

Brain-derived Tau And Phosphorylated Tau Markers Outperform Total Versions In Predicting Clinical Diagnosis



Michel N. Nafash, Marissa F. Farinas, Theresa E. Boots, Xuemei Zeng, Ruyu Shi, Annie Bedison, Cristy Matan, Neelesh K. Nadkarni, Alexandra Gogola, C. Elizabeth Shaaban, Jennifer Lingler, Howard J. Aizenstein, Dana L. Tudorascu, Tharick A. Pascoal, Victor L. Villemagne, Sarah B. Berman, Milos D. Ikonovic, Robert A. Sweet, Julia Kofler, Beth E. Snitz, M. Ilyas Kamboh, Ann D. Cohen, Oscar I. Lopez, Thomas K. Karikari

INTRODUCTION

- Plasma tau/p-tau species have been established as fluid markers for Alzheimer's disease (AD), with p-tau217 being the golden standard due to its high sensitivity.
 - Others include p-tau181 and p-tau231.
- Circulating tau in the blood is subject to peripheral contamination.
 - Heart, pancreas, and kidney release p-tau species.
 - Comorbid conditions (e.g., diabetes) increase circulating tau/p-tau.
 - Increase false positives and complicate diagnosis and treatment eligibility determination.
- BD-tau/BD-p-tau assays have emerged to measure CNS-specific tau/p-tau, which lacks exon 4a in peripheral tau, and demonstrated
- BD-tau/BD-p-tau species show promise with better diagnostic performance than their respective total counterparts because they are resistant to peripheral contamination.
- Recent biomarker tests are incorporating BD-tau/BD-p-tau into new multiplex assays, (e.g. the NULISeq CNS 120).

METHODS AND PARTICIPANTS

- Biomarker measurements were obtained using the NULISeq CNS 120 Panel.
- Diagnostic parameter point estimates and 95% CI's were obtained using bootstrap logistic regression with 1000 iterations.

	AD Dementia N = 485 ¹	Cognitively Normal N = 417 ¹	MCI N = 322 ¹	non-AD Dementia N = 210 ¹	p-value ²
Sex					< 0.0001
Female	270 (56%)	264 (63%)	142 (44%)	83 (40%)	
Race					< 0.0001
Non-Hispanic White	454 (94%)	348 (83%)	307 (95%)	202 (96%)	
Black/African American	26 (5.4%)	62 (15%)	10 (3.1%)	8 (3.8%)	
Other	4 (0.8%)	7 (1.7%)	5 (0.15%)	0 (0%)	
APOE					< 0.0001
ε4/ε4 homozygous	47 (9.8%)	16 (3.9%)	41 (13%)	10 (4.8%)	
ε4 heterozygous	234 (49%)	125 (30%)	114 (36%)	63 (30%)	
Non-carrier	201 (42%)	272 (66%)	163 (51%)	136 (65%)	
Education (years)	14 (4)	16 (4)	16 (5)	14 (5)	< 0.0001
Age (years, at visit)	74 (14)	68 (10)	72 (12)	68 (14)	< 0.0001
Amyloid PET					< 0.0001
Present	27 (5.6%)	41 (9.8%)	47 (14.6%)	21 (10%)	
BD-pTau-217	13.08 (1.35)	11.70 (0.65)	12.34 (1.28)	11.97 (1.06)	< 0.0001
pTau-217	12.93 (1.30)	11.61 (1.02)	12.37 (1.33)	11.94 (1.24)	< 0.0001
BD-pTau-181	15.61 (1.39)	14.19 (1.15)	14.91 (1.48)	14.58 (1.49)	< 0.0001
pTau-181	14.34 (1.16)	13.51 (1.10)	14.01 (1.19)	13.75 (1.09)	< 0.0001
BD-pTau-231	14.02 (0.76)	13.40 (0.44)	13.68 (0.67)	13.55 (0.62)	< 0.0001
pTau-231	14.62 (1.20)	13.84 (1.24)	14.42 (1.46)	14.19 (1.37)	< 0.0001
BD-MAPT	13.11 (0.59)	12.83 (0.37)	12.96 (0.44)	12.94 (0.38)	< 0.0001
MAPT	13.02 (1.05)	12.65 (1.15)	12.99 (1.19)	12.90 (1.04)	< 0.0001

¹N(%); Median (IQR)
²Pearson's Chi-squared test; Kruskal-Wallis rank sum test

RESULTS

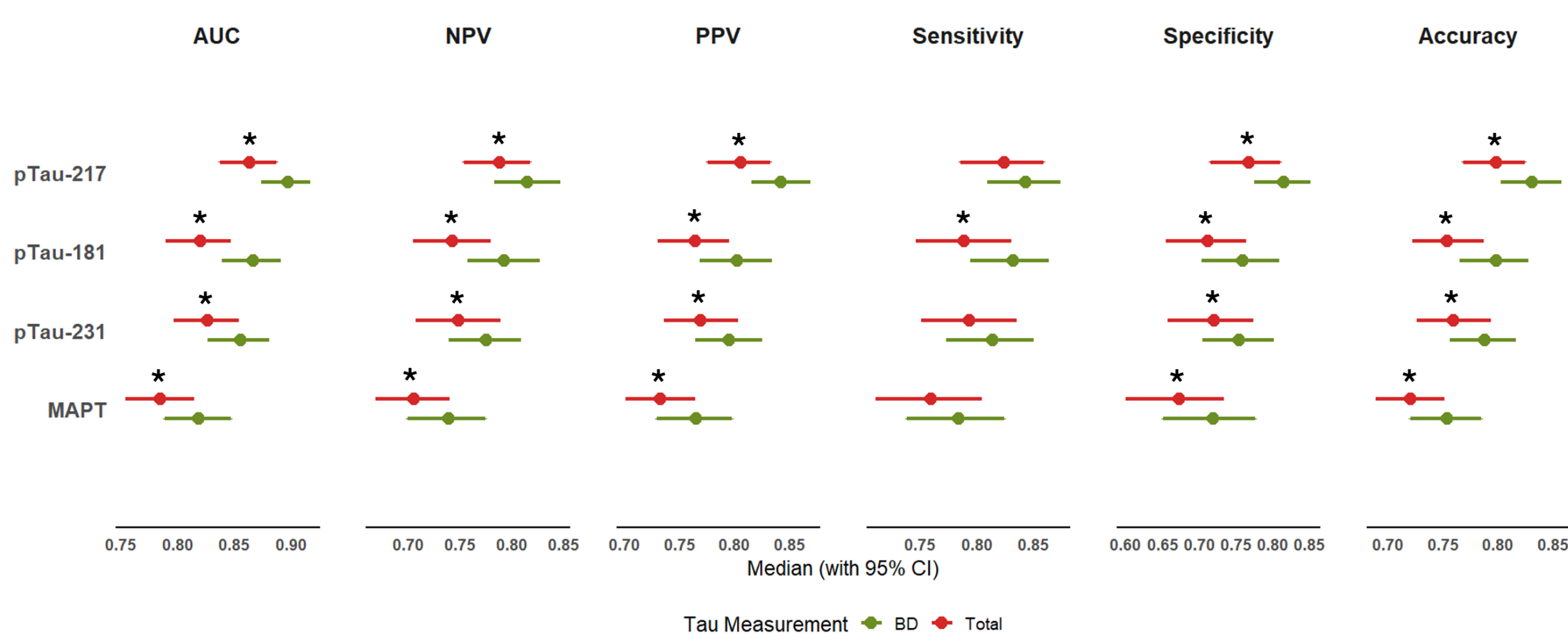


Figure 1. Differences in diagnostic parameters between BD-tau/p-tau and total tau/p-tau at distinguishing AD dementia patients from cognitively unimpaired individuals.

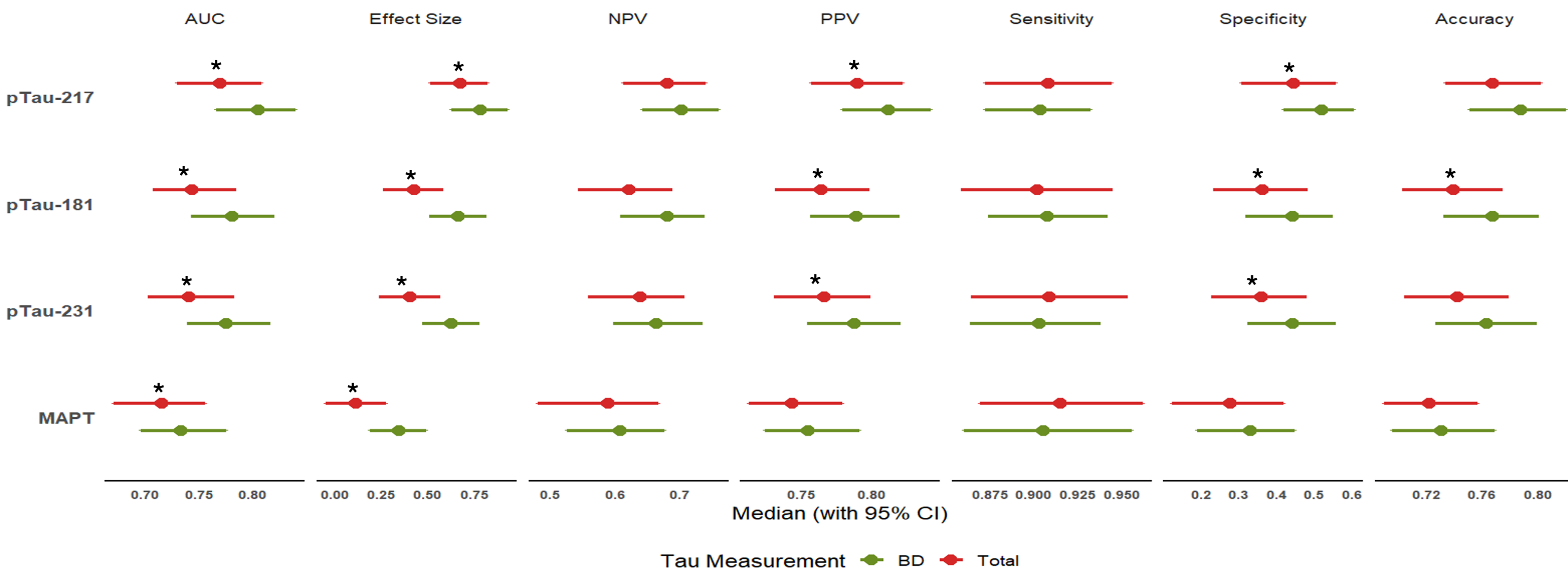


Figure 3. Differences in diagnostic parameters between BD-tau/p-tau and total tau/p-tau at distinguishing AD dementia from non-AD dementia.

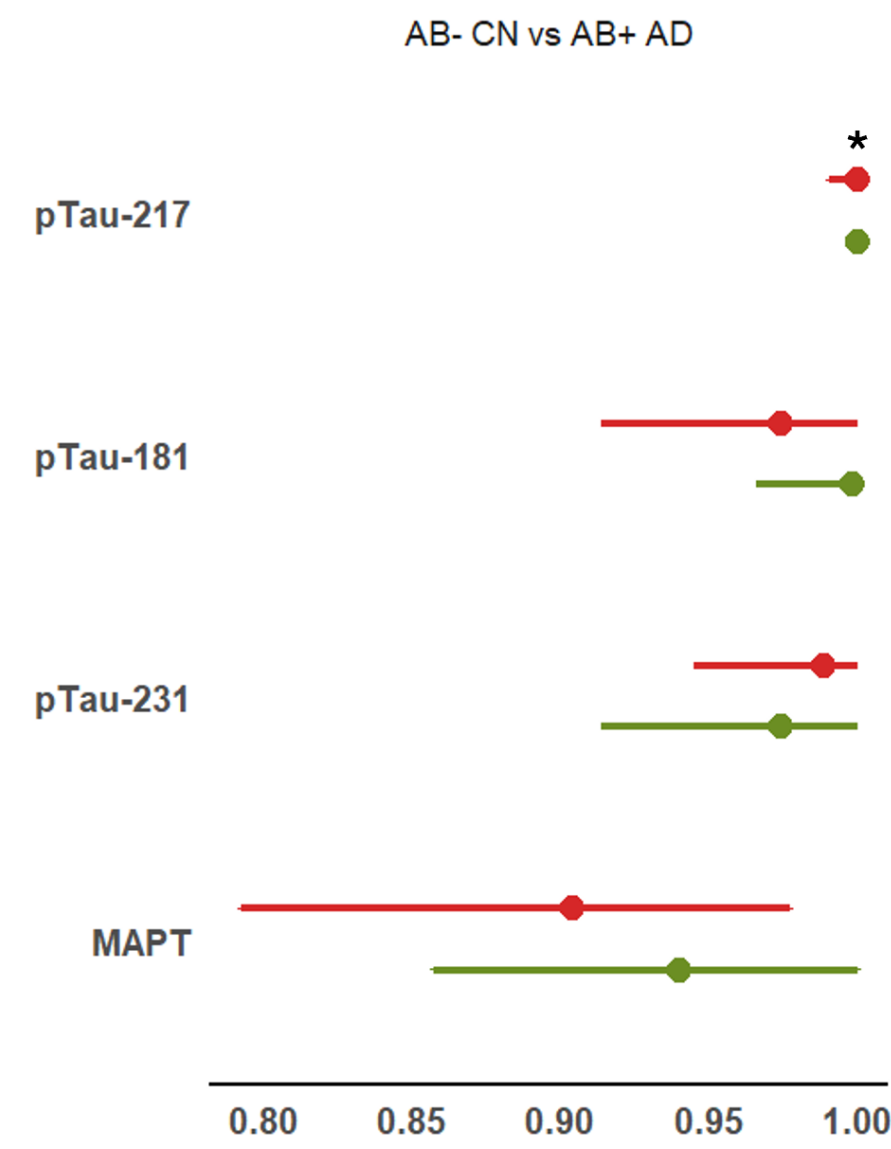


Figure 4. AUC of BD-tau/p-tau vs total tau/p-tau in discriminating Aβ+ AD patients from Aβ- controls.

In a subcohort with confirmed Aβ-PET status, BD-p-tau217 was significantly more able to distinguish Aβ+ AD patients than Aβ- controls, suggesting an improved surrogate marker for Aβ status.

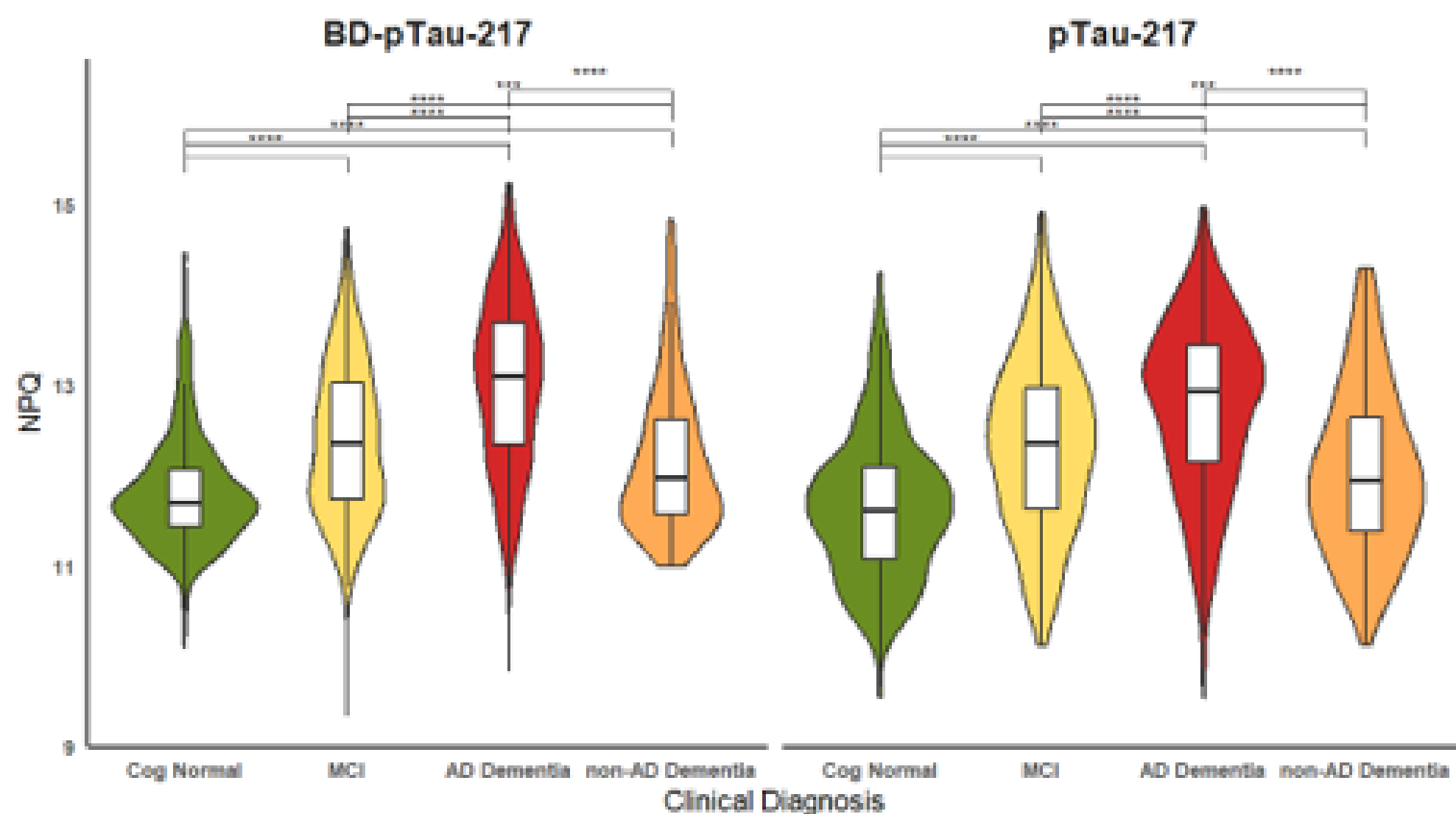


Figure 5. Distributions of BD-p-tau217 and total p-tau217 by cognitive status obtained via clinical diagnosis.

- Superior performance of BD-p-tau compared to total p-tau at distinguishing AD-dementia from normal controls
- Higher AUC, effect size, specificity, and accuracy across all isoforms.
- Sensitivity of BD-p-tau isoforms show an increasing trend, with significance only present with p-tau181.

- BD-p-tau isoforms demonstrate a better discriminative accuracy between dementia caused by AD and other pathologies.
- Significantly higher AUC, effect size, and specificity across all isoforms.
- p-tau181's accuracy significantly improved with BD measurement.

All BD-p-tau and total p-tau isoforms follow the same patterns, with highest measurements seen in AD patients, followed by patients with MCI, then non-AD dementia patients, then cognitively normal individuals, as measured by clinical

CONCLUSIONS

- Brain-derived p-tau measurements deliver superior discriminative performance to distinguish Alzheimer's dementia from non-AD dementia and cognitive unimpairment.
- BD-p-tau217 emerges as a marker with confirmed improvement in performance over its total counterpart, corroborated by Aβ-PET data.
- More analyses with comorbid conditions and their treatments are needed to evaluate the true advantage of measuring BD-p-tau isoforms over conventional p-tau measurements.

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