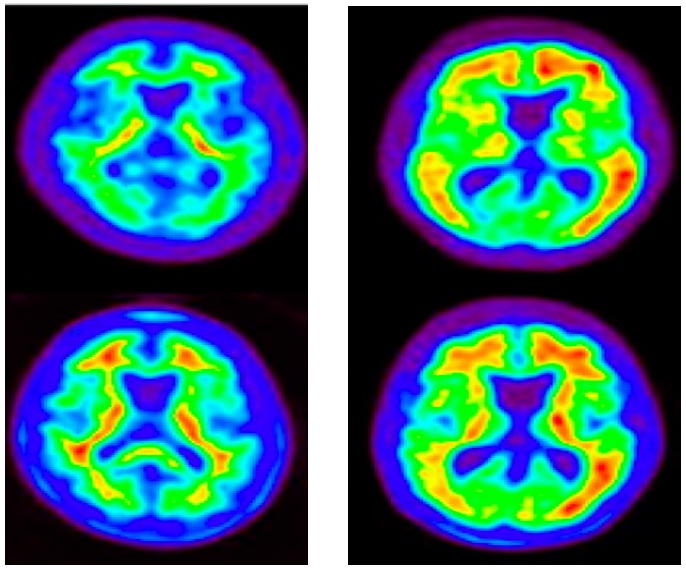
(First research amyloid scans=2004)

Florbetapir (Amyvid) 2012

Aβ- Aβ+

C11 PIB

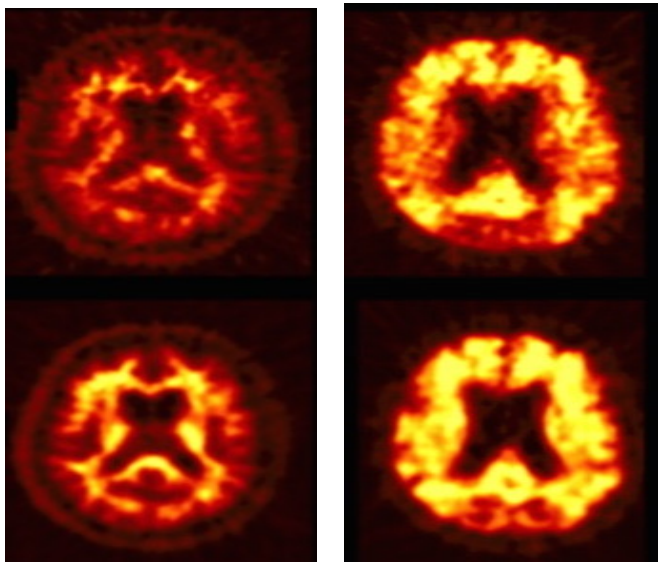
F18 tracer



Landau 2015

Flutemetamol (Vizamyl) 2013

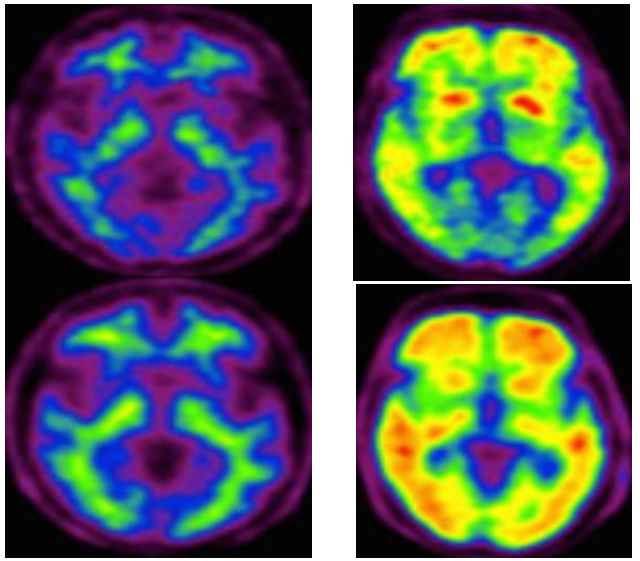
Aβ- Aβ+



Mountz 2015

Florbetaben (Neuroceq) 2014

Aβ- Aβ+

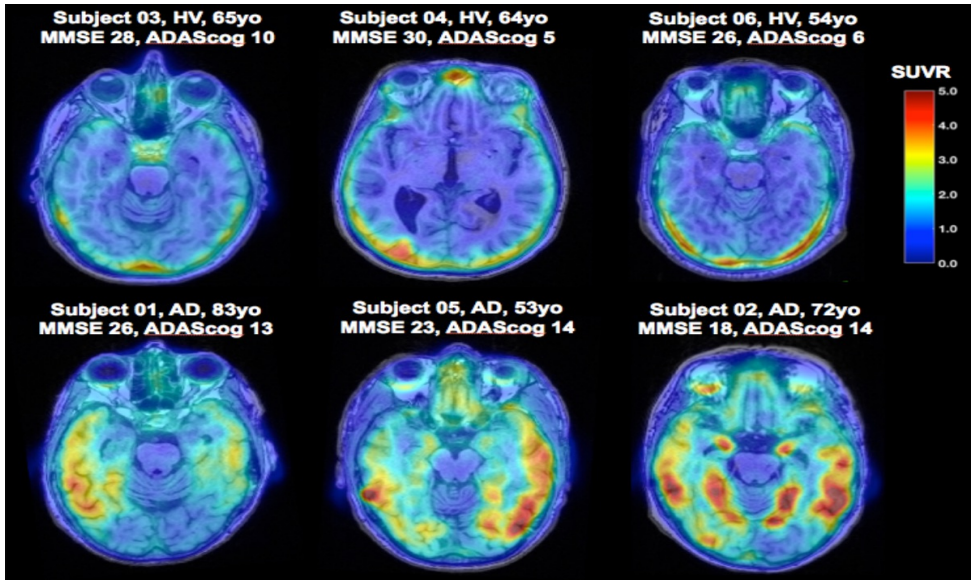


Villemagne 2012

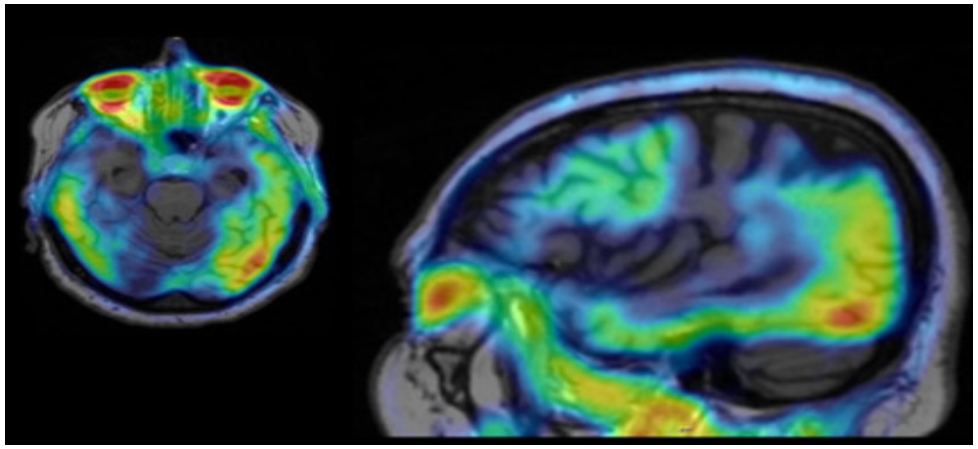
→F18 tracers highly correlated with postmortem amyloid neuritic plaques (moderate/frequent).

Tau Ligand Timeline

- 2013: T807/AV1451/Flortaucipir publication
- 2014: T808 publication (→GTP-1)
- 2016: THK5351 publication
- 2017: THK5351 MAO-B binding discovered
- 2016/17: First MK6240 scans
- 2017: First PI2620 scans presented
- 2020: First JNJ scans presented
- 2020: Flortaucipir FDA approved (Tauvid)

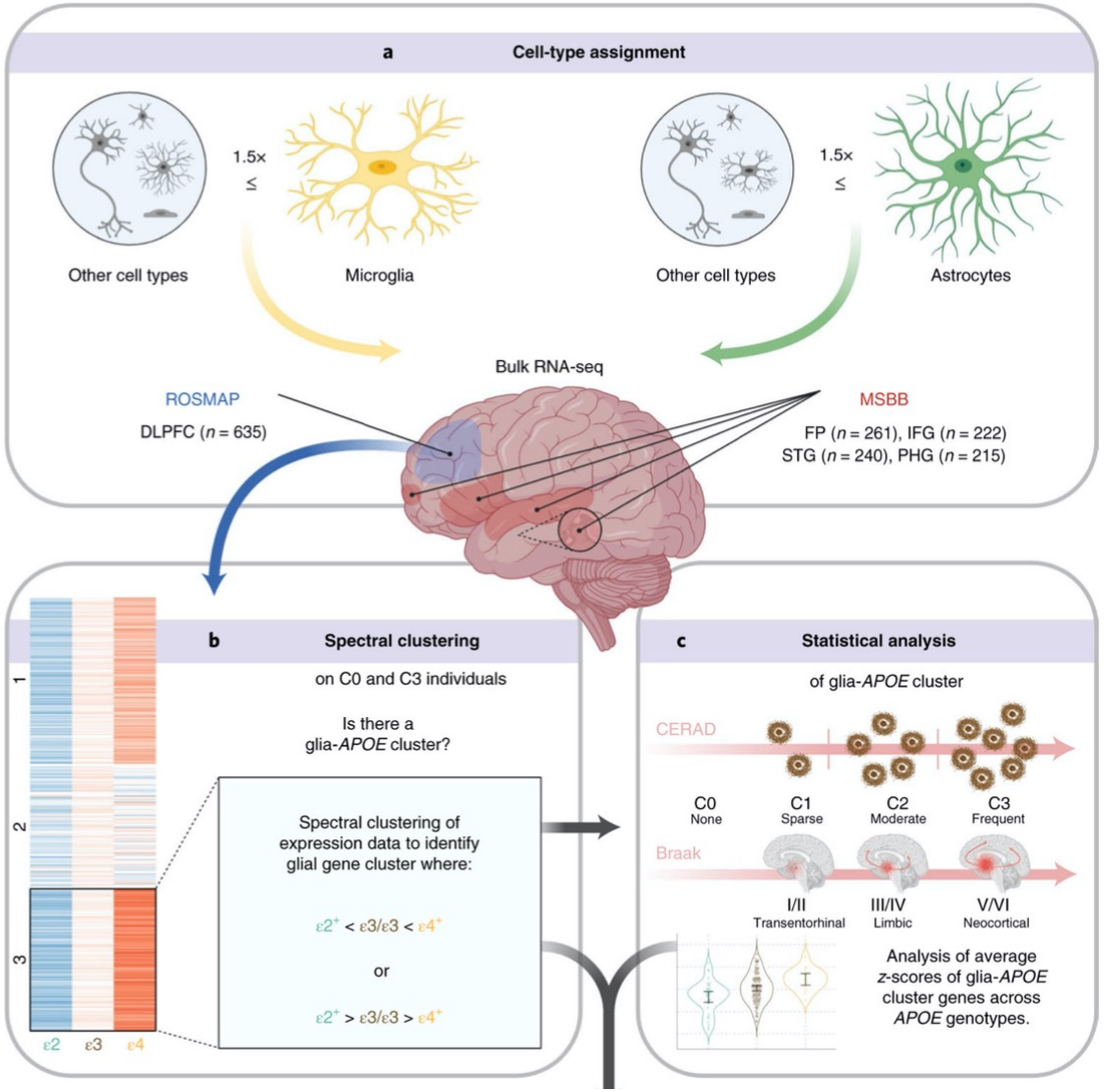


MK6240: HAI 2017

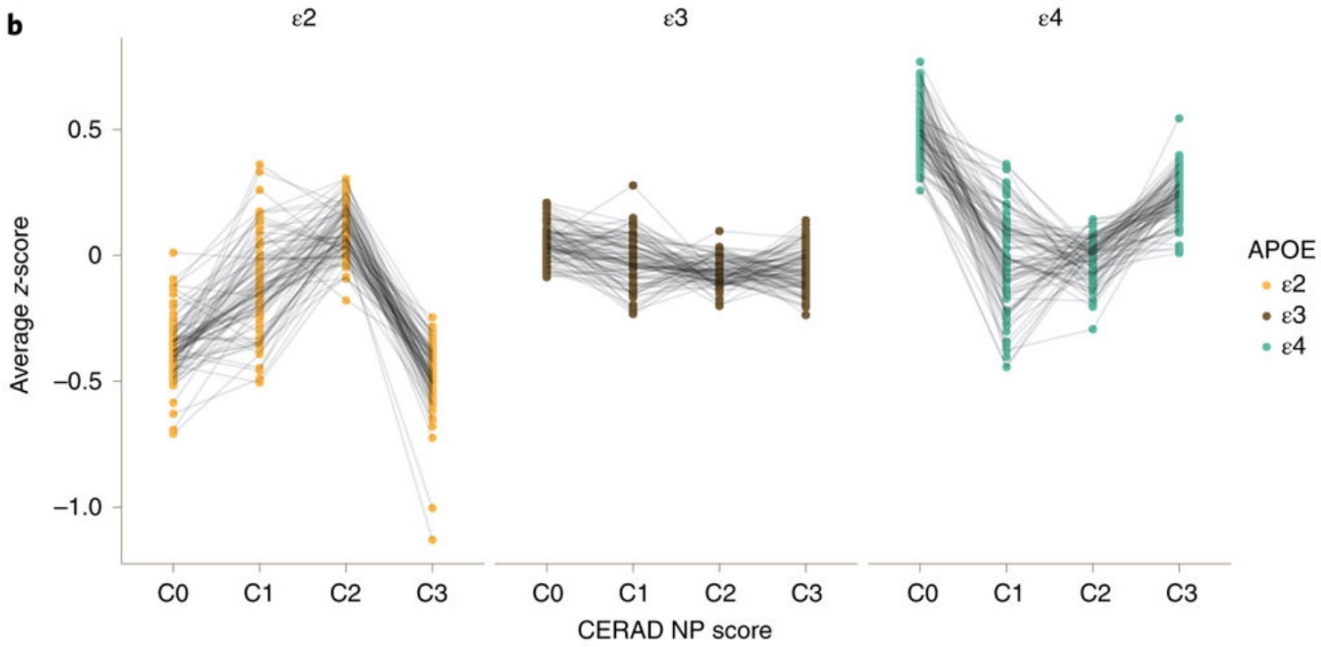


PI2620: ADPD 2017

Additional APOE Effects among Amyloid- : Microglia gene expression



“microglia-APOE cluster”
phagocytosis & proinflammatory genes



Serrano-Pozo 2021