The 'when' matters: evidence from memory markers in the clinical continuum of Alzheimer's disease

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Abstract

Objective: Cognitive assessment able to detect impairments in the early neuropathological stages of Alzheimer's disease (AD) are urgently needed. The Visual Short-Term Memory Binding Task (VSTMBT) and the Free and Cued Selective Reminding Test (FCSRT) have been recommended by the Neurodegenerative Disease Working Group as promising tests to aid in the early detection of AD. In this study, we investigated their complementary value across the clinical stages of the AD continuum. ***Methods:*** 117 older adults with subjective cognitive complaint (SCC), 79 with mild cognitive impairment (MCI), 31 patients with AD dementia (ADD) and 37 cognitively unimpaired (CU) subjects, underwent assessment with the VSTMBT and the Picture version of the Spanish FCSRT. ***Results:*** After controlling for multiple comparisons, significant differences were found across groups. The VSTMBT was the only test that 'marginally' differentiated between CU and SCC ($d = 0.47$, $p = 0.052$). Moreover, whereas the FCSRT showed a gradient (CU = SCC) > MCI > ADD, the VSTMBT gradient was CU > SCC > (MCI = ADD) suggesting that conjunctive binding deficits assessed by the latter may be sensitive to the very early stages of the disease. ***Conclusions:*** Our results suggest that the VSTMBT and the FCSRT are sensitive to the clinical continuum of AD. Whereas the former detects changes in the early prodromal stages, the latter is more sensitive to the advanced prodromal stages of AD. These novel tests can aid in the early detection, monitor disease progression and response to treatment, and thus support drug development programs.

Keywords: Alzheimer's disease continuum, early detection, memory binding, relational memory, cognitive complaint.

Key Points

Question: Are the VSTMBT and the FCSRT sensitive to the earliest cognitive impairments observed in the AD continuum? ***Findings:*** While the VSTMBT is sensitive to the early prodromal stages, the FCSRT is sensitive to the advanced prodromal stages. ***Importance:*** These findings are relevant for the stratification of the clinical stages of AD using cognitive assessment tools. ***Next Steps:*** To investigate the ability of the VSTMBT to predict dementia among older adults with SCC and MCI from the GERO cohort.

Introduction

The development and availability of in-vivo Alzheimer's disease (AD) biomarkers targeting amyloid β, tau, and neurodegeneration, is creating unprecedented opportunities for the early detection of neuropathological changes from the preclinical stages (Dubois et al., 2021; Jack et al., 2016; 2018). Although appealing, adhering to such a novel biomarker framework comes with several challenges. In-vivo biomarkers of AD are commonly found in other neurodegenerative diseases (Robinson et al., 2018). Moreover, their limited specificity considering the heterogeneity of AD and related disorders (Khoury & Ghossoub, 2019) as well as unknown sensitivity to factors affecting diverse populations (Duran-Aniotz et al., 2021; Parra et al., 2018; 2020; 2022a), render their cost-benefit questionable.

As biomarkers for AD meet the above challenges, complementary approaches such as novel neuropsychological tests sensitive to the early stages of AD need more attention and efforts (Schindler et al., 2017). Evidence suggesting that very early cognitive deficits can be identified with appropriate test before the clinical manifestations of the disease become apparent is accruing (Hassenstab et al., 2016; Jack et al., 2019; Koppara et al., 2015; McKay et al., 2022; Papp et al., 2015; Parra et al., 2010a, 2011). Assessment of such functions would provide unique opportunities to identify at risk individuals who would then benefit from more costly biomarker assessments. Such cognitive assessments would not replace biomarker approaches but would complement them by providing community-based non-invasive cost-effective screening methods (Parra et al., 2010b, 2018, 2019a&b, 2020, 2022b,c). For instance, (Cummings et al., 2019) suggested that clinical trials could target secondary prevention in preclinical AD participants who are cognitively normal but have positive biomarkers (e.g., amyloid PET). The Visual Short-Term Memory Binding Task (VSTMBT) could help address such a need inasmuch as it has shown impairment in otherwise completely asymptomatic individuals who will inevitably develop AD dementia (Parra et al., 2010a) and in those in prodromal stages who show brain amyloidosis without overt neurodegeneration (Cecchini et al., 2021). Sevigny et al. (2016) reported that around 39% of 278 patients with an evaluable PET scan were excluded from an AD clinical trial due to amyloid-negative scans. The A4 trial (Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease) conducted amyloid PET on 4,486 individuals of whom 1,323 were Aβ+. This reflects an amyloid PET screen fail rate of 71% (Sperling et al., 2020) with 3.39 individuals screened to identify one Aβ+ individual. Amyloid PET cost-effectiveness for diagnosis (Barthel & Sabri, 2017) and clinical management (Lee et al., 2021) remains low. The advent of blood-based biomarkers (Thijssen

et al., 2020) and effective cognitive screening can represent a turning point in dementia research and clinical practice.

Clinical and neuropsychological assessments continue to be the gold standard in low- and middle-income countries (LMIC, Parra et al., 2018, 2020). Yet, newly developed tests (e.g., Rentz et al., 2013) still lack harmonization (Costa et al., 2017; Parra et al., 2018) and there is little evidence of their usefulness along the disease continuum. The Joint Program for Neurodegenerative Diseases Working Group (Costa et al., 2017) suggested that efforts should be directed to the harmonization of domain specific cognitive assessments. The Working Group recommended two memory tests that have proved informative in the early detection of AD, namely the VSTMBT and the Free and Cued Selective Reminding Test (FCSRT). Costa et al.'s call was aimed mainly at European Countries. However, we are aware that a similar call has been made in Latin America (e.g., Parra et al., 2018, 2019a, 2020). A handful of studies have now looked at the validity of these two new cognitive tests both in Europe and in Latin America. However, none to date has combined the two in a single study protocol in Latin America (but see Parra et al., 2022b for recent evidence from Europe).

The VSTMBT (Parra et al., 2010a&b) and the FCSRT (Grober et al., 1988) have proved effective to identify at risk individuals throughout the AD continuum with high sensitivity and specificity, particularly in the early stages of the disease (Cecchini et al., 2021; Grober et al., 2021; Rentz et al., 2010). Although, these tests tap into memory binding abilities, they inform about different binding functions (Parra, 2022; Parra et al., 2022b). The VSTMBT assesses conjunctive binding functions responsible for holding integrated features within object representations in VSTM (i.e., shape-colour, Parra et al., 2010a&b). The VSTMBT discriminates participants with and without significant brain amyloid deposits (Cecchini et al., 2021; Norton et al., 2020). The test has proved sensitive to identify subtle cognitive deficits in otherwise asymptomatic mutation carriers caused by the E280A single presenilin-1-mutation more than 10 years before the average age of dementia onset (Parra et al., 2010a, 2011). The FCSRT assesses relational binding, which supports the formation and retention of associative memories (i.e., construction-house). It seems that the FCSRT detects the earliest cognitive symptoms associated with neurofibrillary tangle (NFT) pathology and thus predicts Braak's stages (Grober et al., 2021). The test has shown associations between cognitive deficits and CSF biomarkers indicative of AD in the prodromal stages of the disease (Wagner et al., 2012).

Binding is a relative new memory construct, especially in short-term memory (Wheeler & Treisman, 2002). Previous studies in AD samples have demonstrated that dissociations found with this new paradigm (i.e., selectively impaired binding abilities with relatively preserved memory for individual features) are a hallmark of the disease. Such dissociations entail that in those affected, processing features binding is a more cognitively costly operation that just processing the individual features (Parra et al., 2010a&b). Hence, it is the cost of binding what has proved a cognitive marker for AD (Cecchini et al., 2017; Della Sala et al., 2012). Selective reminding tests, such as the FCSRT are also considered memory binding tests (Buschke, 2014) but such binding functions occur in long-term memory.

As we argued earlier, these new cognitive assessments can support the early diagnosis of AD across developed and developing countries, not only because of their affordability and reliability, but also due to their cultural validity (Della Sala et al., 2016; Parra et al., 2011; Slachevsky et al., 2018; Yassuda et al., 2019). However, it is not clear if both tests are sensitive enough to detect the very subtle memory impairment associated to the earliest stages of AD (i.e., preclinical AD) or if they index cognitive deficits of more advanced disease stages. As Parra (2022) recently suggested, these tests may hold a complementary value to assess different stages of the disease continuum whereby the VSTMBT would reveal subclinical prehippocampal stages (see also Didic et al., 2011; Parra, 2022b&c) and the FCSRT would inform about the hippocampal stages (Grober et al., 2021; Slachevsky et al., 2018). Recent evidence suggests that the VSTMBT can be performed by individuals without intact hippocampi who normally fail associative memory tests such as the FCSRT (Jonin et al., 2019; Parra et al., 2015). Patients who will inevitably develop familial AD due to the mutation E280A-PSEN1 show significant impairments on the VSTMBT when their episodic and associative memory functions known to be linked to the hippocampus remain intact (Parra et al., 2010a; Parra et al., 2011). As Didic et al. (2011) suggested, context-free memory tests such as the VSTMBT appear to tax the function of regions of the anterior medial temporal lobe network (i.e., entorhinal and perirhinal cortices) which are affected by AD prior to the hippocampus (Braak et al., 1999; Braak & Braak, 1996; Juottonen et al., 1998). Thus, by selecting the correct combination of tests we may be able to reveal not only “which” but also ‘when’ memory decline becomes informative of the disease presence. This would greatly support early detection of patients attending memory clinics.

Despite the recommendations by Costa et al. (2017), no study to date has investigated the complementary value of these tests to detect impairments in the clinical continuum of AD in Latin American countries. The Geroscience Center for Brain Health and Metabolism (GERO) cohort (Slachevsky et al., 2020) offers a suitable context to address this outstanding need. Briefly, GERO is a population-based study that aims to investigate the rate of functional decline and progression to clinical dementia and their associated risk factors in community-dwelling older adults (70 years or older) with subjective cognitive complaints (Slachevsky et al., 2020). The rationale is based on the higher risk that patients with subjective cognitive complaints (SCC) have to progress to a dementia syndrome when compared with subjects without such complaints (Kielb et al., 2017; Rabin et al., 2015). Given the association of SCC and AD biomarkers (Amariglio et al., 2012; van Harten et al., 2013), the National Institute on Aging and the Alzheimer's Association preclinical AD working group have highlighted the importance of including this group in disease prevention studies (Sperling et al., 2011). SCC holds an uncertain prognostic value as it has been associated with depression (Zlatar et al., 2018), migraine (Lee et al., 2017), psychosocial factors like professional activity and neuroticism (Zullo et al., 2021), poor sleep quality (Xu et al., 2021), physical health problems and anxiety symptoms (Comijs et al., 2002). Using memory markers that have proved sensitive and specific to AD would help refine risk profiling among members of this group.

Previous studies have already showed memory binding deficits in SCC (Koppara et al., 2015) and preliminary data showed marginal differences between older adults with cognitive complain and healthy controls (Forno et al., 2021, conference proceeding). Moreover, Parra and colleagues (Parra et al., 2017, conference proceeding, *full report submitted*) previously showed that healthy older adults assessed with a high memory load task whose binding cost was greater than 20% (weak binders - WB), had significant increase in amyloid deposits compare to those whose binding functions were preserved (strong binders - SB) (Parra et al., 2017, conference proceeding, *full report submitted*). Given this evidence, WB may have a greater risk to progress to AD relative to SB (Hassenstab et al., 2016; McKay et al., 2022). The present study aimed to investigate the ability of the VSTMBT and the FCSRT to detect and discriminate early cognitive deficits in a population at risk of AD. We sought to investigate if conjunctive binding deficits assessed via the VSTMBT anticipate relational memory impairments as assessed by the FCSRT thus informing about different stages of the clinical continuum of AD.

Methods

Transparency and Openness

The research protocol on which this study relied was preregistered (Slachevsky et al., 2020). In that protocol, sample size estimation, task manipulations, background and experimental tests were described. Data for the present studies were analysed using the Statistical Package for the Social Sciences (SPSS) version 25 for Windows (Corp., 2017). Data used to generate the results reported here can be accessed on request (see corresponding authors).

Participants

A subsample of 264 participants was recruited from the GERO cohort and the Memory and Neuropsychiatric Clinic (CMYN) at Hospital Salvador, Santiago, Chile. In this study, we reported the first wave of the GERO cohort that recruited participants from 2017 to the end of 2021. Importantly, we extended the recruitment period due to the pandemic. Participants were recruited from the general population, using a door-to-door strategy as reported in (Slachevsky et al., 2020). Inclusion in the cohort follows a three-step process. First, selection of eligible participants, i.e. subjects with the following characteristics: 70 years or older, the presence of a knowledgeable informant and/or presence of a contact that allows the follow up of the participants and affiliated to the public health insurance. Second, eligible subjects were evaluated by a psychologist with a set of questionnaires to verify if they fulfilled the inclusion criteria of the cohort: cognitive complaint reported by the participant or a reliable proxy and absence of dementia according to the MMSE and Pfeffer questionnaire (MMSE < 21 (Folstein, 1975); Pfeffer > 2 (Pfeffer et al., 1982)). Third, participants were evaluated by a neurologist to check if participants fulfilled the inclusion or exclusion criteria. Of these, 117 were classified as subjective cognitive complaint (SCC) and 79 mild cognitive impairment (MCI). The final sample was complemented by 31 Alzheimer's disease dementia (ADD) and 37 cognitively unimpaired (CU) participants. All participants were matched by age. The diagnosis was based on a multidisciplinary consensus (neurologist and neuropsychologist) based on extensive clinical protocols, interviews with a reliable proxy, laboratory test and global cognitive functions (Slachevsky et al., 2020).

Briefly, SCC were considered when either self- or informant-reported cognitive complaints were present and accompanied by normal performance on cognitive tests according to age, gender and education, as well as unimpaired basic and Instrumental Activities of Daily

Living (BADL and IALD respectively) as recommended by the Subjective Cognitive Decline Initiative (SCD-I) Working group (Molinuevo et al., 2017). Those with MCI or dementia distinguished themselves as different from CU and SCC groups because they performed below the expected cut-off on a cognitive screening test sensitive to cognitive decline. MCI patients performed below the cut-off point for MCI drawn from a validated Chilean version of the Montreal Cognitive Assessment (MoCA) (Delgado et al., 2017). MoCA has proved effective for detecting MCI (AUC ± 0.903). With a sensitivity and specificity rate of 75% and 82%, the optimal cut-off point for MCI has been set at 20 points or lower (Delgado et al., 2017). As education has a big repercussion on scores, participants with 8 years of education or lower received 2 extra points whereas participants with 8-12 years of education received 1 extra point (Delgado et al., 2017). MCI patients differentiated from the dementia group because they did not have marked functional impairment in everyday activities whereas those with dementia did have such a functional decline. ADD patients met the Alzheimer's clinical syndrome criteria according to NIA-AA Research Framework (Jack et al., 2018). CU had no self- or informant-reported cognitive complaints, unimpaired cognition according to age and education in standard neuropsychological assessment and no functional impairment.

Ethical approval for this study was obtained from the Ethical and Scientific Committees of the East Metropolitan Health Service, Santiago, Chile. All participants had capacity and provided informed consent in accordance with Helsinki's Declaration.

Neuropsychological Assessment

Participants underwent neuropsychological assessment as part of the GERO Cohort (Slachevsky et al., 2020). Global cognitive function was assessed with the Montreal Cognitive Examination (MoCA) (Delgado et al., 2017) and the Chilean's version of Addenbrooke's Cognitive Examination (ACE III) (Bruno et al., 2020). These scales provide scores for cognitive subdomains which were used to support the diagnosis. We additionally assessed attention and executive function using the Chilean's version of the INECO Frontal Screening (IFS) (Jory et al., 2013), the Verbal Fluency Test (Olabarrieta-Landa et al., 2015), and the two parts of the Colour Trail Making Test (TMT-A and TMT-B) (Dugbartey et al., 2000). Finally, functional decline in activities of daily living was assessed using the Technological—Activities of Daily Living Questionnaire (T-ADLQ) (Muñoz-Neira et al., 2012; Slachevsky et al., 2019).

VSTMBT and FCSRT

Neither the VSTMBT nor the FCSRT was used for diagnosis or classification purposes. The VSTMBT is based on the change detection paradigm (Figure 1). It assesses the ability to integrate and temporarily hold colours and shapes as unified representations (Parra et al., 2010a&b; Parra et al., 2009). A perceptual condition was given before the memory tests. This consisted of 10 trials in which two arrays of three coloured shapes (abstract shapes, six-sided polygons) were presented simultaneously above and below a horizontal black line. Participants had to detect whether the coloured shapes below and above the line were the same or different, independently of their location (Della Sala et al., 2018; Parra et al., 2009). This test was used to screen for perceptual binding or colour vision deficits (>=80% correct) which were exclusion criteria for the memory assessment.

During the memory task, participants were presented with abstract shapes displayed in random positions of a 3x3 virtual grid. After an initial fixation cross (1000ms), a study display was presented for 2000ms followed by a 900ms unfilled retention interval. The test display was then presented and remained on until participants responded. Participants were asked to detect whether a change occurred between the study and the test display *('say different')* or if the stimuli remained the same *('say same')*. In 50% of the trials the stimuli remained the same and in the other half, items in the test display were different. The task consisted of two conditions. The Single Shape condition assessed VSTM for single features (i.e., shapes). The Binding condition assessed VSTM for shape-colour bindings. During the Single Shape condition, participants were presented with either two or three black shapes. In the test array for the different trials, two of the previously presented shapes were replaced with new shapes drawn from the same set of eight shapes. In the Binding condition, two or three shapes were presented in a different colour each (from a set of eight non-primary colours). In the test array for the different trials, two of the previously presented coloured shapes swapped their colours.

To be able to detect such changes, participants had to remember either the individual shapes (i.e., Single Shape condition) or the combinations of shape and colour (i.e., Binding condition) presented in the study display. Each condition consisted of 32 trials of which 50% presented arrays of two stimuli and the remaining 50% presented three stimuli. The rationale for the use of these two set sizes was presented by (Parra et al., 2019b). The test took around 15 minutes to be administered.

Insert Figure 1 about here

The picture version of the Spanish FCSRT (black and white line drawings, (Slachevsky et al., 2018) (Figure 2) was applied according to the procedure defined by Grober and colleagues (Grober et al., 1988). A study phase was first applied in which 16 drawings were presented in four groups of successive cards. Items associated to a semantic category were first presented in each quadrant of the card. Participants were asked to name these aloud after each semantic cued was presented (i.e., "Which of these drawings correspond to a part of the body?"). Once the four items of the first card were appropriately encoded, the card was removed and encoding was immediately tested by providing the cues and requesting recall of the associated items. If the subject was not able to recall some items, the encoding procedure was repeated for those items. After the participant was able to recall the first four items of the card, the procedure was repeated for the remaining cards. This study phase allows encoding to be controlled and provided the first variable, Immediate Recall (IR). The subsequent memory phase consisted of three successive recall trials. The first recall trial was presented after 60s, whereas the second and third trial were conducted after 20s. Participants were asked to count backwards from 100 while they waited for each trial to begin. Each recall trial consisted of up to two minutes of a freely recall items, were participants have to recall as many items as possible from the four cards. Items that were not spontaneously recalled were reminded by the examiner by giving the respective semantic cue (i.e., "What was the name of the fish?"). This phase provided two scores, the Total Free Recall (TFR) consisting of the total items spontaneously recalled across the three trials, and the Total Immediate Recall (TIR) (maximum score = 48) consisting of the sum of the free recalled items and the cued recalled items across the three trials. After a 20min delayed, the procedure was repeated. The delayed phase provided a Delayed Free Recall (DFR) score and a Total Delayed Recall ((TDR) maximum score = 16). We did not include the recognition phase to avoid extending the neuropsychological assessment.

Insert Figure 2 about here

Data Analyses

Groups (CU, SCC, MCI and ADD) were compared using a one-way ANOVA followed by Tukey's post-hoc tests to correct for Type I errors. Gender was analysed with the Pearson chi-squared (χ^2) test. When significant differences were found in education level between groups, an analysis of covariance (ANCOVA) was conducted with years of education as covariate of no interest. The effect size (Cohen's *d* (Cohen, 1988)) was calculated for group differences using G*Power 3 (Faul et al., 2007). An effect of $d = 0.2$ was considered a small effect, $d = 0.5$ as a medium effect, $d = 0.8$ and above a large effect.

Recent evidence has shown that the VSTMBT is able to identify memory impairments as early as SCC (Koppara et al., 2015) and even in completely asymptomatic carriers of an autosomal dominant mutations that inevitably leads to ADD (E280A-PSEN1, Parra et al., 2010a). Such binding deficits in E280A-PSEN1 carriers were found at the age at which amyloid reaches a plateau (Fleisher et al., 2012). Following this evidence, we wanted to investigate if our experimental tests (VSTMBT and FCSRT) could identify participants who may hold different risk levels for ADD. For this purpose, we first calculated the Cost of Binding, which provides information on the cognitive resources needed to hold integrated information in VSTM (Binding) relative to those needed to hold individual features (Single Shape) (Della Sala et al., 2018; Parra et al., 2017), conference proceeding, *full report submitted*). This cost was calculated as follows:

Binding Cost = ((Score on Single Shape – Score on Shape—Colour Binding)/ Score on Single Shape)) *100.

Parra and colleagues (Parra et al., 2017, conference proceeding, *full report submitted*) previously showed that healthy older adults assessed with a high memory load task (set size 3) whose binding cost was greater than 20% (weak binders - WB), had significant increase in amyloid deposits compare to those whose binding functions were preserved (strong binders - SB) (Parra et al., 2017). We expanded such an approach in our study and applied it to data collected with the VSTMBT (set size 3) and with the FCSRT. Following previous research (Parra et al., 2017), we selected a cut-off of 20% drop in VSTMBT and we calculated the standard deviations (SD) that such a drop represented in CU. We applied such SD to TFR data from the FCSRT (Auriacombe et al., 2010; Grober et al., 2010) providing an equivalent cut-off score for this test of 12.79%. CU and SCC were divided in WB/Week Recallers (WR) and SB/Strong Recallers (SR), thus following the same procedures across tests.

We controlled for experiment-wise and family-wise error rates (Benjamini & Hochberg, 1995; Blakesley et al., 2009) by applying FDR corrections to p-values resulting from the one-way ANOVA/ANOCOVA models and Tukey's post-hoc tests to explore the sources of the significant effects. Effect sizes (i.e., Cohen-*d*) were used to explore differences between SB/SR and WB/WR, SB/SR and MCI; and WB/WR and MCI. ANCOVA models were used to control for years of education as a covariate of no interest. As significant age differences were found between SR and MCI, this variable was also added to the ANCOVA as a covariate of no interest. The aim of this analysis was to explore if subjects classified based on cut-off scores of a given cognitive marker (e.g., VSTMBT) would differ in their performance on the other maker (e.g., FCSRT). All statistical analyses were performed using The Statistical Package for the Social Sciences (SPSS) version 25 for Windows (Corp., 2017.).

Results

Neuropsychological data

Detailed results of the neuropsychological assessment are presented in Table 1. Briefly, FDR corrected ANOVA models and Tukey's post hoc tests confirmed significant impairments of ADD and MCI in global cognitive function, executive function, attention, and episodic memory. As expected, ADD patients performed worse than MCI on global cognitive and functional scales (see Table 1 for descriptive and inferential statistics).

Most significant differences were confirmed after adjusting for educational level (ANCOVAs) in the comparisons between ADD, MCI, CU, and SCC. Other than attention, phonemic fluency, global cognition, and executive function remained significant when comparing MCI with CU, and SCC. No significant differences on standard neuropsychological tests and functional scales were found between CU and SCC after adjusting by educational level. ADD was the only group that significantly differ in ADL when compared with CU, SCC and MCI, showing poorer results across all ADL measures (see Table 1).

VSTMBT

When comparing CU, SCC, MCI and ADD, the mean performance on the Single Shape condition for both low (i.e., 2 items) and high (i.e., 3 items) memory load showed the following gradient ((CU = SCC) > (ADD > MCI) (see Table 1). VSTM Binding showed a slightly

different gradient (CU > SCC > ADD > MCI) with low memory load and the following gradient (CU > SCC > (ADD = MCI) for high memory load. Notably, the VSTM shape-colour Binding condition with high memory load was the only experimental task that could marginally differentiate between CU and SCC *(d = 0.47, p = 0.052),* results that were confirmed by Tukey's post hoc tests. Of note, education was not associated with VSTM for single shape or shape—colour binding. This is in line with previous evidence showing that this function is not affected by education (Brockmole et al., 2008; Parra et al., 2009; Yassuda et al., 2019). Nevertheless, to further rule out the influence of education, we ran a set of parallel analyses. The first analysis relied on mixed-ANCOVAs models including Groups as the between-subjects factors, Condition (Shape only vs Shape-Colour Binding, set size 3) as the repeated-measures, and Education as the covariable. These results proved that education did not remove the Group x Condition Interaction consistently reported by previous studies (see Supplementary Figures 1 and 2). The second approach was to match groups according to the years of Education. This replicated our current findings and highlighted some of the effects observed with the entire sample (see Supplementary Tables 1 to 3). We therefore decided to retain the entire dataset and report on the whole sample for the sake of representativeness.

Picture version of FCSRT

No significant differences were found when comparing CU and SCC in any measures of the FCSRT. The TFR and the DFR of the FCSRT discriminate between CU and MCI [*(d = 0.7, p < 0.001), (d = 0.7, p < 0.01)* respectively] and between SCC and MCI patients [*(d = 0.5, p < 0.001), (d = 0.4, p < 0.05)* respectively]. These results remained significant after adjusting for years of education for all the variables, with the exception of the TFR between CU and MCI patients. When comparing MCI with ADD patients, the former performed significantly better than the latter in all the variables of the FCSRT. These differences remained significant after adjusting for years of education (see Table 1).

Analysis of SB/SR vs WB/WR

We ran a two-way ANOVA with Group (SB vs WB) as the between-subjects factors and Condition (Single Shape vs Shape—Colour Binding) as the within-subjects' factors. The results previously reported by (Parra et al., 2017, conference proceeding, *full report submitted*) were replicated. There was no effect of Group [$F(1,152) = 0.64$, $p = 0.425$, $\eta 2 = 0.004$, β=12%], a significant effect of Condition [$F(1,152) = 223.01$, $p < 0.001$, $\eta 2 = 0.559$, β=100%] and a significant Group x Condition interaction [$F(1,152) = 243.91$, $p < 0.001$, $\eta 2 = 0.616$, β=100%]

(Figure 3). As expected, WB were disproportionally poorer than SB in the Shape-Colour Binding Condition (*t=7.32, p<0.001*) (this was the classification variable). However, WB were significantly better than SB on the Single Shape Condition (*t=5.48, p<0.001*). WB showed a significant performance drop on the Shape-Colour Binding Condition relative to the Single Shape (*t=24.55, p<0.001*), an effect not observed in SB (*t=0.44, p=0.661*). Therefore, for WB, binding shape and colour in VSTM was a very challenging task relative to processing individual features.

Insert Figure 3 about here

Notably, the comparison between SB and WB showed no significant differences when variables form either the FCSRT or classical neuropsychological tests were used (see Table 2). MCI patients performed significantly poorer than both SB and WB on the Single Shape and Shape-colour Binding condition with both low and high memory load. Significant differences were also found when comparing WB and MCI patients on the FCSRT TFR *(d = 0.5, p < 0.001),* FCSRT DFR *(d = 0.4, p < 0.05),* global cognitive function (ACE-III *(d = 1.4, p < 0.001))*, executive function *(d = 1.3, p < 0.001)* and attention *(d = 0.5, p < 0.001)* with the latter performing significantly poorer than the former. Although, no significant results were found in the FCSRT TFR and FCSRT DFR between WB and MCI patients after adjusting for years of education, global cognitive function, executive function, and attention remained significant. As expected, SB outperformed MCI patients across all cognitive tests including the FCSRT TFR *(d = 0.7, p < 0.001),* FCSRT DFR *(d = 0.6, p < 0.01),* global cognitive function *(*ACE-III (*d = 1.3, p < 0.001),* and executive functions *(d = 1.2, p < 0.001).* Results that were confirmed after adjusting for years of education (Table 2).

When WR and SR were compared, the former group performed significantly poorer than the latter in global cognitive function *(*ACE-III (*d = 0.8, p < 0.001)* and phonemic verbal fluency *(d = 0.6, p < 0.05)* thus suggesting that deficits identified by the FCSRT TFR appear to be linked to advanced prodromal stages of the disease. Relative to WR, MCI patients had poorer results in global cognitive function *(*ACE-III (*d = 0.7, p < 0.05),* executive function *(d = 0.9, p < 0.001)* and VSTM single shape for low memory load *(d = 0.7, p < 0.05).* After adjusting for years of education, WR outperformed MCI patients only in executive function test and in the VSTM single shape for low memory load (see Table 3). Relative to SR, MCI

patients showed significant differences for all experimental measures and several standard neuropsychological assessments. Briefly, MCI patients showed poorer results on the VSTM Single Shape and Shape-Colour Binding for low *(d = 0.8, p < 0.001)* and high *(d = 0.7, p < 0.001)* memory load, global cognitive function *(*ACE-III (*d = 1.5, p < 0.001),* executive function *(d = 1.3, p < 0.001)* and attention *(d = 0.5, p < 0.001).* These results were confirmed after running ANCOVAs.

Discussion

The aim of the study was to investigate the ability of the VSTMBT and the FCSRT to identify early cognitive deficits in a population at risk of ADD. We further compared the complementary values of these tests to detect deficits that are likely underpinned by the different neuropathological changes across the AD continuum, with an emphasis in its prodromal stage. We found that the VSTMBT and the FCSRT are sensitive to the clinical continuum of AD. Whereas the former detects changes in the early prodromal stages, the latter is more sensitive to the advanced prodromal stages of the AD continuum, i.e. VSTMBT discriminated between CU and SCC and the FCSRT discriminated between CU and MCI.

Although both the VSTMBT and the FCSRT proved sensitive to cognitive deficits associated with early ADD, crucial differences between both tests were observed. The VSTMBT was able to identify individuals with poor abilities in conjunctive binding in a population who may be at a higher risk of ADD. Deficits were detected in CU subjects and in SCC, even when standard neuropsychological assessment proved uninformative, and these would unlikely reflect Type I errors (see Methods, FDR corrections). Previous studies have consistently reported that the VSTMB paradigm is a preclinical cognitive marker for AD (Cecchini et al., 2021; Koppara et al., 2015). This proposal has stemmed from the observation that the ability to bind information in VSTM is severely affected even when VSTM for individual features remains relatively preserved. Our data confirmed this notion and revealed that patients in the very early stages of the disease can outperform healthy controls on the baseline conditions (i.e., Shape Only) despite showing significant binding impairments. Together with the existing literature, such an observation grants us confidence that these patients present with a profile compatible to that seen in AD.

Notably, the cost of binding analysis comparing SB vs WB yielded a significant Group x Condition Interaction previously reported (Parra et al., 2017) showing selective VSTM shape-colour binding impairment with preserved memory for single feature in WB. The

behavioral pattern shown in Figure 3 has been previously observed in asymptomatic older adults who have significant accumulation of amyloid -β in their brain (Parra et al., 2022c) and in asymptomatic carriers of a mutation (i.e., E280A-PSEN1) that inevitably leads to familial AD (Parra et al., 2010a). The literature on associative memory (a form of relational binding) in ageing and dementia has failed to consistently demonstrate that such binding deficits (e.g., object-location association) are unaccounted for by limitations in processing individual parts (i.e., object or locations alone). By dissociating this construct in short-term memory, we have found that contrary to associative memory, which declines steadily with age (Naveh-Benjamin et al., 2003; Rhodes et al., 2019), shape-colour binding in STM remains preserved throughout the lifespan (Hoefeijzers et al., 2017; Parra et al., 2009). Such a property is proving clinically meaningful because this test can help separate normal and abnormal ageing trajectories before people become aware of any cognitive deficits, as shown by our studies in completely asymptomatic or very mildly impaired individuals (Parra et al., 2022b&c). Furthermore, neither standard neuropsychological assessments nor the FCSRT TFR was able to differentiate between SB and WB. These results suggests that the VSTMBT and the FCSRT index different binding functions with those assessed be the former being targeted by AD in earlier stages. The facts that such deficits were found when no other standard cognitive assessment revealed significant results, makes this test a suitable preclinical cognitive marker for the AD continuum.

On the contrary, the FCSRT discriminate CU and MCI, but no significant results emerged when comparing CU and SCC. Moreover, SR vs WR comparison showed significant deficits in several cognitive domains including global cognition and phonemic fluency, with the latter performing worse than the former. It seems that deficits identified by the FCSRT TFR are associated to more advanced stages in the AD continuum. Of note, VSTM shape-colour binding deficits were also present in WR relative to SR. Such a discrepancy was not observed when comparing SB and WB using FSCRT variables. This reinforces the notion of different binding mechanisms taxed by these tests, which are differentially vulnerable to different disease stages (Della Sala et al., 2018; Parra et al., 2022b&c). As we hypothesised, conjunctive binding deficit as revealed by the VSTMBT seem to anticipate binding deficits identified by the FCSRT. These results suggests that the VSTMBT and the FCSRT hold complementary value to track at risk individuals as they progressed from the early (SCC, VSTMBT) to the more advanced prodromal (FSCRT, MCI) stages of the AD continuum a proposal that is in line with (Parra, 2022; Parra et al., 2022b). Interestingly, recent evidence has shown that FCSRT TFR is able to discriminate Braak stage III from Braak stage 0/I being the earliest and most

sensitive variable of the FCSRT to detect NFT pathology (Grober et al., 2021). Subjects that have been classified as amnesic or non-amnesic MCI already evidence AD pathology corresponding to Braak limbic stage (III and IV) (Riley et al., 2002). Moreover, NFT pathology in the medial temporal lobe in stage III reflects a burden that cause the typical clinical course associated with early AD cognitive symptoms (Nelson et al., 2012), supporting the idea that the FCSRT is sensitive to more advanced prodromal stages of the AD continuum.

This current study expands the scope of Costa et al.'s call by contributing data that will allow cross-cultural comparison in future studies. As Parra (2022) recently highlighted, the lack of such data has proved a long standing barrier to the wider implementation of neuropsychological assessments to tackle dementia with true global strategies. Future studies will need to further consider this proposal in groups of older adults better defined in terms of health history, cognitive and biomarker profiles. Our study has some limitations. Frist, we did not follow the classification of MCI into subtypes (amnestic and non-amnestic) but rather focused on evidence of impairments in general cognitive and functional abilities. Our results from the experimental tests (i.e., VSTMBT and FCSRT) do suggest that our group of MCI patients presented with memory problems. However, future studies should explore if the pattern of results here presented holds when MCI sub-types diagnosed ad-hoc are considered. Second, our participants had no biomarkers confirmation of AD pathology. Due to the high heterogeneity, this is more of an issue for SCC and MCI participants rather than clinically defined patients with dementia likely linked to an AD aetiology. Notwithstanding, we provide robust and strong evidence on the utility of the VSTMBT and the FCSRT as "cognitive markers" for the AD continuum. Following recent recommendations (Jack et al., 2016), our findings could be interpreted as part of the Alzheimer's Clinical Syndrome. In addition, our sample include mostly female participants thus future investigation should consider more sex-balanced samples. Nonetheless, participants were recruited from the GERO cohort which recruit participants through a population—based study (Slachevsky et al., 2020). The GERO cohort provides an excellent opportunity to analyze the conversion rate of these participants and the predictively power of the VSTMBT and the FCSRT due to its longitudinal methodology. Future studies are expected to investigate this issue when the GERO cohort final assessment concludes (Slachevsky et al., 2020).

In conclusion, our study confirms the complementary value of the VSTMBT and the FCSRT to detect cognitive deficits associated with the early stages of AD. To the best of our knowledge, this is the first study that compares the ability of the VSTMBT and the FCSRT to

detect cognitive impairments in the clinical continuum of AD in Latin American cohorts. We highlight the complementary value of both tests with the VSTMBT being sensitive to detect early cognitive deficit associated with the transition from normal aging to early symptomatic stages (SCC) of the AD continuum, while the FCSRT could help monitor the disease progression and response to treatment in more advanced prodromal stages of the disease. Our findings support the proposal that the combination of both tests would greatly support early diagnosis of AD and prevention trials.

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Table 1

Descriptive statistics and results of cognitive assessments

	CU (n = 37)	SCC (n = 117)	MCI (n = 79)	ADD (n = 31)	ANOVA *F* (p-value)	ES (CU vs SCC)	ES (CU vs MCI)	ES (SCC vs MCI)	ES (CU vs ADD)	ES (SCC vs ADD)	ES (MCI vs ADD)
Age, mean (SD) years	75.62 (4.11)	76.16 (4.89)	77.56 (4.88)	78.16 (7.63)	2.491	0.119	0.430	0.286	0.414	0.312	0.093
Education	12.70 (4.97)	9.97 (4.53)	7.58 (4.16)	12 (3.97)	14.422***	0.573**	1.116***	0.549**	0.155	0.476	1.086***
Gender (F:M)	26:11	91:26	68:11	16:15	χ^2 = 15.431***	-	-	-	-	-	-
ACE III Total Score	87.41 (6.91)	83.03 (8.34)	70.70 (10.71)	65.74 (11.87)	56.272***	0.571	1.854*** (+++)	1.284*** (+++)	2.231***	1.685***	0.438 (+++)
MoCA Total Score	24.43 (4.83)	24.71 (2.39)	15.58 (3.83)	16.03 (4.92)	131.822***	0.073	2.030*** (+++)	2.861*** (+++)	1.723***	2.245***	0.102
IFS Total Score	19.79 (3.27)	18.14 (4.26)	12.80 (4.59)	13.69 (4.72)	35.818***	0.434	1.751*** (+++)	1.209*** (+++)	1.502***	0.990***	0.191
Total FAS	36.16 (11.16)	29.69 (11.89)	22.10 (10.82)	29.26 (11.2)	14.205***	0.561* (−)	1.279*** (+)	0.667*** (+)	0.617	0.037	0.650* (−)
TMT-A	72.83 (26.035)	85.96 (40.874)	119.81 (93.604)	121.13 (52.096)	8.228***	0.383	0.683*** (−)	0.468*** (−)	1.172**	0.751*	0.017
TMT-B	155.56 (55.344)	183.32 (101.264)	316.23 (156.961)	262.23 (138.047)	23.820***	0.340	1.365*** (+++)	1.006*** (+++)	1.019**	0.651**	0.365
VSTM 2 'Single Shapes' performance (%)	91.39 (11.539)	91.39 (8.478)	79.91 (16.435)	84.07 (17.066)	14.565***	0	0.808***	0.877***	0.502	0.542*	0.248
VSTM 3 'Single Shapes' performance (%)	80.57 (13.881)	80.18 (12.801)	70.65 (12.947)	72.98 (16.001)	9.812***	0.029	0.739***	0.740***	0.506	0.496*	0.160
VSTMB 2 Binding performance (%)	76.12 (20.087)	72.17 (14.645)	61.08 (13.387)	66.94 (15.578)	11.617***	0.224	0.881***	0.790***	0.510	0.345	0.403
VSTMB 3 Binding performance (%)	70.27 (14.687)	63.97 (12.162)	57.19 (13.052)	57.45 (13.827)	10.738***	0.467 [m]	0.941***	0.537**	0.898***	0.500	0.019
Visual-FCSRT Total Free Recall (TFR)	33.78 (4.283)	32.80 (5.160)	29.27 (6.939)	11.42 (6.556)	119.152***	0.206	0.782*** (−)	0.577*** (+)	4.038***	3.624***	2.644*** (+++)

Visual-FCSRT Total Immediate Recall (TIR)	47.86 (0.419)	47.41 (1.682)	46.65 (3.9)	34.16 (9.526)	96.282*** ‖	0.367	0.436	0.253	2.031***	1.937***	1.716*** (+++)
Visual-FCSRT Delayed Free Recall (DFR)	12.98 (2.105)	12.17 (2.317)	11.01 (3.111)	3 (3.120)	107.593*** ‖	0.365	0.741** (+)	0.422* (+)	3.749***	3.336***	2.571*** (+++)
Visual-FCSRT Total Delayed Recall (TDR)	15.97 (0.164)	15.82 (0.519)	15.35 (2.317)	10.52 (4.946)	57.569*** ‖	0.389	0.377	0.279	1.557***	1.507***	1.250*** (+++)
T-ADLQ BALD (%)	1.07 (3.03)	0.82 (2.37)	2.73 (7.36)	8.94 (11.52)	15.236*** ‖	0.091	0.295	0.349	0.934***	0.976***	0.642*** (+++)
T-ADLQ IADL (%)	8.32 (8.65)	8.93 (11.48)	12.26 (13.69)	43.25 (16.35)	63.088*** ‖	0.068	0.344	0.263	2.670***	2.429***	2.055*** (+++)
T-ADLQ a-ADL (%)	20.17 (16.65)	21.43 (18.58)	28.87 (21.26)	50.34 (24.36)	18.047*** ‖	0.071	0.455	0.372	1.446***	1.334***	0.939*** (+++)
T-ADLQ Total Score (%)	9.27 (8.12)	9.55 (9.36)	12.96 (11.79)	38.67 (14.71)	61.340*** ‖	0.031	0.364	0.320	2.475***	2.362***	1.928*** (+++)

Note. CU: Cognitively Unimpaired; SCC: Subjective Cognitive Complaint; MCI: Mild Cognitive Impairment; ADD: Alzheimer Disease Dementia; ES: Effect Size; ^{m} $p = 0.052$; * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$. (After ANCOVA adjusted by education for variable of no interest: $^{-}$ $p \geq 0.05$; $^{+}$ $p \leq 0.05$; $^{++}$ $p \leq 0.01$; $^{+++}$ $p \leq 0.001$; ‖ Survived FDR correction).

Missing data for Education: 1 MCI.

Missing data for ACE III: 3 SCC, 2 MCI.

Missing data for IFS: 1 CU, 3 SCC, 1 MCI.

Missing data for Total FAS: 3 SCC, 1 MCI.

Missing data for TMT A: 1 CU, 1 SCC, 5 MCI.

Missing data for TMT B: 1 CU, 1 SCC, 5 MCI, 1 AD.

Missing data for T-ADLQ BADL: 6 CU, 4 SCC, 6 MCI, 1 AD.

Missing data for T-ADLQ IADL: 6 CU, 4 SCC, 6 MCI, 1 AD.

Missing data for T-ADLQ a-ADL: 6 CU, 4 SCC, 6 MCI, 1 AD.

Missing data for Total T-ADLQ: 6 CU, 4 SCC, 6 MCI, 1 AD.

Table 2

Strong Binders vs. Weak Binders

	SB (n = 58)	WB (n = 96)	MCI (n = 79)	ADD (n = 31)	ANOVA *F* (p-value)	ES (SB vs WB)	ES (SB vs MCI)	ES (WB vs MCI)	ES (SB vs AD)	ES (WB vs AD)
Age, mean (SD) years	76.02 (4.70)	76.04 (4.73)	77.56 (4.88)	78.16 (7.63)	2.387	0.004	0.346	0.316	0.337	0.334
Education	10.50 (4.98)	10.70 (4.67)	7.58 (4.16)	12 (3.97)	10.438***¶	0.041	0.636***	0.705***	0.333	0.300
Gender	46:12	71:25	68:11	16:15	χ^2 = 15.129**¶	-	-	-	-	-
ACE III Total Score	83.64 (8.95)	84.39 (7.58)	70.70 (10.71)	65.74 (11.87)	53.110***¶	0.090	1.311*** (+++)	1.475*** (+++)	1.703***	1.873***
MoCA Total Score	24.62 (3.65)	24.66 (2.81)	15.58 (3.83)	16.03 (4.92)	131.685***¶	0.012	2.417*** (+++)	2.707*** (+++)	1.983***	2.156***
IFS Total Score	18.08 (4.11)	18.82 (4.08)	12.80 (4.59)	13.69 (4.72)	34.417***¶	0.180	1.211*** (+++)	1.384*** (+++)	0.992***	1.162***
Total FAS	31.52 (12.62)	31.13 (11.68)	22.1 (10.82)	29.26 (11.2)	10.838***¶	0.032	0.801*** (+)	0.768*** (++)	0.189	0.163
TMT-A	83.68 (44.915)	82.36 (33.961)	119.81 (93.604)	121.13 (52.096)	7.769***¶	0.035	0.492** (—)	0.531*** (+)	0.769*	0.881*
TMT-B	177.30 (105.468)	176.42 (85.583)	316.23 (156.961)	262.23 (138.047)	23.197***¶	0.009	1.038*** (+++)	1.105*** (+++)	0.691**	0.747**
VSTM 2 'Single Shapes' performance (%)	91.27 (10.202)	91.47 (8.704)	79.91 (16.435)	84.07 (17.066)	14.569***¶	0.021	0.830***	0.879***	0.512*	0.546*
VSTM 3 'Single Shapes' performance (%)	73.49 (14.305)	84.37 (10.259)	70.65 (12.947)	72.98 (16.001)	19.541***¶	0.874***	0.208	1.174***	0.033	0.847***
VSTMB 2 Binding performance (%)	72.95 (16.406)	73.22 (16.059)	61.08 (13.387)	66.94 (15.578)	10.915***¶	0.016	0.792***	0.821***	0.375	0.396
VSTMB 3 Binding performance (%)	74.03 (11.754)	60.32 (10.941)	57.19 (13.052)	57.45 (13.827)	25.185***¶	1.207***	1.355***	0.259	1.292***	0.230
Visual-FCSRT Total Free Recall (TFR)	33.57 (4.096)	32.72 (5.423)	29.27 (6.939)	11.42 (6.556)	119.132***¶	0.176	0.754*** (+)	0.554*** (—)	4.052***	3.540***
Visual-FCSRT Total Immediate Recall (TIR)	47.83 (1.558)	47.33 (1.427)	46.65 (3.9)	34.16 (9.526)	96.412***¶	0.334	0.400	0.231	2.002***	1.933***
Visual-FCSRT Delayed	12.69 (2.104)	12.14 (2.369)	11.01 (3.111)	3 (3.120)	107.222***¶	0.245	0.632** (++)	0.408* (—)	3.641***	3.299***

Free Recall (DFR)										
Visual-FCSRT Total Delayed Recall (TDR)	15.83 (0.596)	15.88 (0.363)	15.35 (2.317)	10.52 (4.946)	57.495***⁋	0.101	0.283	0.319	1.507***	1.528***
T-ADLQ BALD (%)	0.37 (1.56)	1.17 (2.91)	2.73 (7.36)	8.94 (11.52)	15.455***⁋	0.342	0.443	0.278	1.042***	0.924***
T-ADLQ IADL (%)	8.78 (11.78)	8.81 (10.43)	12.26 (13.69)	43.25 (16.35)	63.055***⁋	0.002	0.272	0.283	2.979***	2.512***
T-ADLQ a-ADL (%)	20.15 (17.08)	21.75 (18.78)	28.87 (21.26)	50.34 (24.36)	18.096***⁋	0.089	0.452	0.354	1.435***	1.314***
T-ADLQ Total Score (%)	9.36 (10.11)	9.57 (8.49)	12.96 (11.79)	38.67 (14.71)	61.337***⁋	0.022	0.327	0.330	2.322***	2.423***

Note. SB: Strong Binders; WB: Weak Binders; MCI: Mild Cognitive Impairment; AD: Alzheimer Disease; ES: Effect Size; * $p \leq 0.05$; * $p \leq 0.059$; ** $p \leq 0.01$; *** $p \leq 0.001$. (After ANCOVA adjusted by education for variable of no interest: ¯ $p \geq 0.05$; $^{+}$ $p \leq 0.05$; $^{++}$ $p \leq 0.01$; $^{+++}$ $p \leq 0.001$; ⁋ Survived FDR correction)

Missing data for Education: 1 MCI.
Missing data for ACE III: 3 WB, 2 MCI.
Missing data for IFS: 4 WB, 1 MCI.
Missing data for Total FAS: 3 WB, 1 MCI.
Missing data for TMT A: 2 SB, 5 MCI.
Missing data for TMT B: 2 SB, 5 MCI, 1 AD.
Missing data for T-ADLQ BADL: 5 SB, 5 WB, 6 MCI, 1 AD.
Missing data for T-ADLQ IADL: 5 SB, 5 WB, 6 MCI, 1 AD.
Missing data for T-ADLQ a-ADL: 5 SB, 5 WB, 6 MCI, 1 AD.
Missing data for Total T-ADLQ: 5 SB, 5 WB, 6 MCI, 1 AD.

Table 3

Strong Recallers vs. Weak Recallers

	SR (n =131)	WR (n = 23)	MCI (n = 79)	ADD (n = 31)	ANOVA *F* (p-value)	ES (SR vs WR)	ES (SR vs MCI)	ES (WR vs MCI)	ES (SR vs ADD)	ES (WR vs ADD)
Age, mean (SD) years	75.73 (4.56)	77.74 (5.22)	77.56 (4.88)	78.16 (7.63)	3.731*¶	0.417	0.395*	0.035	0.392	0.064
Education	10.56 (4.74)	10.61 (5.27)	7.58 (4.16)	12 (3.97)	9.644***¶	0.009	0.667***	0.637*	0.329	0.297
Gender (M:F)	102:29	15:8	68:11	16:15	χ^2 = 16.281***¶	-	-	-	-	-
ACE III Total Score	84.98 (7.96)	77.82 (8.47)	70.70 (10.71)	65.74 (11.87)	56.247***¶	0.871**	1.513*** (+++)	0.737* (—)	1.903***	1.171***
MoCA Total Score	24.83 (3.23)	23.26 (2.45)	15.58 (3.83)	16.03 (4.92)	132.365***¶	0.546	2.608*** (+++)	2.389*** (+++)	2.114***	1.860***
IFS Total Score	18.77 (4.01)	16.98 (4.33)	12.80 (4.59)	13.69 (4.72)	35.357***¶	0.429	1.386*** (+++)	0.936*** (+)	1.160***	0.726*
Total FAS	32.37 (11.46)	25.22 (13.39)	22.10 (10.82)	29.26 (11.2)	13.691***¶	0.573*	0.921*** (+++)	0.256	0.274	0.327
TMT-A	80.32 (37.868)	99.91 (38.171)	119.81 (93.604)	121.13 (52.096)	8.180***¶	0.515	0.553*** (+)	0.278	0.896**	0.464
TMT-B	167.35 (76.846)	232.87 (145.675)	316.23 (156.961)	262.23 (138.047)	25.710***¶	0.562	1.186*** (+++)	0.550* (—)	0.849***	0.206
VSTM 2 'Single Shapes' performance (%)	91.52 (9.399)	89.67 (9.536)	79.91 (16.435)	84.07 (17.066)	13.825***¶	0.195	0.867***	0.726**	0.540*	0.405
VSTM 3 'Single Shapes' performance (%)	81.01 (13.006)	75.82 (12.256)	70.65 (12.947)	72.98 (16.001)	10.891***¶	0.410	0.798***	0.410	0.550*	0.199
VSTMB 2 Binding performance (%)	73.61 (16.258)	69.02 (16.043)	61.08 (13.387)	66.94 (15.578)	10.687***¶	0.248	0.841***	0.537	0.418	0.131
VSTMB 3 Binding performance (%)	66.88 (12.919)	57.61 (10.652)	57.19 (13.052)	57.45 (13.827)	12.305***¶	0.782**	0.746***	0.035	0.704**	0.012
Visual-FCSRT Total Free Recall (TFR)	34.55 (3.533)	24.52 (2.874)	29.27 (6.939)	11.42 (6.556)	178.892***¶	3.114***	0.958*** (+++)	0.894*** (+++)	4.392***	2.588***
Visual-FCSRT Total Immediate Recall (TIR)	47.70 (1.262)	46.48 (1.755)	46.65 (3.9)	34.16 (9.526)	97.378***¶	0.798	0.362	0.056	1.992***	1.798***
Visual-FCSRT Delayed Free Recall (DFR)	12.84 (1.888)	9.52 (2.313)	11.01 (3.111)	3 (3.120)	131.546***¶	1.572***	0.711*** (+++)	0.543(+)	3.815***	2.374***

Visual-FCSRT Total Delayed Recall (TDR)	15.92 (0.411)	15.52 (0.593)	15.35 (2.317)	10.52 (4.946)	57.930***⁋	0.784	0.342	0.100	1.538***	1.419***
T-ADLQ BALD (%)	0.82 (2.51)	1.15 (2.58)	2.73 (7.36)	8.94 (11.52)	15.320***⁋	0.129	0.347	0.286	0.974***	0.933***
T-ADLQ IADL (%)	8.21 (9.99)	11.55 (14.78)	12.26 (13.69)	43.25 (16.35)	64.164***⁋	0.264	0.337	0.049	2.586***	2.034***
T-ADLQ a-ADL (%)	20.26 (17.49)	25.48 (20.87)	28.87 (21.26)	50.34 (24.36)	18.779***⁋	0.271	0.442* (¯)	0.160	1.418***	1.096***
T-ADLQ Total Score (%)	8.89 (8.66)	11.91 (10.94)	12.96 (11.79)	38.67 (14.71)	62.544***⁋	0.305	0.393* (¯)	0.092	2.467***	2.064***

Note. SR: Strong Recallers; WR: Weak Recallers; MCI: Mild Cognitive Impairment; ADD: Alzheimer Disease Dementia; ES: Effect Size*; * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.* (After ANCOVA adjusted by education for variable of no interest: ¯ $p \geq 0.05$; $^{+}$ $p \leq 0.05$; $^{++}$ $p \leq 0.01$; $^{+++}$ $p \leq 0.001$; ⁋ Survived FDR correction. SR vs MCI ANCOVA model include education and age as variables of no interest).

Missing data for Education: 1 MCI.
Missing data for ACE III: 2 SR, 1 WR, 2 MCI.
Missing data for IFS: 3 SR, 1 WR, 1 MCI.
Missing data for Total FAS: 3 SR, 1 MCI.
Missing data for TMT A: 2 SR, 5 MCI.
Missing data for TMT B: 2 SR, 5 MCI, 1 AD.
Missing data for T-ADLQ BADL: 10 SR, 6 MCI, 1 AD.
Missing data for T-ADLQ IADL: 10 SR, 6 MCI, 1 AD.
Missing data for T-ADLQ a-ADL: 10 SR, 6 MCI, 1 AD.
Missing data for Total T-ADLQ: 10 SR, 6 MCI, 1 AD.

Figure 1

Examples of trial design for the different conditions of the VSTMBT across the two memory loads (set size 2 and 3).

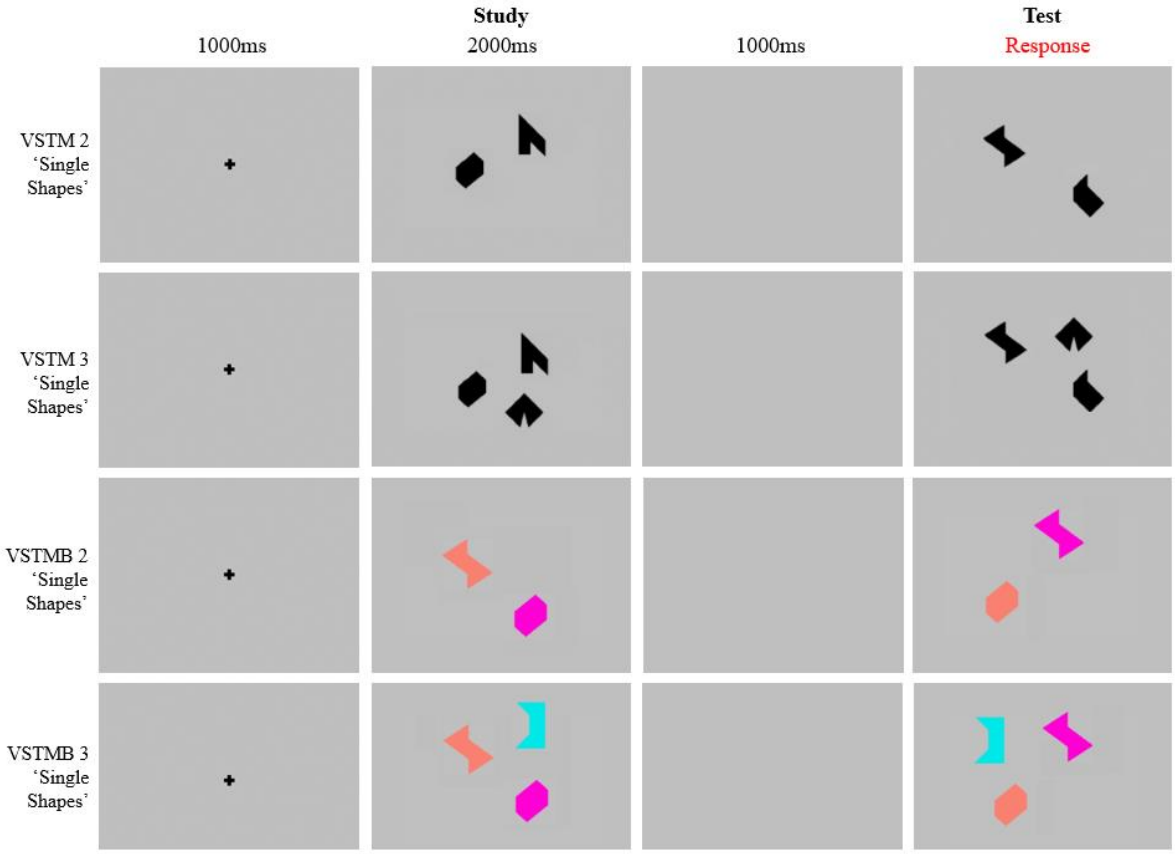

Figure 2

Administration sequence for the FCSRT. After the four Cards were presented, Total Free Recall and Total Cued Recall (TFR and TCR), Total Immediate Recall (TIR = TFR + TCR), Delayed Free Recall (DFR) and Total Delayed Recall (TDR) were calculated (see text for more details).

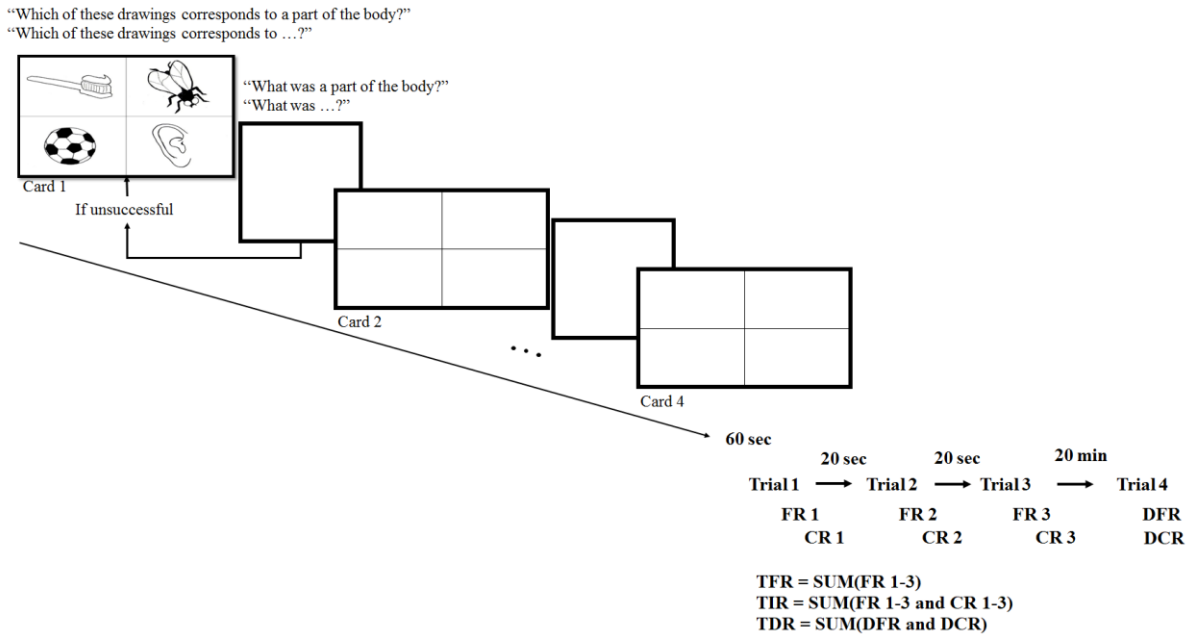

Figure 3.

Analysis of the interaction between Group (SB vs WB) and Condition (Single Shape vs Shape-Colour Binding).