

BIOMARKERS (NON-NEUROIMAGING)

Targeting pre-symptomatic AD individuals: Deep cognitive assessment and plasma biomarkers to predict tau aggregation

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Abstract

Background: Cognitively unimpaired (CU) individuals with both elevated brain amyloid load and tau burden in the medial temporal (MTL) and temporal neocortex (NEO) face high risk of short-term cognitive decline (≤ 5 years; risk=50%). However, identifying these individuals in the population remains challenging due to their low prevalence (8-10%), the cost and invasiveness of validated biomarkers. Cognitive measures and blood-based biomarkers offer promising scalable alternatives, but most plasma biomarkers are more closely associated with amyloid than tau aggregates, and tau-specific measures remain poorly defined. This study assessed whether specific cognitive tasks, including tasks targeting the functions of the first affected regions by tauopathy, and blood-based biomarkers can predict early tau aggregation.

Method: Seventy-seven CU participants completed the Visual Short-Term Binding Test (VSTMBT), the Conceptual Matching Task (CMT), the cognitive tests required for the Preclinical Alzheimer's Cognitive Composite (PACC5), a blood-test, [¹⁸F]-MK6240 tau-PET imaging, 3T-MRI, and amyloid (A) status determination (A+ for Centiloid ≥ 20 or cerebrospinal fluid amyloid-beta₄₂ ≤ 437 pg/mL). The VSTMBT and CMT (Figure 1) involve fine-grained perceptual and conceptual discrimination, respectively, supposedly relying on the transentorhinal cortex. The sample included 55 A- CU and 22 A+ CU (Table 1). Standard Uptake Value ratios (SUVR) were computed for MTL and temporal NEO region of interests (ROI; Ossenkoppele et al., 2022; reference=grey cerebellar). Plasma *p*-tau₂₁₇ and *p*-tau₁₈₁ levels were quantified using Lumipulse and SIMOA. Univariate regression models predicting ROI tau burden based on demographics (age, sex, education), cognitive performance (VSTMBT, CMT, PACC5), and plasma *p*-tau species (2 ROIs x 8 predictors) were conducted to select contributing

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predictors (highlighted in green in Table 2) for further stepwise regression analyses (both directions).

Result: For MTL tau burden, optimal model fit (initial AIC=4.88, final AIC=3.55) was found with the VSTMBT ($b = -0.01$, $SE=0.004$, $p = .004$) and plasma p -tau₂₁₇ level ($b = 1.18$, $SE=0.276$, $p <.001$) as predictors. For temporal NEO tau burden (initial AIC=41.04, AIC=-44.92), best fit was found with the PACC5 ($b = -0.09$, $SE=0.04$, $p = .027$) plasma p -tau₂₁₇ ($b = 0.77$, $SE=0.15$, $p <.001$; $b = 0.76$) and p -tau₁₈₁ ($b = -0.003$, $SE=0.002$, $p = .125$) levels as predictors.

Conclusion: Plasma p -tau₂₁₇ predicted tau burden across both ROIs, alongside different cognitive tasks depending on the ROI, likely reflecting their associated cognitive functions.

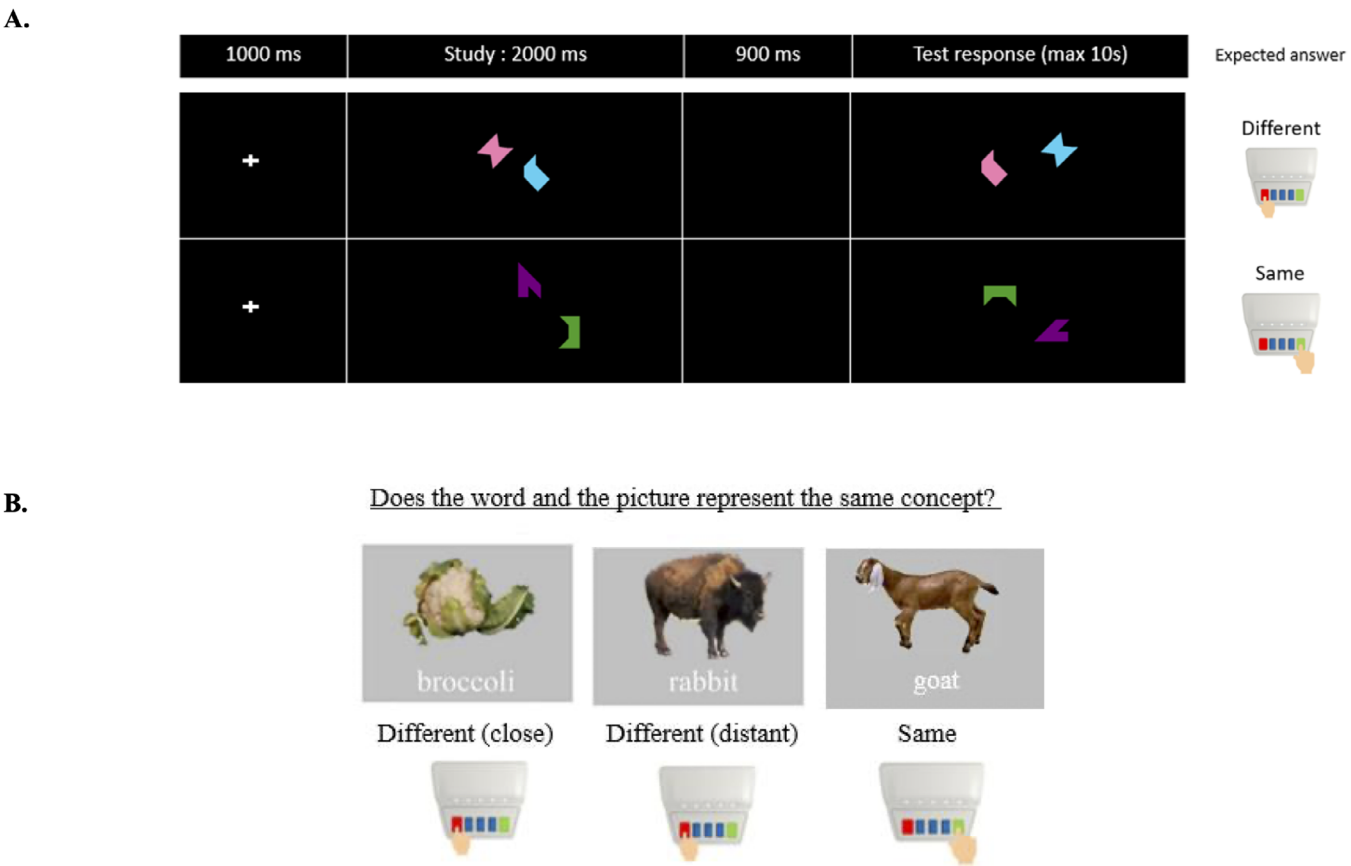


Figure 1. A. Visual Short Term Memory Binding Test: participants are shown sets of two or three colored shapes. After a short delay, they are asked whether another set of colored shapes match the previous one. **B. Conceptual Matching Task:** the tasks consists in indicating whether the picture and the word refer to the exact same concept. The task includes closely related semantic items.

Table 1. Demographics, cognitive performance, plasma biomarkers, and ROI tau burden

	A- CU (n = 55) <i>Mdn (Q1-Q3)</i>	A+ CU (n = 22) <i>Mdn (Q1-Q3)</i>	<i>p</i>
Demographics			
Age (years)	67.0 (60.5–73.0)	74.5 (68.5–76.8)	.002
Sex (% female)	56%	54%	1.00
Education (years)	17.0 (16.0–18.5)	16.0 (15.0–18.8)	.601
APOE ε4 carriers (%)	42%	63%	.139
Cognition			
MMSE (/30)	29.0 (28.0–30.0)	29.0 (28.0–29.0)	.185
PACC5 (z-score)	0.11 (-0.26–0.33)	-0.15 (-0.66–0.09)	.027
VSTMBT (%)	84.4 (75.0–90.6)	71.9 (66.4–81.3)	.005
CMT (%)	93.5 (89.7–95.4)	89.4 (84.7–93.2)	.011
Plasma (pg/mL)			
p-tau ₂₁₇	0.10 (0.08–0.13)	0.21 (0.17–0.40)	< .001
p-tau ₁₈₁	18.0 (14.10–24.83)	32.29 (24.30–39.57)	< .001
ROI tau burden (SUVr)			
MTL	0.79 (0.73–0.85)	1.17 (0.90–1.55)	< .001
Temporal NEO	0.96 (0.88–1.02)	1.08 (1.01–1.21)	< .001
AT stratification			
MTL	52 A-T- 3 A-T+	9 A+T- 13 A+T+	-
Temporal NEO	55 A-T- 0 A-T+	14 A+T- 8 A+T+	-

Note. Group comparisons were performed using Mann-Whitney tests. The sample was enriched in APOE ε4 carriers. A- = amyloid negative; A+ = amyloid positive (for cerebrospinal fluid Aβ42 level < 437 pg/ml or Centiloid ≥ 20), CU = cognitively unimpaired (MMSE ≥ 24/30 and z-scores > -1.5 for memory, executive, language and visuo-spatial domains), Mdn = median; Q1-Q3 = first and third quartiles; MMSE = Mini-Mental State Examination; PACC5 = Preclinical Alzheimer's Cognitive Composite 5 (Papp et al., 2017; averaged z-score across the MMSE, Logical Memory Delayed Recall Story A from the Weschler Memory Scale-III, Digit-Symbol Substitution Test, sum of free and total recalls from the French-version of the Free and Cued Selective Reminding Test and category fluency) ; VSTMBT = Visual Short-Term Memory Binding Test (Parra et al., 2010); CMT = Conceptual Matching Task (Frick et al., 2023); pg = picogram; mL = milliliter; ROI = region of interest; SUVr = Standard Uptake Value ratio; **MTL** = medial temporal lobe ROI (unweighted average of bilateral entorhinal cortex and amygdala; Ossenkoppele et al., 2022) ; **NEO** = temporal neocortex ROI (weighted average of bilateral middle temporal and inferior temporal cortices; Ossenkoppele et al., 2022); AT = amyloid-tau; T+ for SUVr > cut-off corresponding to Mean SUVr + 2 SD across all A- CN (1.33 for both MTL and temporal NEO ROIs).

Table 2. Univariate regression models predicting ROI tau burden, aimed at selecting contributing predictors (highlighted in light green) for further stepwise regression analyses

	β	95% CI	FDR adjusted <i>p</i>
MTL SUVR			
Age	0.01	0.00 – 0.03	.059
Male sex	0.01	-0.17 – 0.23	.899
Education	-0.01	-0.04 – 0.02	.593
PACC5	-0.27	-0.41 – -0.12	.007
VSTMBT	-0.02	-0.02 – -0.01	< .001
CMT	-0.02	-0.04 – 0.00	.163
p-tau ₂₁₇	1.68	0.91 – 2.65	< .001
p-tau ₁₈₁	0.01	0.004 – 0.02	.007
Temporal NEO SUVR			
Age	0.01	-0.002 – 0.02	.196
Male sex	0.02	-0.11 – 0.16	.815
Education	0.004	-0.15 – 0.02	.813
PACC5	-0.16	-0.24 – -0.07	.007
VSTMBT	-0.01	-0.01 – -0.002	.018
CMT	-0.02	-0.07 – -0.004	.017
p-tau ₂₁₇	0.83	0.53 – 1.18	< .001
p-tau ₁₈₁	0.01	0.001 – 0.01	.026

Note. We performed Generalized Linear Models (GLMs) with an inverse Gaussian distribution and a log link, since tau burden data were positively skewed, and these models provided lower AICs compared to Gaussian models.

ROI = region of interest; SUVR = Standard Uptake Value ratio; MTL = medial temporal lobe ROI (unweighted average of bilateral entorhinal cortex and amygdala; Ossenkoppele et al., 2022) ; NEO = temporal neocortex ROI (weighted average of bilateral middle temporal and inferior temporal cortices; Ossenkoppele et al., 2022); PACC5 = Preclinical Alzheimer's Cognitive Composite 5; VSTMBT = Visual Short-Term Memory Binding Test ; CMT = Conceptual Matching Task.