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Research Article

Entorhinal tau impairs short-term memory binding in preclinical Alzheimer's disease

Lara Huyghe[1], Lisa Quenon[1,2], Yasmine Salman[1], Lise Colmant[1,2], Thomas Gérard[1,4], Vincent Malotaux[1], Emilien Boyer[1,2], Laurence Dricot[1], Renaud Lhommel[1,4], John L. Woodard[1,5], Adrian Ivanoiu[1,2] and Bernard Hanseeuw[1,2,3,6]

[1]Institute of Neuroscience (IoNS), UCLouvain, Brussels, Belgium, [2]Neurology Department, Saint-Luc University Hospital, Brussels, Belgium, [3]Radiology Department, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, [4]Nuclear Medicine Department, Saint-Luc University Hospital, Brussels, Belgium, [5]Department of Psychology, Wayne State University, Detroit, MI, USA and [6]WELBIO department, WEL Research Institute, Wavre, Belgium

Abstract

Objective: The entorhinal cortex (EC) is the first cortical region affected by tau pathology in Alzheimer's disease (AD), but its functions remain unclear. The EC is thought to support memory binding, which can be tested using the Visual Short-Term Memory Binding Test (VSTMBT). We aimed to test whether VSTMBT performance can identify individuals with preclinical AD before noticeable episodic memory impairment and whether these performances are related to amyloid (Aβ) pathology and/or EC tau burden. **Methods:** Ninety-four participants underwent the VSTMBT (including a shape-only condition (SOC) and a shape-color binding condition (SCBC)), standard neuropsychological assessment including the Preclinical Alzheimer Cognitive Composite (PACC5), an Aβ status examination, a 3D-T1 MRI and a [^{18}F]-MK-6240 tau-PET scan. Participants were classified as follows: 54 Aβ-negative cognitively normal (Aβ − CN), 22 Aβ-positive CN (Aβ + CN, preclinical AD), and 18 Aβ + individuals with Mild Cognitive Impairment (Aβ + MCI, prodromal AD). **Results:** Aβ + CN individuals performed worse than Aβ-CN participants in the SCBC while the SOC only distinguished Aβ − CN from MCI participants. The SCBC performance was predicted by tau burden in the EC after adjusting for Aβ, white matter hypointensities, inferior temporal cortex (ITC) tau burden, age, sex, and education. The SCBC was more sensitive than the PACC5 in identifying CN individuals with a positive tau-PET scan. **Conclusion:** Impaired visual short-term memory binding performance was evident from the preclinical stage of sporadic AD and related to tau pathology in the EC, suggesting that SCBC performance could detect early tau pathology in the EC among CN individuals.

Keywords: Short-term memory binding; preclinical Alzheimer's disease; cognition; PACC; entorhinal cortex; tau

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Statement of Research Significance

Topic: Standard neuropsychological tests lack sensitivity in the early stages of Alzheimer's disease. In this study, we evaluated whether assessment of conjunctive binding abilities could reveal cognitive changes earlier than in standard assessment. Main findings: We demonstrated that impaired binding performance in visual short-term memory was evident as early as the preclinical stage of sporadic Alzheimer's disease and was linked to tau pathology in the entorhinal cortex. These results suggest that binding performance could detect early tau pathology in the entorhinal cortex in cognitively normal individuals. Study contribution: Assessment of this conjunctive binding abilities could enable diagnosis earlier than standard neuropsychological assessment.

Introduction

Alzheimer's disease (AD) is characterized by two proteinopathies acting synergistically in the brain: the amyloid (Aβ) and the tau pathologies (Hanseeuw et al., 2019; Nelson et al., 2012). These neuropathological changes accumulate slowly, years before the onset of cognitive symptoms, defining a silent asymptomatic or preclinical phase (Jack et al., 2013). Currently, preventive clinical trials administer anti-Aβ or anti-tau drugs during this window to halt the neurodegenerative processes before cognition starts declining (Rafii & Aisen, 2023). This approach necessitates screening older adults to identify asymptomatic individuals with the highest risk of rapid clinical progression. Previous studies have consistently demonstrated that cognitively normal (CN) individuals with high Aβ burden are at higher risk of future cognitive decline than CN

Corresponding author: Lara Huyghe; Email: lara.huyghe@uclouvain.be

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individuals with low Aβ levels (Donohue et al., 2017; Hanseeuw et al., 2021). However, not all CN individuals with elevated Aβ burden experience similar patterns of cognitive decline. A recent study demonstrated that CN individuals with both abnormal global Aβ deposition and tau burden in the medial temporal lobe (Aβ + Tau + MTL), as evidenced using positron emission tomography (PET) imaging, had a six-fold increased risk (risk = 50%) of short-term conversion (within 3–5 years) to symptomatic AD, compared to those CN individuals with only high Aβ burden (Aβ + Tau−, risk = 8%) (Ossenkoppele et al., 2022). Therefore, identifying Aβ + Tau + CN individuals could enrich clinical trials with persons at risk for rapid cognitive decline (Ossenkoppele et al., 2022). However, PET imaging techniques can hardly be used as a general screening tools due to their cost, invasiveness, and limited availability. Thus, cognitive tests are promising alternatives for this purpose (Parra et al., 2010) as they might be cost-effective, non-invasive, rapid, and widely accessible. Despite this potential, the cognitive endpoints that best reflect AD pathology during the preclinical phase are still unknown.

Standard cognitive measures, including episodic memory tests such as the Free and Cued Selective Reminding Test (FCSRT, Grober et al., 1988), were designed to distinguish Mild Cognitively Impaired (MCI) or dementia patients from CN individuals (Lemos et al., 2015). These metrics have proven effective in identifying MCI patients progressing to dementia (Grande et al., 2018; Grober et al., 2022). However, standard cognitive tests lack sensitivity to detect subtle cognitive changes during the preclinical stage of AD (Johnson et al., 2016; Parra et al., 2022; Rentz et al., 2013). To address this limitation, cognitive composite scores that aggregate standard measures, such as the Preclinical Alzheimer Cognitive Composite (PACC, Donohue et al., 2014), have been proposed to increase the sensitivity of these measures to detect early preclinical cognitive decline. However, cross-sectional studies involving CN individuals are inconsistent, and those that evidenced differences between Aβ+ and Aβ- individuals often show only small effect sizes (AUC between 0.580 and 0.630) (Papp et al., 2022). Furthermore, due to its multidomain properties, the PACC likely lacks the specificity to detect early tau aggregation, beyond the effects of amyloidosis at the preclinical stage (McKay et al., 2024). This issue is critical because tau pathology significantly impacts brain function and cognition (Hanseeuw et al., 2023; Ossenkoppele et al., 2016). Autopsies studied by Braak and Braak outlined the staging progression of tau pathology ranging from stage 0 to VI. Tau first accumulates in the transentorhinal cortex (tEC, comprising the medial portion of the perirhinal and anterolateral entorhinal cortices, alEC; Braak stage I) before extending to the MTL (Braak stage II) and subsequently to the rest of the temporal lobe (Braak stage III-IV) (Braak & Braak 1991). This typical spatial spreading of tau pathology has been primarily confirmed through tau-PET studies (Pascoal et al., 2021). There is a need to validate cognitive tasks that may engage the tEC (Bastin & Delhaye 2023) to identify who will progress to symptomatic AD more effectively. The tEC is involved in context-free memory functions, such as familiarity-based recognition (Parra et al., 2024). It is also necessary to create, store, and retrieve unique representations of objects, allowing one to distinguish between very similar entities by integrating all their characteristics (Bastin & Delhaye 2023; Bussey & Saksida 2002). This ability can be assessed by the Visual-Short Term Memory Binding Test (VSTMBT, Parra et al., 2010), which evaluates conjunctive binding skills by requiring the retention of integrated features (e.g., shapes and colors) within object representation in short-term memory. This ability enables us to integrate the different features that we perceive from an object (color, shape, size, texture, smell) into a unique and unified memory representation, allowing us to later recognize and differentiate these complete entities from similar items (e.g., such as when we memorize the car of a friend by integrating its size, shape, color, license plate, and brand into a unified memory representation). The VSTMBT has been shown to distinguish MCI (Cecchini et al., 2020) and patients with subjective cognitive impairment (SCI) (Koppara et al., 2015; Valdés Hernández et al., 2020) from CN individuals. Deficits in the VSTMBT were also observed in CN carriers of a presenilin 1 mutation leading to familial AD, compared with CN non-carriers (Parra et al., 2010; Parra et al., 2019). Furthermore, performance on this task correlated with the Aβ burden in this population (Norton et al., 2020) and in prodromal sporadic AD patients (Cecchini et al., 2021). Moreover, Parra and colleagues (2024) found that CN participants with binding difficulties had higher Aβ deposits in the lateral-occipital cortex, fusiform gyrus, and EC than those with a low binding cost. In addition, VSTMBT scores were shown to correlate with tEC atrophy (Valdés Hernández et al., 2020). While the VSTMBT appears promising for detecting cognitive correlates of early AD pathology, it has been chiefly used by the team that developed the test, and the sensitivity to identify individuals with preclinical AD individuals is not yet established. Moreover, the relationship between VTSMBT performance and EC tau burden (EC_{tau}) has rarely been investigated in preclinical AD.

In the current study, we investigated VSTMBT performance in a sample of CN individuals with both Aβ and tau-PET imaging. We also included a group of patients with prodromal AD (Aβ+ MCI) as a positive control group assessing individuals further along in the AD spectrum. Our primary objectives were to evaluate the associations of VSTMBT performance with (1) the Aβ status in CN individuals and (2) with tau aggregation in the MTL (EC) and the ITC. Additionally, we compared the sensitivity and specificity of the VSTMBT and the PACC5 for identifying CN individuals with abnormal Aβ or tau burden.

Methods

Participants

One hundred and three individuals (aged 52–86) participated in this study, including 76 cognitively normal (CN) individuals and 27 patients with MCI (Mini-Mental State Examination (MMSE) ≥23 (Ruchinskas & Curyto 2003)). MCI patients were recruited at the Memory Clinic of the Cliniques Universitaires Saint-Luc in Brussels, Belgium. CN volunteers were enlisted via other clinical 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 for carriers of the Apolipoprotein E ε4 allele (*APOE* ε4) to match the frequency of *APOE* ε4 carriership observed in patients. Recruitment and examinations were conducted between June 2019 and May 2024. Exclusion criteria were non-AD neurodegenerative pathologies, focal brain lesions, major depression or 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).

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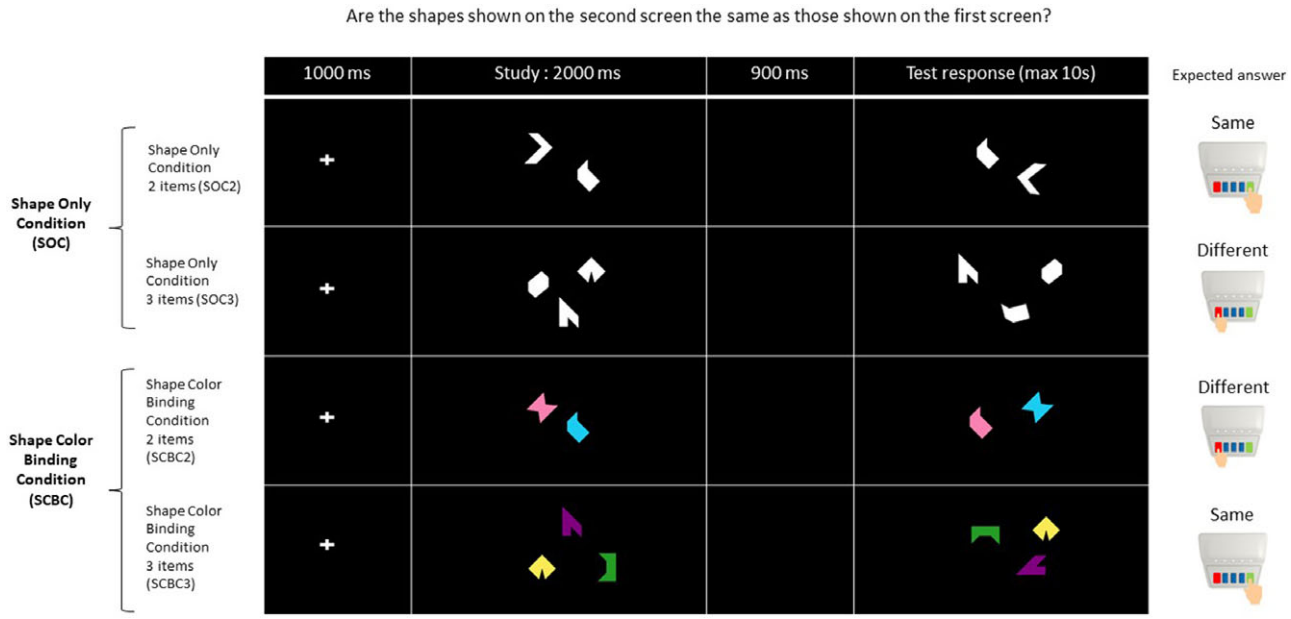

Figure 1. Illustration of the conditions of the Visual-Short-Term Memory Binding Test (VSTMBT). The VSTMBT had four conditions: two with two items; and two with three items. In shape only conditions (SOC), participants had to determine whether the shapes presented on the test display were identical to the ones given earlier on the study display. In the shape color binding conditions (SCBC), participants had to judge whether the shapes and their respective colors on the test display were the same as on the study display. The orientation and position of the shapes on the screen were irrelevant in each condition. To respond, participants used the E-Prime Chronos device. If they judged the sets of shapes as identical, they were asked to press the green button and the red one otherwise.

All participants underwent the VSTMBT (Parra et al., 2010), a standard neuropsychological assessment to determine their cognitive status, a 3D-T1 brain Magnetic Resonance Imaging (MRI), a [^{18}F]-MK-6240 Tau-PET scan, and an examination of the Aβ status either PET or cerebrospinal fluid (CSF).

Visual short-term memory binding test (VSTMBT)

Participants were assessed using a 16-inch laptop running an E-prime script (v.3.0, Psychological Software Tools, Pittsburgh, PA). Responses were collected using the E-prime Chronos device which records reaction times with millisecond accuracy.

The trial design for each condition of the VSTMBT is shown in Figure 1. The task was based on a change detection paradigm. Each trial began with a fixation cross that remained on the screen for 500 ms, followed by the study display presented for 2000ms. The study display presented two or three shapes the participant had to remember. After a 900 ms unfilled retention interval, the test display appeared, and participants had to determine whether the shapes presented in the test display were identical to those given in the study display, regardless of their position and orientation changes. Shapes were similar in 50% of the trials. Participants were instructed to press the green button on the E-prime Chronos device as fast as possible to indicate whether the shapes were identical and the red button if they were different.

There were four conditions, varying the number of shapes (two or three) and their color (white for the "Shape-Only condition" (SOC) or colored). The colored conditions required binding in memory of the shapes with their respective color ("Shape-Color Binding condition" (SCBC)), whereas the SOC assesses visual short-term memory for a single feature. The shapes presented within a trial were selected among a sample of eight non-verbalizable polygons combined with eight colors in the SCBC. The combination of shapes and colors was predefined and consistent across participants. No shape or color was repeated within a given array. All participants started with a two-item condition, followed by the same three-item condition. Half of the participants started with the SOC and the other half with the SCBC. Each condition included one practice trial followed by 16 test trials presented randomly. The accuracy score (AS) was calculated as the percentage of correct answers for each condition and the entire task (total AS). We also calculated the binding cost (Forno et al., 2023), which offers insights into the cognitive resources required to maintain integrated information (SCBC) compared to those needed for storing individual features (SOC). The results about binding cost can be found in supplementary materials (S2, S3, S4).

A perceptual binding task was used as a screening test to rule out perceptual binding deficits of color and shape (see Parra et al., 2010 for more details). The data for the perception condition are not presented, but all the participants in this study obtained a performance above the 80% cut-off (Forno et al., 2023).

Due to difficulties in correctly distinguishing certain contrasts observed during a pre-test phase with healthy older individuals ($n = 2$), the color of some shapes and the background (changed from gray to black) were adapted from the original task. For a full description of the modified colors, see figure S1. The instructions were also translated in French, and the response modality was adjusted from a keyboard to the Eprime Chronos device to enable millisecond reaction times to be recorded. Despite these modifications, the performance of our sample is broadly comparable to that obtained in other studies (see for instance (Forno et al., 2023; Parra et al., 2010; Valdés Hernández et al., 2020).

The VSTMBT was performed within a year relative to the tau-PET scan and the standard cognitive assessment.

Neuropsychological assessment

The neuropsychological testing evaluated four cognitive domains: (1) verbal episodic memory (FCSRT, French version (Van der Linden et al., 2004)), (2) language (Lexis Naming Test, Category

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and Letter Fluency Test for animals and letter' P,' (de Partz de Courtray et al., 2001)), (3) executive functions (Trail Making Test part A and B (Reitan, 1955) and Luria's Graphic Sequences (Weiner et al., 2011)), and (4) visuospatial functions (Clock Drawing Test (Rouleau et al., 1992) and Praxis part of the CERAD battery (Morris et al., 1988)). *Z*-scores were computed for each cognitive domain based on three measures within each domain and averaged to create a global cognitive *Z*-score (see (Ivanoiu et al., 2015) for more information about cognitive testing). A cognitive domain was considered impaired if the *Z*-score fell below −1.5 standard deviations of the mean of an independent sample composed of 32 CN individuals who remained cognitively stable over an eight-year period. Patients were considered to have MCI if at least one *z*-score was below this cut-off and as being CN otherwise.

CN Volunteers also completed the Digit-Symbol Coding test (WAIS-IV, (Wechlser, 2011)) and the Logical Memory Test (WMS-III, (Wechsler, 2001)), which are classically used to calculate the PACC5 (Papp et al., 2017). In the current study, the PACC5 was computed as the average of five *Z*-scores calculated based on the MMSE (0-30) (Folstein et al., 1975), the Logical Memory Delayed Recall Story *A* (0-25) (WMS-III, (Wechsler, 2001)), the Digit-Symbol Coding Test (0-135, (Wechlser, 2011)), the sum of free and total recall from the French-version of the FCSRT (0-96) (Van der Linden et al., 2004) and categorical fluency (animals, 2 minutes, (de Partz de Courtray et al., 2001)). The *Z*-scores were calculated by referring to the performance obtained by all the CN individuals ($n = 76$). The PACC5 was not available for MCI patients.

MRI

We acquired three-dimensional (3D) T1-weighted and T2-weighted sequences for each participant at the Saint-Luc University Hospital (UCLouvain, Belgium) using a 3T head scanner (Signa™ Premier, General Electric Company, USA). The T1 MRI was segmented with Freesurfer (version 7.2), using the T2 sequence to improve the segmentation. MRI enabled us to determine EC and ITC volume and quantify WMH. WMH lesion load (mm3) was extracted from T1-weighted MRIs. WMH were identified by using spatial intensity gradients across tissue classes (Fischl et al., 2004).

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-minute 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 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-registered with a 3D-T1 MRI using the PetSurfer pipeline, a set of tools within FreeSurfer for end-to-end integrated MRI-PET analysis (Greve et al., 2016). Standardized Uptake Value ratio (SUVr) values were extracted for all regions from the Desikan-Killiany Atlas (Desikan et al., 2006) using cerebellum gray matter as a reference region. The Braak 5 region was calculated following previously defined regions-of-interest (Schöll et al., 2016). The interest of including a Braak 5 ROI was to show that our participants did not have extensive tauopathy. Our regions of interest were the EC and the ITC. We selected the EC because our hypothesis was to test whether VSTMBT performance could reflect early tauopathy. The ITC was selected because it is a region adjacent to the EC that is affected later in the course of the disease. By including this region in our models, we were able to demonstrate the specificity of the EC on VSTMBT performance.

Individuals were classified as Tau+ when the Braak stage was rated superior to 0 on visual read by the nuclear medicine physician.

Amyloid status

The Aβ status was determined either by lumbar puncture ($n = 17$) or Aβ PET-scan with [^{18}F]-Flutemetamol (Vizamyl™, GE Healthcare, $n = 68$) or Pittsburgh compound B (PIB) ($n = 18$). The Aβ-PET burden was calculated and expressed in the Centiloid scale (Hanseeuw et al., 2021; Klunk et al., 2015). In CSF, measurements of Aβ42 were conducted using Lumipulse automated assays. Participants were considered amyloid positive (Aβ+) if at least one of the following criteria was met: Centiloid >20 (Amadoru et al., 2020) or CSF Aβ42 < 437pg/ml (Bayart et al., 2019). Fourteen participants with borderline Aβ42 CSF levels (between 437pg/ml and 650pg/ml) also underwent PIB-PET, which proved positive in all these participants.

Clinical classification

Based on the neuropsychological examination and the Aβ status, three clinical groups were defined as follows: (1) amyloid-negative cognitively normal individuals (Aβ − CN, $n = 54$); (2) amyloid-positive cognitively normal individuals (Aβ + CN, considered as having preclinical AD, $n = 22$); (3) amyloid-positive MCI participants (Aβ + MCI, considered as having prodromal AD, $n = 18$). As this research focused on AD early diagnosis, Aβ − MCI participants ($n = 9$) were excluded from the analyses.

Among the 94 participants, one Aβ + MCI participant had no available tau-PET data because he moved during the acquisition. Moreover, another Aβ + MCI individual only had data for the SOC because of color perception deficits.

Statistical analyses

The accuracy score (AS) for the SOC was calculated by averaging performance on the two-items SOC and the three-items SOC. Similarly, the AS score for the SCBC was computed by averaging performance on the two and three-items SCBC. The total AS score was obtained by averaging these four conditions.

All analyses were computed using SPSS 28.0.1.1 Statistics for Windows (Armonk, NY: IBM Corp.) with two-tailed *p*-values reported. Data were tested for normality using the Shapiro-Wilk test (data not shown).

To investigate whether VSTMBT conditions could distinguish Aβ+CN from Aβ−CN individuals, we first compared VSTMBT performance across clinical groups using parametric or non-parametric ANOVA's, with post hoc multiple comparisons tests adjusted using Bonferroni correction. Second, we performed multiple linear regression models to test whether EC_{tau} or ITC_{tau} explains VSTMBT performance in the entire sample, and specifically with CN participants (Aβ − CN and Aβ + CN). All regression models were adjusted for age, sex, and education and time between VSTMBT administration and tau-PET. We also

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Table 1. Demographic characteristics and biomarkers values

	Aβ-CN ($n = 54$)	Aβ+CN ($n = 22$)	Aβ+MCI ($n = 18$)	p-val
Age – Mean (SD)	68.11 (7.77)	72.50 (7.33)	70.61 (8.22)	.074
Education years – Mean (SD)	17.31 (2.83)	17.05 (3.27)	15.33 (4.35)	.086
Sex - % of women	55%	55%	50%	.919
APOE ε4 carriers – n (%)	25 (46.3%)	16 (72.7%)	9 (50%)	.140
MMSE - mean (SD)	29.15 (0.86)	28.68 (0.89)	26.33 (1.88) *, $	< .001
PACC5 - mean (SD)	−0.01 (0.49)	−0.36 (0.51) *	–	.020
Global cognitive z-score - mean (SD)	0.18 (0.37)	−0.05 (0.42)	−1.31 (0.69) *, $	< .001
Aβ method – CSF/PET/CSF + PET (n)	2/50/2	1/17/4	10/1/7	–
Tau entorhinal SUVr – mean (SD)	0.90 (0.17)	1.43 (0.64) *	2.15 (0.76) *	< .001
Tau inferior temporal SUVr - mean (SD)	0.94 (0.11)	1.10 (0.44)	2.01 (1.13) *, $	< .001
Tau in Braak 5 regions SUVr – mean (SD)	0.84 (0.09)	0.92 (0.10) *	1.33 (0.70) *	< .001

SD = Standard deviation; CN = cognitively normal; MCI = mild cognitive impairment; Aβ = amyloid-β; CSF = cerebrospinal fluid; SUVr = Standard Uptake Value ratio; * significantly different from Aβ-CN; $ significantly different from Aβ + CN. Seven MCI patients and six CN individuals with borderline amyloid CSF results underwent Aβ-PET. In these cases, the Aβ classification was based on PET data.

controlled for cognitive status to ensure that MCI patients did not drive the analysis. Additionally, amyloid burden (as measured by PET and expressed in Centiloids) and white matter hypointensities (WMH) were introduced as covariates in separate models. Participants who only underwent a lumbar puncture were therefore excluded from this analysis ($n = 10$). Third, mixed-effect models were used to determine whether the effect of regional tauopathy on VSTMBT performance varied by conditions. Linear mixed-effects regression was conducted with the clinical group as the between-subject factor and condition as the within-subject factor (SOC vs. SCBC and two items vs. three items) to evaluate if the associations between regional tau burden and performance varied according to the groups and conditions. Finally, we computed ROC curve analyses to compare the sensitivity and the specificity of the VSTMBT conditions, the FCSRT, and the PACC5 to discriminate Aβ+CN from Aβ-CN and Tau+CN from Tau-CN.

Results

Characteristics of participants

The 94 participants included 54 Aβ − CN (57%), 22 Aβ + CN (23%), and 18 Aβ + MCI (19%). Groups did not significantly differ in terms of age ($p = .074$, $\eta^2 = .054$), education ($p = .086$, $\eta^2 = .052$), sex ($p = .919$, $V = .068$) or percentage of APOE ε4 carriers (p = .140, see Table 1). Regarding cognitive measures, Aβ + CN had similar MMSE and global cognitive composite scores to those of Aβ − CN ($p = .223$, $\eta^2 = .04$ and $p = .122$, $\eta^2 = .04$, respectively), but Aβ + CN performed significantly worse than Aβ-CN on the PACC5 ($p = .020$, $\eta^2 = .082$). As expected, Aβ + MCI performed substantially worse on all cognitive measures than both CN groups (all $p < .05$). Aβ+ CN had a higher tau burden than Aβ − CN in the EC ($p < .001$, $\eta^2 = .19$), but not in the ITC ($p = .237$, $\eta^2 = .04$). Aβ + MCI had higher EC_{tau} and ITC_{tau} (both $p < .001$, $\eta^2 = .33$ and $\eta^2 = .24$, respectively), compared to Aβ-CN and higher ITC_{tau} than Aβ+CN ($p = .023$, $\eta^2 = .15$), but non-significantly higher EC_{tau} ($p = .169$, $\eta^2 = .08$). All groups had less tau-pet signal in Braak 5 regions than in EC and ITC.

Group differences in visual short-term memory binding performances

AS was comparable across the groups in the shape-only condition with two items (two-items SOC) ($p = .219$). In contrast, there was a group difference in the AS when three items were used (three-items SOC) or in the shape-color binding conditions (SCBC) with either two or three items (all p's < .001). Post-Hoc tests revealed that Aβ+CN participants performed worse than Aβ-CN individuals in the three-items SOC ($p = .028$), in the two-items SCBC ($p = .001$), and in the three-items SCBC ($p = .038$) conditions.

When averaging performance across the two- and three-items conditions, Aβ+CN individuals did not significantly differ from Aβ − CN participants in the SOC ($p = .114$), but they did in the SCBC ($p < .001$; see Figure 2). Aβ+MCI had a lower performance than Aβ-CN in both SOC ($p = .001$) and SCBC ($p < .001$). Averaging AS across all four conditions revealed a significant difference in total AS by Aβ status in CN ($p < 0.001$). Reaction times did not distinguish groups in any condition. Moreover, there was no effect on the order of the conditions presented to the participants (SOC versus SCBC) ($p = .822$).

Association between performance and demographics

The total AS was significantly predicted by age, with older age associated with lower performance ($\beta = -.297$, SE = .097, partial $\eta^2 = .094$, $p = .003$) but not by education nor sex ($\beta = .271$, SE = .241, partial $\eta^2 = .014$, $p = .265$ and $\beta = 1.498$, SE = 1.615, partial $\eta^2 = .010$, $p = .356$ respectively). An interaction was found between condition (SOC versus SCBC) and age ($F(1,91) = 5.917$, partial $\eta^2 = .061$, $p = .017$). Specifically, age was related to AS in SCBC ($\beta = -.454$, SE = .131, partial $\eta^2 = .117$, $p < .001$) but not in SOC ($\beta = -.154$, SE = .095, partial $\eta^2 = .028$, $p = .106$).

When only considering CN participants, the association between age and performance was not significantly different across conditions ($F(1,74) = 1.717$, partial $\eta^2 = .023$, $p = .194$).

Association between total accuracy score and regional tau burden

The total AS was significantly associated with EC_{tau} and ITC_{tau} across the entire sample ($\beta = -4.028$, SE = 1.082, partial $\eta^2 = .137$, $p < .001$ and $\beta = -3.366$, SE = 1.236, partial $\eta^2 = .079$, $p = .008$, respectively). The delay between VSTMBT administration and tau-PET has no effect on performance ($\beta = .001$, SE = .001, partial $\eta^2 = .001$, $p = .741$). An interaction effect was observed between

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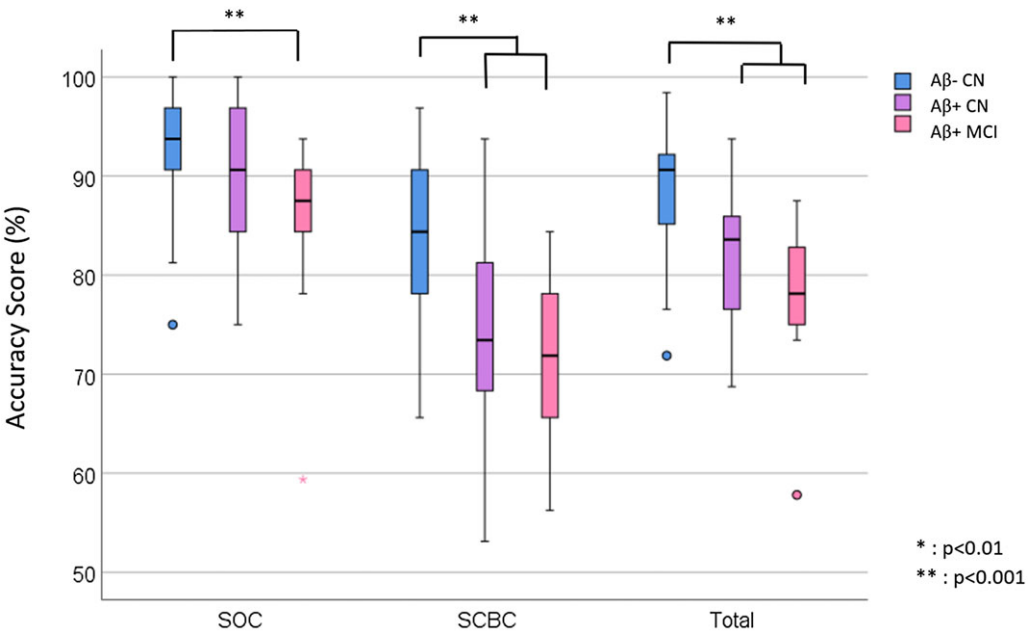

Figure 2. Boxplots of Visual-Short-Term Memory Binding Test performances in each group. SOC = shape-only condition; SCBC = shape-color binding condition; CN = cognitively normal; MCI = mild cognitive impairment; Aβ = amyloid-β. Each participant is therefore represented twice on this graph: once for his performance in the SOC, and once for his performance in the SCBC. Aβ + CN did not differ from Aβ – CN participants in SOC ($p = .114$), but they did in SCBC ($p < .001$) and in total score ($p < .001$), which is the average between the SOC and SCBC scores.

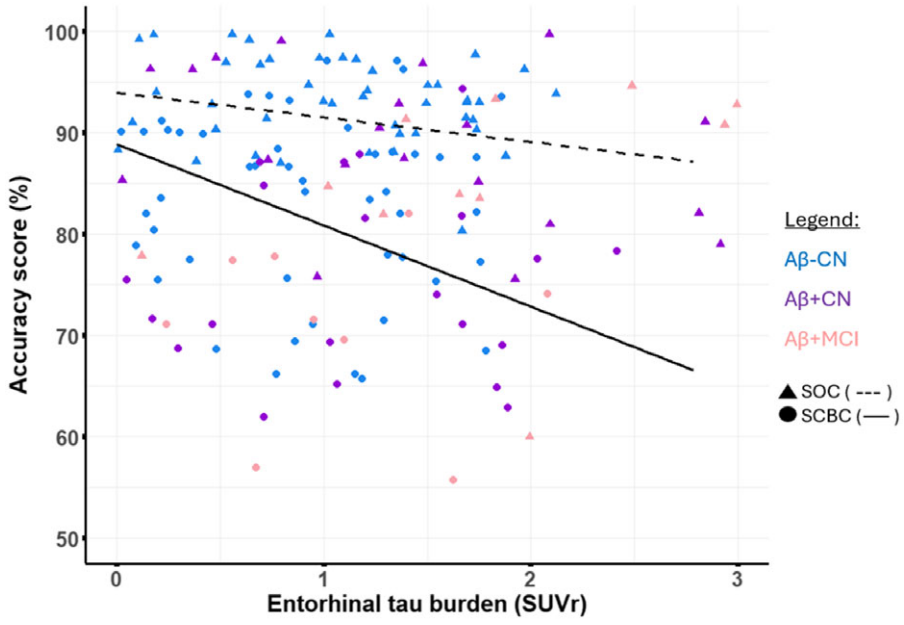

Figure 3. Association between entorhinal tau PET signal and accuracy score in each condition of the Visual-Short-Term Memory Binding Test. SOC = shape-only condition (dotted line); SCBC = shape-color binding condition (plain line); CN = cognitively normal; MCI = mild cognitive impairment; Aβ = amyloid-β. Each participant is represented twice on this graph: once for SOC, and once for SCBC performance. This graph highlights a stronger relationship between AS and entorhinal tau PET signal in the SCBC (plain line) than in the SOC (dotted line).

EC_{tau} and condition ($F(1,87) = 12.29$, partial $\eta^2 = .124$, $p < .001$, see Figure 3), indicating that the association between the EC_{tau} and the AS was more robust in the SCBC ($\beta = -6.594$, $SE = 1.457$, partial $\eta^2 = .191$, $p < .001$) than in the SOC ($\beta = -1.497$, $SE = 1.121$, partial $\eta^2 = .020$, $p = .185$). There was no interaction between EC_{tau} and the number of items ($F(1,86) = .005$, partial $\eta^2 = .000$, $p = .946$) nor between EC_{tau}, the condition (SOC versus SCBC), and the number of items ($F(1,87) = 1.021$, partial $\eta^2 = .012$, $p = .315$). Finally, no interaction was found between ITC_{tau} and any conditions (all p's $> .05$).

Association between binding performance and regional tau burden

We then focused on binding performance, as this condition was more strongly associated with EC_{tau} than the non-binding SOC subtask.

Over the entire sample, the SCBC AS was associated with EC_{tau} and ITC_{tau} ($\beta = -6.594$, $SE = 1.457$, partial $\eta^2 = .191$, $p < .001$ and $\beta = -4.313$, $SE = 1.731$, partial $\eta^2 = .067$, $p = .015$ respectively). While EC_{tau} remained a significant predictor after adjusting for cognitive status, ITC_{tau} did not (Table 2, model 1), suggesting that MCI participants drove the effect of ITC_{tau} on binding

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performance. In contrast, there was no interaction between EC_{tau} and clinical group ($F(2,92) = 1.464$, partial $\eta^2 = .034$, $p = .237$), indicating that a specific group did not drive the association between tau and binding performance.

When analyzing CN only, EC_{tau} was associated with SCBC AS ($\beta = -10.561$, SE = 2.54, partial $\eta^2 = .198$, $p < .001$), while the ITC_{tau} was not ($\beta = -9.542$, SE = 5.199, partial $\eta^2 = .041$, $p = .071$; Table 2, model 3).

Association between binding performance and entorhinal tau after adjusting for amyloid load and white matter hypointensities

EC_{tau}, amyloid PET signal and WMH were independently associated with SCBC AS when included in a model predicting binding performance in the entire sample (Table 2, model 2). In this model, the EC_{tau} explained the highest percentage of variance. Similar results were observed when restricting the analysis to CN participants (Table 2, model 4). In this subgroup, EC_{tau} only explained more than two times as much variance of binding performance (17%) compared to amyloid or WMH (7.8% and 8.2%, respectively). Similar results were obtained when considering two- or three-items SCBC, with slightly smaller effect sizes for EC_{tau} in the three items SCBC, when considering the entire sample ($\beta = -7.089$, SE = 2.612, partial $\eta^2 = .095$, $p = .008$ and $\beta = -8.377$, SE = 5.129, partial $\eta^2 = .050$, $p = .059$, respectively) or CN only ($\beta = -3.396$, SE = 4.479, partial $\eta^2 = .116$, $p = .005$ and $\beta = -3.10$, SE = 5.081, partial $\eta^2 = .107$, $p = .007$, respectively).

EC_{tau} burden remains significant after adjusting for the effect of ITC_{tau} in the entire sample and in CN participants ($\beta = -8.857$, SE = 2.778, $\eta^2 = .125$, $p = .002$ and $\beta = -11.022$, SE = 2.950, $\eta^2 = .181$, $p < .001$, respectively).

Association between non-binding performance and regional tau burden

Neither EC_{tau} nor ITC_{tau} was associated with SOC performance in either model (Table 2, right panel). Non-binding (SOC) performance was thus only influenced by the cognitive status in Model 1 and age in Model 3 in CN participants.

ROC curves

We finally aimed to evaluate which measure among the FCSRT, the PACC5, and VSTMBT performance best distinguished Aβ+MCI from CN (Aβ + and Aβ−), Aβ + CN from Aβ− CN, and Tau + CN ($n = 12$) from Tau − CN ($n = 64$). As a reminder, the PACC5 was not available for MCI participants. For distinguishing Aβ+MCI individuals from CN participants (both Aβ+ and Aβ−), the FCSRT (AUC = 0.947, $p < .001$, best threshold = −1.28 *Z*-score, Sensitivity (Sn) = .76, Specificity (Sp) = .98) showed the greatest AUC, surpassing the SCBC (AUC = 0.772, $p < 0.001$, best threshold = 82.8%, Sn = .94, Sp = .49), which is consistent with the use of this test to highlight episodic memory impairment, the more frequent deficit observed in symptomatic AD patients.

To distinguish Aβ + CN from Aβ − CN, the highest AUC was found for the AS in the VSTMBT two-items SCBC (AUC = 0.773, $p < .001$, best threshold = 90.5%, Sn = .77, Sp = .65; Figure 4a). In contrast, the PACC5, with a threshold of -0.155 *Z*-score, had a lower AUC (AUC = 0.697, $p = .007$, Sn = .72, Sp = .68).

To distinguish CN with a positive tau-PET visual read (Braak >0) from CN with a negative tau-PET (Braak 0), the AS in the two-items SCBC was the most sensitive measure (AUC = 0.841, $p = <.001$, best threshold = 80%, Sn = .92, Sp = .61). In contrast, all other metrics, including PACC5 had lower AUC (AUC = .654, $p = .020$, best threshold = −.33 *Z*-score, Sn = .61, Sp = .73; Figure 4b).

Discussion

Detecting early changes in cognitive performances in individuals with preclinical AD is essential for early diagnosis, prevention and clinical trials. The present study investigated whether VSTMBT could identify early AD, including Aβ pathology and EC_{tau}. We found that Aβ + CN individuals had lower VSTMBT SCBC performance than Aβ− CN and that binding performance was associated with EC_{tau}. Moreover, binding performance distinguished CN individuals with Aβ or tau better than the PACC5.

Our observations are consistent with previous studies demonstrating reduced binding performance in individuals with autosomal-dominant AD mutations (E280A-PSEN1) (Parra et al., 2010; 2019), and in sporadic SCI and MCI patients (Cecchini et al., 2020, 2021, 2023; Koppara et al., 2015; Valdés Hernández et al., 2020). Thanks to our large dataset of well-characterized CN individuals, our study adds to these previous findings by showing a decline in SCBC performance during the preclinical stage of sporadic AD, where most cognitive tests remain in the normal range. Our study highlights the superiority of SCBC over SOC (i.e., binding of multiple features over single-feature memory) to distinguish preclinical AD from Aβ-CN. In line with Koppara and colleagues' findings in SCI participants (2015), the SOC condition lacks the sensitivity to differentiate preclinical AD from CN individuals. As our results showed that this condition is less sensitive than the SCBC alone, it seems clinically unnecessary to administer the SOC. This condition mainly served in this work as a comparison for SCBC and to calculate the binding cost, which did not demonstrate increased sensitivity compared to the SCBC alone (for more details see supplementary S2, S3, S4).

Second, we observed that the EC_{tau} was associated with VSTMBT SCBC performance, but not in the SOC. Only one study has previously investigated the link between VSTMBT performance and regional tau deposits in familial AD (Norton et al., 2020). Unlike our findings, their results indicated a stronger association between EC_{tau} and performance in SOC than in SCBC. This discrepancy could be due to differences in the studied populations, the task conditions, and the tau-PET radiotracer used. Norton and colleagues included CN participants who were significantly younger, less educated, and had familial AD, which is more frequently associated with an atypical distribution of tau pathology (with more extensive tau burden in the parietal lobe and relatively lower tau burden in the MTL (Gordon et al., 2019)). Most importantly, their subjects showed comparable tauopathy between the EC and ITC, suggesting that their participants already had more advanced tauopathy than our sample. This argument, combined with the fact that they only used the most challenging condition (3 items), leads us to believe that the SCBC was already too complex, and that SOC performance led to fewer ceiling effects than in our study. Finally, Norton and colleagues used [^{18}F]-Flortaucipir whereas we used [^{18}F]-MK-6240 as a tau-PET radiotracer, which could explain the differences in our results as [^{18}F]-MK-6240 has a more extensive dynamic range in SUVr, improving early EC_{tau} detection (Gogola et al., 2022).

EC_{tau} better explained binding performance than Aβ, WMH, or age. Previous studies have shown that participants with more significant difficulties in the SCBC compared to the SOC ("high

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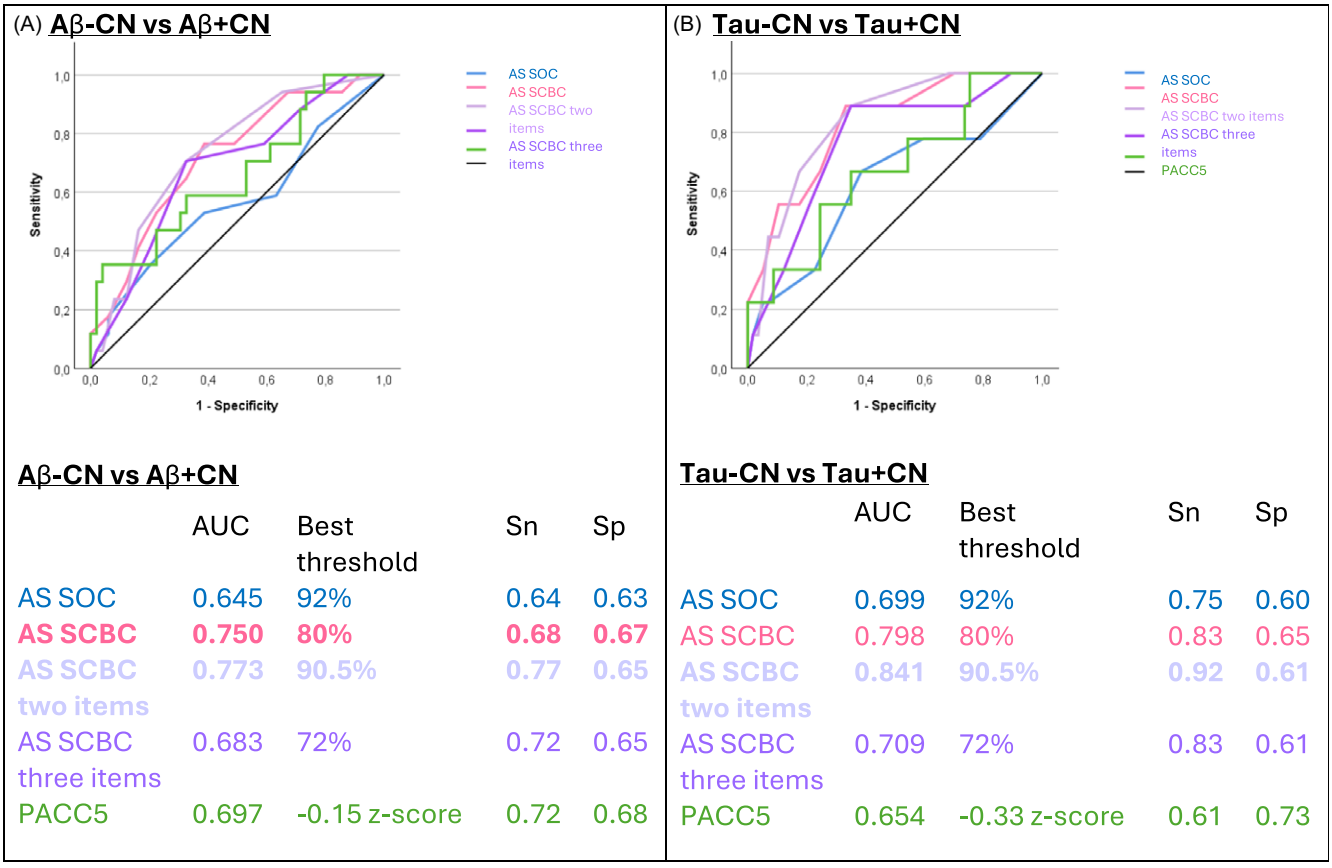
Table 2. Multiple regression models predicting the accuracy score in the shape-color binding condition and in shape-only condition

	Shape-Color Binding Condition				Shape-Only Condition			
	Entorhinal Cortex Tau		Inferior Temporal Cortex Tau		Entorhinal Cortex Tau		Inferior Temporal Cortex Tau	
	β (SE)	p-val (η^2p)	β (SE)	p-val (η^2p)	β (SE)	p-val (η^2p)	β (SE)	p-val (η^2p)
Entire sample								
Model 1 (n = 91) (R^2)		< .001(.310)		< .001 (.243)		.013 (.181)		.014 (.182)
Intercept	102.974 (11.649)	< .001 (.531)	98.721 (12.294)	< .001 (.493)	87.243 (8.664)	< .001 (.602)	88.914 (8.749)	< .001 (.607)
Tau (SUVr)	−5.002 (1.779)	.006 (.085)	−.723 (2.223)	.776 (.001)	.271 (1.33)	.839 (.000)	−1.197 (1.557)	.444 (.007)
Age (y)	−.289 (.130)	.028 (.055)	−.359 (.134)	.009 (.078)	−.099 (.097)	.312 (.012)	−.086 (.096)	.375 (.009)
Education (y)	−.111 (.311)	.721 (.002)	−.094 (.329)	.776 (.001)	.178 (.233)	.446 (.007)	.185 (.234)	.432 (.007)
Sex	.304 (4.664)	.629 (.003)	−.255 (5.238)	.732 (.001)	3.629 (3.392)	.352 (.010)	4.813 (3.584)	.236 (.016)
Cognitive Status	3.799 (3.965)	.132 (.027)	7.834 (4.097)	.012 (.072)	7.447 (2.847)	.017 (.065)	6.286 (2.873)	.130 (.027)
Delay VSTMBT-PET	−.001 (.311)	.856 (.000)	− 001 (.001)	.675 (.002)	.001 (.001)	.147 (.024)	.001 (.001)	.178 (.021)
Model 2(n = 81) (R^2)		< .001 (.467)		< .001 (.406)		.016 (.242)		.024 (.247)
Intercept	109.368 (12.349)	< .001 (.574)	105.149 (13.692)	< .001 (.507)	89.135 (10.235)	< .001 (.586)	92.012 (10.719)	< .001 (.575)
Tau (SUVr)	−6.455 (2.197)	.004 (.110)	−2.235 (3.028)	.463 (.008)	.263 (1.821)	.885 (.000)	−1.526 (2.370)	.522 (.006)
Age (y)	−.103 (.142)	.473 (.007)	−.171 (.149)	.256 (.018)	−.008 (.118)	.945 (.000)	−.011 (.117)	.922 (.000)
Education (y)	−.377 (.320)	.244 (.019)	−.273 (.337)	.420 (.009)	.065 (.266)	.806 (.001)	.069 (.264)	.794 (.001)
Sex	3.682 (7.225)	.471 (.007)	2.917 (7.761)	.526 (.006)	4.387 (5.988)	.595 (.004)	5.267 (6.075)	.509 (.006)
Cognitive Status	−3.893 (4.457)	.328 (.014)	−1.350 (4.850)	.767 (.001)	4.83 (3.694)	.593 (.004)	3.751 (3.797)	.880 (.000)
Aβ-PET (Centiloid)	−.127 (.051)	.015 (.081)	−.178 (.052)	.001 (.143)	−.082 (.042)	.058 (.050)	−.071(.041)	.087 (.041)
WM Hypointensities	−.001 (.00)	.023 (.071)	−.001 (.00)	.090 (.040)	.00 (0.00)	.255 (.018)	.00 (0.00)	.259 (.018)
Delay VSTMBT-PET	−0.001 (.001)	.623 (.003)	−.001 (.001)	.697 (.002)	.001 (.001)	.309 (.015)	.001 (.001)	.377 (.011)
CN only								
Model 3 (n = 73) (R^2)		< .001 (.278)		.055 (.141)		.107 (.119)		.047 (.145)
Intercept	116.508 (12.251)	< .001 (.578)	116.033 (14.344)	< .001 (.497)	109.254 (8.751)	< .001 (.699)	114.198 (9.253)	< .001 (.693)
Tau (SUVr)	−10.561 (2.54)	< .001 (.198)	−9.542 (5.199)	.071 (.046)	−2.349 (1.814)	.200 (.023)	−6.594 (3.554)	.053 (.053)
Age (y)	−.207 (.138)	.136 (.031)	−.272 (.149)	.073 (.045)	−.183 (.098)	.067 (.047)	−.177 (.096)	.071 (.046)
Education (y)	−.612 (.371)	.103 (.037)	−.440 (.410)	.287 (.016)	−.116 (.265)	.662 (.003)	−.185 (.264)	.488 (.007)
Sex	1.392 (2.130)	.516 (.006)	1.746 (2.323)	.455 (.008)	−.609 (1.521)	.690 (.002)	−.688 (1.499)	.648 (.003)
Delay VSTMBT-PET	−.001 (.001)	.742 (.002)	−.001 (.001)	.947 (.000)	.001 (.001)	.549 (.005)	.001 (.001)	.773 (.001)
Model 4 (n = 71) (R^2)		< .001 (.438)		< .001 (.327)		.026 (.213)		.024 (.215)
Intercept	109.818 (11.378)	< .001 (.605)	107.002 (13.868)	< .001 (.495)	103.816 (8.305)	< .001 (.714)	106.128 (9.241)	< .001 (.677)
Tau (SUVr)	−9.314 (2.557)	< .001 (.172)	−4.220 (5.496)	.445 (.009)	−1.115 (1.866)	.552 (.006)	−2.726 (3.662)	.459 (.009)
Age (y)	−.044 (.145)	.764 (.001)	−.154 (.155)	.326 (.015)	−.061 (.106)	.564 (.005)	−.072 (.104)	.490 (.007)
Education (y)	−.648 (.341)	.062 (.053)	−.392 (.373)	.298 (.017)	−.179 (.249)	.474 (.008)	−.189 (.149)	.450 (.009)
Sex	1.432 (2.014)	.480 (.008)	2.249 (2.189)	.308 (.016)	−1.410 (1.470)	.341 (.014)	−1.357 (1.459)	.356 (.013)
Aβ-PET (Centiloid)	−.122 (.052)	.023 (.078)	−.182 (.057)	.002 (.138)	−.079 (.038)	.043 (.063)	−.077 (.038)	.048 (.060)
WM Hypointensities	−.001 (.000)	.016 (.088)	−.001 (.00)	.308 (.016)	.00 (.00)	.220 (.023)	.00 (.00)	.264 (.019)
Delay VSTMBT-PET	−.001 (.001)	.354 (.013)	−.001 (.001)	.501 (.007)	.001 (.001)	.614 (.004)	.001 (.001)	.726 (.002)

Models 3 and 4 only present the results in CN participants (Aβ-CN and Aβ+CN). Models 2 and 4 are adjusted for amyloid-PET. In CN individuals, the EC_{tau} remains associated with binding (SCBC score) even after adjusting for amyloid burden. The EC_{tau} and ITC_{tau} did not contribute to explaining performance in SOC.



Aβ-CN vs Aβ+CN

	AUC	Best threshold	Sn	Sp
AS SOC	0.645	92%	0.64	0.63
AS SCBC	**0.750**	**80%**	**0.68**	**0.67**
AS SCBC two items	0.773	90.5%	0.77	0.65
AS SCBC three items	0.683	72%	0.72	0.65
PACC5	0.697	-0.15 z-score	0.72	0.68

Tau-CN vs Tau+CN

	AUC	Best threshold	Sn	Sp
AS SOC	0.699	92%	0.75	0.60
AS SCBC	0.798	80%	0.83	0.65
AS SCBC two items	0.841	90.5%	0.92	0.61
AS SCBC three items	0.709	72%	0.83	0.61
PACC5	0.654	-0.33 z-score	0.61	0.73

Figure 4. ROC curves comparing the different tests in cognitively normal individuals. CN = cognitively normal; MCI = mild cognitive impairment; Aβ = amyloid-β; AS = accuracy score; SOC = shape only condition; SCBC = shape-color binding condition; PACC5 = Preclinical Alzheimer Cognitive Composite; AUC = area under the curve; Sn = sensitivity; Sp = specificity. ROC curves data table evaluating the cognitive metrics to distinguish Aβ − CN vs Aβ + CN (left side) and tau − CN vs tau + CN (right side). The presence of amyloid is established based on the CL >20 threshold, and the presence of tau is established by a Braak stage >0. The best AUC curve for each comparison is in bold.

binding cost") were more likely to have Aβ pathology (Parra et al., 2024) and/or WMH (Parra et al., 2015). This finding suggests that Aβ deposits and/or WMH might impair binding capacities, although their study did not test. Our analyses revealed that EC_{tau} accounted for more variance in SCBC than Aβ or WMH. Moreover, EC_{tau} remained significant after adjusting for ITC_{tau}, suggesting that SCBC is specifically sensitive to the EC_{tau} and not to more widespread tauopathy, making it possible to diagnose the disease at the preclinical stage as soon as tauopathy appears in this region.

Consistent with our correlational analyses, we observed that the SCBC (and especially the two-items SCBC) had the highest AUC for distinguishing Tau + CN from Tau − CN, using the tau-PET visual read to define tau positivity (Braak stage >0). This result is noteworthy as Aβ + Tau + CN individuals are six times more likely to develop cognitive impairment within five years than Aβ + Tau- individuals (Ossenkoppele et al., 2022). In addition, VSTMBT SCBC, and especially the two-items condition had a higher AUC and sensitivity than PACC5 to distinguish Aβ+ from Aβ− CN individuals. Of note, the PACC5 was designed initially to separate Aβ− from Aβ+ CN individuals but requires a more extended administration time than the VSTMBT SCBC (30 vs. less than 5 minutes). Moreover, the VSTMBT is more straightforward to implement remotely than the PACC5, as recently demonstrated in a VSTMBT self-administration study (Butler et al., 2024).

Limitations

Although the shapes were selected to be infrequent and non-verbalizable polygons (to minimize the impact of verbal working memory on visual working memory), some participants reported relying on verbalization by assigning a label to specific shapes. Verbalization has been shown to facilitate memory (Nedergaard et al., 2023) as well as problem-solving ability (Baldo et al., 2005). We did not control for the strategies used, which may have led to overestimating participants' performance using specific strategies.

Second, Aβ-MCI participants were excluded due to the small sample size. Thus, this study did not determine whether SCBC low performance is specific to AD. However, previous research has already demonstrated that performance in a color-object binding task, relatively similar to the VSTMBT, was not affected in other pathologies such as frontotemporal dementia, vascular dementia, Lewy body dementia and dementia associated with Parkinson's disease (Della Sala et al., 2012; Kozlova et al., 2021).

Third, our sample is not representative of the general population, as it mainly consisted of white individuals with a high level of education and APOE ε4 carriers were over-represented compared to the general population. Indeed, in the general population, only 23% of individuals carry at least one ε4 allele (Régy et al., 2024)(versus 46 to 72% in our sample, see table 1). Further research should be conducted in more diverse populations.

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Fourth, the colors currently used in this test make it unsuitable for colorblind patients. However, the task could easily be adapted with a color palette tailored to those with color vision deficiencies.

Fifth, participants were asked to respond by pressing a green or red button to record their answers and response time. Still, this procedure led to some errors (with some participants spontaneously reporting they aimed to press the other button during the task). We could not take the oral responses into account. However, we do not believe this limitation significantly impacts our findings, as it comprised less than 2% of the responses. Moreover, it has been shown that there was no difference in performance in this task compared to the same task with oral responses (Cecchini et al., 2023).

Finally, despite this task appearing robust across various administration procedures (for instance self-administration (Butler et al., 2024), flash cards (Della Sala et al., 2018) or computer tablets (Weir et al., 2014)) we still lack standardized cut-offs enabling to implement this task in clinical practice. Our study suggests the use of a 90.5% threshold for the two-items SCBC to detect both amyloid and tau pathologies in a CN population. Moreover, all the studies that have assessed the value of this task so far, including the current one, are cross-sectional. Future work should investigate how performance evolves over time, in association with biomarkers, and test whether it is predictive of future patient outcomes.

Perspectives

While the VSTMBT appears promising in identifying individuals at the preclinical stage of AD, further studies are needed to support the validation of this task as a screening tool (e.g., replication within larger preclinical samples, determining the specificity of this task to screen for a potential underlying AD pathology, standardization of the task design and administration procedures, assessing the test-retest reliability, development of normative data).

Moreover, longitudinal studies should be carried out to determine whether VSTMBT can predict clinical conversion and how VSTMBT performances evolve with disease progression.

Conclusion

In conclusion, our analyses show that conjunctive binding abilities, enabling us to integrate all the features of objects into unified representations, seems sensitive to early tau burden in preclinical AD. Assessing this ability seems therefore promising for large-scale early diagnosis of the disease.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1355617725000165.

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