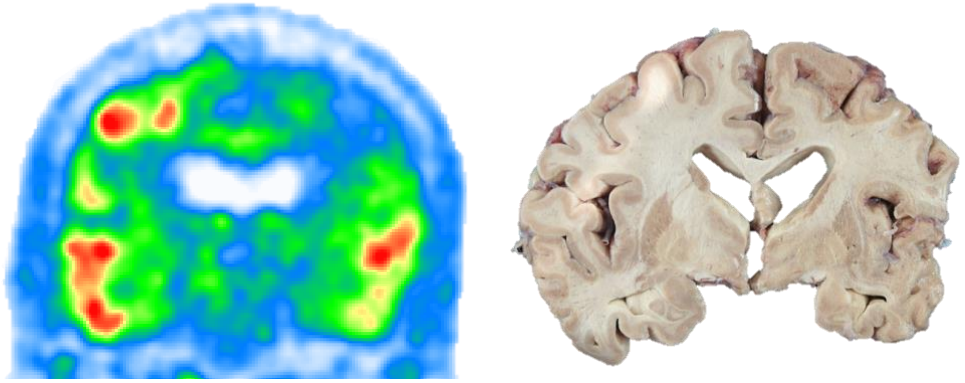
UCSF Weill Institute for Neurosciences
Memory and Aging Center



Neuropathological validation of AD biomarkers

past - present - future

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Disclosures

No personal disclosure

Research funding from

- NIH
- US department of Defense
- Alzheimer's Association

Neuroimager by training

Neuropathology enthusiast

Fluid biomarker adopter

Neuropathological validation

Not a comprehensive review (10-15 min!) – few key points

Neuropath validation is crucial when using biomarkers to

- determine the presence/absence of AD neuropathology
- study pathophysiology of disease

But not all biomarkers need neuropathological validation to be clinically relevant and useful

Neuropathological validation & FDA approval of PET

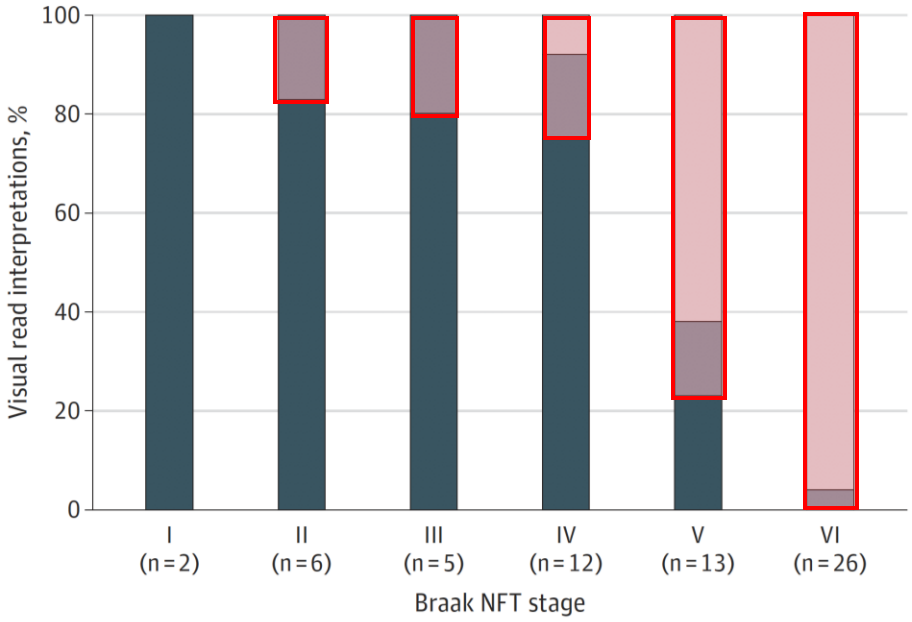
Amyloid-PET

Based on correspondence between
- PET **binary visual read**
- CERAD mod-to-freq, i.e. C2
(neuritic plaque density)

tracer	n	Se	Sp	reference
Florbetapir	59	92%	95%	Clark et al., Lancet Neurol 2012
Flutemetamol	68	88%	88%	Curtis et al., JAMA Neurol 2015
Florbetaben	74	98%	89%	Sabri et al, Alz&Dem 2015

Tau-PET (Flortaucipir)

Based on correspondence between
- PET **binary visual read**
- Braak stage V/VI, i.e. B3
(advanced tau tangle stage)



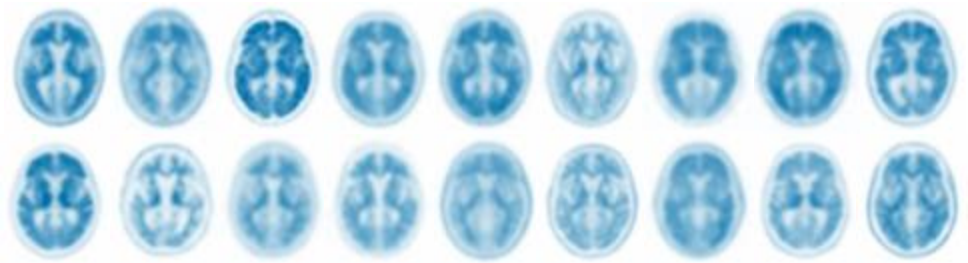
N = 64

Se = 92-100%
Sp = 52-92%

Fleisher et al,
JAMA Neurol 2020

Amyloid-PET is **more than a binary outcome**

Amyloid-PET / neuropathology across centers
(UCSF, UC Davis, UPitt, Mayo, AIBL)
n = 179 patients



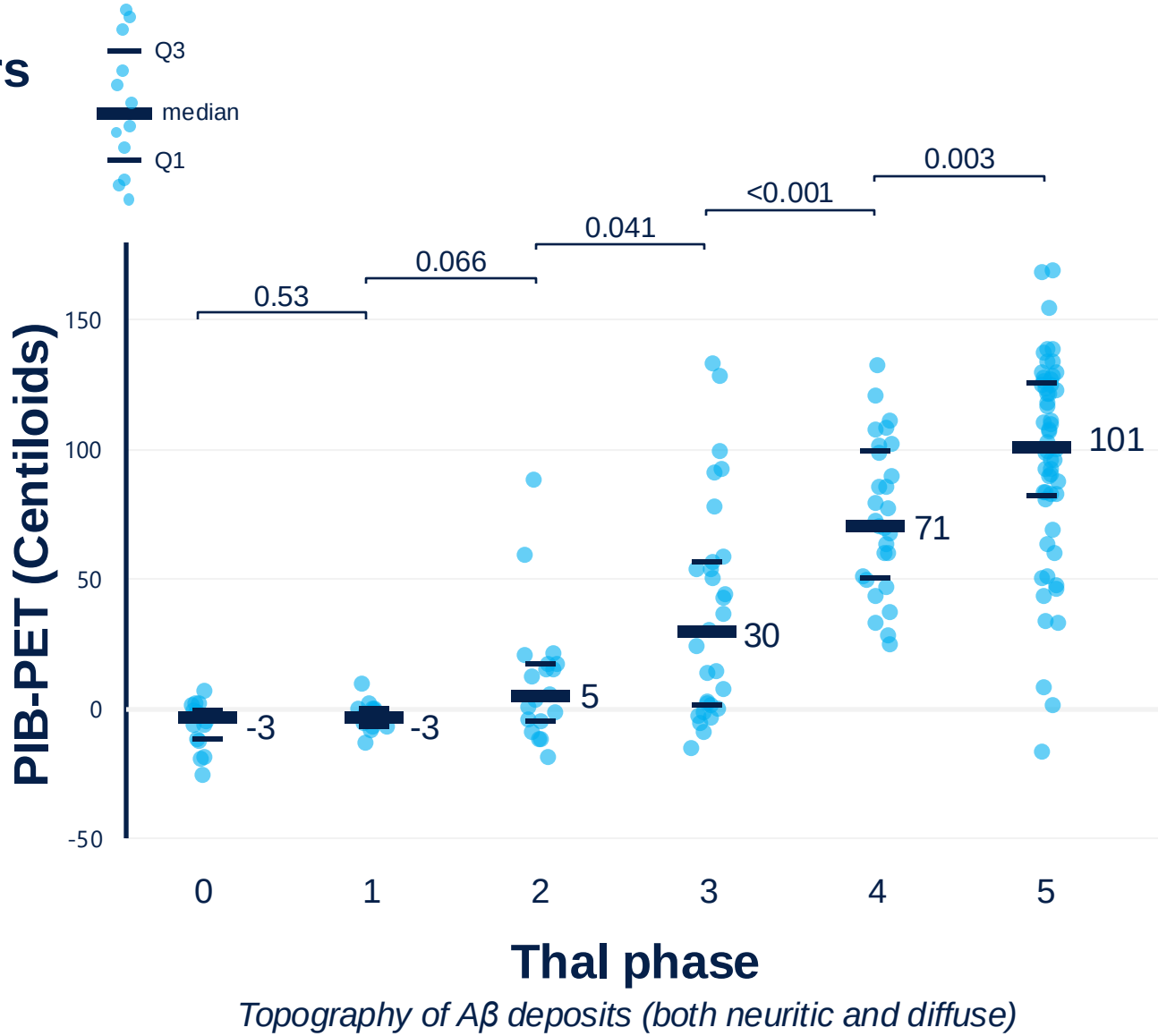
Amyloid-PET quantified in Centiloids
(Klunk et al, Alz&Dem 2015)

Average signal in Aβ-negative individuals (controls in their 20s)

0 CL

100 CLs

mean signal in patients with typical mild-to-moderate AD dementia



Topography of Aβ deposits (both neuritic and diffuse)

La Joie, Ayakta et al, Alz&Dem 2019

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Amyloid-PET is **more than a binary outcome**

Thresholds depend on your standard of truth

ROC analyses based on multiple pathological standards of truth

Standard of truth	N	AUROC	Threshold	Accuracy	Sensitivity	Specificity
CERAD score						
None versus sparse-to-frequent[a]	41 versus 138	0.919 [0.869-0.955]	12.2			
None-sparse versus moderate-frequent [b]*	59 versus 120	0.910 [0.858-0.948]	12.2	88.3 [82.6-92.6]	89.2 [82.2-94.1]	86.4 [75.0-94.0]
None-to-moderate versus frequent[c]	96 versus 83	0.857 [0.797-0.905]	32.4	87.7 [82.0-92.1]	88.0 [79.0-94.1]	71.9 [61.8-80.6]
Thal phase						
0 versus 1-to-5[d]	17 versus 157	0.891 [0.835-0.933]	7.4	78.2 [71.3-84.0]	75.8 [68.3-82.3]	100 [80.5-100]
0-1 versus 2-to-5	30 versus 132	0.920 [0.868-0.957]	12.0	85.2 [78.7-90.3]	81.8 [74.2-88.0]	100 [88.4-100]
0-to-2 versus 3-to-5[e]*	49 versus 113	0.923 [0.871-0.959]	23.5	88.9 [83.0-93.3]	85.8 [78.0-91.7]	95.9 [86.0-99.5]
0-to-3 versus 4-5[f]	78 versus 84	0.913 [0.858-0.951]	24.4	87.7 [81.6-92.3]	96.4 [89.9-99.3]	78.2 [67.4-86.8]
0-to-4 versus 5	106 versus 56	0.860 [0.797-0.910]	79.9	81.5 [74.6-87.1]	76.8 [63.6-87.0]	84.0 [75.6-90.4]
ADNC levels						
None versus low-to-high	17 versus 157	0.891 [0.835-0.933]	7.4	78.2 [71.3-84.0]	75.8 [68.3-82.3]	100 [80.5-100]
None-low versus intermediate-high*	66 versus 113	0.894 [0.840-0.935]	24.4	85.5 [79.5-90.3]	84.1 [76.0-90.3]	87.9 [77.5-94.6]
None-to-intermediate versus high	114 versus 59	0.887 [0.830-0.930]	59.3			

Early stages of amyloid deposits

Amyloid + advanced tau NFT (B3)

La Joie, Ayakta et al, Alz&Dem 2019

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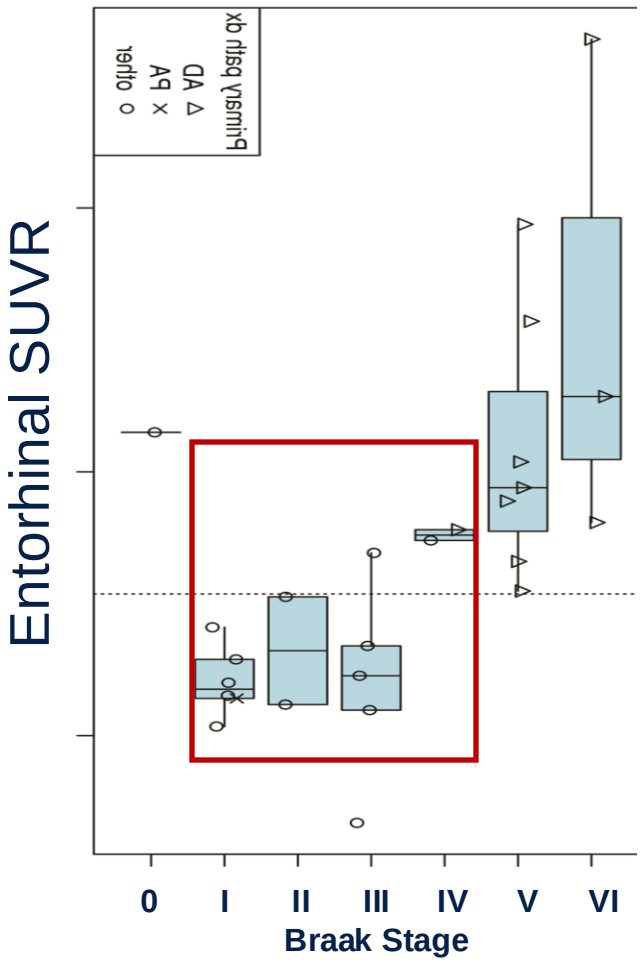
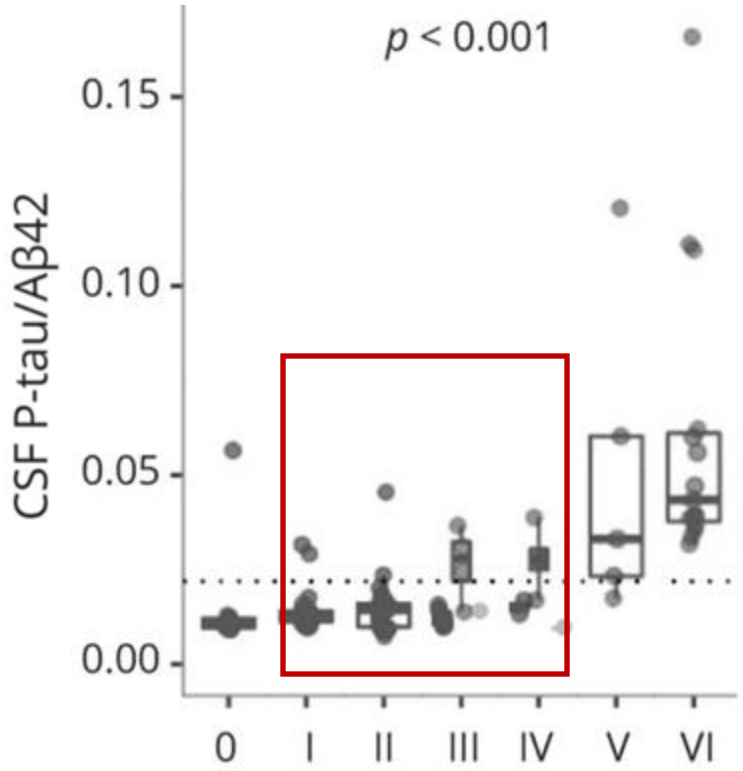
Sensitivity to mild-to-moderate neuropathological stages?

Flortaucipir PET



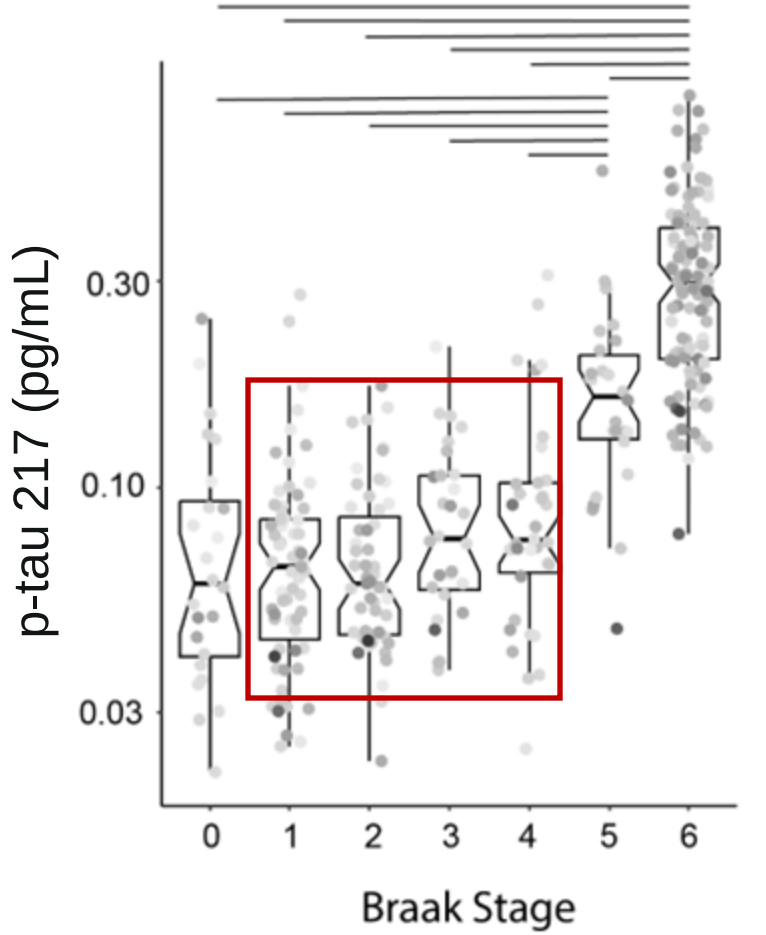
Lowe et al,
Alz & Dem 2020 (Mayo ADRC)

CSF Roche Elecsys



Mattsson-Carlgren *et al,*
Neurology 2022 (UCSF ADRC)

Blood (Ptau217 Janssen)



Vandevrede et al,
in revision (UCSF ADRC)

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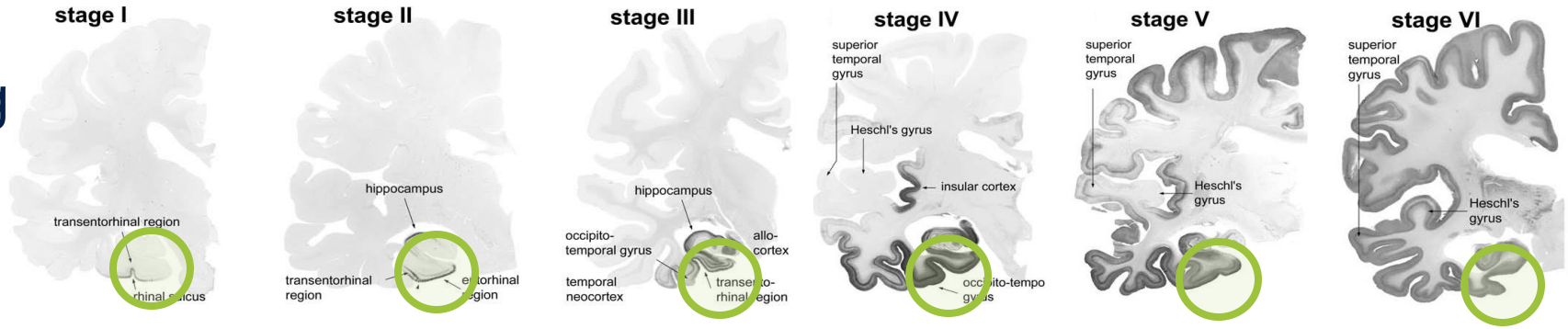
Neuropathology is more than an ordinal outcome

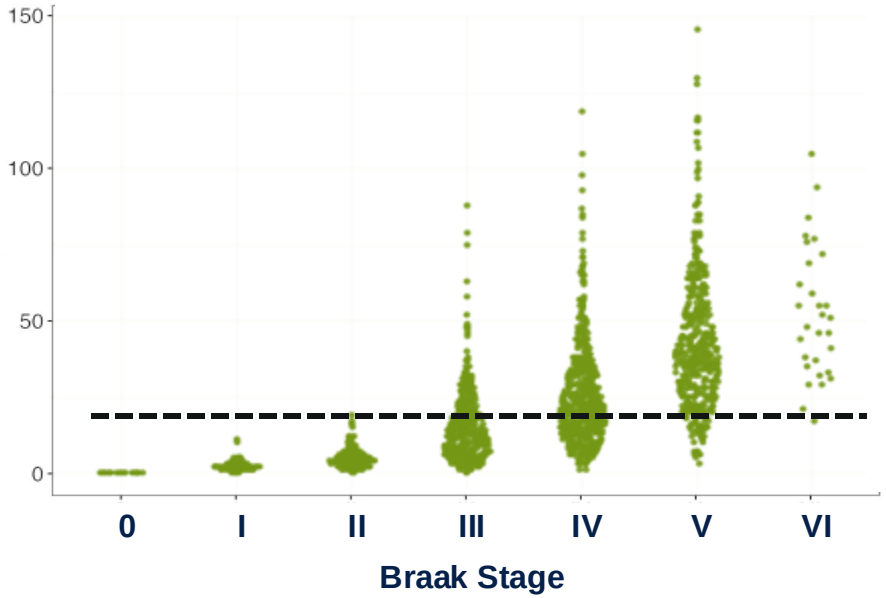
Braak et al, Acta Neuropathol (2006)

Stereotypical Braak staging for **neurofibrillary tangle topography**



Braak staging is a **poor proxy for tangle burden**

Entorhinal neurofibrillary tangle density



In vivo detection threshold?

Data from Rush center (1,828 cases with quantitative neuropath)

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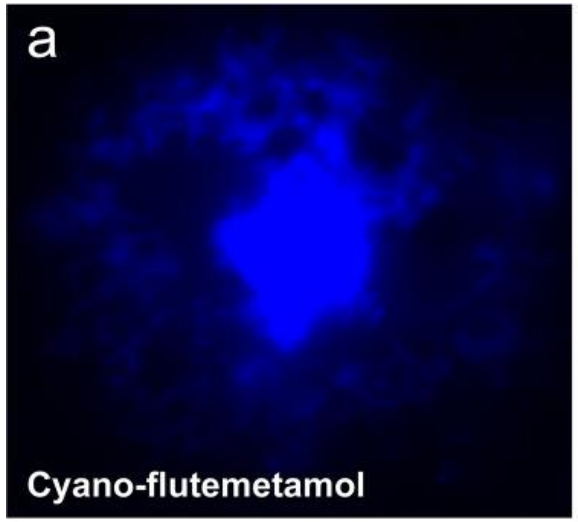
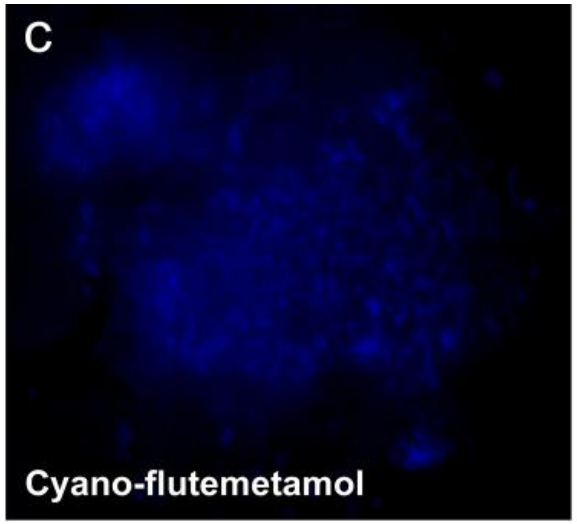
Neuropathology is more than an ordinal outcome - Aβ

Cored Aβ plaque



Diffuse Aβ plaque



total fluorescence of 1 cored plaque
= total fluorescence of ~3 diffuse plaques of similar volume

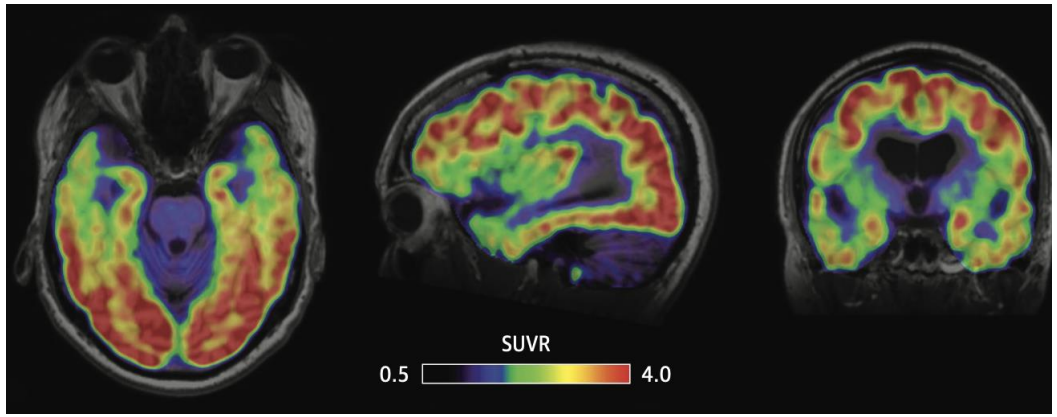
PET signal is likely a function of plaque size and density of Aβ fibrils in plaques

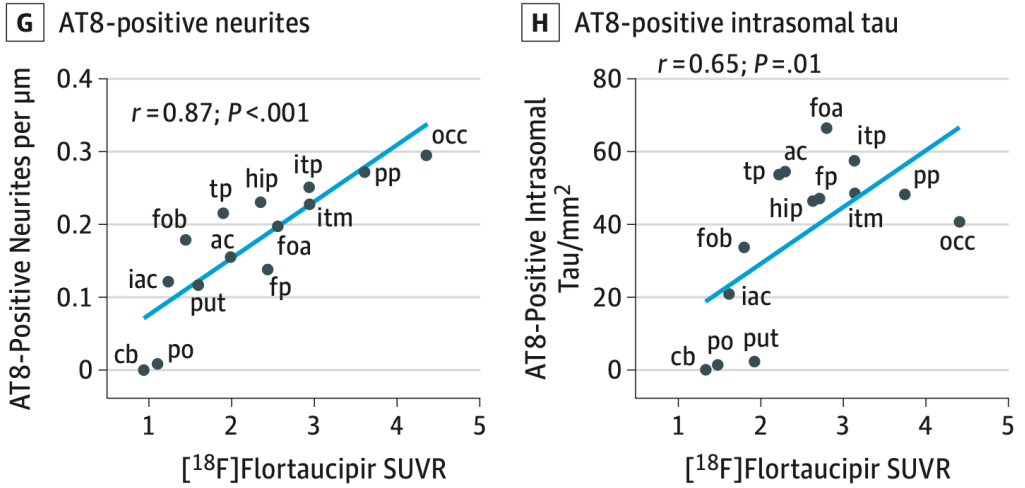
University of Pittsburgh ADRC brain bank

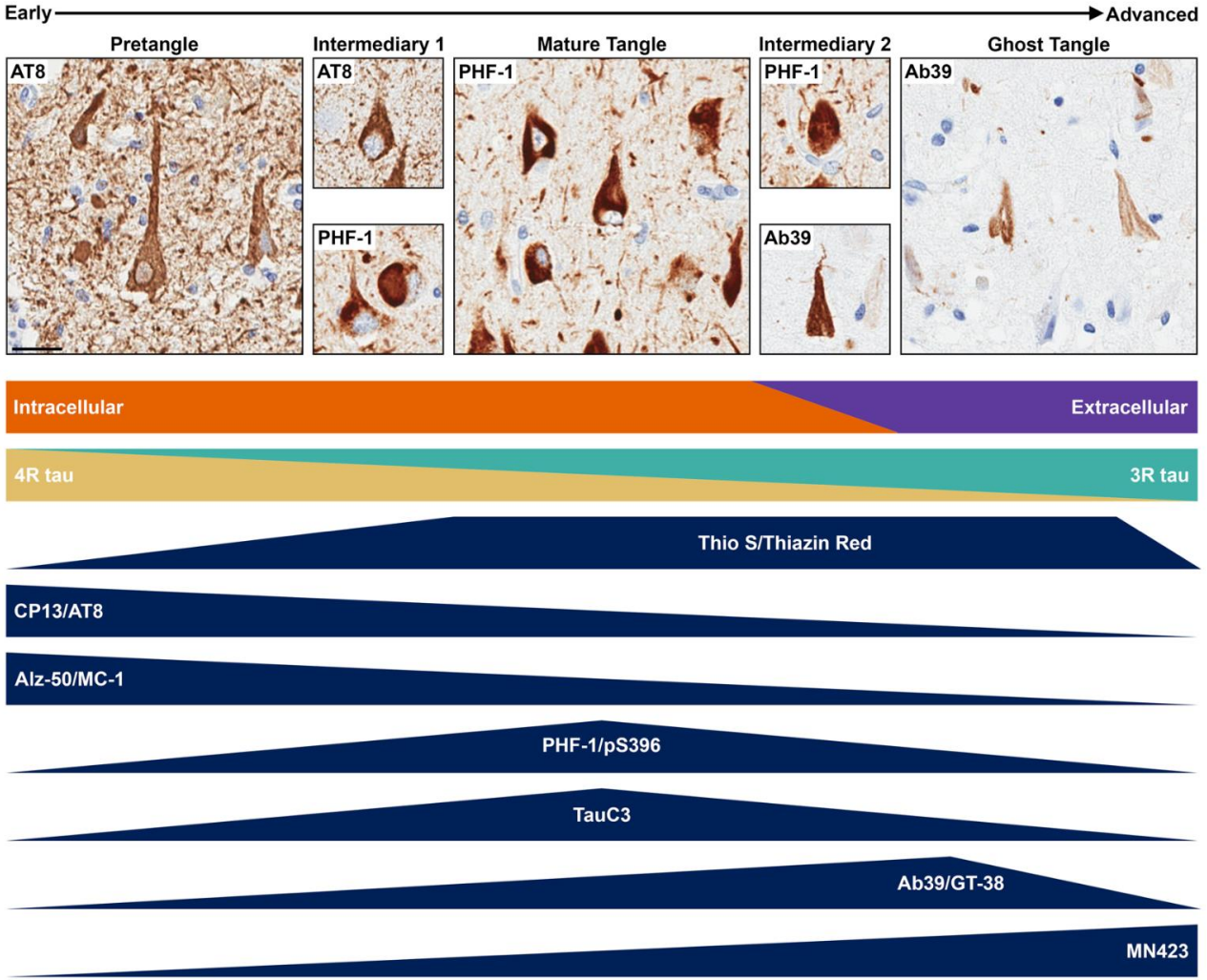
Ikonomovic et al,
Acta Neuropathologica 2020

UCSF

Neuropathology is more than an ordinal outcome - tau







Smith et al, JAMA Neurology 2018

Moloney et al, Alz & Dem 2021

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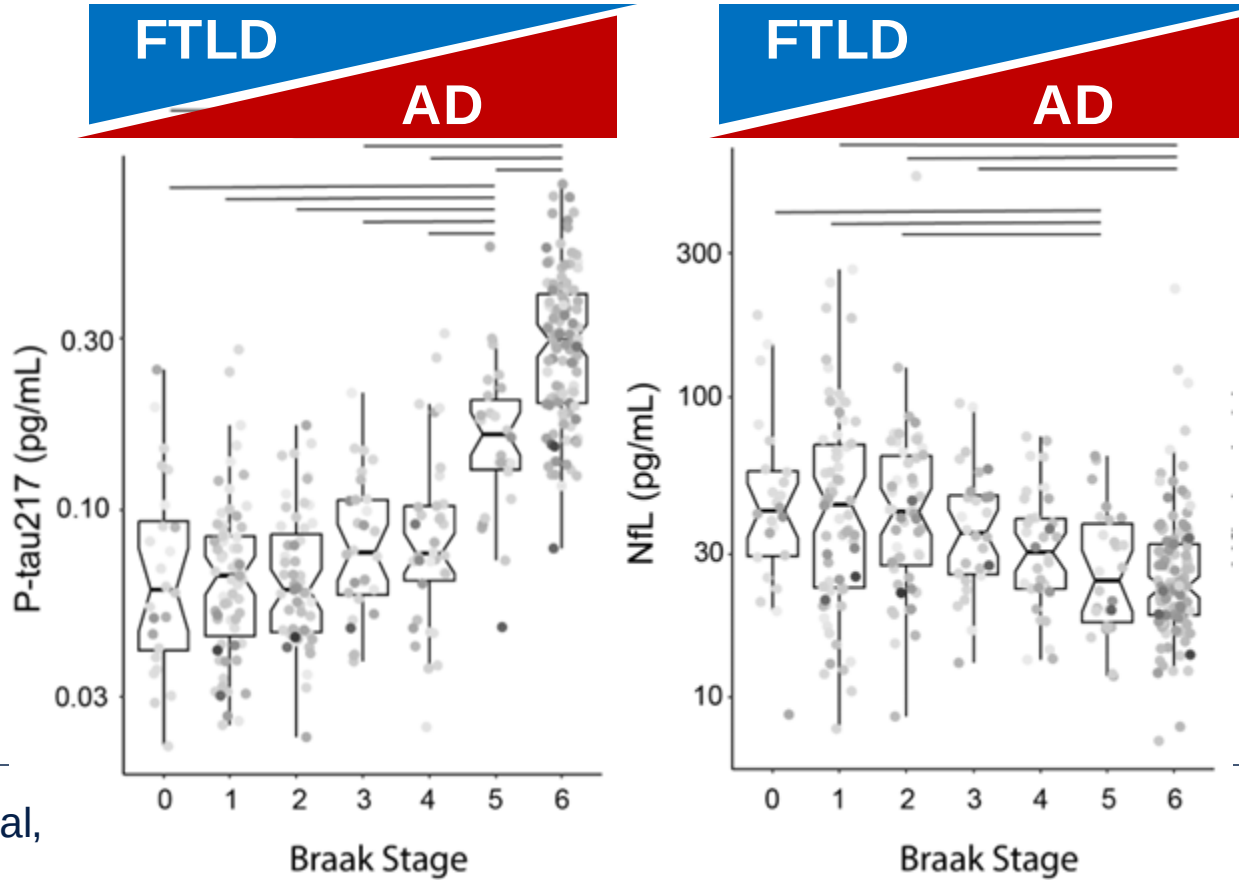
Fundamental/methodological issues with study samples

Time between biomarker test and death

Who is in your biomarker/brain donation study?

- White, educated, urban - Lack of representativeness/inclusivity in general
- Who are the participants with no/low AD pathology?



Cohort-specific collider bias ++

NfL: FTLD > AD > controls

Vandevrede et al, in revision

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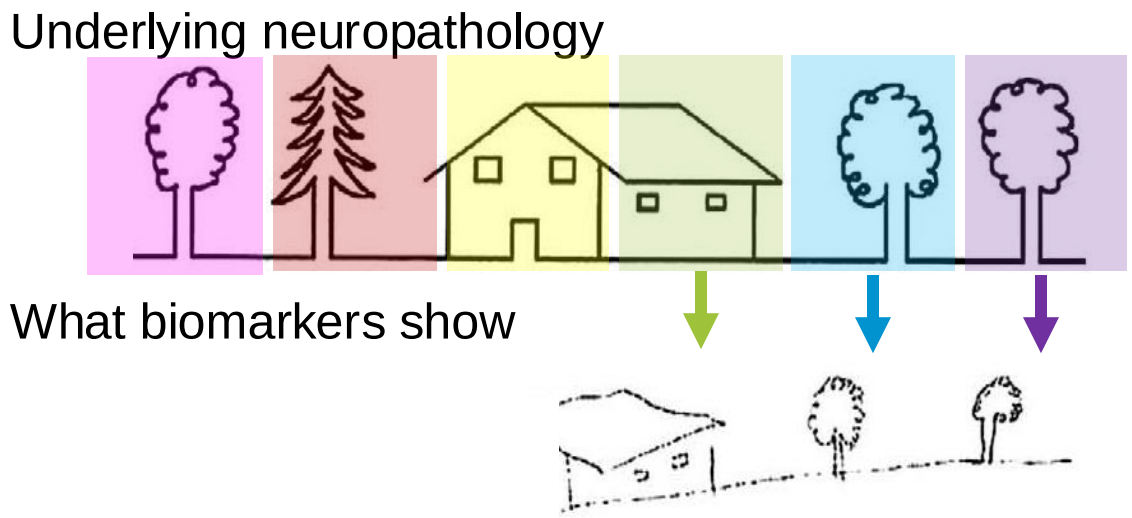
Relative contribution of AD versus co-pathologies: in vivo?



No direct markers

TDP-43
(FTLD-TDP, LATE-NC)

Non-AD tauopathies
(Picks, PSP, CBD, AGD, CTE…)

Lewy Body Disease/α-syn
*major progress (cf later in the session)

negative AD biomarkers in a patient with clinical decline

→ some (unmeasured) non-AD etiologies are involved

Specific markers

AD Tau

Aβ deposits

Cerebrovascular lesions

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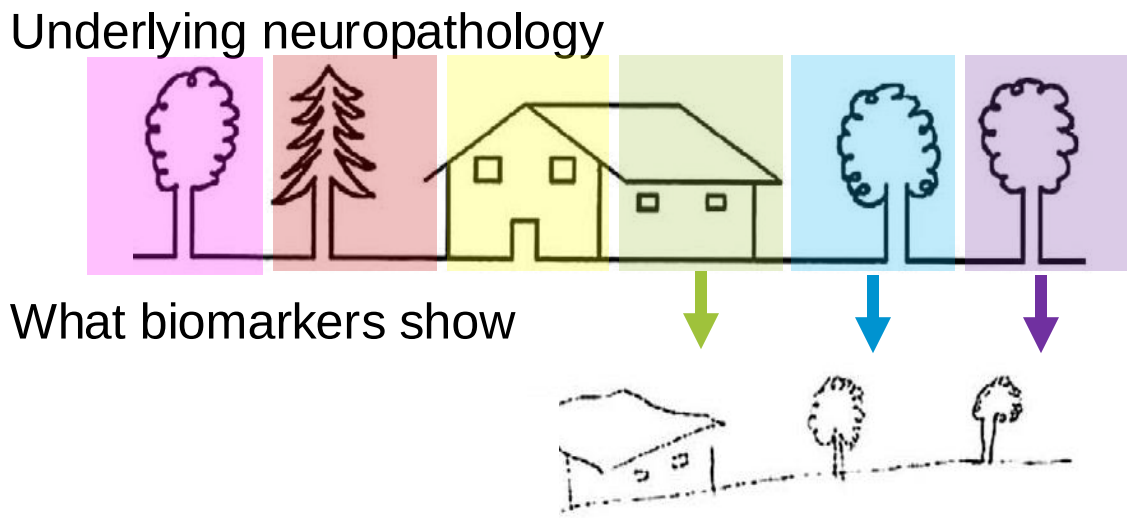
Relative contribution of AD versus co-pathologies: in vivo?



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Non-AD tauopathies
(Picks, PSP, CBD, AGD, CTE…)

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positive AD biomarkers
→ we don't know if it is the only or even the primary neuropathology

Importance of clinical context and pretest probability of AD

Specific markers

AD Tau

Aβ deposits

Cerebrovascular lesions

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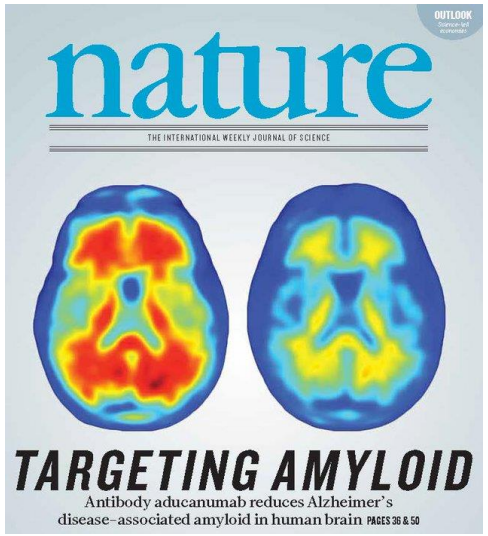
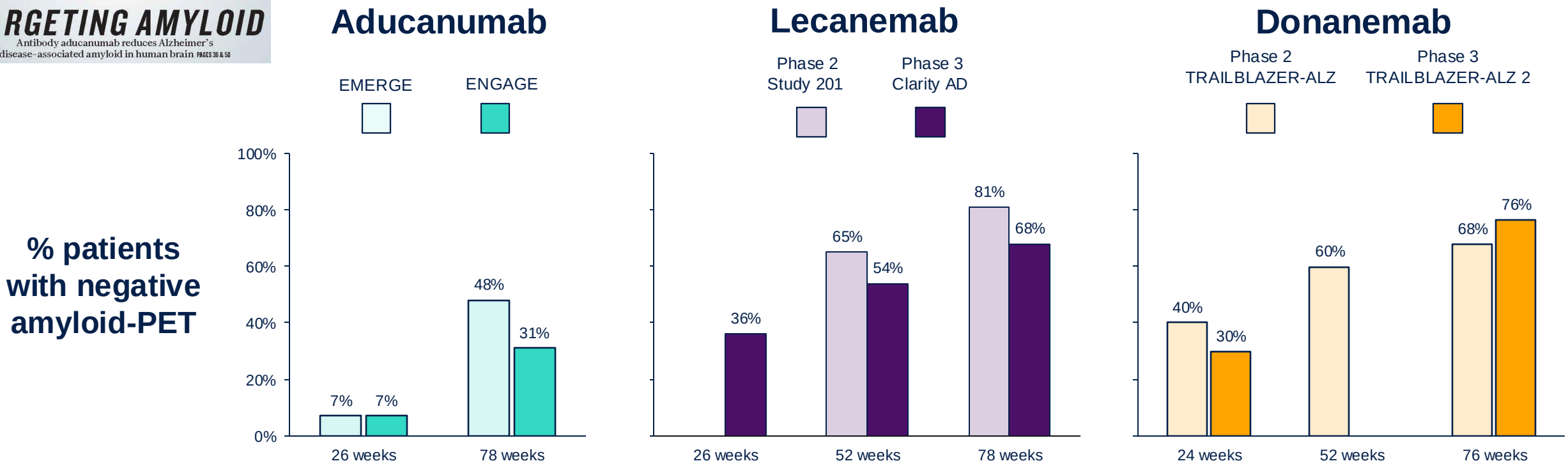
Treatment Related Amyloid plaque Clearance (TRAC)



After anti-Aβ MABs, Aβ-PET can become negative

(but fluid markers do not fully normalize)



La Joie et al, in preparation

UCSF

Neuropathology of TRAC?

Crucial to understand what TRAC reflects in the brain

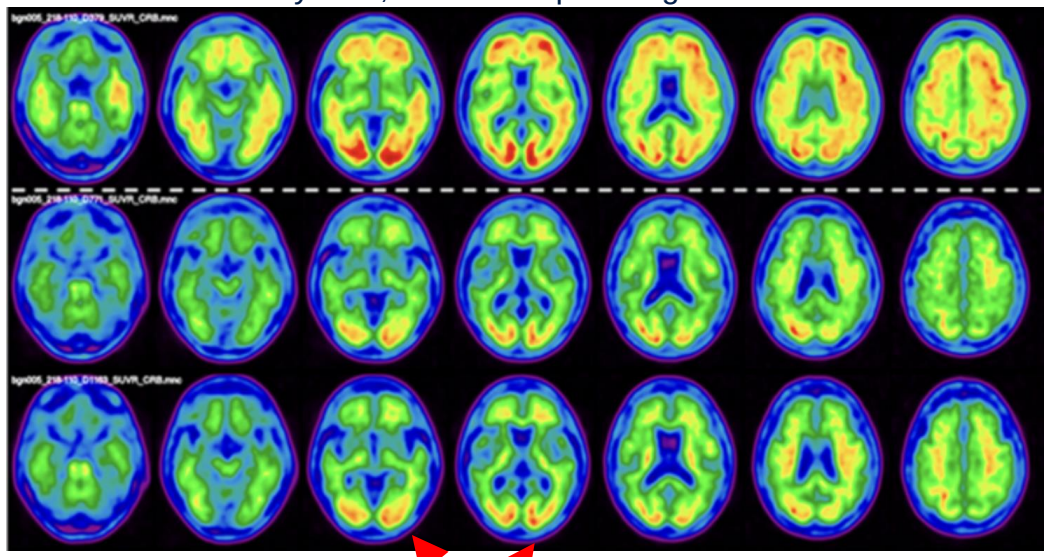
How much *Aβ plaque pathology can remain in the brain while being undetected?*

What kind *of Aβ deposits are particularly affected by the MABs?*

To day, no report of participants with full TRAC who came to autopsy

Plowey et al, Acta Neuropathologica 2022

aducanumab



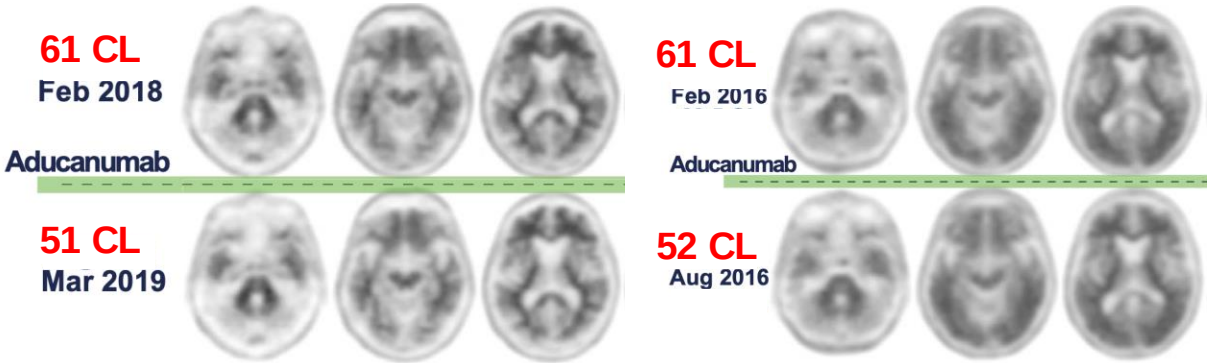
residual PET positivity
(partial clearance)

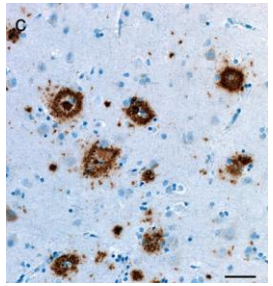
Passed away 4 months after last IV

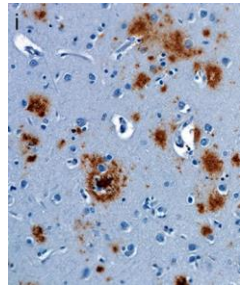
- "***sparse residual Aβ plaque*** *morphologically comprised predominantly of dense cores that* ***lacked rims of non-compact Aβ***"
- "*The highest density of residual Aβ plaques, [...] was present in the occipital cortex*".

VandeVrede et al, Acta Neuropathologica 2023

2 cases with moderate exposure to aducanumab







*"**Amyloid plaque abundance and morphology were typical** […] at this clinicopathological stage, without reported changes to plaque morphology"*

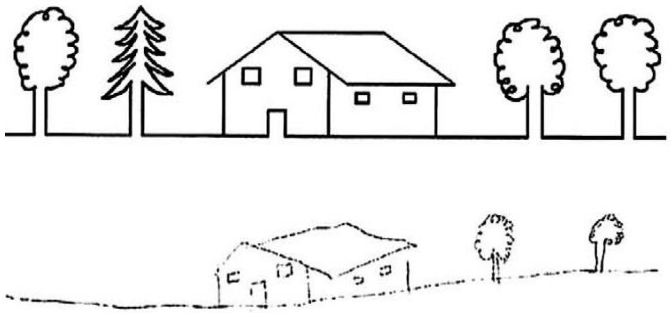
Looking forward

More diversity in samples used to validate biomarkers *(Brickman er al, Alz&Dem 2021)*

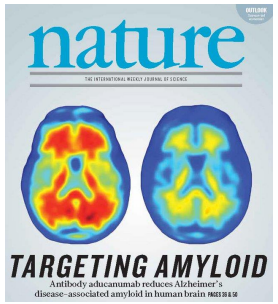
More nuanced analysis of both

- Biomarker outcomes (not just binary)
- neuropathology (quantitative & qualitative measures – digital pathology)

Clinical interpretation will be limited until we have **good biomarkers of common copathologies**
(No matter how good AD biomarkers are at detecting ADNC)



Not only for detection of natural disease mechanisms, but also to **better characterize biomarker results during/after anti-Aβ MABs**



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Patients, families, caregivers

UCSF Memory & Aging Center / ADRC

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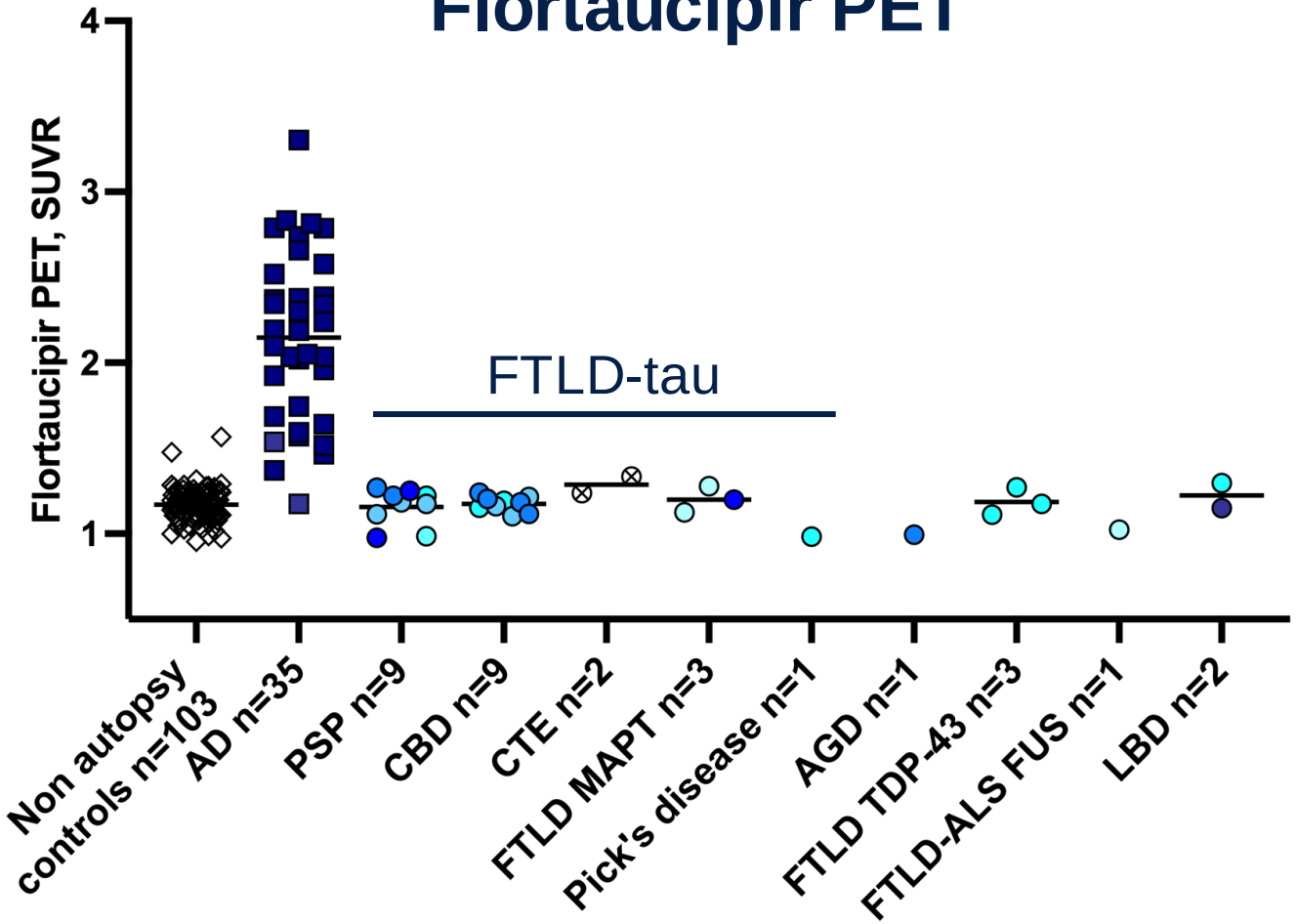
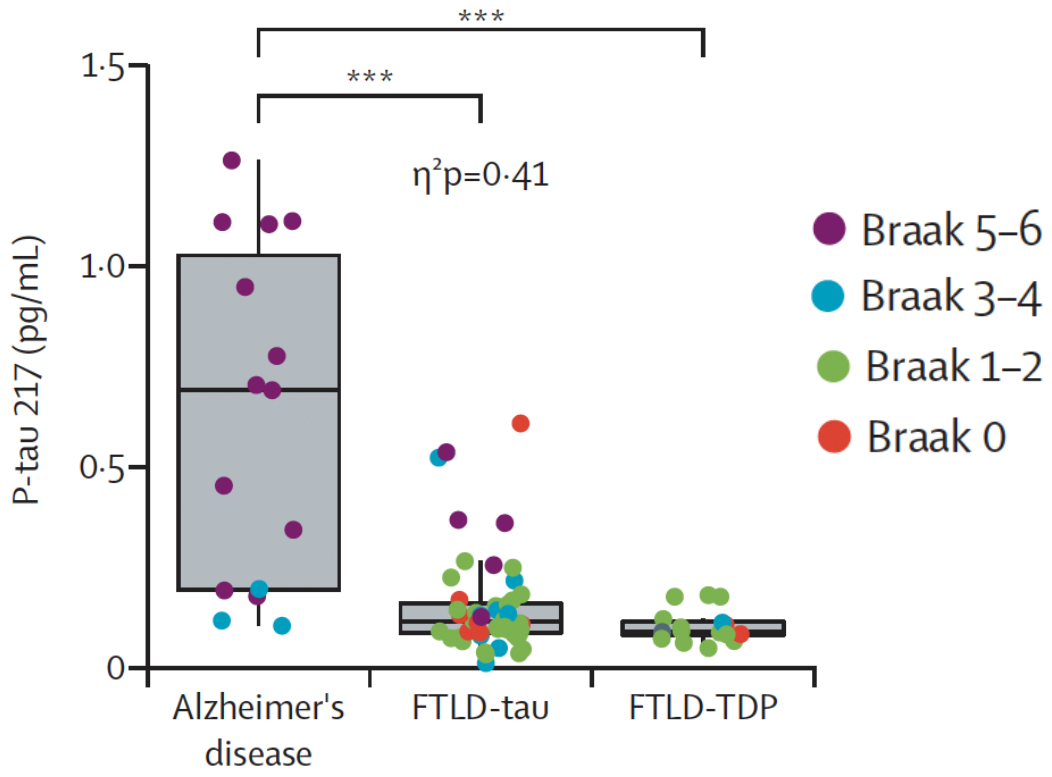
‘Tau’ biomarkers = AD Tau biomarkers

Flortaucipir PET



Vrillon et al,
In preparation

Blood (Lilly ptau217)



Thijssen, La Joie et al,
Lancet Neurol 2021

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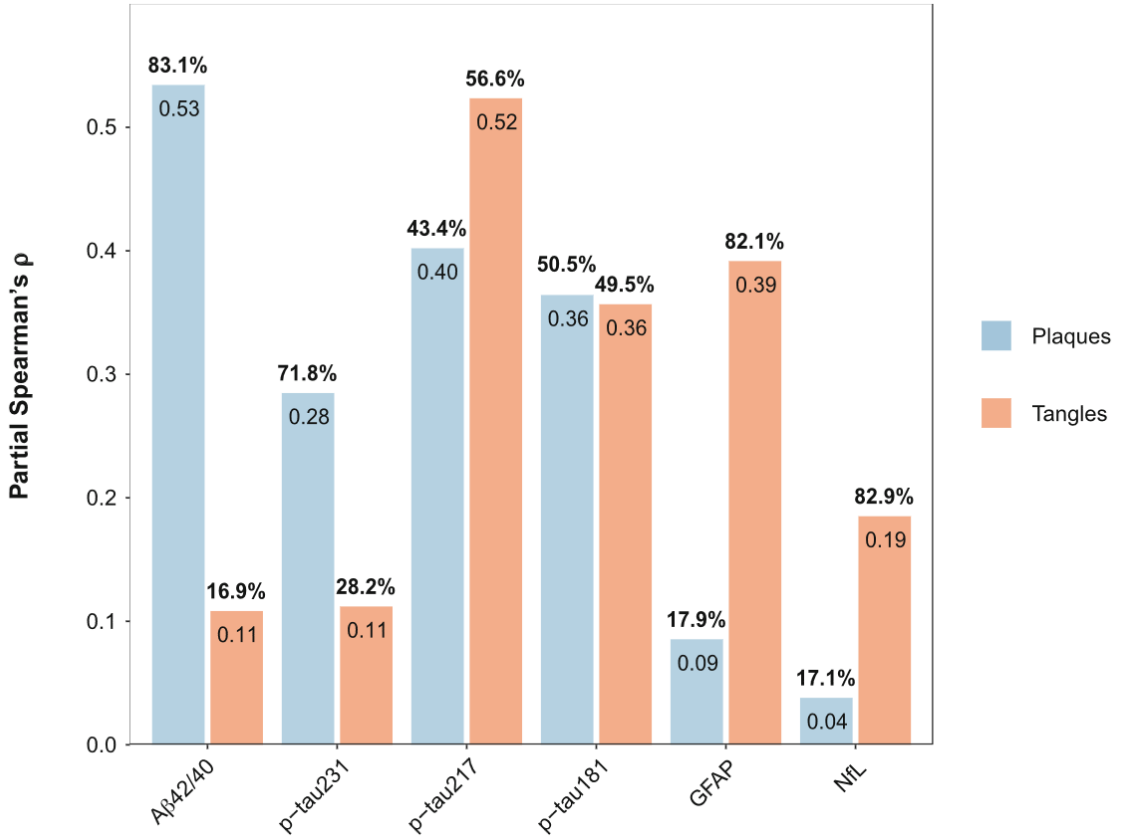
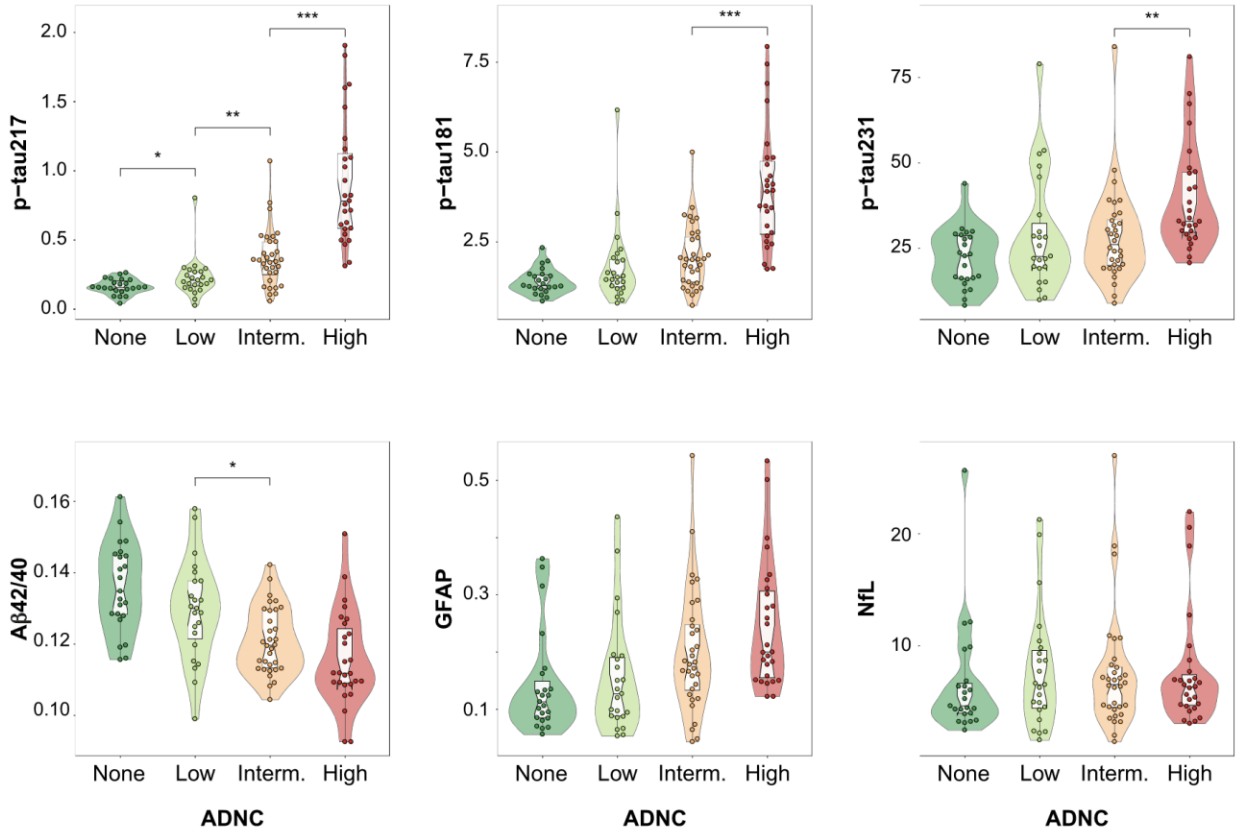
Emerging plasma biomarker panels?





105 participants from the Arizona Study of Aging and Neurodegenerative Disorders

Salvado et al, EMBO Molecular Medicine 2023

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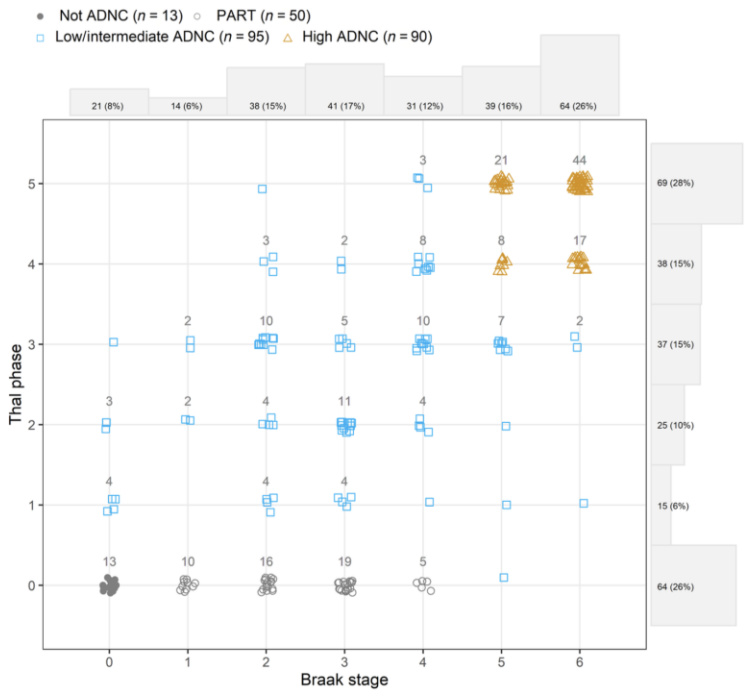
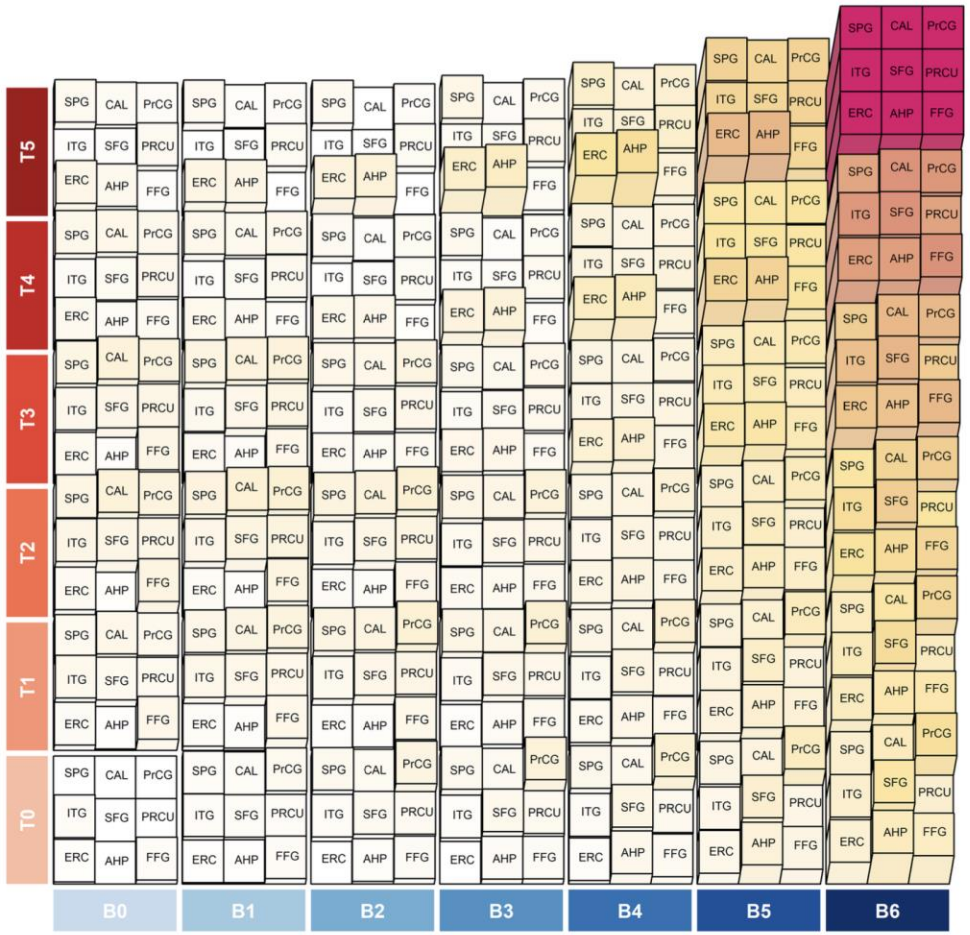
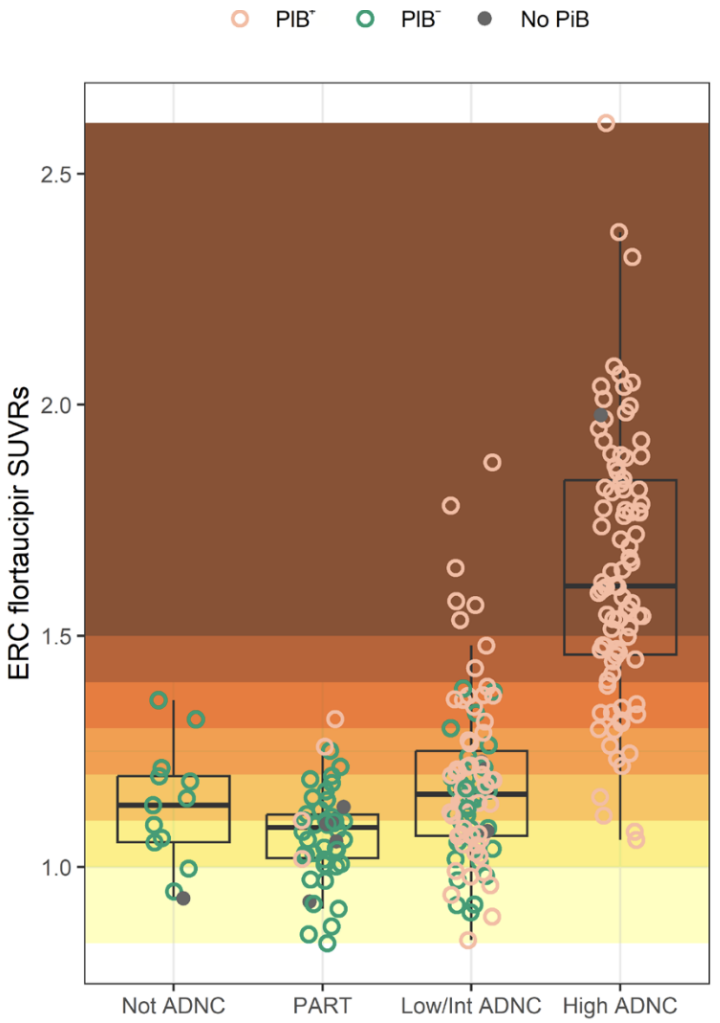
Tau PET signal driven by amyloid and tau staging?







Josephs et al, Sci Trans Med 2024

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