

Supplementary Information

Supplementary Table 1. Demographic characteristics of participants that did not fit the NIA-AA based profiles or the A-T- group

	A- $T_{Me+Te-R-}$	A- $T_{Me-Te+R-}$	A- $T_{Me-Te-R+}$	A- $T_{Me-Te+R+}$	A- $T_{Me+Te+R-}$	A- $T_{Me+Te+R+}$
n	11	2	6	3	4	5
Age (years)	76.4 ± 5.8	79.0 ± 3.0	74.7 ± 5.2	67.0 ± 5.0	78.0 ± 4.1	70.2 ± 4.3
Education (years)	13.5 ± 4.3	12.0 ± 3.0	15.0 ± 2.2	16.0 ± 4.5	14.0 ± 1.7	11.0 ± 2.8
Gender, F (%)	45%	50%	83%	67%	7%	40%
MMSE	26.4 ± 3.6	29.5 ± 0.5	29.2 ± 0.7	27.3 ± 2.1	25.5 ± 3.4	24.0 ± 2.6
CDR-SoB	1.4 ± 2.0	0.2 ± 0.2	0.1 ± 0.2	2.5 ± 2.5	1.4 ± 1.0	3.0 ± 1.7
Tau PET SUVR (MetaT)	1.2 ± 0.1	1.1 ± 0.1	1.0 ± 0.1	1.1 ± 0.0	1.3 ± 0.2	1.8 ± 0.9
Centiloid (CL)	5.6 ± 8.0	-6.2 ± 1.2	-4.1 ± 5.1	-3.1 ± 3.4	-0.6 ± 9.2	9.2 ± 7.6
Plasma p217+tau (fg/ml)	85.8 ± 48.2	126.2 ± 57.9	57.8 ± 25.5	63.0 ± 30.0	112.8 ± 31.2	159.3 ± 94.7
MCI or Dementia (%)	45%	0%	17%	67%	75%	80%

Values presented as mean ± SD for all variables except n, Gender, Apolipoprotein E (APOE) ε4 and MCI or Dementia (%). *MMSE* mini-mental state examination; *CDR-SoB* clinical dementia rating sum of boxes; *SD* Standard deviation; *Me* mesial temporal ROI; *Te* temporoparietal ROI; *R* rest of neocortex. Positive sign denotes being above the pre-defined thresholds and negative below the pre-defined thresholds outlined in the Methods section. *Tau PET SUVR (MetaT)* Tau ¹⁸F-MK6240 SUVR estimated in a standard meta-temporal composite region, comprising entorhinal cortex, parahippocampus, amygdala, inferior temporal, fusiform, and middle temporal cortex ROI.

12 Supplementary Table 2. Demographic characteristics, breakdown by clinical diagnosis

		CU	MCI	Dementia
n		248	144	83
Age (years)		75.6 ± 6.2	73.8 ± 7.7	71.5 ± 8.2
Education (years)		13.7 ± 3.0	12.6 ± 3.1	12.2 ± 2.9
Gender, Female (%)		54%	45%	43%
<i>APOE</i> ε4 (%)		30%	40%	55%
MMSE		28.6 ± 1.4	26.4 ± 2.6	22.2 ± 5.0
CDR_SoB		0.2 ± 0.5	1.2 ± 0.8	5.6 ± 3.0
Centiloid (CL)		32.9 ± 50.6	90.2 ± 56.1	103.5 ± 52.6
Aβ+ PET (%)		37%	81%	90%
Tau PET, meta temporal (SUVR)		1.0 ± 0.2	1.6 ± 0.6	2.0 ± 0.8
Plasma p217+tau (fg/ml)		99.3 ± 76.4	197.4 ± 123.3	243.1 ± 144.4
AT biomarker groups	A-T- (%)	63%	19%	10%
	A+T- (%)	19%	16%	11%
	A+T _{MTL} + (%)	6%	7%	8%
	A+T _{MOD} + (%)	11%	49%	36%
	A+T _{HIGH} + (%)	1%	9%	35%

13 Values presented as mean ± SD for all variables except n, Gender, Apolipoprotein E
14 (*APOE*) ε4, Aβ+ PET% and AT biomarker groups. Total n = 475. Aβ+ PET based on a
15 threshold of 25 CL. *MMSE* mini-mental state examination; *CDR-SoB* clinical dementia
16 rating sum of boxes; *SD* Standard deviation; *CU* Cognitively Unimpaired; *MCI* Mild
17 Cognitive Impairment; A-T- amyloid negative and tau negative; A+T- amyloid positive and
18 tau negative; A+T_{MTL}+ amyloid positive with tau uptake limited to medial temporal region;
19 A+T_{MOD}+ amyloid positive with moderate tau uptake in temporo-parietal region; A+T_{HIGH}+
20 amyloid positive with high tau uptake in temporo-parietal region.

21 Supplementary Table 3. The *p*-values and Cohen's *d* effect sizes for differences in plasma
 22 p217+tau concentration

Comparisons	Adjusted <i>p</i> values	Cohen's <i>d</i>
A-T- vs. A+T-	<0.001	1.3
A-T- vs. A+T _{MTL} +	<0.001	2.0
A-T- vs. A+T _{MOD} +	<0.001	2.3
A-T- vs. A+T _{HIGH} +	<0.001	3.8
A+T- vs. A+T _{MTL} +	0.731	0.4
A+T- vs. A+T _{MOD} +	<0.001	1.2
A+T- vs. A+T _{HIGH} +	<0.001	2.2
A+T _{MTL} + vs. A+T _{MOD} +	<0.001	0.9
A+T _{MTL} + vs. A+T _{HIGH} +	<0.001	1.6
A+T _{MOD} + vs. A+T _{HIGH} +	<0.001	1.1

23 Multiple comparison of group means, using Tukey HSD. A-T- amyloid negative and tau
 24 negative; A+T- amyloid positive and tau negative; A+T_{MTL}+ amyloid positive with tau
 25 uptake limited to medial temporal region; A+T_{MOD}+ amyloid positive with moderate tau
 26 uptake in temporo-parietal region; A+T_{HIGH}+ amyloid positive with high tau uptake in
 27 temporo-parietal region.

Supplementary Table 4. Statistics of the ROC analysis to predict disease stage using p217+tau Youden threshold, *CU and CI participants combined*

	AUC	Youden threshold	Sensitivity	Specificity	PPV	NPV
Model 1	0.92 [0.90 - 0.94]	99.38 [89.75 - 102.45]	0.87 [0.83 - 0.91]	0.84 [0.78 - 0.88]	0.89 [0.85 - 0.92]	0.81 [0.77 - 0.87]
Model 2	0.92 [0.90 - 0.94]	168.04 [131.83 - 177.38]	0.77 [0.73 - 0.90]	0.91 [0.80 - 0.95]	0.84 [0.71 - 0.89]	0.88 [0.85 - 0.93]
Model 3	0.91 [0.88 - 0.95]	205.43 [173.18 - 257.86]	0.89 [0.79 - 0.97]	0.82 [0.75 - 0.9]	0.33 [0.25 - 0.47]	0.99 [0.98 - 1.0]

Values reported with bootstrapped 95% confidence intervals, shown in square brackets.

Model 1: A-T- vs. A+T-/A+T_{MTL}+/A+T_{MOD}+/A+T_{HIGH}+. The reported AUC value was slightly higher and Youden's index threshold lower than previously reported for this p-tau assay when discriminating based on A β status (which was based on cohort 1 p217+tau data) [4]. This is attributed to the cohort 2 differences due to between-lab variations (for details on cohort 1 and cohort 2, see Methods). It is less likely to be due to exclusion of A-T+ individuals from the current study, as repetition of this analysis, with the 31 A-T+ included, yielded an AUC of 0.91 [0.89 - 0.93] and Youden threshold of 99.38 fg/ml [89.75 - 126.68]. PPV and NPV reported at A+ observed prevalence of 58%.

Model 2: A-T-/A+T-/A+T_{MTL}+/A+T_{MOD}+/A+T_{HIGH}+. PPV and NPV reported at A+T_{MOD}+/A+T_{HIGH} observed prevalence of 33%.

Model 3: A-T-/A+T-/A+T_{MTL}+/A+T_{MOD}+/A+T_{HIGH}+. PPV and NPV reported at A+T_{HIGH} observed prevalence of 24%.

A-T- amyloid negative and tau negative; A+T- amyloid positive and tau negative; A+T_{MTL} amyloid positive with tau uptake limited to medial temporal region; A+T_{MOD} amyloid positive with moderate tau uptake in temporo-parietal region; A+T_{HIGH} amyloid positive with high tau uptake in temporo-parietal region; PPV positive predictive value; NPV negative predictive value.

Supplementary Table 5. Statistics of the ROC analysis to predict disease stage using p217+tau Youden threshold, in *CI* participants

	AUC	Youden threshold	Sensitivity	Specificity	PPV	NPV
Model 1	0.93 [0.89 - 0.96]	126.68 [94.83 - 149.88]	0.83 [0.69 - 0.95]	0.86 [0.79 - 1.0]	0.97 [0.96 - 1.0]	0.48 [0.34 - 0.74]
Model 2	0.89 [0.86 - 0.93]	177.38 [168.04 - 179.39]	0.78 [0.74 - 0.86]	0.92 [0.85 - 0.96]	0.94 [0.89 - 0.97]	0.72 [0.66 - 0.81]
Model 3	0.84 [0.78 - 0.89]	230.29 [205.43 - 299.52]	0.84 [0.69 - 0.95]	0.71 [0.64 - 0.88]	0.39 [0.31 - 0.58]	0.95 [0.92 - 0.98]

Values reported with bootstrapped 95% confidence intervals, shown in square brackets.

Model 1: A-T- vs. A+T-/A+T_{MTL}+/A+T_{MOD}+/A+T_{HIGH}+. PPV and NPV reported at A+ observed prevalence of 72%.

Model 2: A-T-/A+T-/A+T_{MTL}+ vs. A+T_{MOD}+/ A+T_{HIGH}+. PPV and NPV reported at A+T_{MOD}+/A+T_{HIGH}+ observed prevalence of 51%.

Model 3: A-T-/A+T-/A+T_{MTL}+/A+T_{MOD}+ vs. A+T_{HIGH}+. PPV and NPV reported at A+T_{HIGH}+ observed prevalence of 39%.

A-T- amyloid negative and tau negative; A+T- amyloid positive and tau negative; A+T_{MTL}+ amyloid positive with tau uptake limited to medial temporal region; A+T_{MOD}+ amyloid positive with moderate tau uptake in temporo-parietal region; A+T_{HIGH}+ amyloid positive with high tau uptake in temporo-parietal region; PPV positive predictive value; NPV negative predictive value.

Supplementary Table 6. Discrimination between only two stages at a time, *CU and CI participants combined*

	AUC	Youden threshold	Sensitivity	Specificity	PPV	NPV
A+T- vs. A+T _{MTL} +	0.57 [0.43 - 0.71]	164.10 [80.17 - 266.58]	0.41 [0.25 - 1.00]	0.79 [0.16 - 0.97]	0.46 [0.22 - 0.75]	0.73 [0.65 - 1.0]
A+T _{MTL} + vs. A+T _{MOD} +	0.78 [0.68 - 0.87]	178.91 [144.24 - 179.98]	0.73 [0.67 - 0.87]	0.82 [0.62 - 0.95]	0.96 [0.92 - 0.99]	0.34 [0.24 - 0.51]
A+T _{MOD} + vs. A+T _{HIGH} +	0.74 [0.67 - 0.82]	299.52 [230.29 - 358.75]	0.63 [0.51 - 0.89]	0.77 [0.53 - 0.9]	0.53 [0.39 - 0.7]	0.83 [0.79 - 0.93]

To discriminate between only two biological PET stages at a time, the sample sizes were smaller, thus we performed this analysis only on the combined CU and CI participants. The AUC values were expectedly lower when using plasma p217+tau to discriminate between only two stages at a time. Values reported with bootstrapped 95% confidence intervals, shown in square brackets. A+T- amyloid positive and tau negative; A+T_{MTL} + amyloid positive with tau uptake limited to medial temporal region; A+T_{MOD} + amyloid positive with moderate tau uptake in temporo-parietal region; A+T_{HIGH} + amyloid positive with high tau uptake in temporo-parietal region.