Short-Term Memory Binding is insensitive to the socioeconomic status of older adults with and without Mild Cognitive Impairment

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This is a peer-reviewed, accepted author manuscript of the following article: Martínez-Flórez, J. F., Belalcázar, M., Alvarez, A., Erazo, O., Sevilla, S. T., & Parra Rodriguez, M. (in press). Short-term memory binding is insensitive to the socioeconomic status of older adults with and without mild cognitive impairment. The Clinical Neuropsychologist.

Abstract

Objective: The Visual Short-Term Memory Binding (VSTMB) Test is a useful tool in the assessment of Alzheimer's disease (AD). Research has suggested that short-term memory binding is insensitive to the sociocultural characteristics of the assessed individuals. Such earlier studies addressed this influence by considering years of education. The current study aims to determine the influence of sociocultural factors via a measure of Socioeconomic Status (SES) which provides a more holistic approach to these common confounders.

Methods: A sample of 126 older adults, both with (n = 59) and without (n = 67) amnestic mild cognitive impairment (aMCI), underwent assessment using a neuropsychological protocol including VSTMB test. All participants were classified as either high SES or low SES, employing the Standard Demographic Classification from the European Society for Opinion and Marketing Research.

Results: ANOVA/ANCOVA models confirmed that performance of healthy and aMCI participants on traditional neuropsychological tests were sensitive to SES whereas the VSTMB Test was not. The results add to the growing array of evidence suggesting that there are cognitive abilities which are unaffected by socioeconomic factors, regardless of clinical condition.

Conclusions: The lack of sensitivity to sociocultural factors previously reported for the VSTMB test is accompanied by a lack of sensitivity to socioeconomic factors thus broadening the scope of this test to aid in the detection of dementia across populations with different backgrounds. Future studies should take these findings forward and explore the potential influences of AD biomarkers (A/T/N) on the association between cognitive functions and demographic variables.

- **Key Words:** Cognitive Aging, Alzheimer Disease Early Onset, Neuropsychological Tests, Short-Term memory binding, Socioeconomic Factors, Neuropsychology.

Introduction

Aging impacts cognitive functioning, and a significant percentage of older people will experience cognitive decline linked to dementia risk. The onset and rate of cognitive decline in aging can be influenced by external factors such as level of education (Rosselli et al., 2022), economic status (Ibanez et al., 2023), cultural beliefs (Cipriani & Borin, 2015), ethnic and racial disparities (Babulal et al., 2019), and internal factors such as a genotypes (Bellenguez et al., 2022) linked to dementia risk (Jack et al., 2018), comorbidities (Livingston et al., 2020), and others. Disentangling the influence of Alzheimer's Disease (AD) on brain changes from the influence of socio-contextual factors in cognitive aging is a key challenge that the field of neuropsychological assessment currently faces (Parra, 2014, 2022a).

Currently, aging research aims to identify cognitive markers that can support the detection of early disease stages. Such tools can aid health professionals and stakeholders to work in global teams with the goal of using research to create interventions and tools that might improve disease management, delay symptom onset, and slow the progression of the disease. Different cognitive functions such as spatial navigation (Sensitivity 0.92; Specificity = 0.92) (Segen et al., 2022; Wiener et al.,2020), phonological (Sensitivity: 0.89; Specificity, 0.85) (Wright et al., 2023) and semantic fluency (Sensitivity 0.75; Specificity 0.81) (Marra et al., 2021; Payton et al., 2020) or visual short term memory binding (Sensitivity 0.90; Specificity 0.78) (VSTMB, (Cecchini et al., 2021; Parra et al., 2010a)) have been identified as cognitive markers to detect early AD-associated cognitive impairment. Cognitive assessment and the correct identification of dementia symptoms are further challenged by issues such as cultural diversity and social disparities (Parra

et al., 2018; Parra et al., 2019; Quiroz et al., 2022). In this context of diversity, the effects of cultural backgrounds, socioeconomic factors, including the educational and socioeconomic status of individuals being assessed play a pivotal role. At least, two major issues can be identified in this area. One relates to how such socio-contextual constructs are defined. The other is linked to appropriate and situated forms of neuropsychological assessment in older adults.

Socioeconomic Status (SES) is a construct that encompasses educational, income and occupational resources and is a factor that influences individuals' life outcomes (Farah, 2017). Lower SES has been recognized as a risk factor for AD, which impacts the severity and speed of cognitive decline and increases the risk of death from disease (Cadar et al., 2018; Petersen et al., 2021). Older individuals with low socioeconomic status may experience a life path characterized by limited cognitive engagement and access to environmental resources. This could lead to poorer cognitive functioning and a faster decline in cognitive abilities as they age (Darin-Mattsson et al., 2017; Steptoe & Zaninotto, 2020). Furthermore, older adults with low SES show poorer performance on cognitive assessment tasks, making it difficult to discern their premorbid cognitive profile from early stages of AD with the current neuropsychological tests used in clinical practice (Ardila et al., 1989; Ortega et al., 2021). This influence may be modulated by mechanisms associated with the concept of cognitive reserve (Stern, 2012). Socio-contextual conditions, including SES, can profoundly impact brain health over time, accumulating their effects through critical periods leading up to different life trajectories into older age (Elbejjani et al., 2017). Also, low SES has effects at a macroscopic level on the brain (Brito & Noble, 2014), alterations in physiological brain dynamics, levels of biomarkers, and allostatic overload (Ibanez et al., 2023) but studies in this regard are usually interested in healthy adults (Elbejjani et al., 2017) and are rare in the Latin American context. Recent studies have started to raise awareness

about this long-standing barrier and urged to identify methodologies to overcome it (Ibanez et al., 2021; Parra et al., 2021).

Different strategies have been used to overcome socioeconomic and cultural barriers in the cognitive assessment of MCI. These include translating cognitive tests and adapting their cut-off scores for different populations. However, despite being the most widely used strategies, these approaches have been criticized for language translation errors, loss of original meaning in verbal subtests, and, in many cases, the familiarity required with concepts from Western and educated culture (such as the alphabet, names of prominent figures, and historical background) to assess domains like memory or language, resulting in loss of sensitivity, specificity, validity, and consistency of cognitive outcome measures (Mirza, Waheed & Waheed 2022; Milani et al., 2018). Another strategy has been the development of specific cross-cultural tools. Some tools as the Rowland Universal Dementia Assessment Scale (RUDAS) (Nielsen & Jørgensen, 2020), the Cross-Cultural Dementia Screening (CCD) (Goudsmit et al., 2017) and the Cross-Cultural Neuropsychological Test Battery (CNTB) (Nielsen et al., 2019) have been recently proposed as screening tools for dementia symptoms (Custodio et al., 2020; Custodio et al., 2021). Although these tests have demonstrated favorable sensitivity and specificity values for detecting symptoms of dementia, their validation in the case of CCD and CNTB has been restricted to migrant populations in the European context. Concerning RUDAS, due to the verbal load of the test, the potential need for an interpreter in some instances has been reported for a comprehensive assessment, which could pose a limitation (Delgado-Álvarez et al., 2023).

The VSTMB Test (Parra et al., 2010) assesses *conjunctive binding* functions, which consist of the ability to integrate and maintain object's features into unified representations. In its visual recognition version, which relies on the change detection paradigm (Parra et al., 2010a; Wheeler & Treisman, 2002), *conjunctive binding* is assessed by detecting changes across two consecutive

arrays displaying either single features such as shapes, or feature bindings i.e., colored shapes. This cognitive function is preserved in healthy aging (Brockmole et al., 2008; Isella et al., 2015; Parra et al., 2010a; Rhodes et al., 2016). In the last decade, it has been reported as a sensitive cognitive marker for pathological cognitive decline and AD in aging (Cecchini et al., 2021; Parra et al., 2010a). Experimental evidence drawn from the VSTMB test, based on the change detection paradigm, has shown specific deficits in binding functions in individuals with AD in its sporadic (Parra et al., 2010a) and familial clinical variants (Parra et al., 2010b). This sensitivity holds in the early stages of memory decline as in amnestic Mild Cognitive Impairment (aMCI) and Subjective Cognitive Decline (Koppara et al., 2015; Martínez-Florez et al., 2021; Parra et al., 2019). More recent results (Parra et al., 2022; Parra et al., 2024) (Forno et al., 2022b) showed that it can help trace the transition from normal aging to AD dementia. Interestingly, VSTMB has proved to be insensitive to the educational background of individuals being assessed whether via its change detection version (Parra et al., 2011), free recall (Yassuda et al., 2020), or memory reconstruction (Hoefeijzers et al., 2017). The performance on the VSTMB test engages the brain regions of the ventral visual stream instead of the hippocampus, which supports its potential for early detection of AD (Parra et al., 2014b; Martinez et al., 2019). The potential of the VSTMB test lies in the fact that the task presents nonverbal simple stimuli and colors. The stimuli presented in the task are not dependent on education or a particular cultural context. The administration is based on straightforward instructions and does not require specific knowledge. Therefore, it can also be used to assess people with low and high literacy levels and diverse sociocultural backgrounds. This evidence reinforces the notion that binding function is a suitable cognitive marker to distinguish healthy cognitive from pathological aging in a culture-free manner (Della Sala et al., 2018).

Recently, there has been a growing discussion about the limited scope of the variable education level to capture the multitude of factors that underlie socio-contextual abilities. For example, in a recent meta-analysis, Maccora et al. (2020) concluded that while the evidence of an association between low education and dementia incidence is robust, inconsistency in the definition, measurement and operationalization of education hinders the translation of this evidence into practical policy recommendations to reduce dementia risk (see Bodryzlova et al. (2022) for a similar view). Therefore, we decided to expand this study's approach by focusing on SES, which is a construct that has been operationalized as a composite variable for research in an international standardized questionnaire with consistent results (Hoffmeyer-Zlotnik, 2008; Lizana et al., 2018; Migeot et al., 2022; Wolf & Hoffmeyer-Zlotnik, 2003). As noted above, the impact of SES on cognitive markers for dementia, such as the VSTMB test, has not been widely researched to date. Therefore, this paper aimed to investigate the effect of SES on cognition and VSTMB in older adults with and without aMCI. Based on existing evidence, it was predicted that contrary to traditional neuropsychological tests, which can be highly sensitive to SES, the VSTMB test would not be sensitive to SES.

Methods

Participants and Sample configuration

The sample consisted of 176 participants recruited from the Ambulatory and Residence service of the "San Miguel" geriatric hospital in Cali, Colombia, the Care Center of Older People (COMFANDI) and old age university programs in the city. Inclusion criteria for both groups were to be ≥ 60 years old and healthy according to a self-reported questionnaire. None of the participants reported a history of neurological or psychiatric disorders or substance abuse, as

assessed by a semi-structured clinical interview. This study was approved by the Ethics Committee of the Health Faculty of Universidad Santiago de Cali and Geriatric Hospital "San Miguel" in Cali, Colombia. The study follows the ethical principles of the Declaration of Helsinki (2013). All participants gave their written informed consent to take part in the study.

The first step in the sample configuration was to classify participants' SES level according to the Standard Demographic Classification from the European Society for Opinion and Marketing Research (ESOMAR) (Wolf & Hoffmeyer-Zlotnik, 2003). This questionnaire has proven to be a useful tool for measuring SES internationally, including the Latin American population (Celis-Morales et al., 2012; Migeot et al., 2022). The estimation of SES provided by the ESOMAR classification derives from a dimensional guideline that includes information about the education level and occupation history and status of the main income earner of the household, and in the case of unemployed or retired participants, the economic status defined according to the ownership of specific material goods. The ESOMAR includes six classifications: A=very high, B=high, Ca=medium–high, Cb=medium, D=medium–low, and E=low. Based on Migeot et al. (2022) and Lizana et al. (2018), this study merged levels D and E into the low-SES group and levels B and Ca into the high-SES group (total n=69) (see figure 1 for sample configuration). None of the participants were classified as level A, and a small number of participants (n=4) classified at the CB medium level were excluded to ensure the accurate categorization of individuals as high or low SES avoiding the risk of bias.

[INSERT FIGURE 1 HERE]

The second step aimed to identify participants who might have aMCI at the time of recruitment according to the core clinical criteria proposed by NIA-AA guidelines (Jack et al.,

2018; Petersen et al., 2013; Albert et al., 2011; Sperling et al., 2011). These criteria included: subjective cognitive complaints and concerns about cognitive impairment in the past year in relation to a preexisting pattern, objective cognitive decline in one or more cognitive domains (-1.5 SD compared with normative data), preservation of functional independence in daily activities, and no evidence of dementia. The Mini-Mental State Examination (MMSE) (Upton, 2013) and the Addenbrooke's Cognitive Examination Revised (ACE-R) (Mioshi et al., 2006) were used to ascertain normal cognitive performance. We relied on the scores for the subscales of ACE-R to detect cognitive impairment in specific cognitive domains, and to ascertain that our participants have an objective memory impairment we used the scores of the Memory domain of ACE-R and the Rey Auditory Verbal Learning Test (RAVLT) delayed recall (Bean, 2011). The Functional Activities Questionnaire (FAQ), Lawton-Brody Instrumental Activities of Daily Living Scale (IADL) (Fish, 2011; Lawton & Brody, 1969), and the Physical Self-Maintenance Scale (PMMS) (Pfeffer et al., 1982) were used to check for the absence of severe impairments in functional abilities. The Geriatric Depression Scale (GDS) (Yesavage et al., 1982) was used to rule out depression, and the Hachinski Ischemic Score (HIS) (Pantoni & Inzitari, 1993) was used to discard signs of vascular pathology. Previously translated and adapted to Colombian and/or Latin-American population versions of these tests were used. The cut-off scores according to local normative data were: MMSE: ≥25 (For those with + 9 years of education, ≥24 for 5-9 years, and ≥23 for 1-5 years) (Roselli et al., 2000); ACE-R: ≥82 (for ages 60-69, ages 70-75 ≥78), ACE-R MD: ≥19 (for ages 60-69, ages 70-75 ≥17) (Ospina-Garcia, 2015), RAVLT delayed recall: 4, FAQ: <5, GDS: ≤4, HIS: ≤4 (Henao-Arboleda et al., 2010; Lasprilla, 2015). The control group was defined based on self-reported good health, and in accordance with the specified cut-off scores and inclusion criteria.

It is worth noting that recent evidence suggests that control participants that are defined based on self-report and even on standardized neuropsychological tests, may not be true controls (Bos et al., 2018; Hassenstab et al., 2016). For instance, Parra et al. (2022) recently reported that of 70 self-reported healthy participants who entered their study, 27 met criteria for objective cognitive decline. Those participants had significant VSTMB deficits as the most silent cognitive feature. More recently, Forno et al. (2022a) divided controls and older adults with subjective cognitive decline (SCD) based on VSTMB test performance classifying them into Strong Binders and Weak Binders. These authors discovered that individuals classified within the Weak Binders category were the sole group displaying signs of very early (still subjective) cognitive decline. This evidence suggests that VSTMB abilities can assist in the identification of individuals who can be categorized as true controls (in line with Bos et al., 2018). In this regard, recent evidence suggests that a binding cost >20% (a drop in performance on the Shape-Color Binding condition relative to the Shape Only condition) is highly indicative of AD risk or the presence of dementia (see also Parra et al., 2017; Parra et al., 2024). Consequently, we decided to follow the methodology used by Forno et al. (2022a) and Parra et al. (2024) to exclude Weak Binders from our control group. To calculate the binding cost, we employed the formula as reported by Forno et al. (2022a) and Parra et al. (2024): [Binding cost = ((Shape-only - Shape-color Binding)/ Shape-only) * 100].

After (1) classifying and merging participants' SES level according to the study's objective, (2) confirming the presence of the aMCI clinical criteria, and (3) excluding Weak Binders, our final sample was composed by the following groups: 40 Low SES controls, 33 Low SES aMCI, 27 high SES controls, and 26 high SES aMCI. The demographic, clinical and cognitive characteristics of these groups are presented in Table 1 (see Supplementary Table S.1 for the full set of data).

Finally, an *a priori* power analysis was conducted using GPower version 3.1.9.7 (Faul et al., 2007) to ensure an adequate sample size. The results indicated that, for a medium effect size (η^2 = 0.25), a probability of error of $\alpha = 0.05$, a moderate correlation between repeated measures (r = 0.5), and a 4-group design with 2 repeated measures, a total sample size of 48 participants would suffice to achieve a power of 80%. Hence, we achieved adequate statistical power.

Assessments

Background assessment

The clinical evaluation included a semi structured sociodemographic and health interview, the functional and clinical tests previously mentioned such as the HIS, GDS, FAQ, PSMS, IADL. To rule out color blindness, participants were assessed with the Ishihara Test for Color Blindness (Pickford, 1944). The clinical neurocognitive protocol, as mentioned before, included the ACE-R, the MMSE, the Rey Auditory Verbal Learning Test (RAVLT) (Bean, 2011), Rey–Osterrieth Complex Figure Test (ROCF) (Berry et al., 1991; McKinlay, 2011), the phonological and semantic verbal fluency tasks (Nass, 1984), the Trail Making Test Form A and B (Bucks, 2013; Tombaugh, 2004), the Digit Symbol Substitution Test from the Wechsler Adult Intelligence Scale (WAIS-IV) (Bettcher et al., 2011), the digit span test (Wambach et al., 2011) and an abbreviated version of the Boston Naming Test (Roth, 2011) consisting of 20 items.

The Visual Short Term Memory Binding Test (VSTMB)

The VSTMB, which is based on a change detection paradigm, was presented on an HP laptop with a 15-inch monitor, following the methodology outlined in previous studies (Della Sala et al., 2012; Parra et al., 2010b; Parra, et al., 2009; Parra et al., 2019). The task started with a fixation screen and required participants to memorize visual arrays containing three black shapes (Shape-

only condition) and colored shapes (Shape-color binding condition) presented for 2 seconds on a study display. Following a 1-second delay, a probe screen emerged, presenting either the same or a different stimulus in new random positions. Participants were instructed to verbally indicate whether the stimuli on the probe visual array were the same or different to those presented on the study array. Thirty-two trials were presented in random order for each condition (shape condition; shape-color binding), with 50% being "different trials" i.e., changes occurred in the probe display whereby two new shapes (Shape-only condition) or two new bindings (Shape-color binding condition) were presented. The completion time for the task typically ranged from 10 to 15 minutes per participant. The proportion of correct responses was the dependent variable.

[INSERT FIGURE 2 HERE]

Data Analysis

First, to test the effect of SES on older adults' cognition with and without aMCI, a two-way ANOVA (Clinical Group (aMCI vs Controls) x SES (Low vs High)) was conducted to compare clinical and neuropsychological data, with Bonferroni corrections applied to post-hoc tests to control for multiple comparisons.

Next, a 3-way mixed ANOVA model was formulated to determine whether clinical status and SES exerted any influence on binding performance. In this model, we incorporated two levels of the Experimental condition as the within-subjects factor (Shape vs Shape-color binding), as well as two levels of each between-subjects factor, Clinical Group (aMCI vs Controls) and SES (Low vs High). Finally, a variation of this model was used, a 3-way mixed ANCOVA with ACE-R as a

covariate which aimed to investigate whether the severity of cognitive decline could be considered an explanatory variable of the observed effects. Effect sizes were calculated and the significance level was set at 0.05 for all analyses. In the presence of significant effects and interactions, Bonferroni-corrected post-hoc comparisons were conducted. We reported on the core ANOVA outcomes (F, df, and p-value) and the associated effect size (partial eta squared η^2 = 0.01 small, 0.06 medium, 0.14 large). The procedures were performed using SPSS v25.

Results

The results of the sociodemographic, clinical, and cognitive assessments are summarized in Table 1. There were no significant differences in age between the groups, and no differences in gender composition of the sample by clinical ($\chi2(1, n=126) =0.72$, $p=0.39$) or SES group ($\chi2(1, n=126) =1.32$, $p=0.25$). As education is inherently included in the SES definition, we observed differences in this variable when considering the SES main effect. Additionally, the functional scales used (i.e., FAQ, PMMS, Lawton & Brody) confirmed that the groups showed equivalent functional performance and did not show depression (GDS) or evidence of cerebrovascular pathology (HIS), thus endorsing the status of early aMCI.

Results of the neuropsychological assessment revealed that, in comparison to the control groups, the aMCI groups exhibited lower performance in all tasks. In relation to the influence of SES, the results showed a significant effect of SES, regardless of the clinical condition, on almost all conventional neuropsychological tasks, except for the TMT-B, and a marginal effect on the MMSE. The scores from the VSTMB test (% of Correct Recognition and the binding cost) showed an effect of Group but not of SES. Concerning the Clinical Group*SES interaction, a significant effect was observed for the ACE-R, MMSE, ACE-R (MD) and digit span, seemingly

driven by the lowest scores achieved by aMCI from the low SES Group. However, this interaction effect was absent in other related tasks, including RAVLT, RAVLT DR, ROCF immediate and delayed recall, TMT-A, DS, phonological and semantic fluency (see Table 1), denoting a general impact of SES on such abilities, which was independent of group membership.

[INSERT TABLE 1 HERE]

A three-way mixed ANOVA was conducted to determine the potential influence of the Clinical Group and SES conditions on binding performance.

[INSERT FIGURE 3 HERE]

The main effects of the model demonstrate that there was a main effect of the Experimental Condition [F (1.122) =513483, $p < 0.001$, $\eta^2 = 0.274$]. There was also an effect of the Clinical Group condition [F (1.122) = 141.587, $p < 0.001$, $\eta^2 = 0.346$] and a marginal non-significant effect for the SES condition [F (1.122) = 3.399, p 0.068, $\eta^2 = 0.008$]. The only interaction that reached the threshold of significance was the Clinical Group*Experimental Condition [F (1.122) = 12.638, $p < 0.001$, $\eta^2 = 0.007$]. None of the remaining interactions reached the significance threshold (SES*task condition [F (1.122) = 1.182, p 0.279, $\eta^2 =0.00006$]; Clinical Group*SES [F (1.1) = 0.077, $p = 0.782$, $\eta^2 = 1.875e\text{-}4$]; Experimental Condition*Clinical Group*SES [F (1.122) = 3.483, $p = 0.064$, $\eta^2 = 0.002$]). Lastly, a post-hoc analysis was performed to evaluate the group*task condition interaction. The results showed that, for the control group, the binding condition was significantly more demanding than the shape condition [$t = 13.871$, $p < 0.001$]. However, this discrepancy was significantly more pronounced in the aMCI groups [$t = 18.078$, p

< 0.001]. (Table 1 shows data from the Shape-color binding condition i.e., VSTMBT and the Binding Cost, as these inform on the core function investigated here i.e., binding).

In the mixed ANCOVA model, covarying for ACE-R showed that the only main effect that remained significant after this control was the Clinical Group [F (1.121) = 3.087, p < 0.001, η^2 = 0.199]. Neither SES [F (1.122) = 0.715, p= 0.400, η^2 = 0.004] nor Task Condition [F (1.121) = 1.233, p = 0.269, η^2 = 0.001] proved significant. Regarding interactions, the core Clinical Group*Experimental Condition remained significant [F (1.121) = 4.988, p < 0.027, η^2 = 0.006]. No other interaction reached the significance threshold: SES*Clinical Group; [F (1.121) = 0.546, p= 0.461, η2 = 0.003]; Experimental condition*SES [F (1.121) = 0.925, p= 3.338, η^2 = 0.001; Experimental Condition*Clinical Group*SES [F (1.121) = 3.208, p= 0.076, η^2 = 0.004]. These results support the hypothesis that SES does not disproportionately impact the participants' performance on the VSTMB test and that it holds regardless of the disease severity.

Discussion

The current study aimed to investigate the influence of SES on cognitive makers for dementia, including the VSTMB test, in older adults with and without aMCI. We predicted that this recently identified cognitive ability would not be sensitive to such a demographic factor. The key findings from the study are as follows: (1) SES significantly impacted performance on almost every traditional neuropsychological task we used for assessment. (2) Interestingly, the VSTMB test proved to be insensitive to the influence of SES, suggesting that this cognitive measure remains robust across different socioeconomic backgrounds. We will now discuss these findings in detail.

Sensitivity of Traditional Neuropsychological Tests to SES

Our results support the hypothesis that low SES negatively impacts general cognitive abilities and memory in older adults. Moreover, low SES groups, independent of their clinical condition, tend to perform poorly compared to high SES groups. These findings are consistent with previous research studies, which have now regularly reported a cognitive disadvantage among both young and older individuals with low SES compared to those with high SES (Migeot et al., 2022; Noble et al., 2012; Shi et al., 2023; Zhang et al., 2022; Elbejjani et al., 2017). Therefore, we suggested that the sensitivity of traditional neuropsychological tests could reflect a significant bias, capturing the influence of sociodemographic factors that distinguish healthy cognition from cognitive impairment in aging. Growing evidence suggests that this bias not only affects the association of sociodemographic factors and behaviors, but also complicates the interpretation of the stage of brain pathology underlying said associations (Mungas et al., 2009).

VSTMB and SES

The key hypothesis of the present study concerned the relationship between performance on the VSTMB test and SES. We predicted that SES would not differentially impact VSTMB performance in a sample consisting of both aMCI participants and healthy controls. The results from our mixed models supported this prediction. Our findings confirmed that the binding condition of the VSTMB is more cognitively demanding than the shape-only condition, and this experimental condition proves highly sensitive to clinical cognitive impairment, in line with previous studies (Cecchini et al., 2022; Isella et al., 2015; Koppara, et al., 2015; Parra et al., 2010a; Parra et al., 2010b; Parra, et al., 2019; Parra et al., 2011a; Parra et al., 2011b). Our results demonstrate that this observed effect did not significantly interact with SES, indicating that the

VSTMB test is insensitive to the demographic variations encompassed by SES. Our study added novel insights on the influence of sociodemographic variables on VSTMB performance. We do not consider our finding a replication of previously described results, as those studies explored sociodemographic factors only from the perspective of years of education (e.g., Yassuda et al., 2020). We feel confident that our study strengthens and expands the existing evidence by providing a more multidimensional measure such as SES that, in addition to education, includes occupational history and status. It is worth noting that even during the sample configuration process, we observed that SES would unlikely interact with the binding cost variable as the number of controls excluded due to a high binding cost (as suggested by Forno et al.,2022b and Parra et al., 2024) was higher in the high SES group compared to the low SES group. We have shown in Supplementary Table S.1 that keeping such participants in the sample would not modify the results supporting the sensitivity of the VSTMB test to MCI and its lack of sensitivity to SES. Following recent evidence (Parra, et al., 2024) and recommendations (Bos et al., 2018, who recommended biomarker-adjusted norms to establish normality), we decided to report on the data excluding such participants.

The results from this study are in line with those reported by Parra, et al. (2011a) and Yassuda et al. (2020) which confirmed that education does not differentially affect the binding cost. In fact, our results expand those earlier findings, since education is just a component entering our operationalization of the SES variable (Ardila, 2020; Bodryzlova et al., 2022; Rosselli & Ardila, 2003). Therefore, we feel confident to suggest that the VSTMB test is not only insensitive to education, but in a broader sense, to the effect of socio-contextual variables like SES. This has significant implications for addressing contemporary challenges in the fight against neurodegenerative disorders within diverse populations, as this test serves as a highly sensitive

and less biased tool for the early detection of AD. Additionally, it can be easily implemented at a lower cost compared to biomarkers (Butler et al., 2022; Parra et al., 2022). This makes the VSTMB test a valuable asset in the early diagnosis and monitoring of AD, especially in resource-limited settings or when considering diverse and economically varied populations in a broader context of brain health, as exemplified by the Colombian sample recruited in this study.

Another interesting observation was that the above-described results from the VSTMB test were independent of the disease severity. The core Group*Task Condition interaction consistently reported in the literature on VSTMB deficits in AD risk was observed in the present study with and without correction for disease severity (covarying for ACE-R), and in neither analysis SES impacted such outcomes (no three-way interactions). This is relevant too as a neuropsychological test that identifies individuals with aMCI independently of their socio-cultural background and disease severity, would aid in the very early detection of AD. That is exactly what Parra et al. (2022) recently demonstrated. Furthermore, Parra et al. (2024) recently showed that such behavioral patterns indicating risk of AD are independent of Cognitive Reserve and seemingly associated with increased brain amyloid deposits.

We would like to acknowledge some limitations in our study. First, although we administered some traditional neuropsychological tests known to be sensitive to AD, there are other promising tests also recommended by consensus groups such as the Free and Cued Selective Reminding Test (FCSRT) (Costa et al., 2017), which has been used in Latin American settings (Forno et al., 2022b). Given the relevance of these tests in informing the transition from normal to pathological aging (i.e., VSTMB) and the progression through the prodromal and early clinical stages (see Parra et al., 2022), future studies are needed to investigate whether the latter test is also insensitive to SES, as we explored in this study. Second, our final sample size was relatively

small. This was due to the strict inclusion and exclusion criteria we applied (e.g., Parra et al., 2024 and Bos et al., 2018), which resulted in a smaller healthy control group. Based on recent evidence (Forno et al., 2022b), we feel confident that these individuals are true control participants. Nevertheless, future studies will be required to explore if these recent notions (i.e., Bos et al., 2018) and methodological approaches (i.e., Forno et al., 2022b; Parra et al., 2024) will improve the prediction of future AD dementia among older adults at risk. Furthermore, to strengthen the generalizability of our findings, we need replication studies in larger samples of participants from various diverse and underrepresented settings.

In conclusion, using a reliable measure of SES for the first time, we have demonstrated that such a sociodemographic factor does not differentially affect performance on a cognitive task widely regarded as a maker for the preclinical detection of AD. Future studies should take this observation forward and explore the effects of SES on the brain-behavior association via pipeline AD biomarkers such as the A/T/N framework (Jack et al., 2016). Furthermore, our methodology should be generalized to other samples collected from more diverse cultures with different socio-contextual conditions. This will broaden our understanding of whether and to what extent these factors, either individually or in combination, impact neuropsychological assessment and cognitive performance in the context of aging.

Founding

This work was founded by the Direccion General de Investigaciones of Universidad Santiago de Cali (Grant number 450-621121-2927 call No. 11- 2021 & call No. 10-2023).

Disclosure of interest

All authors declare that they have no conflicts of interest.

Acknowledgements

This work is dedicated to the older adults of the San Miguel Geriatric Hospital and to all people who, for whatever reason, have grown old in conditions of poverty and inequality.

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Tables

Table 1. Means and standard deviations for demographic, clinical and cognitive scores with the sample divided into groups according to SES and MCI status.

	Low SES Controls (n=40)	Low SES aMCI (n=33)	High SES Controls (n=27)	High SES aMCI (n=26)	Main effect SES		Main effect group		Interaction SES*group	
					F	*p*-value	*F*	*p*-value	*F*	*p*-value
Age	71.00(7.26)	70.36(5.47)	69.92(4.12)	70.46(5.90)	.205	.651	.002	.963	.296	.587
Education	4.15(1.07)	3.57(1.30)	15.96(2.00)	15.73(1.51)	2051.02	.001	2.32	.130	.418	.519
Yesavage	1.35(0.92)	1.69(1.23)	.85(1.06)	1.26(1.88)	3.98	.048	2.71	.102	.023	.880
Hachinski	1.32(0.61)	1.75(.86)	1.18(.87)	1.30(1.08)	3.66	.058	3.24	.74	1.04	.316
FAQ	.92(1.74)	1.84(3.75)	.07(0.38)	.30(0.61)	9.13	.003	2.13	.146	.760	.385
ACE-R	90.70(3.88)[bd]	77.84(4.99)[acd]	92.74(3.55)[bd]	84.61(4.50)[abc]	32.56	.001	184.70	.001	9.37	.003
ACE-R (MD)	22.50(1.67)[bc]	17.54(1.09)[acd]	23.48(1.86)[bd]	20.46(2.37)[abc]	37.34	.001	156.34	.001	9.20	.003
MMSE	28.20(1.40)[bd]	24.18(1.97)[ac]	28.14(1.37)[bd]	25.23(1.27)[ac]	3.18	.077	154.00	.001	3.88	.051
RAVLT	5.20(.93)	3.54(1.00)	7.66(1.54)	5.96(1.58)	116.09	.001	54.96	.001	.012	.911
RAVLT DR	5.17(2.06)	2.48(1.46)	7.55(2.15)	5.26(1.09)	55.81	.001	51.81	.001	.341	.560
ROCF	20.79(9.12)	15.15(7.87)	29.83(7.81)	25.92(7.63)	44.10	.001	10.25	.002	.338	.562
ROF IR	9.37(6.32)	6.30(3.73)	13.63(6.30)	10.90(4.78)	20.22	.001	8.650	.004	.030	.862
ROF DR	5.56(3.34)	4.30(3.36)	12.25(6.43)	8.82(4.83)	47.30	.001	8.27	.005	1.772	.186
TMT-A	89.22(42.86)	134.48(77.34)	60.29(22.81)	89.30(59.86)	13.98	.001	14.04	.001	.672	.414
TMT-B	197.07(95.20)	238.19(91.42)	149.66(66.00)	244.53(113.97)	1.46	.228	16.09	.001	2.512	.116
Digit span	5.07(1.07)[b]	4.09(1.84)[acd]	5.66(1.27)[b]	5.69(1.25)[b]	19.08	.001	3.64	.059	4.406	.046
DS	22.00(11.69)	15.39(13.06)	34.22(12.46)	22.96(11.11)	20.37	.001	16.60	.001	1.12	.291
Boston NT	15.37(2.74)	14.72(2.51)	18.11(2.81)	16.03(2.82)	16.94	.001	7.65	.007	2.101	.150
VF	12.92(3.99)	9.42(5.86)	16.55(6.63)	11.92(4.81)	10.17	.002	17.90	.001	.347	.557
SF	15.42(4.08)	11.51(5.52)	19.92(5.31)	14.26(3.91)	17.87	.001	31.07	.001	1.03	.311
VSTMBT	65.70(4.30)	54.21(4.57)	68.00(5.39)	54.38(4.09)	2.22	.139	229.05	.001	1.64	.202
Binding Cost	11.37(4.37)	15.51(5.09)	9.92(7.87)	18.27(7.53)	.348	.557	31.52	.001	3.59	.060

* Notice the F and p values reported refers to Group * SES interaction. *Note*. GDS= Geriatric Depression Scale; FAQ=Functional Activities Questionnaire; ACE-R = Addenbrooke Cognitive Examination Revised (MD= Memory Domain); MMSE = Mini-Mental State Examination; RAVLT= Rey Auditory Verbal Learning Test (DR= Delayed Recall); ROCF= Rey–Osterrieth Complex Figure Test (IR= Immediate Recall; DR= Delayed Recall); DS= Digit Symbol Test (WAIS IV); VF= Verbal Fluency; SF= Semantic Fluency; VSTMBT = performance on the Shape-color binding condition. PMMS and Lawton & Brody test report variance equal to 0, so they are not reported in the table. Letters denote significant group differences in group*SES interactions a = differ from “Low SES control” group; b = differ from “Low SES aMCI” group; c = differ from “High SES control”; d = differ from “High SES aMCI”. VSTMBT: % of Correct Recognition. (see Supplementary Table S.1 for the full set of data).

Figure Legends

Figure 1. Workflow of sample configuration from the initial entering point to the final group allocation. Highlight the criteria used to generate each sample group (Total -> SES -> aMCI/Controls -> binding cost > [SES + MCI/Controls]) *Notice that of the total of 33 excluded controls, 25 are from High SES and 8 are Low SES (see Supplementary Table S.1 for the full set of data).

Figure 2. An example trial for each condition of the Short-Term Memory Binding Test using all Set Sizes (A=Shape only; B= Shape colour Binding 3 items; C= Shape-colour Binding 2 items).

Figure 3. Means and standard errors for the VSTMB according to aMCI and SES.

Figures

Figure 1

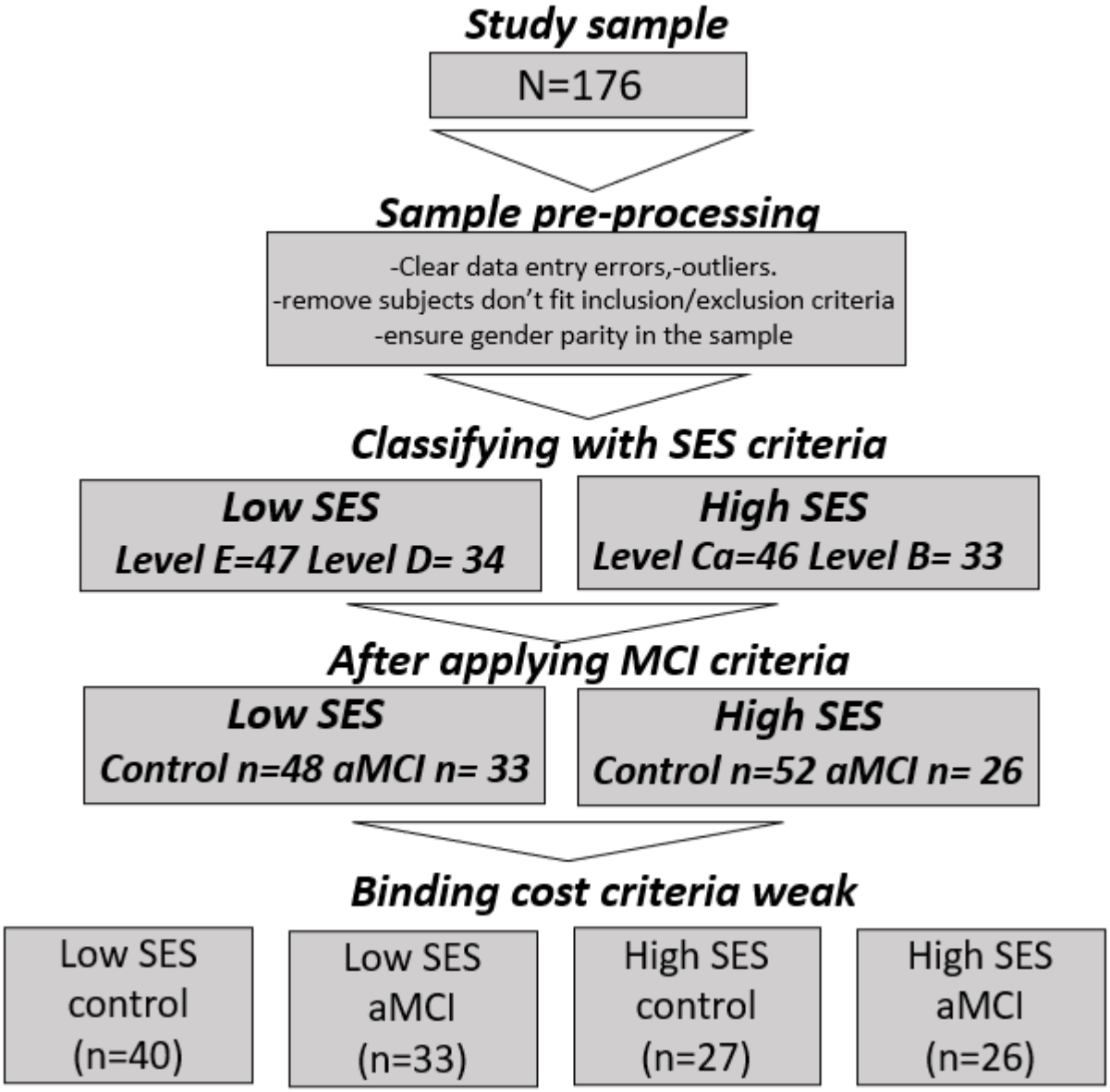


Figure 2

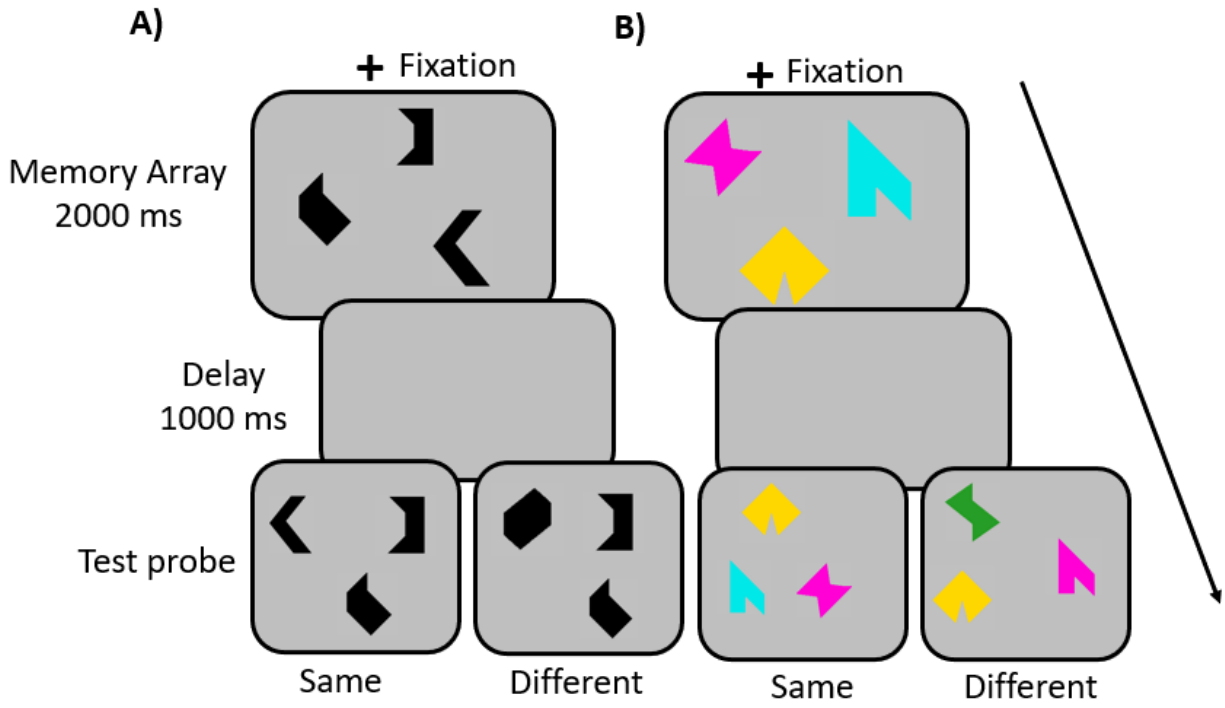
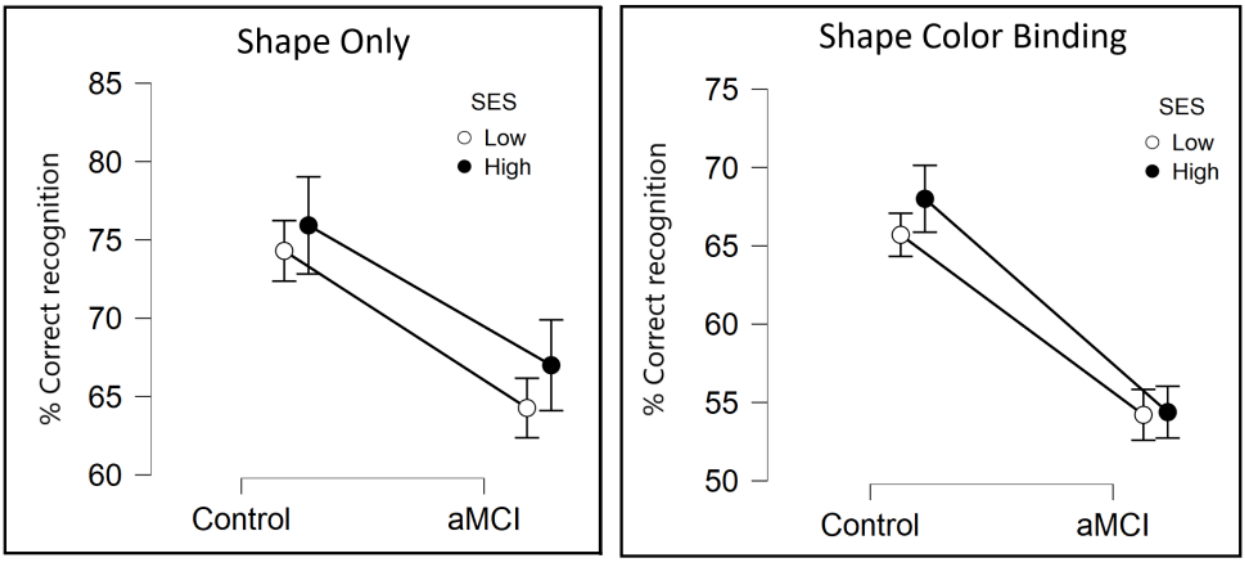

A)
B)
Fixation
Fixation
Memory Array
2000 ms
Delay
1000 ms
Test probe
Same
Different
Same
Different

Figure 3


Shape Only
% Correct recognition
85
80
75
70
65
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SES
Low
High
Control
aMCI
Shape Color Binding
% Correct recognition
75
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SES
Low
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Supplementary Material

Table S.1. Means and standard deviations for demographic, clinical, and cognitive scores, with the sample divided into groups according to SES (Low vs. High), cognitive status (Controls vs. aMCI), and cost of binding (Strong vs. Weak Binders).

	Low SES Controls Strong Binders (n=40)	Low SES Controls Weak Binders (n=8)	Low SES aMCI (n=33)	High SES Controls Strong Binders (n=27)	High SES Controls Weak Binders (n=25)	High SES aMCI (n=26)	Main effect SES		Main effect group		Interaction SES*group	
							F	*p*-value	*F*	*p*-value	*F*	*p*-value
Age	71.00(7.26)	68.25(6.11)	70.36(5.47)	69.92(4.12)	69.48(4.73)	70.46(5.90)	.006	.936	.749	.474	.387	.679
Education	4.15(1.07)	4.50(2.67)	3.57(1.30)	15.96(2.00)	13.60(3.35)	15.73(1.51)	973.08	.001	2.42	.092	5.624	.004
Yesavage	1.35(0.92)	1.87(1.12)	1.69(1.23)	.85(1.06)	.76(.87)	1.26(1.88)	9.48	.003	1.50	.225	.023	.483
Hachinski	1.32(0.61)	1.00(1.19)	1.75(.86)	1.18(.87)	.92(1.11)	1.30(1.08)	1.80	.181	3.63	.034	.567	.568
FAQ	.92(1.74)	1.25(1.08)	1.84(3.75)	.07(0.38)	.40(.20)	.30(0.61)	11.13	.001	1.34	.264	.462	.631
ACE-R	90.70(3.88)^{cef}	91.37(3.77)^{cef}	77.84(4.99) ^{aef}	92.74(3.55)^{af}	94.36(3.93)^{abcf}	84.61(4.50)^{acde}	26.62	.001	116.73	.001	5.07	.007
ACE-R (MD)	22.50(1.67)^{bcef}	23.12(1.35)^{a}	17.54(1.09)^{abf}	23.48(1.86)^{cf}	24.28(1.74)^{cf}	20.46(2.37)^{abc}	28.37	.001	102.47	.001	5.16	.007
MMSE	28.20(1.40)	27.50(1.41)	24.18(1.97)	28.14(1.37)	28.84(2.49)	25.23(1.27)	6.21	.014	71.03	.001	2.23	.114
RAVLT	5.20(.93)	6.50(0.92)	3.54(1.00)	7.66(1.54)	8.20(1.78)	5.96(1.58)	81.93	.001	40.75	.001	.786	.457
RAVLT DR	5.17(2.06)	6.37(1.59)	2.48(1.46)	7.55(2.15)	9.72(10.99)	5.26(1.09)	11.13	.001	8.07	.001	.097	.908
ROCF	20.79(9.12)	27.37(6.50)	15.15(7.87)	29.83(7.81)	29.58(7.66)	25.92(7.63)	44.66	.001	6.25	.002	.282	.754
ROF IR	9.37(6.32)	7.37(3.58)	6.30(3.73)	13.63(6.30)	15.68(7.70)	10.90(4.78)	29.70	.001	4.41	.014	1.15	.318
ROF DR	5.56(3.34)	5.50(3.38)	4.30(3.36)	12.25(6.43)	15.00(8.06)	8.82(4.83)	53.80	.001	5.38	.006	2.05	.132
TMT-A	89.22(42.86)	91.25(35.49)	134.48(77.34)	60.29(22.81)	59.80(15.53)	89.30(59.86)	15.19	.001	9.65	.001	.434	.649
TMT-B	197.07(95.20)	146.25(48.15)	238.19(91.42)	149.66(66.00)	142.60(70.27)	244.53(113.97)	.863	.354	13.79	.001	1.50	.225
Digit span	5.07(1.07)	5.12(.99)	4.09(1.84)	5.66(1.27)	5.52(1.497	5.69(1.25)	11.77	.001	1.99	.140	2.62	.075
DS	22.00(11.69)	24.25(17.16)	15.39(13.06)	34.22(12.46)	38.88(12.96)	22.96(11.11)	25.50	.001	11.58	.001	.870	.421
Boston NT	15.37(2.74)	16.00(2.72)	14.72(2.51)	18.11(2.81)	18.36(2.05)	16.03(2.82)	14.84	.001	14.38	.001	.633	.532
VF	12.92(3.99)	13.62(4.04)	9.42(5.86)	16.55(6.63)	19.12(6.85)	11.92(4.81)	10.17	.002	17.90	.001	.347	.557
SF	15.42(4.08)	16.75(5.80)	11.51(5.52)	19.92(5.31)	19.84(4.89)	14.26(3.91)	15.55	.001	18.67	.001	.539	.585
VSTMBT	65.70(4.30)	60.50(3.58)	54.21(4.57)	68.00(5.39)	63.88(5.61)	54.38(4.09)	5.19	.024	108.75	.001	1.27	.284
Binding Cost	11.37(4.37)	25.910(5.68)	15.51(5.09)	9.92(7.87)	26.56(4.75)	18.27(7.53)	.732	.543	62.83	.001	1.93	.148

Notice the F and p values reported refers to Group * SES interaction. *Note*. Yesavage= Geriatric Depression Scale; FAQ=Functional Activities Questionnaire; ACE-R = Addenbrooke Cognitive Examination Revised (MD= Memory Domain); MMSE = Mini-Mental State Examination; RAVLT= Rey Auditory Verbal Learning Test (DR= Delayed Recall); ROCF= Rey–Osterrieth Complex Figure Test (IR= Immediate Recall; DR= Delayed Recall); DS= Digit Symbol Test (WAIS IV); VF= Verbal Fluency; SF= Semantic Fluency; VSTMBT = performance on the Shape-color binding condition. PMMS and Lawton & Brody test report variance equal to 0, so they are not reported in the table. Letters denote significant group differences in group*SES interactions a= differ from low SES control, b= differ from Weak Binders Low SES, c= differ from Low SES aMCI (n=33), d= differ from High SES control, e= differ from Weak Blinders High SES, f= differ from High SES aMCI (n=26).

The Table above shows descriptive data from all the groups, including control participants excluded from the primary analysis reported in the manuscript due to their weak Visual Short-Term Memory Binding abilities. These supplementary results confirm that removing such participants from the primary analysis does not modify the core outcomes reported in the manuscript. Only the VSTMBT variable revealed a significant effect of SES not observed initially, but this was explained by a general effect of SES on VSTM, which was observed for shape-only and shape-color binding alike, as confirmed by the lack of significant effects of such a factor on the Binding Cost. These results are in line with those recently reported by Parra et al. (2024), who found that traditional neuropsychological tests failed to detect impairments in cognitively unimpaired older adults whose weak binding abilities were accounted for by increased Amyloid-β in brain regions relevant to this memory function.