



Plasma eMTBR-tau243 as a disease biomarker across Alzheimer's disease clinical phenotypes

Jennifer L. Whitwell¹; Jerusha G. Bhaskaran¹; Ryota Satoh¹; Jonathan Graff-Radford¹; Mary M. Machulda¹; Val J. Lowe¹; Michelle M. Mielke²; Shin-Cheng Tzeng³; John Bui³; Tim West³; Philip Verghese³; Venky Venkatesh³; Keith A. Josephs¹

¹Mayo Clinic, Rochester, MN; ²Wake Forest University, Winston-Salem, NC; ³C2N Diagnostics, LLC, St. Louis, MO

Background

- Phosphorylated species of tau (p-tau) can be measured in plasma, including tau phosphorylated at threonine 217 (p-tau217). However, these p-tau metrics have been more closely associated with A β plaques, rather than tau deposition.
- A new mass-spectroscopy assay has been developed to quantify the tau microtubule-binding region containing residue 243 (MTBR-tau243). Plasma-measured endogenous MTBR-tau243 (eMTBR-tau243) is elevated in Alzheimer's disease (AD) and correlates to quantitative tau PET and cognition, outperforming p-tau217.
- It is unknown, however, how eMTBR-tau243 performs across the phenotypic spectrum of AD, including atypical AD clinical phenotypes.

Objective

To assess eMTBR-tau243 and p-tau217 in a cohort of patients with different clinical phenotypes of AD and to determine whether plasma biomarkers relate to demographics, cognition and A β and tau PET.

Methods

- 20 patients with biomarker-confirmed AD (five amnesic-AD, six language-AD, six visual-AD, two motor-AD, one unclassified-AD) were recruited by the Neurodegenerative Research Group (NRG), Department of Neurology, Mayo Clinic, (**Table 1**).
- These patients were matched by age and sex to 10 A β -negative controls.
- All AD patients had undergone Pittsburgh Compound B (PiB) and flortaucipir PET. Regional standardized uptake value ratios (SUVRs) were calculated using the Mayo Clinic Adult Lifespan Template.
- eMTBR-tau243, p-tau217 and %p-tau217 (the ratio of non-phosphorylated to phosphorylated tau217) were analyzed from plasma samples using validated methods.

Table 1: Cohort Demographics

	Amnesic (n=5)	Language (n=6)	Visual (n=6)	Motor (n=2)	Unclassified (n=1)
Sex, female (%)	2 (40%)	2 (33%)	4 (67%)	1 (50%)	1 (100%)
Age at onset, yrs	71 [67-74]	60 [57-75]	67 [60-74]	58 [57-58]	53
Age at visit, yrs	74 [71-79]	67 [58-79]	70 [62-75]	62 [57-58]	58
Time onset to visit, yrs	3.5 [0.7-5.5]	4.2 [0.6-7.3]	2.9 [0.5-5.4]	4.2 [3.1-5.4]	5
A β PET centiloid	97 [77-134]	105 [76-145]	108 [34-161]	80 [54-105]	203
Tau meta-ROI SUVR	2.0 [1.5-2.2]	2.2 [1.3-2.7]	1.5 [1.3-3.4]	2.2 [1.8-2.5]	2.7
MoCA (/30)	21 [17-23]	19 [7-26]	23 [17-29]	20 [18-21]	18
CDR-SB (/18)	2.0 [0.5-8.0]	3.3 [0.5-11.5]	1.8 [1.0-7.5]	1.8 [1.5-2.0]	1.5

Data shown as median [range] or N (%). MoCA = Montreal cognitive assessment battery; CDR-SB = clinical dementia rating scale sum of boxes; SUVR = Standardized uptake value ratios; tau meta-ROI calculated from the temporal lobe.

Table 2: Plasma biomarker associations

	eMTBR-tau243	p-tau217	%p-tau217
Flortaucipir PET SUVR			
Entorhinal cortex (Braak I-II)	0.45, p=0.05	0.47, p=0.04	0.34, p=0.14
Lateral temporal (Braak III-IV)	0.82, p<0.001	0.70, p<0.001	0.67, p=0.002
Lateral parietal (Braak V)	0.89, p<0.001	0.72, p=0.0005	0.70, p=0.001
Lateral occipital (Braak V)	0.62, p=0.003	0.48, p=0.03	0.46, p=0.04
Sensorimotor (Braak VI)	0.79, p<0.0001	0.57, p=0.01	0.54, p=0.02
Visual cortex (Braak VI)	0.47, p=0.04	0.31, p=0.19	0.30, p=0.20
Global A β SUVR	0.48, p=0.03	0.47, p=0.04	0.34, p=0.14
Age	-0.53, p=0.02	-0.41, p=0.07	-0.49, p=0.03
MoCA	-0.51, p=0.02	-0.40, p=0.08	-0.33, p=0.15
CDR-SB	0.01, p=0.96	-0.001, p=0.99	-0.07, p=0.76

Table shows Spearman rho and p values

CDR-SB = Clinical Dementia Rating Scale sum of Boxes; MoCA = Montreal Cognitive Assessment Battery; SUVR = Standardized uptake value ratios

Results

- Plasma eMTBR-tau243, p-tau217 and %p-tau217 levels were greater in AD than controls, with highest AUROCs obtained for p-tau217 and %p-tau217, followed by eMTBR-tau243 (**Fig. 1**). The highest levels of all three biomarkers were observed in motor-AD and unclassified-AD (**Fig. 1**).
- eMTBR-tau243 levels were below the limits of quantitation in 9/20 patients with AD (45%) – these patients had more focal and milder patterns of tau uptake on PET (**Fig. 2**).
- Strong positive correlations were observed between eMTBR-tau243 levels and tau-PET SUVR in lateral temporal, parietal, occipital and sensorimotor regions (**Table 2**). Weaker correlations were observed with p-tau217 and %p-tau217 (**Table 2**).
- Younger age was associated with greater eMTBR-tau243 and %p-tau217 levels, and global A β SUVR was weakly positively correlated with both eMTBR-tau243 and p-tau217 (**Table 2**).
- Worse performance on the MoCA was associated with greater eMTBR-tau243 levels (**Table 2**).

Figure 1

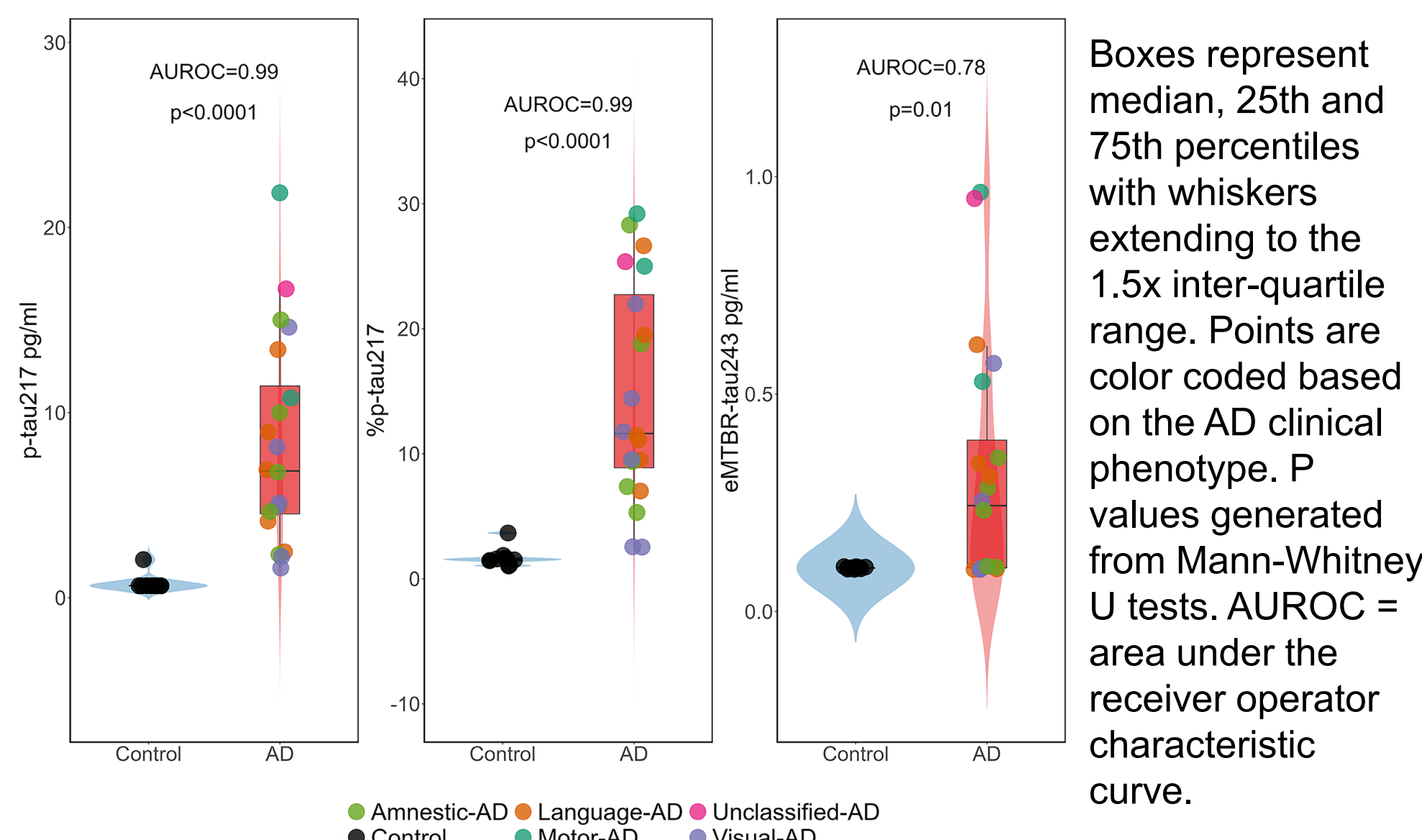
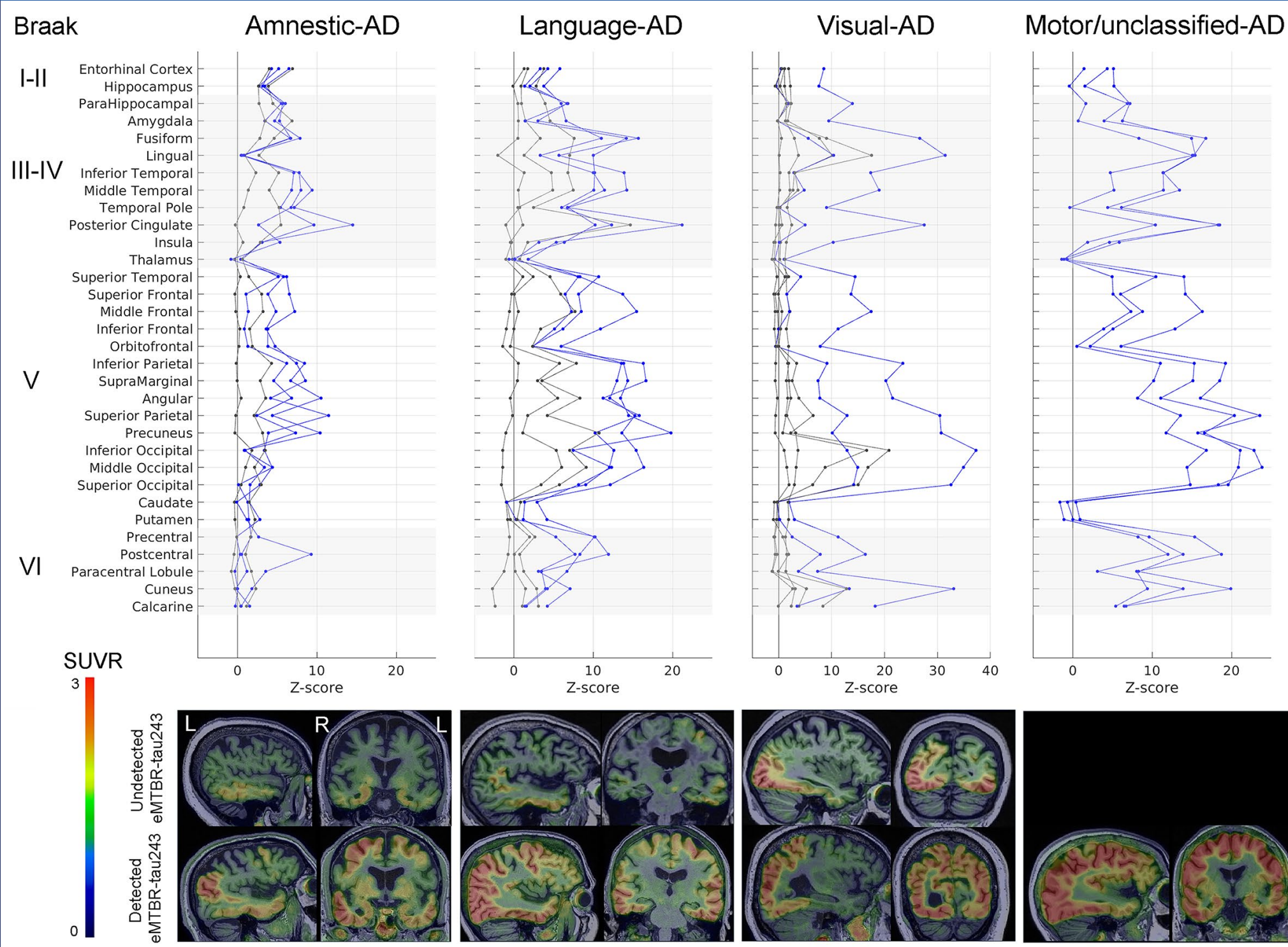


Figure 2



The top panel shows plots of regional tau-PET z scores in each AD patient. Blue = patients with detected eMTBR-tau243 levels; black = patients with undetected eMTBR-tau243 levels. Bottom panel shows representative patient-level SUVR maps.

Conclusion

The p-tau217 and %p-tau217 metrics provide more sensitive diagnostic biomarkers, but eMTBR-tau243 performs better as a disease biomarker of neocortical tau deposition and cognitive impairment in patients with different clinical phenotypes of AD. These findings support the utility of both plasma biomarkers in patients with atypical presentations of AD.

Acknowledgement

National Institutes of Health R01-AG50603 and AVID Radiopharmaceutical for supplying AV1451.