Amyloid and Tau PET for Predicting Progression in Alzheimer's Disease

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Disclosures

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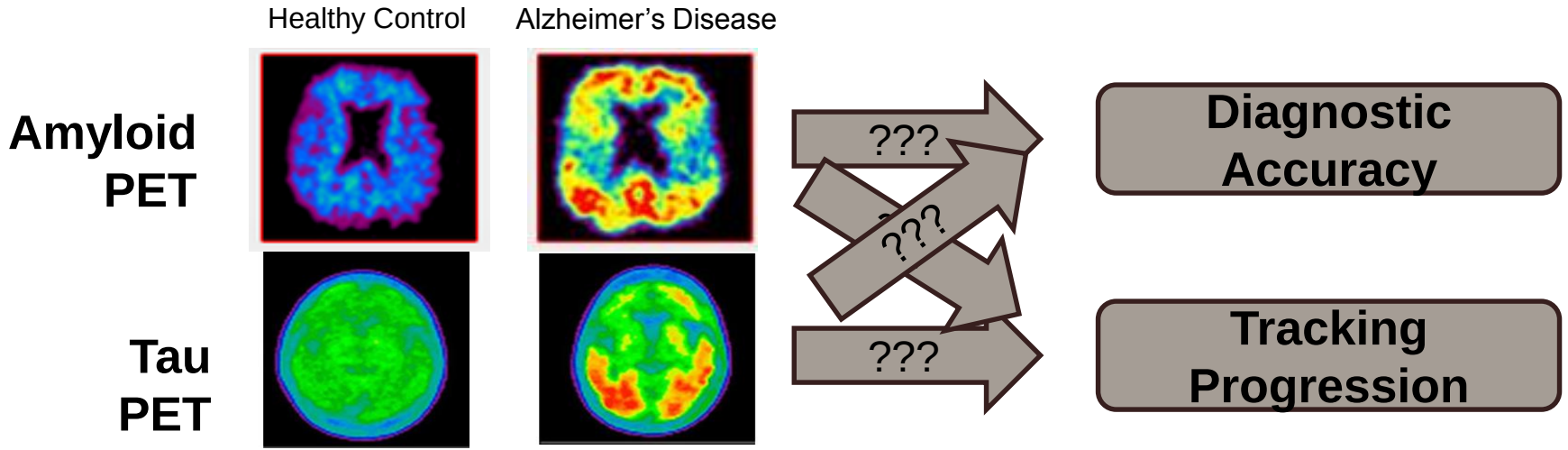
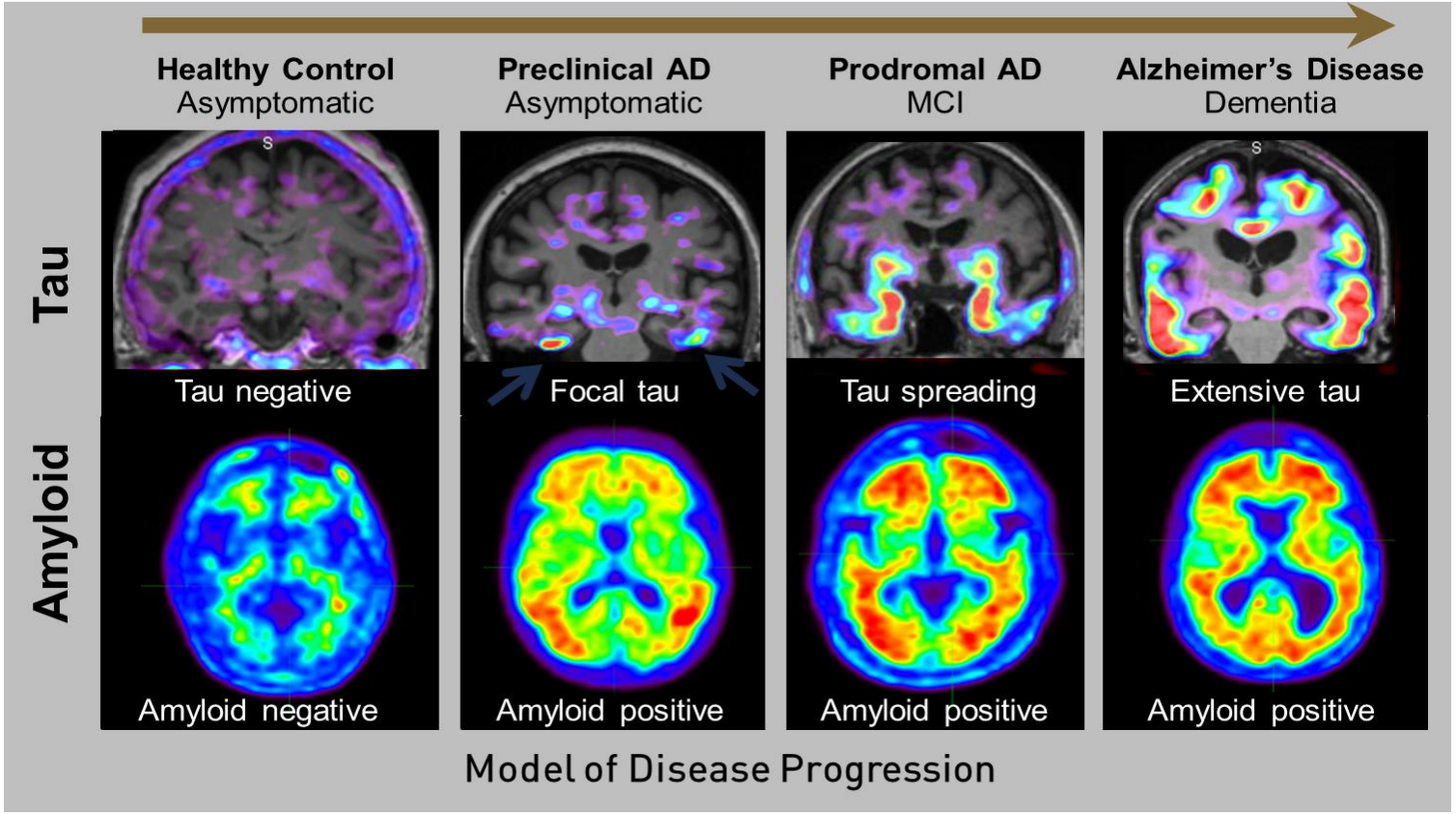
Potential Roles of Amyloid and Tau PET in Predicting Progression in AD

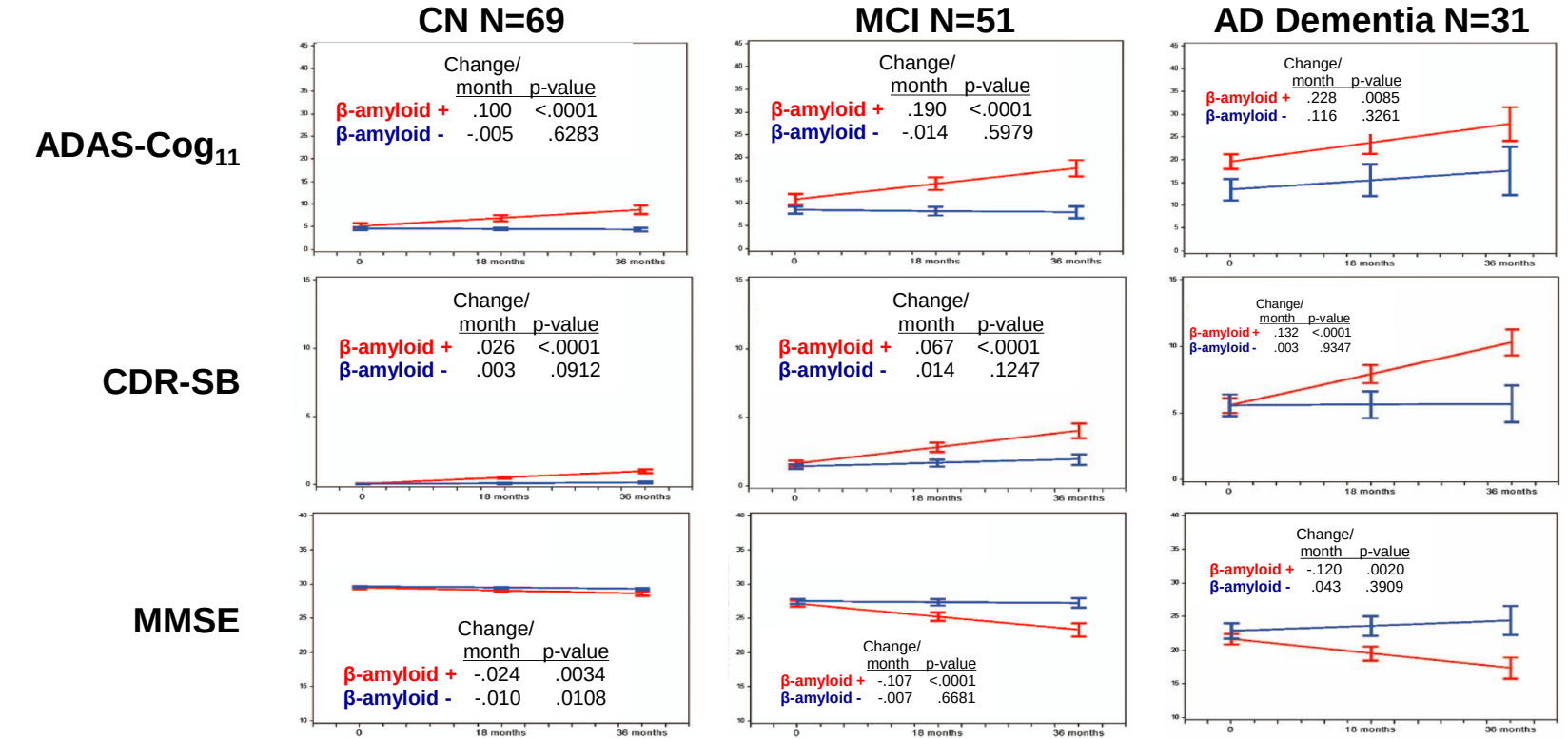
- **Prognostic indicators**
  - **Diagnostic accuracy?**
  - **Tracking disease progression?**



Amyloid and Tau PET Imaging – a Dynamic Duo!



Amyloid Deposition Influences Cognitive Decline at 36 Months



Doraiswamy PM et al. *Mol Psychiatry* 2014;19(9):1044-51

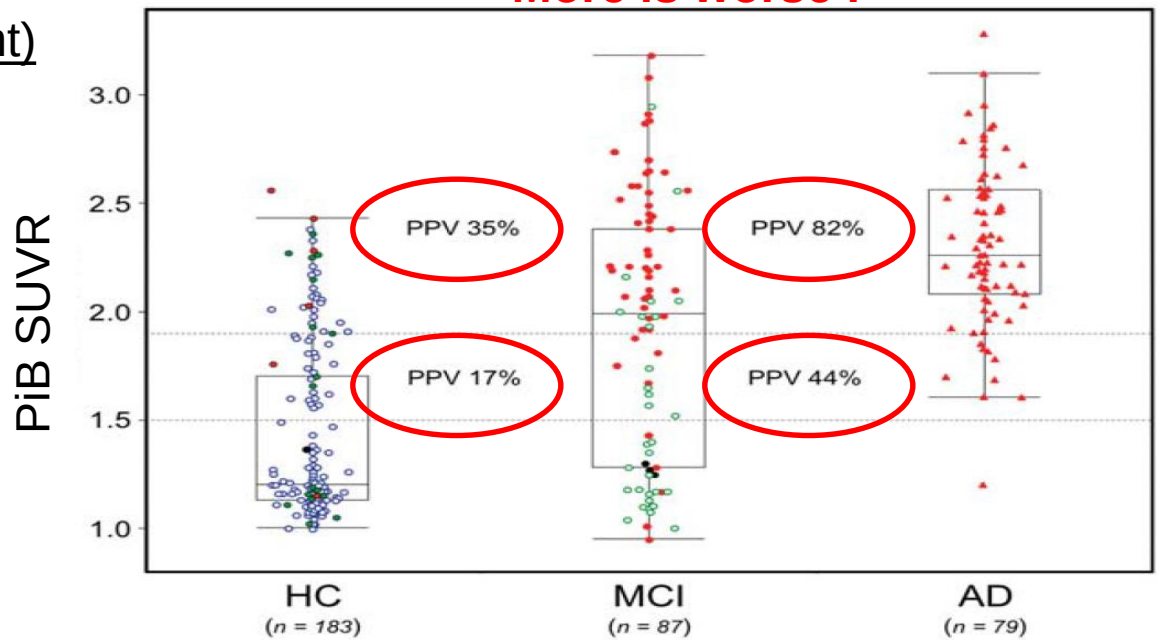
Predicting Alzheimer Disease with β-Amyloid Imaging: Results from the Australian Imaging, Biomarkers, and Lifestyle Study of Ageing

More is worse !

Progression KEY (left → right)

Baseline position retained on graph

- Did not progress
  - HC
  - MCI
- HC → MCI
- HC/ MCI → AD
- HC/ MCI → non-AD (black)
- Positive control*

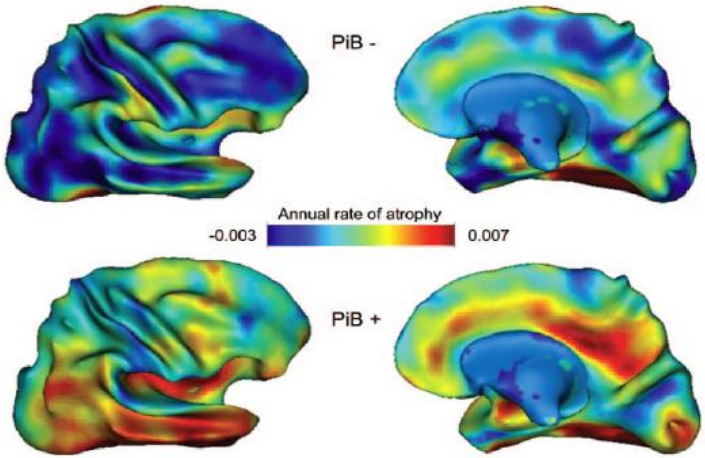


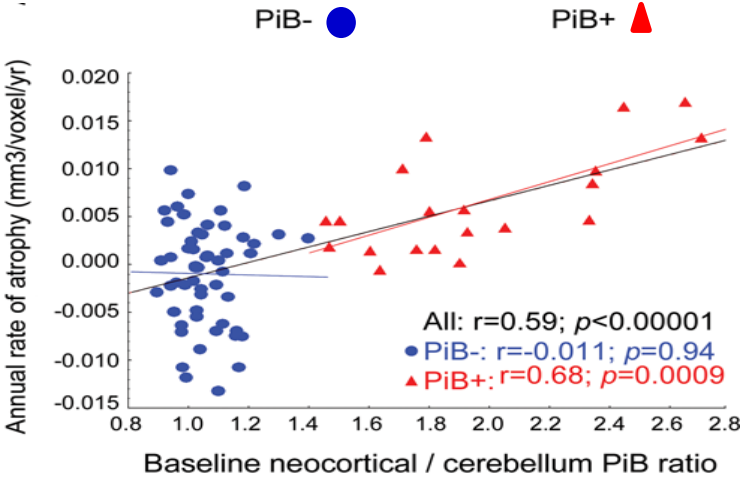
***For comparison, the SUVr values for all subjects with AD at enrollment into the AIBL study of ageing are shown (red triangles) [11C] Pittsburgh compound B SUVr values by baseline clinical diagnosis and status after 3 years.**

AIBL=Australian Imaging, Biomarkers, and Lifestyle; AD=Alzheimer's **disease; HC=healthy controls; MCI=mild cognitive impairment; PPV=positive predictive value**

Rowe C.C. et al, Ann Neurol 2013;74:905–913

Cortical Amyloid is Associated with Increased Annual Rate of Global Atrophy in Cognitively Normal Individuals

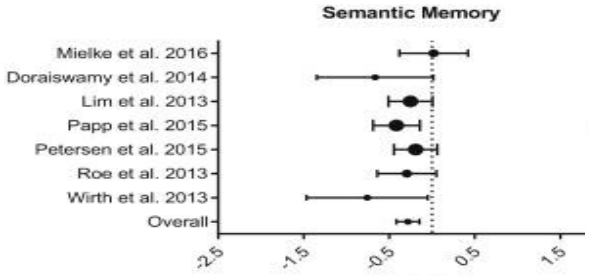


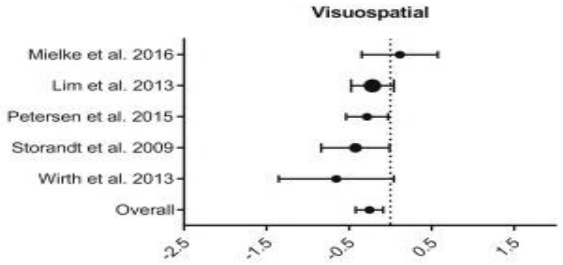


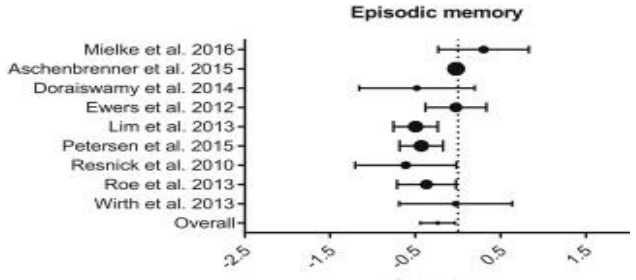
PiB=C[11]Pittsburg compound B

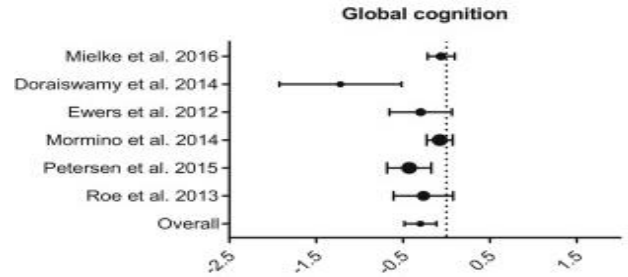
Chetelat G, et al. Neurology 2012;78:477–484

Subtle Changes with Amyloid Positivity and Cognitive Decline (Meta-analysis)









Conclusions:

- **In CN older adults is Aβ+ is associated with subtle cognitive impairment and decline**
- Meta-analysis (of longitudinal studies) show association of Aβ+ with impairments in domains of semantic memory, visuospatial function, episodic memory, and global cognition. **But, effect sizes are small.**
- No Aβ related decline observed for working memory, processing speed or executive function

Cohen's d with 95% CI

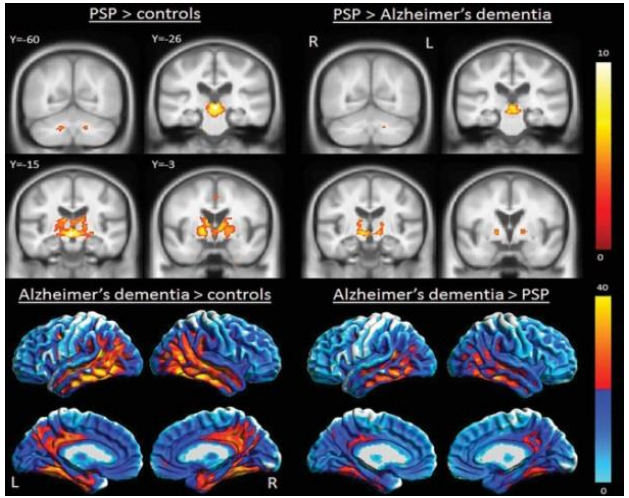
Dotted lines represent no effect of amyloid on cognition. Negative values represent greater decline in performance in the presence of high Aβ, size of dots represents study weighting due to sample size

Aβ=amyloid beta; CN=cognitively normal

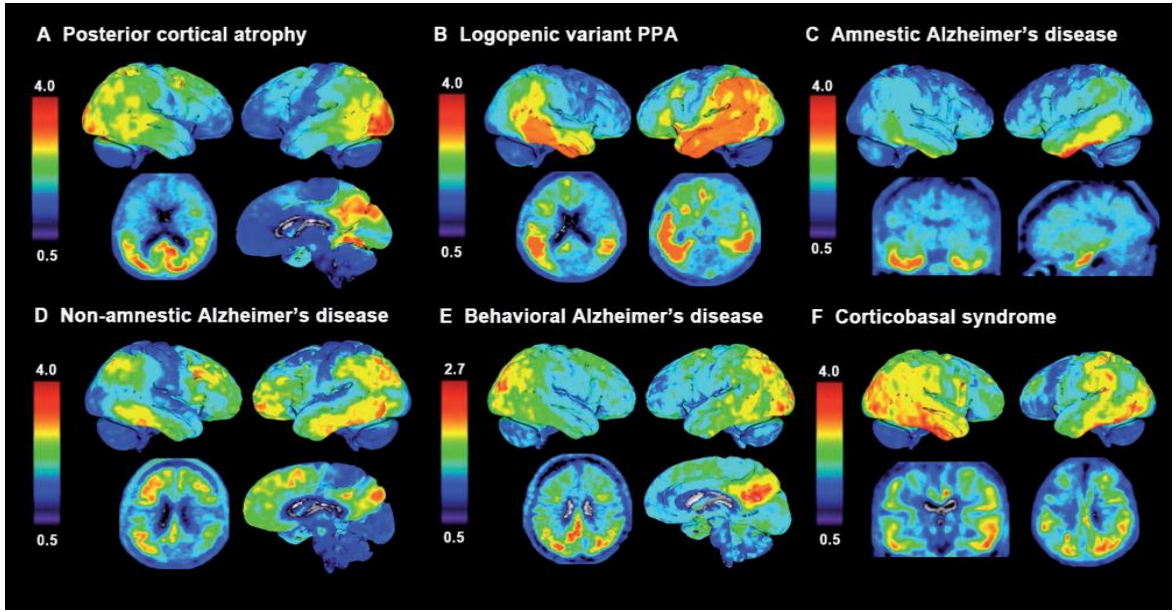
Baker JE, et al. Alzheimer Dement DADM 2016:1-13 (in press). doi: http://dx.doi.org/10.1016/j.dadm.2016.09.002

Tau PET Patterns may distinguish different tauopathies and clinical phenotypes

PSP vs AD



Clinical Variants of AD



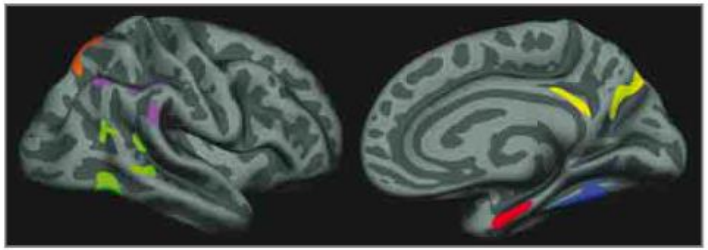
And……..tau PET tracers vary in their specificity to AD

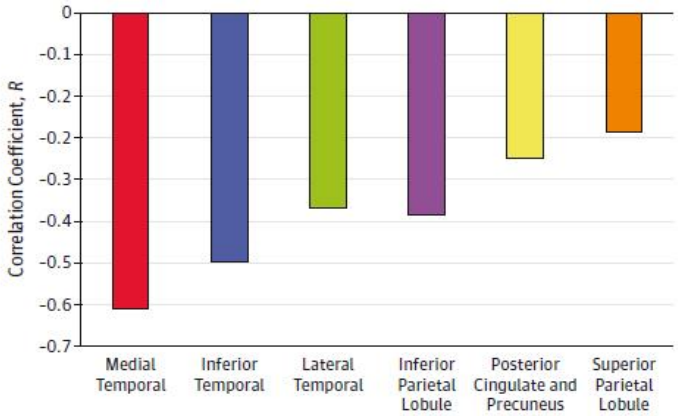
JL Whitwell, et al. **Mov Disord.** , Movement Disorders 2016; **Oct 27. doi: 10.1002/mds.26834. [Epub ahead of print] (Left)**
R Ossenkoppele, et al. , Brain **2016;139(Pt 5):1551-67.** 2016 (**Right**)

Tau PET and AD cortical signature

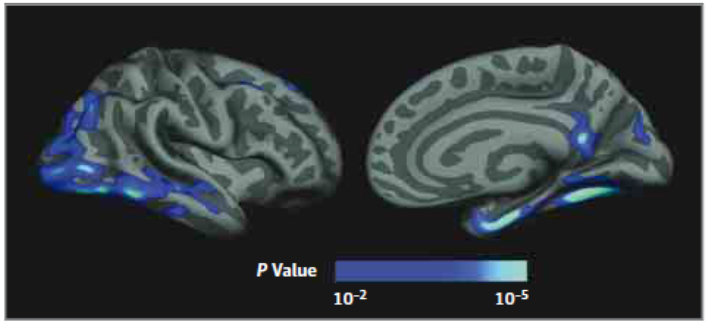
Figure 1. Regional and Vertexwise Associations Between [^{18}F]-AV-1451 Binding and Cortical Thickness

A AD cortical signature





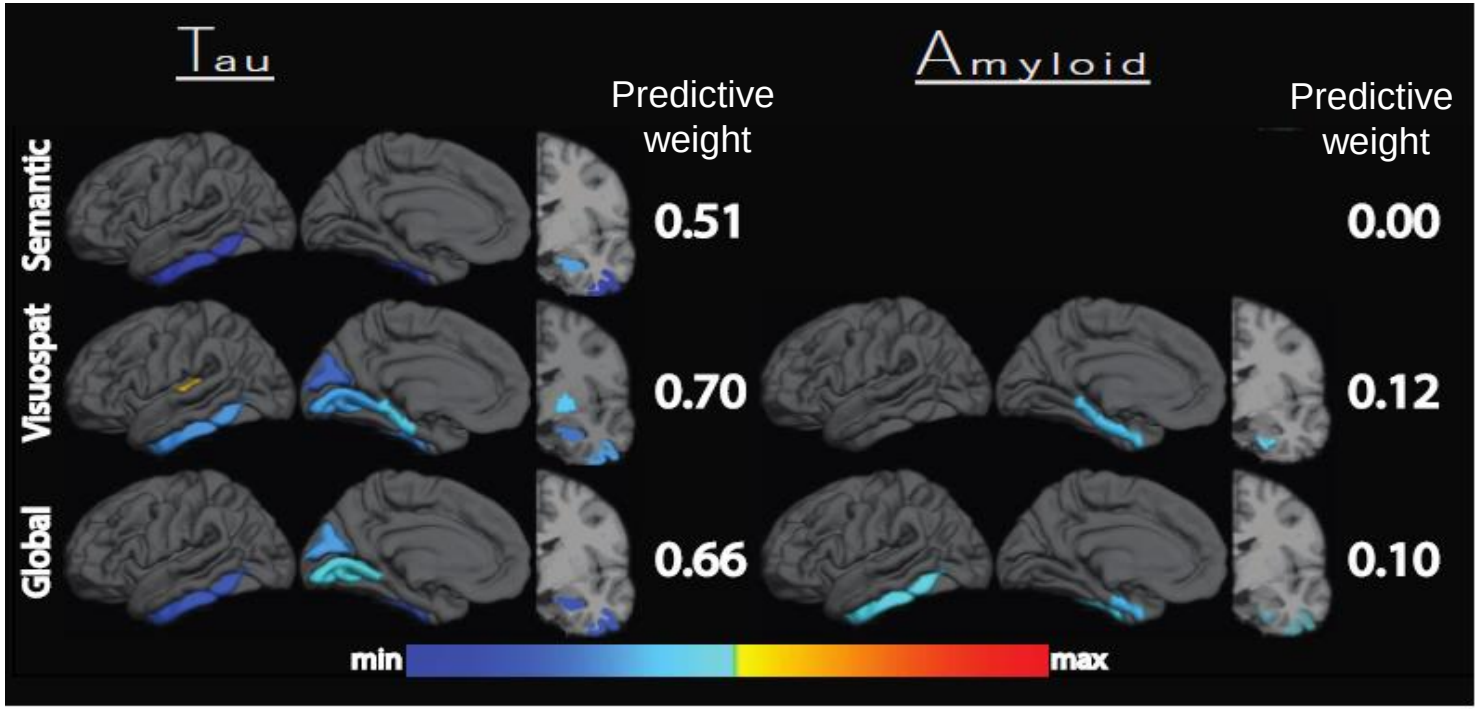
B Cortical mantle



Pearson correlation between [^{18}F]-AV-1451 binding and cortical thickness was assessed for each region of interest that composed the Alzheimer disease (AD) cortical signature (A) and each vertex across the cortical mantle (B). The regional correlation coefficients are showed with a bar graph in an order that is consistent with the hypothetical sequence of neurofibrillary tangles spreading. The color-coded anatomic location of AD cortical signature regions is labeled in the bar graph accordingly. The significance of vertexwise correlation was thresholded at $P < .05$, corrected for multiple comparisons at the cluster level. Both AD cortical signature regions and vertexwise correlation are displayed on the semi-inflated cortical surface of the FreeSurfer average brain, with light gray regions representing gyri and dark gray regions representing sulci.

Liang Wang, JAMA Neurol 2016;73(9):1070-7.

Tau PET Better Predicts Cognitive Performance compared to Amyloid (Cross-sectional data)



Regions with negative values (cooler colors) are where more PET pathology predicts lower cognitive performance
***total predictive weight values for tau (left) and Aβ (right) are shown**
Visuospat = visuospatial
Brier MR, et al. Sci Transl Med 2016;8(338)338ra66

AV-1451-A05 Study - Longitudinal

- Subjects were recruited as healthy controls (HC), patients diagnosed with mild cognitive impairment (MCI) and possible or probable AD (AD) dementia
- The following evaluations were performed at baseline, 9-month, and 18-month visits:
  - 18F-Flortaucipir (18F-AV-1451) scan (10 mCi IV, scanning 80- to 120-min p.i. as 4 x 5 min frames)
  - MRI (volumetric T1-weighted scan)
  - Cognitive (ADAS, MMSE) and Functional (FAQ) scales
- All subjects underwent a single Florbetapir F 18 scan and ApoE genotesting at baseline

10 Baseline Subject Characteristics of Interim Analysis Population

Flortaucipir SUVR by Age: All Subjects at Baseline, 9-Month and 18-Month Visits

Flortaucipir SUVR Change at 18-Month Visit vs Baseline, MCI + AD

Correlation between ^{18}F AV-1451 and Factor Scores

86 Aβ+ subjects (age = 74 ± 9); Inverse Correlations

Individual Subject Average Neocortical Flortaucipir SUVr Values

Amyloid/Tau PET vs Cognition Correlations

Baseline correlations are modeled to adjust for effects of age, and for 18-month change data models include both age and baseline cognition, results are presented for amyloid positive subjects

Cognitive Change as a Function of Amyloid and Tau (+/-)

Diagnostic Accuracy
Summary

Amyloid PET	Tau PET
Diagnostic Accuracy	**Diagnostic Accuracy**
♦ Has a truth standard (autopsy) ✓ ♦ Independently valuable for ruling out AD ✓ ♦ **With caveats**	♦ Lacks truth standard **X** ♦ Independently valuable for diag ✓/ **X** ▪ AD specificity may vary by tracer ▪ Interpretation is more dependent on understanding regional patterns

Tracking Disease Progression
Summary

Amyloid PET	Tau PET
Tracking Disease Progression	**Tracking Disease Progression**
♦ Global plaque load is associated with increased rate of brain atrophy ✓ ♦ Better in preclinical/early AD? ✓ ♦ Presence of amyloid is a weaker predictor of cognitive change ✓ ▪ Cognitive decline may be driven by tau **X** **Amyloid → Tau → decline**	♦ Regional binding associated with incr rate of regional brain atrophy ✓ ♦ Better in later/sympt stage of AD? ✓ ♦ Stronger predictor of cog decline ✓

Conclusions

- **Both Amyloid and Tau PET are valuable as predictors of future cognitive decline**
  - Amyloid PET is *foretelling* of future neurodegeneration and tau pathology even in the absence of cognitive symptoms
  - Tau PET is suggestive of existing regional neurodegeneration and the presence of associated cognitive symptoms
- **This suggests**
  - Amyloid may have more value in the earlier stages of disease for secondary prevention and diagnosis
  - Tau may be more valuable for staging symptomatic disease, understanding its course, and predicting future cognitive course
- **Combining Amyloid and Tau PET may be ideal for defining the overall AD disease state, providing complementary information to inform future decline.**

Acknowledgements

This work would not be possible without the dedication of **research volunteers**

and

all study **site investigator teams**