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BIOMARKERS

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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, [^{18}F]-MK6240 tau-PET imaging, 3T-MRI, and amyloid (A) status determination (A+ for Centiloid≥ 20 or cerebrospinal fluid amyloid-beta$_{42}$≤437 pg/mL). The VSTMBT and CMT (Figure 1) involve fined-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*-tau$_{217}$ and *p*-tau$_{181}$ 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-tau$_{217}$ 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-tau$_{217}$ (b = 0.77, SE=0.15, p <.001; b = 0.76) and p-tau$_{181}$ (b = -0.003, SE=0.002, p = .125) levels as predictors.

Conclusion: Plasma p-tau$_{217}$ predicted tau burden across both ROIs, alongside different cognitive tasks depending on the ROI, likely reflecting their associated cognitive functions.

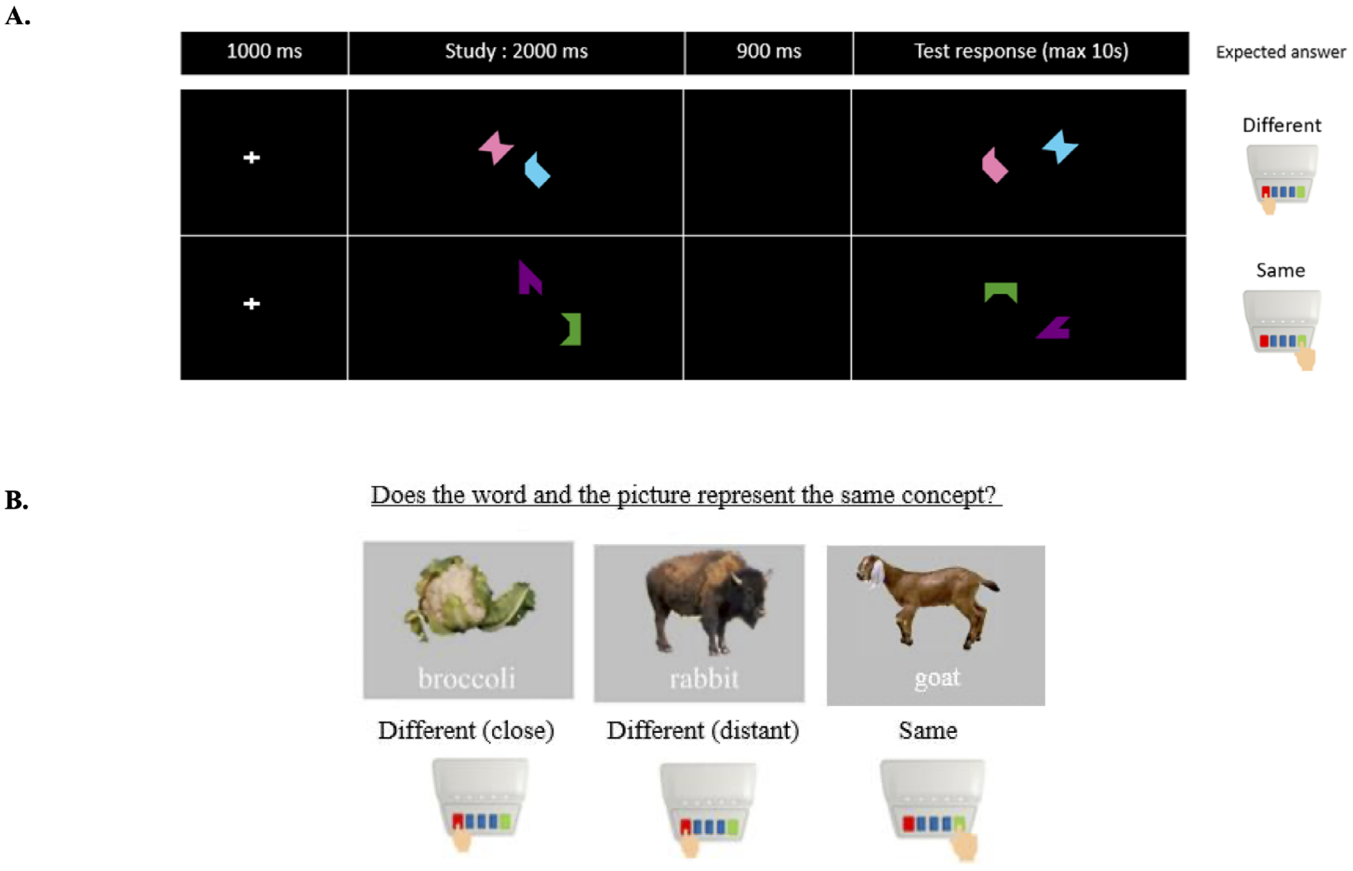

Figure 1. A. *Visual Short Term Memory Binding Test*: participants are shown sets of two or three colored shapes. After a short delay, they are asked whether another set of colored shapes match the previous one. **B.** *Conceptual Matching Task*: the tasks consists in indicating whether the picture and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

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

	A- CU (n = 55) *Mdn (Q1-Q3)*		A+ CU (n = 22) *Mdn (Q1-Q3)*		*p*
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).

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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 p
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.

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