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Original Article

Preclinical detection of Alzheimer's disease pathology using conceptual discrimination abilities

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ABSTRACT

Background: Performance on the Conceptual Matching Task (CMT), a measure of discrimination between conceptually confusable items, has been suggested as a cognitive marker of rhinal cortex atrophy, one of the first brain regions affected by Alzheimer's disease (AD) pathology.
Objectives: We aimed to determine whether CMT can detect preclinical AD, and whether CMT performance is related to regional deposition of tau protein or other AD-associated lesions including amyloid (Aβ) accumulation and white matter hyperintensities (WMH).
Design, setting and participants: This cross-sectional study include 101 participants from the UCL2016–121 cohorts in Brussels, Belgium, classified as 56 Aβ-negative cognitively unimpaired (Aβ-CU), 25 Aβ-positive CU (Aβ+CU, preclinical AD), and 20 Aβ-positive mildly cognitively impaired (Aβ+MCI, prodromal AD) individuals.
Measurements: Participants underwent CMT and a standard neuropsychological assessment that included the Preclinical Alzheimer Cognitive Composite (PACC5), an Aβ status examination, a 3D-T1 MRI and a [^{18}F]MK-6240 tau-PET scan.
Results: CMT performance was lower among Aβ+MCI and Aβ+CU than Aβ-CU individuals. The effect of Aβ on CMT performance was stronger in the presence of WMH, but rhinal tau burden did not explain CMT performance beyond the effects of Aβ and WMH. CMT performance correlated with executive, memory, and language performance. Finally, CMT was more sensitive than PACC5 to detect CU individuals with Aβ or tau pathology.
Conclusion: Given that impaired performance is observed earlier in the CMT than in standard neuropsychological tests, this test shows promise as an early diagnostic tool for AD and may offer significant utility in the context of clinical trials.

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1. Introduction

Alzheimer's disease (AD) proteinopathies, including amyloid-beta (Aβ) plaques and tau neurofibrillary tangles [1,2], accumulate years before the onset of cognitive symptoms, defining a silent preclinical phase [3]. The risk of cognitive decline is higher among cognitively unimpaired (CU) individuals with an high Aβ burden compared with those with low Aβ levels [4,5]. Moreover, the combined impact of abnormal global Aβ deposition and tau burden in the medial temporal lobe (Aβ+Tau+MTL) in CU subjects increases the risk of short-term progression to symptomatic AD six-fold (risk=50 % within 3–5 years), compared with CU individuals with only a high Aβ burden (Aβ+Tau-, risk=8 %) [6]. Therefore, the identification of Aβ+Tau+CU individuals could facilitate the enrichment of clinical trials with persons at risk for rapid cognitive decline [6]. However, a reliable, easy-to-use, rapid, and cost-effective method to identify AD progression at the preclinical stage remains a major research gap. Positron-emission-tomography (PET) imaging for Aβ and tau is unsuitable for large-scale population screening due to its cost and invasiveness. On the other hand, cognitive assessments are good candidates for this purpose. However, the standard cognitive tests usually used clinically in Western Europe, were designed to optimally detect cognitive impairment in the prodromal and dementia stages of AD. Therefore, these tests (e.g., the Free and Cued Selective Reminding Test [7] or Verbal Fluency Test [8]) lack the requisite sensitivity to accurately capture the subtle cognitive correlates of the developing tau pathology in its earliest stages [9]. Various studies have attempted to implement new cognitive tasks to detect cognitive disorders earlier than the standard assessment. One the one hand, cognitive composite scores that aggregate standard measures, such as the Preclinical Alzheimer Cognitive Composite (PACC5, [10]), have been proposed as more sensitive instruments to detect early preclinical cognitive decline. However, cross-sectional performance between Aβ-positive (Aβ+) and Aβ-negative (Aβ-) CU individuals on this metric showed only small effect sizes (AUC between 0.580 and 0.630) [11]. The memory decline observed in AD during the standard neuropsychological assessment is linked primarily to hippocampal pathology [12]. However, deterioration of this region begins during Braak stage II or III whereas other regions such as the trans-entorhinal cortex are affected earlier in disease progression (Braak stage I) [13], which has been parcellated in a PET region-of-interest designated as the rhinal cortex (RC) [14]. One approach to detect subtle cognitive changes in preclinical AD would be to develop cognitive tasks that assess the function of this region [15].

The RC receives inputs from multiple brain areas, establishing this region as a critical node for processing and storing representations of complex perceptual and semantic features [16]. More precisely, the RC has a conjunctive processing function, enabling precise distinctions between highly similar objects with overlapping features [16–18]. Therefore, this region builds unique representations of objects [19] and is implicated in tasks involving discrimination of confusable objects [20,21]. The ability to discriminate conceptually confusable items can be evaluated with the Conceptual Matching Task (CMT, [21]). CMT performance is impaired in patients with mild AD and correlates with atrophy of the left perirhinal cortex (PrC, including the RC) [22]. However, performance of this task in the preclinical stage and its association with early tau protein deposition have not yet been studied. Nonetheless, these initial results and its brief administration time (maximum = 6 min) suggest its potential to facilitate the diagnosis of preclinical AD. Other studies assessing object memory have already shown, for instance, a difference in performance in SCI (Berron et al., 2022) or in Tau+CU subjects (Maass et al., 2019) compared with controls but those tasks are still waiting for validation in preclinical AD. The rhinal cortex is thought to be specific to the treatment of objects, whereas the processing of scenes and space is thought to be underpinned more by posterior-medial regions, and therefore affected later in the course of the disease (Ranganath et al., 2012; Berron et al., 2018). Apart from these studies, which focused on tasks underpinned by the trans-entorhinal cortex, other studies have looked at learning curves and have shown that these curves are reduced in Aβ+CU subjects but only after several days of testing [23–25]. The absence of cross-sectional differences in these studies questioned the clinical utility of this testing method. Finally, very few studies have been able to demonstrate cross-sectional differences between CU individuals with and without Aβ pathology [26–29]. In these studies, the effect sizes for predicting Aβ status are greater than those observed for PACC5 (AUC between 0.63 and 0.77), but sensitivity to tau pathology is generally not assessed while the presence of this pathology is predictive of cognitive decline [6].

The first aim of this study was to determine whether CMT can reveal cognitive decline earlier than the standard neuropsychological tests used in current clinical practice and trials (as early as the preclinical stage). Second, we assessed the association of CMT performance with early tau protein deposition and other AD-associated lesions such as Aβ deposition or white matter hyperintensities (WMH). Finally, we compared the sensitivities of CMT and standard cognitive assessment to detect the presence of Aβ and tau pathologies in CU individuals.

2. Methods

2.1. Participants

Our study population comprised 112 individuals (aged 52–86), including 81 CU subjects and 31 patients with mild cognitive impairment (MCI; Mini Mental State Examination [MMSE] $\geq$ 23 [30]). MCI patients were recruited at the Memory Clinic of the Cliniques Universitaires Saint-Luc in Brussels, Belgium. CU volunteers were enlisted via other academic studies through mailbox announcements and advertisements in the hospital's vicinity. Volunteers were selected from this pool to participate in the current study. Volunteer selection was enriched in carriers of the apolipoprotein ε4 allele (*APOE ε4*) to match the prevalence of *APOE ε4* carriage observed in patients. Recruitment and examinations were conducted between June 2019 and January 2025. Exclusion criteria were focal brain lesions, major depression or other psychiatric diseases, and alcohol or drug abuse. Informed consent was obtained from all participants, adhering to the principles of the Declaration of Helsinki. The Ethical Committee of UCLouvain approved the study (UCL-2016–121, Date: 13/05/2019; Eudra-CT number: 2018–0034/73–94).

All participants underwent the CMT [22], a standard neuropsychological assessment to determine their cognitive status, a [^{18}F]MK-6240 Tau-PET scan, a 3D-T1 brain magnetic resonance imaging (MRI), and an assessment of Aβ status either by PET ([^{18}F]Flutemetamol or [^{11}C]PiB) or lumbar puncture. CMT was performed within a year relative to the tau-PET scan and the standard cognitive assessment.

2.2. Conceptual matching task

CMT [22] is composed of 120 trials in which a word and a picture are simultaneously presented for a maximum of 3 s on the screen (Fig. 1). In our sample, the average completion time was 229 s (min=163, max=320).

In half of the trials, the picture and the word represented the same concept (matching trials), while in the other half, the word and picture did not match the exact same concept, although they belonged to the same superordinate semantic category (non-matching trials). We played on the distance between the concepts (distance condition): half of the non-matching word-picture pairs were very close semantically (close items), while the other half were more distant within the same semantic categories (distant items). Conceptual similarity was computed for each non-matching pair using the cosine between their production frequency vectors extracted from existing feature norms [31,32]. Moreover, each half of the trials utilized either living or non-living pairs (category-domain condition). Conceptual distance did not differ between living and non-living pairs (Living Pairs = 0.34 vs. Non-Living Pairs = 0.35, t =

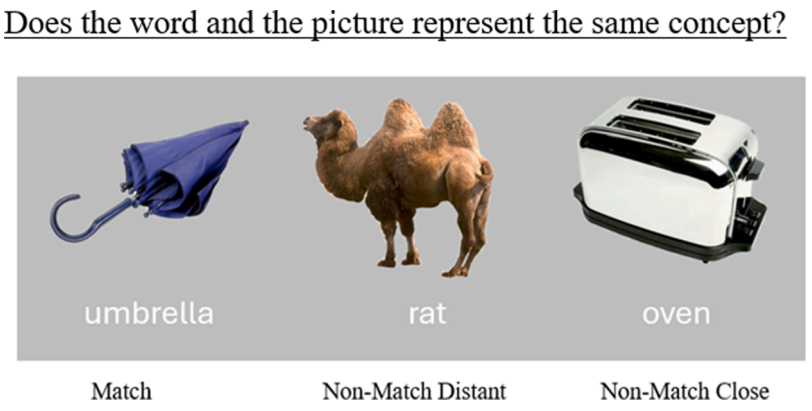


Fig. 1. Example of trials of the Conceptual Matching Task (CMT) [21].
Legend: The participant was instructed to determine whether the word and the picture represented the same concept. The first example illustrates an item from matching trials, the second from the non-match distant trials, and the last one an item from the non-match close trials.

−0.25, df = 118, p = .892, see [22] for further details).

Participants were instructed to indicate whether the word and the picture referred to the same concept by pressing either the far-right button on an Eprime Chronos device (on which we added a green label) if both items corresponded to the same concept, or the far-left button (on which we added a red label) otherwise.

We calculated the accuracy score and the mean reaction time for the subset of items known by the participant among the 120 items comprising the task, and in each condition separately (close versus distant items for the distance condition, matching versus non match items for the matching condition and living versus non-living items in the category-domain condition). To assess the total number of known items, participants completed a prior knowledge questionnaire after the CMT. They were asked whether they had sufficient knowledge of each concept to have a mental representation upon reading it by circling "yes" or "no" next to each item. The total number of known items for each participant was determined by the number of concepts for which they answered "yes." Responses and reaction times to unknown items were not considered. The average total number of known items was 114 words (min=96, max=120, SD= 3.9). The average numbers of known items were similar between groups (p=.351) and this variable did not impact CMT performance (p=.584).

Each participant's mean reaction time was divided by their accuracy score (higher scores indicating poorer efficiency) to compute a Speed-Accuracy Trade-Off (TO) metric. Because TO results were similar to those obtained separately for the accuracy score and the mean reaction time, we only present the TO results in the following sections.

Finally, as in Frick and colleagues' study [22], we computed an ''accuracy sensitivity to conceptual similarity'' metric by correlating each participant's accuracy to the conceptual distance value on a trial-by-trial level using Pearson correlations and a Fisher transformation to convert each Rho-value into a Z-score [21,22].

2.3. Neuropsychological assessment

The neuropsychological testing evaluated four cognitive domains: [1] verbal episodic memory (Free and Cued Selective Reminding Test, FCSRT, French version [33]), [2] language (Lexis Naming Test, Category and Letter Fluency Test for animals and letter 'P', [8]), [3] executive functions (Trail Making Test part A and B [34] and Luria's Graphic Sequences [35]), and [4] visuospatial functions (Clock Drawing Test [36] and Praxis part of the CERAD battery [37]). Composite scores (Z-scores) were computed based on three measures for each cognitive domain, by referring to an independent sample of 32 Aβ- individuals who remained globally cognitively stable (as defined by a MMSE $\geq$ 26/30) over an 8-year period (data collected in UCL-2010–412 study, see [38] for more details). Our Aβ-CN participants had a similar age and MMSE score that the independent sample. A cognitive domain was considered impaired when the corresponding Z-score fell below −1.5 SD. Patients were considered as having MCI if at least one cognitive domain was impaired, and as being CU when all z-scores were above the −1.5 SD threshold. The average of the Z-scores obtained in each of the four cognitive domains enables us to obtain the global cognitive Z-score.

In addition to others tests mentioned above, volunteers also completed the Digit-Symbol Substitution test (WAIS-IV, [39]) and the Logical Memory test (MEM-III, [40]), allowing to calculate the PACC plus a semantic fluency measure (PACC5) [41]. In the current study, the PACC5 was computed as the average of five z-scores calculated based on the MMSE [0–30] [42], the Logical Memory Delayed Recall Story A [0–25] (MEM-III [40],), the Digit-Symbol Substitution Test [0–135] [39], the sums of free and total recalls from the French-version of the FCSRT [0–96] [33] and the category fluency (animals, 2 min, [8]). These Z-scores were calculated by referring to the performance obtained by all CU individuals (n = 81). The PACC5 was not available in MCI patients (because Logical Memory and Digit-Symbol Substitution Test was not administered in this group).

2.4. MRI

Participants underwent three-dimensional (3D) T1-weighted MRI examination at Saint-Luc University Hospital (UCLouvain, Belgium) using a 3 T head scanner (Signa™ Premier; General Electric Company, USA) equipped with a 48-channel coil. 156 slices were acquired using the following parameters: TR = 2188 ms; TE = 2.9 ms; inversion time = 900 ms (MPRAGE), F = 8°; slice thickness = 1 mm; FOV = 256 × 256 mm^2, acquisition matrix = 256 × 256; acquired voxel size = 1 × 1 × 1 mm^3. A 3D T2-weighted sequence was also acquired using the same scanner.

Cortical parcellation of structural MRI data including rhinal cortex (RC, 13) parcellation were performed using FreeSurfer (version 7.2). WMH lesion load (mm^3) was extracted from T1-weighted MRI. WMH was identified by using spatial intensity gradients across tissue classes [43].

2.5. Tau [^{18}F]MK-6240 PET

[^{18}F]MK-6240 (Lantheus Inc.) is an investigational drug studied as a second-generation cerebral tau tangles imaging agent. Radiosynthesis was performed at KULeuven and shipped to our clinic. Ninety minutes after intravenous administration of [^{18}F]MK-6240 (target activity = 185 ±5 MBq), a 30-min dynamic acquisition was performed on a Philips Vereos digital PET-CT. Images were reconstructed using manufacturer's standard reconstruction algorithm (including attenuation, scatter, decay correction, and time-of-flight information). Point spread function (PSF)

Table 1
Demographic characteristics and biomarkers values.

	Aβ-CU (n = 56)	Aβ+CU (n = 25)	Aβ+MCI (n = 20)	p-val
Age – mean (SD)	68.00 (7.91)	72.83 (7.13) *	71.41 (8.08)	.016
Education years – mean (SD)	17.41 (2.82)	16.92 (3.18)	16.10 (4.60)	.315
Sex - % of women	53 %	54 %	50 %	.767
APOE ε4 carriers – n (%)	25 (45.5 %)	19 (76 %)	9 (45 %)	0.140
MMSE - mean (SD)	29.11 (0.88)	28.75 (0.89)	26.33 (1.88) *, **	<0.001
PACC5 - mean (SD)	0.11 (0.45)	−0.19 (0.49) *	–	.019
Global cognitive z-score - mean (SD)	0.17 (0.37)	−0.05 (0.42)	−1.25 (0.73) *, **	<0.001
Aβ method – CSF/PET (n)	1/55	2/23	10/10	–
Centiloid – mean (SD)	6.05 (7.07)	52.47 (28.27) *	71.39 (29.36) *	<0.001
Tau rhinal SUVr - mean (SD)	0.91 (0.12)	1.17 (0.34) *	1.81 (0.82) *	<0.001
WMH – mean (SD)	2423.80 (2204.99)	3877.0 (4213.43)	5139.92 (7324.62) *	.017

Legend: SD= standard deviation; CU = cognitively unimpaired; MCI = mild cognitive impairment; Aβ = amyloid-β; CSF = cerebrospinal fluid; SUVr = standard uptake value ratio; WMH = white-matter hyperintensities volume (mm^3); * = significantly different from Aβ- CU, ** = significantly different from Aβ+CU.

and 1 mm reslicing were also computed using the manufacturer's algorithm to obtain a better resolution recovery.

For all participants, tau-PET images were co-registrated with a 3D-T1 MRI using PetSurfer pipeline, a set of tools within FreeSurfer for end-to-end integrated MRI-PET analysis [44]. Standardized Uptake Value ratio (SUVr) values were extracted for the RC [14] using cerebellum gray matter as reference region. We selected the RC to test whether CMT performance could reflect tauopathy in the very first regions affected in AD.

2.6. Amyloid status

The Aβ status was determined either by lumbar puncture (n = 13) or Aβ PET-scan using [^{18}F]Flutemetamol (Vizamyl™, GE Healthcare, n = 72) or [^{11}C] Pittsburg compound B (PIB) (n = 26). The Aβ-PET burden was expressed in the Centiloid scale [5,45]. In cerebral spinal fluid (CSF), measurements of Aβ42 were conducted using Lumipulse automated assays. Participants were considered amyloid positive (Aβ+) when Centiloid>20 [46] or CSF Aβ42 < 437pg/ml [47].

2.7. Bioclinical classification

Based on cognitive and Aβ statuses, four bioclinical groups were defined as follows: [1] amyloid-negative cognitively unimpaired individuals (Aβ-CU, n = 56); [2] amyloid-positive cognitively unimpaired individuals (Aβ+CU, n = 25); [3] amyloid-positive MCI participants (Aβ+MCI, n = 20) and [4] amyloid-negative MCI participants (Aβ-MCI, n = 11). As this research focused on early AD diagnosis, Aβ-MCI participants were excluded from the analyses.

Participants were also classified according to the visual read of tau-PET images. Individuals were classified as Tau+ when the Braak stage was rated as being superior to 0 on visual read by the nuclearists (T.G and R.L.). Based on the cognitive and the tau-PET statuses, groups were also defined as follows: Tau-CU (n = 66), Tau+CU (n = 15), Tau-MCI (n = 2) and Tau+MCI (n = 18).

Among the 101 analyzed participants, one Aβ+MCI participant had no available tau-PET data because he moved during the acquisition and was therefore only included in the behavioral analyses.

2.8. Statistical analysis

All analyses were computed using SPSS 29.0.2.0 Statistics for Windows (Armonk, NY: IBM Corp) with two-tailed p-values reported. P<.05 was considered to be statistically significant. Data were tested for normality using Shapiro-Wilk test (data not shown). All analyses reported were corrected for the effect of age, sex and education.

CMT performance was compared across bioclinical groups using parametric or non-parametric ANOVA's, with post-hoc multiple comparisons tests adjusted using Bonferroni correction (n = 101). Second, linear mixed-effects regression was conducted with the bioclinical group as the between-subject factor and conceptual distance (close vs distant items) or the category-domain (living vs non-living items) as the within-subject factor (n = 101). Third, we realized multiple linear regression models to test whether tau burden in the RC predicted the CMT performance, first over the entire sample (n = 100) and then in CU participants only (Aβ-CU and Aβ+CU, n = 81). In addition to age, gender and education, these models were corrected for cognitive status and for the time between CMT and tau-PET scan. The Aβ burden (as measured by PET and expressed in Centiloid) and WMH were introduced as covariates in separate models. Subjects who only underwent a lumbar puncture were therefore excluded from this analysis (n = 87 for the entire sample and n = 78 for CU sub-analysis). Fourth, mixed-effect models were used to determine whether the effect of RC tau burden on CMT performance varied by conditions (n = 100). Fifth, we performed partial correlations between CMT performance and cognitive composite z-scores in the entire sample (adjusted for the effect of age, sex, education and time between these examinations, n = 101). These correlations were corrected for multiple comparisons using Bonferroni correction. Then, we ran a linear regression model with all cognitive z-scores included as predictors to assess their independent contribution to CMT performance (n = 101). Finally, we computed ROC curve analyses to compare the sensitivity and the specificity of the CMT compared with PACC5, in the discrimination of Aβ+CU (n = 56) from Aβ-CU (n = 25) and Tau+CU (n = 66) from Tau-CU (n = 15) and we calculated whether the difference in AUC between these tests was significant using De Long test.

3. Results

3.1. Characteristics of participants

The 101 participants included 56 Aβ-CU (55.5 %), 25 Aβ+CU (24.7 %) and 20 Aβ+MCI (19.8 %) individuals. Groups did not differ in education (p=.315) or sex (p=.767; see Table 1), but age was younger in Aβ-CU than Aβ+CU subjects (p=.017). MMSE and global cognitive composite scores were similar between Aβ+CU and Aβ-CU groups (p=.456 and p=.181, respectively), but PACC5 scores were worse in the Aβ+CU than in the Aβ-CU group (p=.019). As expected, global cognitive composite scores were worse in the Aβ+MCI than both CU groups (all p<.01). Centiloid values and RC tau burden were higher in the Aβ+CU compared to the Aβ-CU group (all p<.001), while Aβ+MCI patients exhibited higher centiloid values, WMH load, and RC tau burden than Aβ-CU subjects (all p<.05).

3.2. Group differences in CMT performance

Aβ+CU participants performed worse (higher TO) than Aβ-CU subjects over the entire task (p=.044, η^2p=.054), in matching (p=.048, η^2p=.052), and in non-living conditions (p=.035, η^2p=.057). Performance was similar between those two groups in non-match (p=.138,

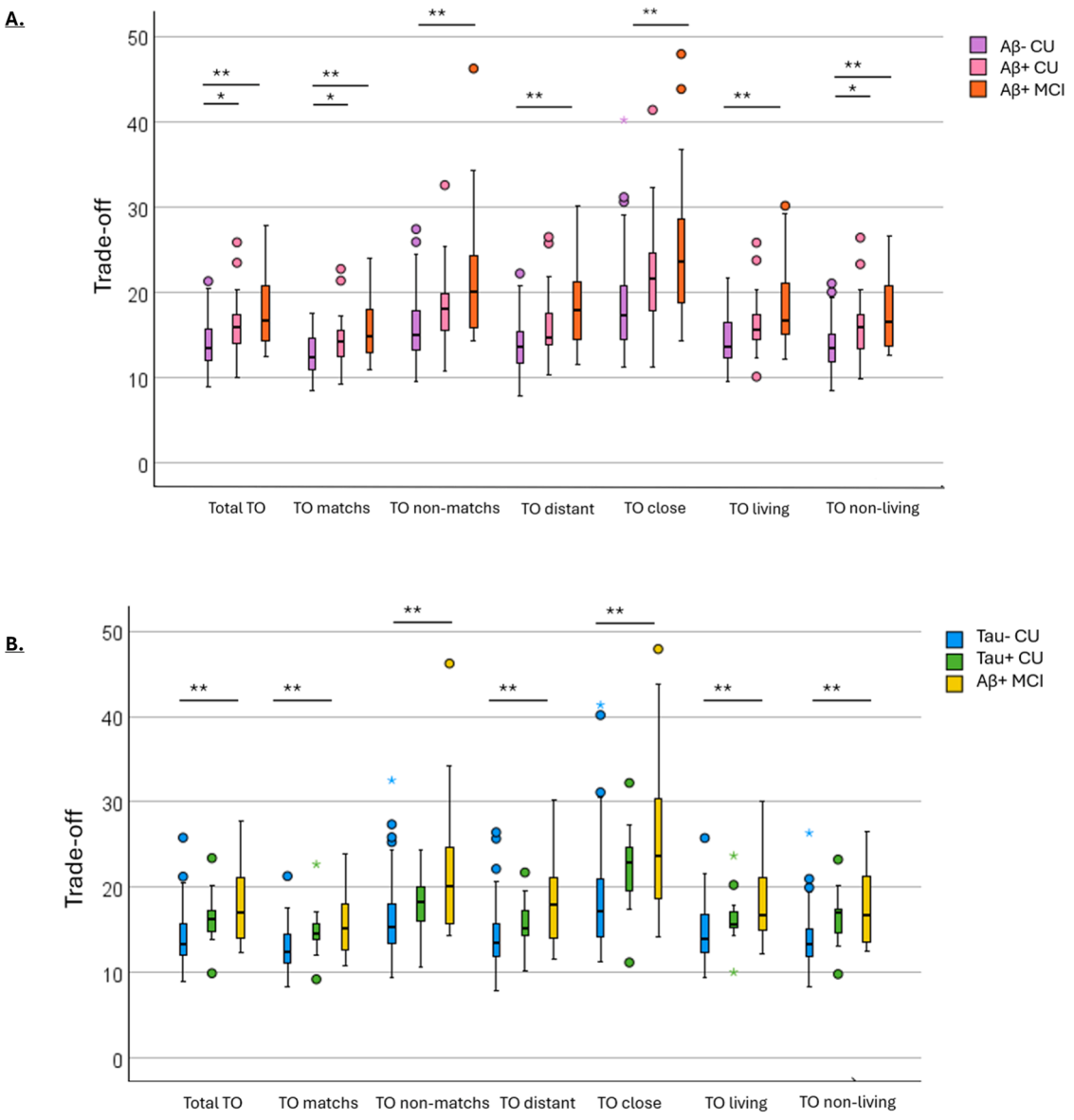


Fig. 2. Boxplots of CMT performance in each group according to condition.

Legend: A. Boxplots of CMT performance according to amyloid and cognitive status. B. Boxplots of CMT performance according to tau and cognitive status. In this analysis, we grouped Tau-MCI and Tau+MCI because of the small number of participants in the first subgroup ($n = 2$). All comparisons were corrected for the effect of age, sex and education.

TO= Trade-Off (higher score reflects poorer performance); Aβ = amyloid; CU = cognitively unimpaired participants; MCI = mild cognitive impaired; *: $p<.05$, **: $p<.01$.

η^2p=.025), distant (p=.066, η^2p=.024), close (p=.347, η^2p=.023) or living (p=.133, η^2p=.024) conditions. TO was worse in the Aβ+MCI compared to the Aβ-CU group in all conditions (all $p<.01$) but similar between the Aβ+MCI and Aβ+CU groups (all $p>.05$) (Fig. 2A).

After stratification by tau and cognitive statuses, performance did not differ between Tau+CU and MCI patients or between Tau-CU and Tau+CU in any CMT conditions (all $p>.05$). However, MCI patients performed worse than Tau-CU subjects in all conditions (all $p<.05$) (Fig. 2B). In this analysis, we combined Tau-MCI ($n = 2$) and Tau+MCI ($n = 18$) groups because of the small sample size of the first group. Excluding Tau-MCI subjects did not change the results.

No intergroup differences in performance were observed when considering the accuracy sensitivity to similarity score (all $p>.100$, Supplementary Material S1).

3.3. Distance and domain effect

To test the performance differences across the three groups according to Aβ and cognitive status, distance conditions (distant vs close items), and category domains (living vs non-living items), we performed a 3 (group) x 2 (distance) x 2 (domain) ANOVA. This analysis revealed a distance effect ($F(1,97)=59.59$, $p<.001$, $\eta^2p=.381$) driven by a worse TO for close items; a domain effect ($F(1,97)=23.97$, $p<.001$, $\eta^2p=.198$) highlighting a better performance for living items; as well as a group effect ($F(2,97)=7.71$, $p<.001$, $\eta^2p=.137$) with worse performance in the MCI group. The analyses also revealed an interaction between distance and group ($F(2,93)=4.74$, $p=.011$, $\eta^2p=.079$). Post-Hoc tests revealed a larger drop in performance in MCI patients compared to CU subjects for both distant and close items (all $p<.05$), but this difference was even more pronounced for close items ($B = -11.43$, $p < 0.001$, $\eta^2p=.141$ and $B = -8{,}09$, $p=.016$, $\eta^2p=.059$ for Aβ-CU and Aβ+CU, respectively) than

Table 2
Regression linear models explaining CMT performance.

	Trade-off			
	β (SE)	p-val (η^2p)	β (SE)	p-val (η^2p)
Model 1	*Entire sample (n = 100)*		*CU only (n = 81)*	
Intercept	3.00 (3.89)	.443 (0.006)	−0.85 (3.83)	.825 (0.001)
RC Tau (SUVr)	1.53 (0.72)	.037 (0.046)	3.76 (1.51)	.015 (0.078)
Age (y)	.14 (0.05)	.003 (0.091)	.13 (0.04)	.004 (0.108)
Education (y)	.05 (0.12)	.671 (0.002)	.14 (0.12)	.263 (0.017)
Sex	−0.67 (0.76)	.375 (0.009)	.23 (0.68)	.731 (0.002)
Delay between CMT and tau-PET	.00 (0.00)	.639 (0.002)	.00 (0.00)	.172 (0.025)
Model 2	*Entire sample (n = 100)*		*CU only (n = 81)*	
Intercept	9.19 (3.93)	.021 (0.057)	−0.85 (3.83)	.825 (0.001)
RC Tau (SUVr)	−1.35 (0.98)	.171 (0.021)	3.76 (1.51)	.015 (0.078)
Age (y)	.13 (0.04)	.004 (0.090)	.13 (0.04)	.004 (0.108)
Education (y)	.12 (0.11)	.271 (0.013)	.14 (0.12)	.263 (0.017)
Sex	−0.12 (0.72)	.869 (0.000)	.23 (0.68)	.731 (0.002)
Cognitive Status	−9.60 (2.63)	<0.001 (0.129)	–	–
RC Tau x Cognitive Status	4.94 (1.93)	.012 (0.068)	–	–
Delay between CMT and tau-PET	.00 (0.00)	.421 (0.007)	.00 (0.00)	.172 (0.025)
Model 3	*Entire sample (n = 87)*		*CU only (n = 78)*	
Intercept	12.82 (4.70)	.019 (0.072)	4.58 (3.98)	.235 (0.021)
RC Tau (SUVr)	−3.16 (1.54)	.511 (0.006)	1.42 (1.65)	.392 (0.011)
Age (y)	.054 (0.044)	.223 (0.020)	.061 (0.05)	.186 (0.026)
Education (y)	.122 (0.103)	.239 (0.018)	.15 (0.11)	.189 (0.026)
Sex	.022 (0.647)	.739 (0.001)	–	–
Cognitive Status	−7.32 (3.53)	.042 (0.054)	.02 (0.66)	.748 (0.002)
Aβ-PET (Centiloid)	.024 (0.015)	.119 (0.032)	.03 (0.02)	.057 (0.053)
WMH	.00 (0.00)	.002 (0.125)	.00 (0.00)	.003 (0.125)
RC Tau x Cognitive Status	4.78 (2.15)	.029 (0.062)	–	–
Delay between CMT and tau-PET	−0.01 (0.01)	.230 (0.019)	−0.01 (0.01)	.418 (0.010)

Legend: A. Regression linear model explaining CMT performance in the entire sample (models 1–3, left side) and in CU only (models 1–3, right side). WMH = white matter hyperintensities volume (mm^3); Aβ = amyloid-beta; CU= cognitively unimpaired participants; MCI= mild cognitively impaired; *B*= unstandardized beta; SE = standard error; p-val= *p*-value; η^2p = partial eta square.

for distant items ($B = -4{,}68$, $p < .001$, $\eta^2p = .191$ and $B = -2{,}27$, p=.046, $\eta^2p = .040$ for Aβ-CU and Aβ+CU, respectively). Finally, there were no interactions between group and domain, domain and distance, or between domain, distance, and group (all p>.170).

3.4. Association between CMT performance and rhinal tau burden

CMT performance was significantly associated with RC tau burden, in the model adjusted for age, sex, education and delay between CMT and tau-PET (Table 2, Model 1, left side). This relationship did not survive when including cognitive status as a covariate (Table 2, Model 2, left side). However, an interaction was observed between RC tau burden and cognitive status (Table 2, Model 2, left side): RC tau burden had a higher predictive value of the CMT TO in CU subjects ($B = 3.35$ p=.028, η^2p=.064) than in MCI participants (β=−0.91 p=.601, η^2p=.020). No interaction was found between RC tau and distance (F(1,94)=0.318, p=.574, η^2p=.003) or category-domain (F(1,94)=0.329, p=.568, η^2p=.003). There was no effect of the delay between CMT and tau-PET (B=−0.01 p=.169, η^2p=.020) on performance nor between CMT and *APOE* status (all p>.730). However, the accuracy sensitivity to similarity score was not explained by RC tau burden (B=−0.01 p=.758, η^2p=.001, **Supplementary Material S2, Model 1 and 2**).

3.5. Association between CMT performance and rhinal tau after adjusting for amyloid load and white matter hyperintensities

After adjusting for the effects of amyloid load and WMH, the association of RC tau burden with CMT performance did not remain significant (Table 2, **Model 3, left side,** n = 87). CMT TO was predicted by WMH (B=−0.000, p=.002, η^2p=.125), by the interaction between RC tau and cognitive status ($B = 4.78$, p=.029, η^2p=.062), and by cognitive status (B=−7.32, p=.042, η^2p=.054).

No interaction was observed between tau and Aβ (F(1,85)=0.492, p=.485, η^2p=.007) or between tau and WMH (F(1,85)=1.91, p=.172, η^2p=.025). However, we observed an interaction between Aβ and WHM (F(1,87)=4.44, p=.038, η^2p=.057). The effect of Aβ on CMT performance was stronger in participants with high WMH ($B = 0.073$, p=.019, η^2p=.314) than with low WMH ($B = 0.018$, p=.283, η^2p=.023) (Fig. 3).

When restricting the analysis to CU participants (Table 2**, Model 3, right side,** n = 78), CMT TO was predicted only by WMH ($B = 0.00$, p=.003, η^2p=.125) and marginally by Aβ load ($B = 0.03$, p=.057, η^2p=.053).

The accuracy sensitivity to similarity score was not explained by any biomarkers when considering the entire sample (Supplementary Material S2, Model 3).

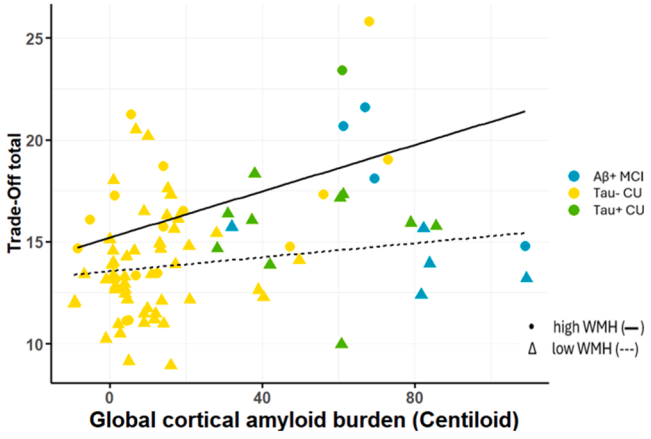


Fig. 3. Illustration of the interaction effect between amyloid load and white matter hyperintensities in the entire sample.
WMH = white matter hyperintensities volume (mm^3); Aβ = amyloid-beta; CU= cognitively unimpaired participants; MCI= mild cognitively impaired.

3.6. Association between CMT performance and cognitive z-scores in the entire sample

Partial correlations were computed between cognitive z-scores and CMT performance in each condition (**Supplementary Material S3**). After correction for multiple comparisons, almost all correlations with memory, language, and the executive z-scores were significant (all $p<.05$). We also observed a relation between close, non-living, and non-match items with the PACC5 as well as a correlation between the non-match items and visuo-constructive z-score (all $p<.05$).

The model including all cognitive composite scores as predictors highlighted that memory, executive, and language z-scores contributed independently to the total TO variance ($\beta=-0.58$, $p=.015$, $\eta^2p=.064$; $\beta=-1.12$, $p=.020$, $\eta^2p=.059$ and $\beta=-1.11$, $p=.039$, $\eta^2p=.047$, respectively).

3.7. ROC curves

To distinguish the Aβ+CU from the Aβ-CU group, CMT TO showed a marginally larger AUC compared to PACC5 (AUC=0.702, $p=.001$ and AUC =0.655, $p=.039$, respectively) (Fig. 4A). The DeLong test disclosed that the difference between these two AUCs was not significant ($p=.770$). To distinguish CU with a positive tau-PET visual read (Braak>0) from CU with a negative tau-PET (Braak 0), CMT TO (AUC =0.733, $p=.001$) was more sensitive than PACC5 (AUC=0.663, $p=.063$) (Fig. 4B), but the difference between these AUCs was not significant ($p=.460$).

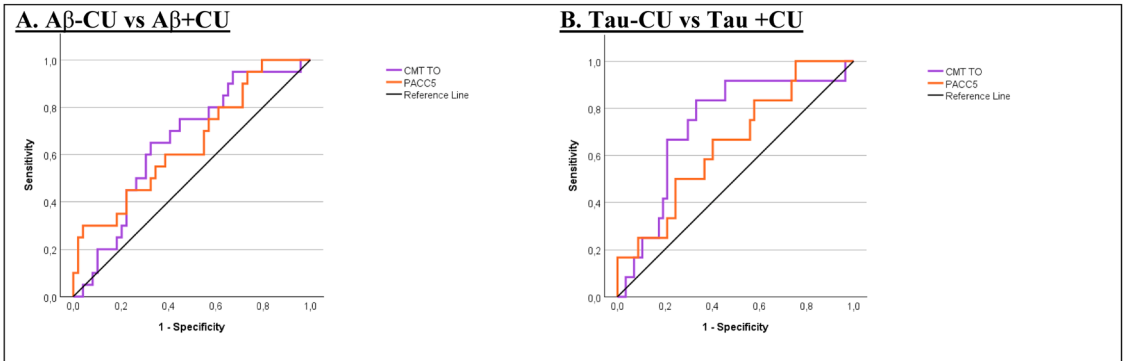
4. Discussion

Detecting the initial cognitive changes of preclinical AD is essential for early diagnosis, prevention, and clinical trial enrolment. The present study investigated whether the CMT, a new short cognitive task that rapidly evaluates the ability to discriminate conceptually confusable items, may identify subtle cognitive impairment starting from the preclinical stage of AD, and whether impaired CMT performance may be associated with AD-related lesions. We found lower CMT performance in Aβ+CU compared to Aβ-CU individuals. This decline was explained primarily by the presence of WMH. Moreover, CMT performance correlated with memory, executive and language cognitive composites scores, and facilitated the identification of CU individuals with elevated Aβ or tau-PET signals as well as than the PACC5 but with a much shorter administration time. Therefore, this test shows promise as a diagnostic tool for preclinical AD and may offer significant utility in the context of clinical trials.

Our results are consistent with those of previous studies that demonstrated reduced CMT performance in samples including patients with AD or PrC lesions [21,22]. Nevertheless, our results evidenced lower performance at the preclinical stage of AD, before deficits become detectable in the standard neuropsychological assessment. To the best of our knowledge, this is one of the first studies showing a difference between Aβ- and Aβ+CU subjects using a cognitive task requiring a very brief completion time (< 6 min) in a single testing session. The sensitivity of the CMT appears comparable to studies that have demonstrated difference between those groups using others remote cognitive tests [26, 27].

Moreover, our study showed that the CMT allows to predicts the tau-PET status in CU participants, a status that is all even more important given that, in the presence of high amyloid burden, it predicts a high risk of short-term (3–5 years) cognitive decline [6]. In an overlapping sample, we previously observed differences in perceptual discrimination performance between A- and *A+* as well as between T- and *T+* CU groups [48], supporting that fine-grained discrimination abilities are impaired as early as the preclinical stage, at both perceptual and conceptual levels. In this study, we highlighted associations between performance on these tasks and early tau protein deposition in the trans-entorhinal cortex. Assessing conceptual or perceptual discrimination abilities with a test of no more than 6 min duration seems a promising strategy for easy-to use, rapid, and cost-effective screening for preclinical AD pathology. Nevertheless, plasma biomarkers also hold promise as scalable screening tools [49], future studies should compare the individual and combined value of such cognitive measures and blood-based biomarkers to identify the individuals presenting a high risk of evolving to symptomatic AD.

Although we highlighted a group, distance, and domain effect in this task [21,22], we did not observe a performance difference between Aβ-CU and preclinical AD subjects in the conditions that were the most demanding in terms of conceptual discrimination (i.e. close and living conditions). We expected a performance difference under these conditions because those items are more difficult to distinguish conceptually as they share more co-occuring features (e.g., "has eyes", "has four leg", etc.) with less distinctive features, than distant or non-living concepts [32,50]. Given that the PrC is predominately involved in fine-grained discrimination of confusable items, and that this region is affected



Aβ-CU vs Aβ+CU

	AUC	Best threshold	Sn	Sp
CMT TO	**0.702**	**14.65**	**0.72**	**0.67**
PACC5	0.655	-0.56	0.69	0.96

Tau-CU vs Tau +CU

	AUC	Best threshold	Sn	Sp
CMT TO	**0.733**	**14.65**	**0.86**	**0.65**
PACC5	0.663	-0.25	0.55	0.76

Fig. 4. ROC Curves comparing performance to distinguish Aβ± or Tau± cognitively unimpaired individuals.
ROC curves data table evaluating the cognitive metrics to distinguish Aβ-CU vs Aβ+CU (left side) and Tau-CU vs Tau+CU (right side). Amyloid positivity was defined as a CL value>20 and Tau positivity was established on the basis of a Braak stage >0. The best AUC curves for each comparison are in bold. Legend: CU = cognitively unimpaired; Aβ = amyloid-β; CMT = Conceptual Matching Task; TO= Trade-Off; PACC5 = preclinical Alzheimer cognitive composite; AUC = area under the curve; Sn = sensitivity; Sp = specificity.

early in the course of AD, we expected lower performance in the close and living conditions in Aβ+CU compared to Aβ-CU individuals. Indeed, studies of patients at different stages of AD had shown the role of the PrC in distinguishing highly confusable compared to less confusable items [51,52]. A possible explanation is that the more difficult conditions were also challenging for low-amyloid participants, and that the difference in performance was therefore only noticeable in the easiest conditions (distant and non-living conditions). This hypothesis is supported by worse performance of Aβ-CU individuals in living and close conditions than in non-living and distant conditions, respectively. Although all conditions were matched in terms of word length and lexical frequency, further studies should investigate the impact of other psycholinguistic variables (e.g. familiarity, age of acquisition, density of orthographic neighbourhood) on our results.

Contrary to our hypothesis, CMT performance was more strongly related to WMH (and marginally linked to Aβ deposition when considering CU individuals only) than to RC tau burden. This result is surprising because the literature has convincingly shown that cognition is more closely linked to tau burden than to Aβ pathology [1,53] and that CMT is correlated with atrophy of the PrC [21,22], a site of early tau accumulation. Beyond differences in imaging methods (tau-PET vs MRI), Frick and colleagues [22] evaluated patients at more advanced disease stages, which may partially explain the discrepancy between their results and our findings. Because they studied patients with more advanced disease, PrC atrophy was probably more severe in their subjects than among our participants. On the other hand, we found that CMT performance correlated with several cognitive domains. These results underscore that this task is multi-determined and relies on widespread neural networks beyond the RC. It therefore makes sense that this task is more sensitive to biomarkers with a general impact on brain function, such as Aβ load or WMH than to regional tau burden. CMT performance correlated primarily with memory and executive composite scores. Executive functions are largely underpinned by the fronto-parietal regions [54]. However, the fronto-parietal networks are less likely to be affected by tauopthy than by Aβ and WMH during preclinical AD [55,56]. Previous studies have associated WMH with various executive tasks, and suggest that executive functioning may be impaired by WMH-induced disruption of neuronal transmission and intraneuronal connectivity [57,58].

We also highlighted an interaction between Aβ and WMH, which is consistent with the fact that WMH worsens cognitive impairment in AD [59–61]. Cognition, and episodic memory in particular, may be impaired by an interaction effect between these two biomarkers in CU individuals [61]. These findings underscore the importance of measuring WMH during the assessment of AD biomarkers.

Finally, we observed a slightly higher AUCs for the CMT than the PACC5 for distinguishing Aβ-CU from Aβ+CU individuals and Tau-CU from Tau+CU subjects (using the tau-PET visual read to define tau positivity: Braak stage >0), but these differences were not statistically significant. Of note, the PACC5 was designed initially to distinguish Aβ- from Aβ+CU individuals [41], but requires a longer administration time (30 vs. less than 6 min) and is less straightforward to implement remotely than the CMT. In addition, CMT performance appears to be more predictive of amyloid or tau status than PACC5 score, and correlates quite well with the different cognitive domains of the standard assessment.

5. Limitations

First, our sample was not representative of the general population, as it consisted primarily of white individuals with a high-level educational level and a high prevalence of *APOE ε4* carriage. Indeed, only 23 % of individuals in the general population carry at least one *ε4* allele [62] (versus 45 to 76 % across our groups, see Table 1). Further research should be conducted in more diverse populations, although we have shown that *APOE* has no impact on performance.

Second, Aβ-MCI participants were excluded from statistical analysis due to the small sample size. Therefore, this study did not determine the specificity of CMT performance to AD pathology.

Third, this study was conducted in French. Translating the items into other languages would be ineffective because word frequency and length effects vary between languages. In addition, it has already been widely demonstrated that cultural differences between people speaking the same language can also have an impact on performance [63]. This would require item adjustement for each language and culture, which would obviously complicate the adaptation process compared with a non-verbal task. Relatedly, some items were unknown to some participants, despite their high educational level. Assessing the appropriateness of the task for participants from more diverse backgrounds and a broader range of French-speaking populations would require further studies using a novel set of stimuli that considers socio-economic and cultural factors. However, the results were only based on known items allowing adjustments for part of these variations and the study was conducted in a quite homogeneous French-Speaking Belgian population

The fourth limitation was its cross-sectional design. Future work should determine how performance evolves over time in association with disease biomarkers, and test whether it is predictive of clinical progression.

6. Perspectives

While the CMT appears promising in identifying individuals with preclinical AD, further work is needed to validate this task as a screening tool (e.g., replication within larger preclinical samples, determination of the specificity of this task to screen for underlying AD pathology, standardization of task design and administration procedures, assessment of test-retest reliability, development of normative data, and longitudinal analysis). Future studies could compare the properties of this test with those of other rapid cognitive batteries and could also explore the benefits of combining this type of rapid test with biological measures such as plasma marker levels. Finally, our results were inconsistent with the hypothesis that we formulated based on previous studies that used this task. Indeed, Frick and colleagues [22] showed that CMT performance, in particular the accuracy sensitivity to similarity score, was related to RC pathology. However, we did not demonstrate a performance difference between Aβ-CU and Aβ+CU individuals when considering this score. Moreover, CMT performance was not correlated with RC tau burden, even before the correction for cognitive status or other biomarkers. Further work is therefore needed to better understand these discrepancies.

Declaration of generative AI and AI-assisted technologies in the writing process

I have not used any AI at all.

CRediT authorship contribution statement

Lara Huyghe: Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Yasmine Salman:** Writing – review & editing, Validation, Data curation. **Lise Colmant:** Writing – review & editing, Validation, Data curation. **Thomas Gérard:** Writing – review & editing, Validation, Data curation. **Vincent Malotaux:** Writing – review & editing, Validation, Data curation. **Gabriel Besson:** Writing – review & editing, Methodology, Conceptualization. **Emma Delhaye:** Writing – review & editing, Validation, Methodology, Conceptualization. **Christine Bastin:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Quentin Dessain:** Writing – review & editing, Methodology. **Laurence Dricot:** Writing – review & editing, Software, Resources. **Renaud Lhommel:** Writing – review & editing, Resources, Data

curation. **Adrian Ivanoiu:** Writing – review & editing, Supervision. **Lisa Quenon:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Data curation, Conceptualization. **Bernard Hanseeuw:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Bernard Hanseeuw reports equipment, drugs, or supplies was provided by Lantheus Medical Imaging Inc. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100332.

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