

Benchmarking the diagnostic accuracies of plasma p-tau205 and p-tau212 against p-tau217 in Alzheimer's disease

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Introduction

Background

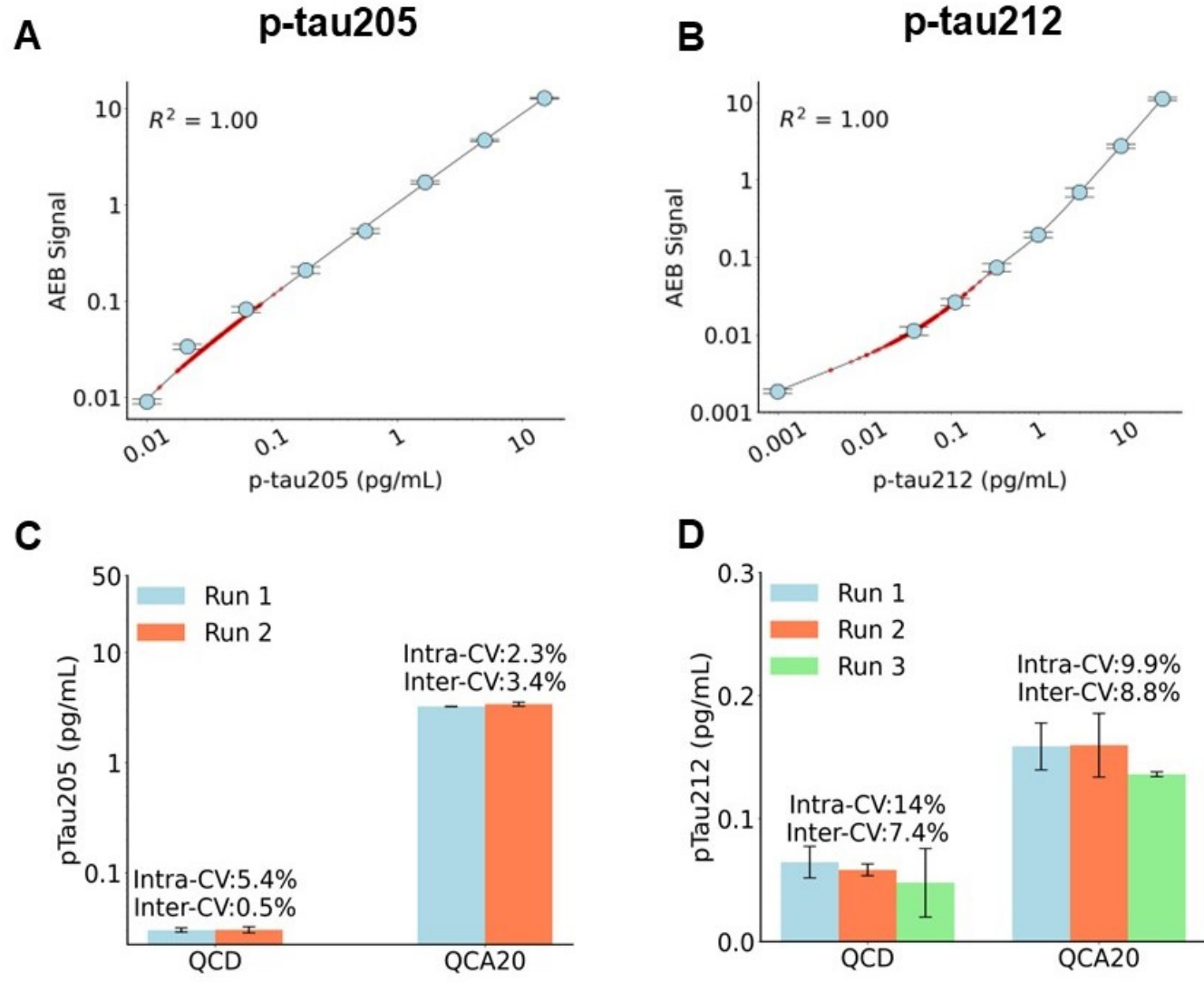
Early changes in tau phosphorylation (p-tau) at selected sites including p-tau217 and p-tau212, in the initial phases of amyloid-beta (A β) plaque accumulation are thought to precede p-tau205 which correlates better with neurofibrillary tangle (NFT) pathology. However, lack of commercial plasma immunoassays for all these p-tau forms prevent direct comparison. We benchmarked the performance of novel ultrasensitive plasma p-tau205 and p-tau212 immunoassays vs p-tau217.

Methods

Participants:

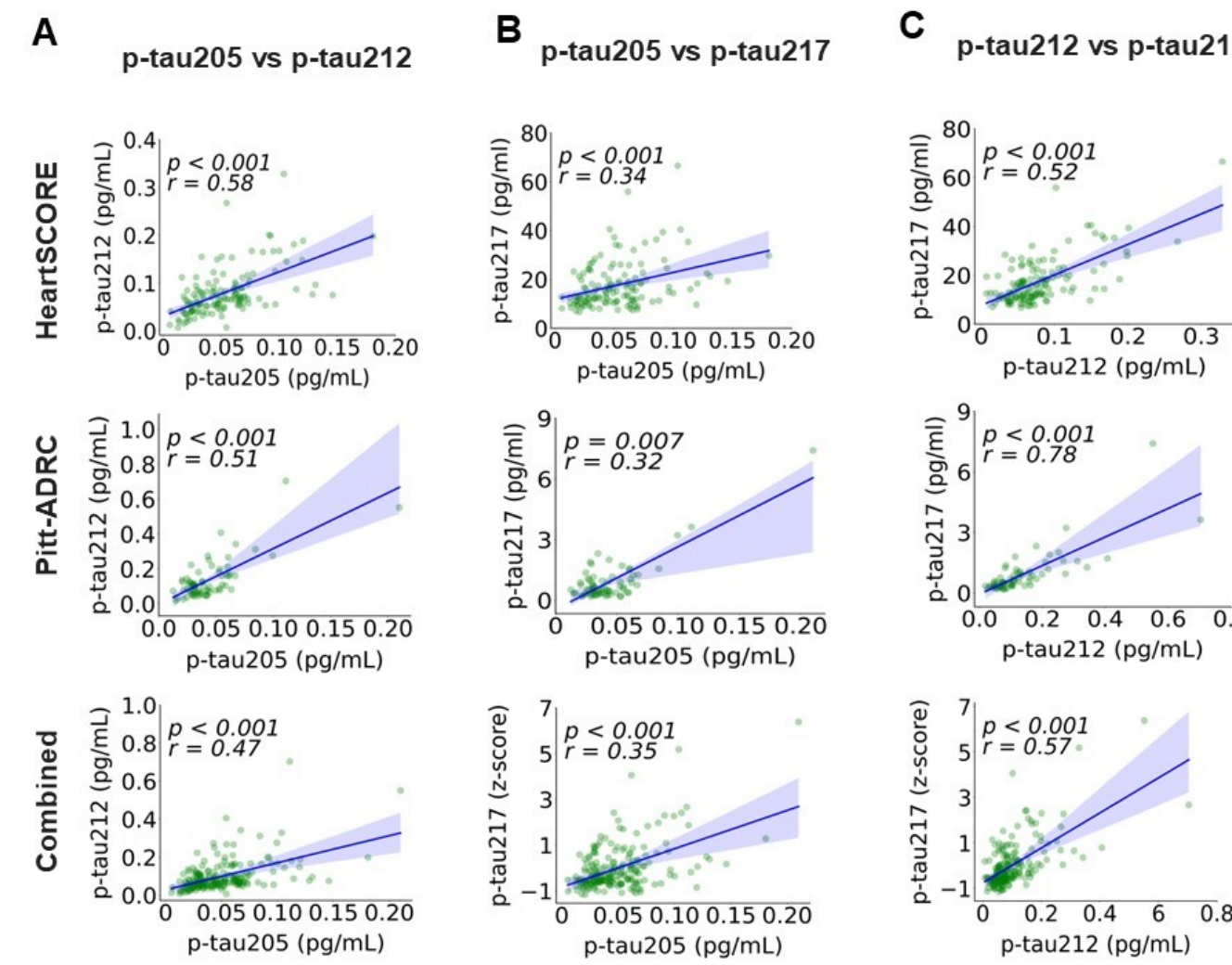
- Heart Strategies Concentrating on Risk Evaluation (HeartSCORE; n = 139), comprising mainly cognitively unimpaired individuals representative of preclinical AD
 - Individuals enrolled at the University of Pittsburgh Alzheimer's Disease Research Center (Pitt-ADRC; n =74), enriched for cognitively impaired participants with mild cognitive impairment and AD dementia.
- Biomarker Quantification (SIMOA platform):** p-tau205, p-tau212, p-tau217 (ALZpath and Pittsburgh assays in HeartSCORE and ADRC, respectively).
- Assessment:** plasma p-tau associations with A β and tau PET imaging, inter-assay correlations, and accuracies to separate clinical groups and identify A β -PET+/tau-PET+ individuals.

Analytical performance of the p-tau205 & p-tau212 assays



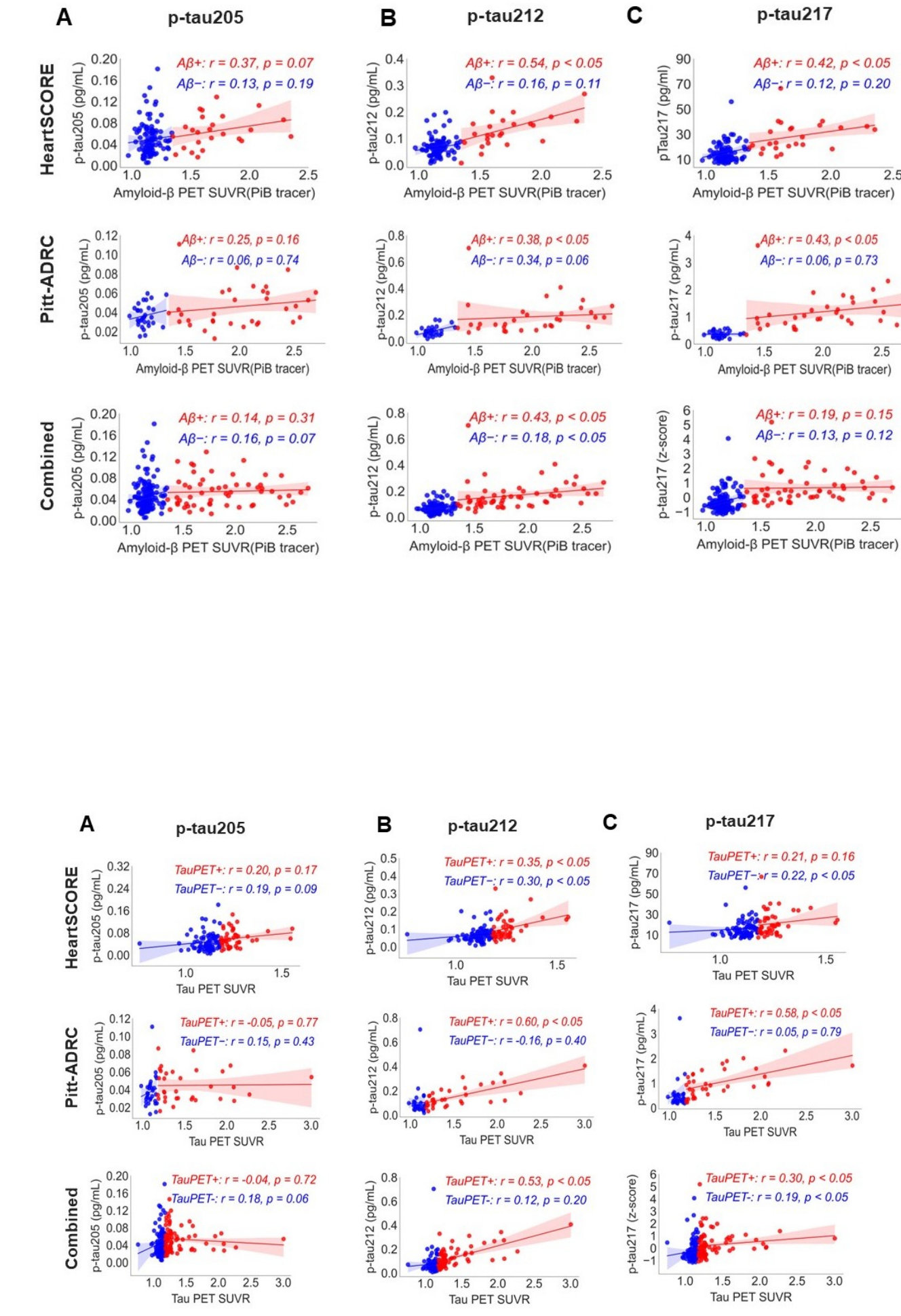
- The calibration curves for p-tau205 and p-tau212 showed sigmoidal responses across the concentration ranges
- p-tau205 and p-tau212 demonstrating excellent repeatability and reproducibility across the tested concentration range

Correlations between plasma p-tau biomarkers



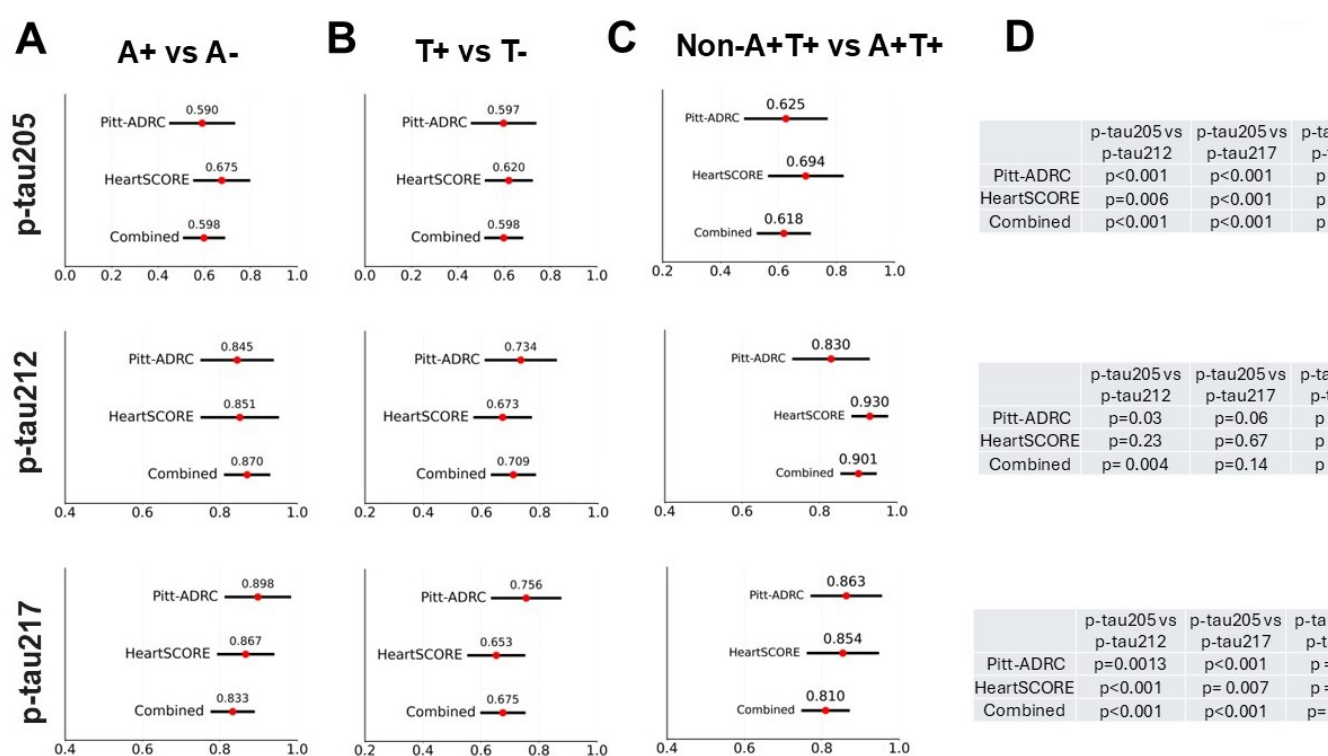
- Strong correlations were observed between p-tau212 and p-tau217
- p-tau205 and p-tau212 concentrations demonstrated a significant moderate positive correlation across cohorts
- correlations between p-tau205 and p-tau217 were weaker but remained significant

Plasma p-tau associations with A β and tau PET



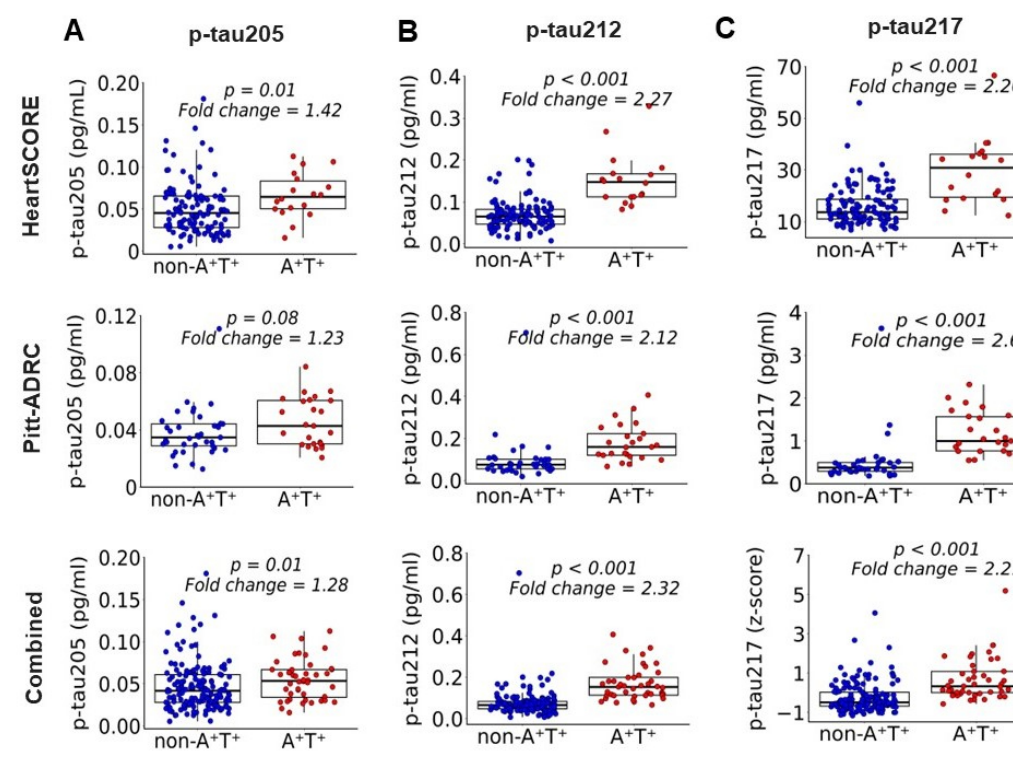
p-tau212 and p-tau217 show stronger and more consistent associations with both A β and tau PET measures than p-tau205

AUC's for predicting A β PET, tau PET, and A $^+T^+$ positivity



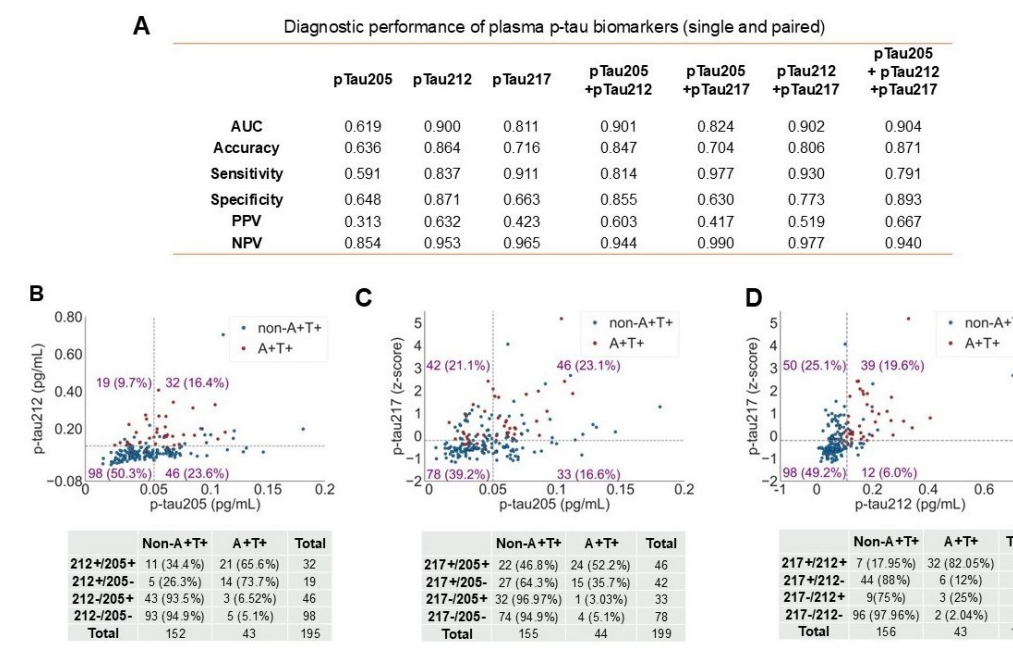
- For identifying A β and tau PET p-tau212 and p-tau217 significantly outperformed p-tau205
- For classification of A β /tau PET positivity p-tau212 achieved the highest AUC, followed by p-tau217, while p-tau205 performed poorly

Plasma p-tau levels differentiate A $^+T^+$ individuals

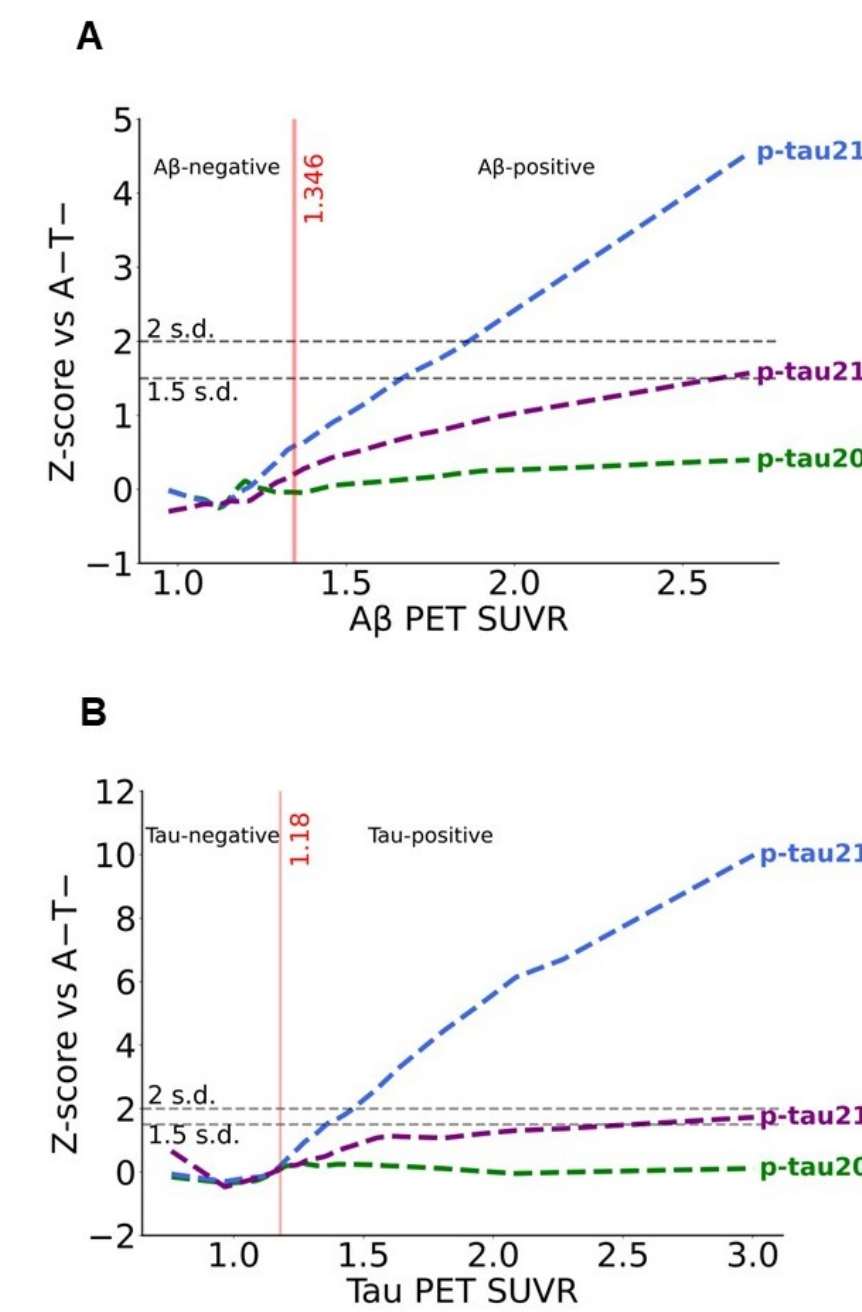


Plasma p-tau205, p-tau212 and p-tau217 was also significantly elevated in the A $^+T^+$ group compared to non-A $^+T^+$ individuals

Performance of combined plasma p-tau biomarkers



Plasma p-tau levels according to A β and tau pathology



p-tau212 demonstrates the earliest and most dynamic increases relative to both amyloid and tau PET, followed by p-tau217, whereas p-tau205 shows limited progression

Demographic characteristics of Pitt-ADRC & HeartSCORE cohort

Cohort	Total	A β PET-	A β PET+ ^a	p-Value ^b
HeartSCORE(n)	139	113	26	
Age (years), median [Q1,Q3]	73.0 [70.0,76.2]	73.0 [70.0,76.0]	75.0 [71.0,79.0]	0.075
Sex, n (%)				0.638
Female	97 (69.8)	80 (70.8)	17 (65.4)	
Male	42 (30.2)	33 (29.2)	9 (34.6)	
Race, n (%)				0.238
Black/African American	42 (30.2)	37 (32.7)	5 (19.2)	
White	97 (69.8)	76 (67.3)	21 (80.8)	
CDR Score, n (%)				0.028
0.0	114 (82.0)	96 (85.0)	18 (69.2)	
0.5	24 (17.3)	16 (14.2)	8 (30.8)	
1.0	1 (0.7)	1 (0.9)		
Tau PET^c, n (%)				<0.001
Negative	88 (63.3)	81 (71.7)	7 (26.9)	
Positive	50 (36.0)	32 (28.3)	18 (69.2)	
Unknown	1 (0.7)		1 (3.8)	
Pitt-ADRC^d (n)	74	34	40	
Age (years), median [Q1,Q3]	70.0 [64.0,75.0]	69.0 [63.0,73.0]	72.0 [69.0,76.0]	0.086
Sex, n (%)				0.087
Female	32 (43.8)	11 (33.3)	19 (55.9)	
Male	41 (56.2)	22 (66.7)	15 (44.1)	
Race, n (%)				1.000
Black/African American	1 (1.4)			
White	72 (98.6)	33 (100.0)	34 (100.0)	
APOE $\epsilon 4$ allele, n (%)				0.216
Absent	44 (60.3)	22 (66.7)	18 (52.9)	
Present	28 (38.4)	10 (30.3)	16 (47.1)	
CDR Score, n (%)				0.017
0.0	7 (9.6)	3 (9.1)	3 (8.8)	
0.5	53 (72.6)	28 (84.8)	24 (70.6)	
1.0	11 (15.1)	2 (6.1)	6 (17.6)	
2.0	2 (2.7)		1 (2.9)	
Tau PET^e, n (%)				<0.001
Negative	31 (42.5)	25 (75.8)	6 (17.6)	
Positive	35 (47.9)	8 (24.2)	27 (79.4)	
Clinical Diagnosis, n (%)				<0.001
Control	17 (23.3)	12 (36.4)	4 (11.8)	
non-AD dementia	11 (15.1)	3 (9.1)	5 (14.7)	
MCI	25 (34.2)	14 (42.4)	11 (32.4)	
AD	19 (26.0)	3 (9.1)	14 (41.2)	
Unkown	1 (1.4)	1 (3.0)		

Results and Conclusion

These findings support plasma p-tau212 as a promising complementary/alternative biomarker to p-tau217 for early detection of A β pathology. Plasma p-tau205 was associated with later-stage tau changes in individuals who were already A β -positive

Acknowledgement

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