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Electrophysiological correlates of visual short-term memory binding deficits in community-dwelling seniors at risk of dementia

Rodrigo Alberto Gonzalez-Montealegre [a], Alfredis González-Hernández [a,b,*], Jasmin Bonilla-Santos [b,c], Dorian Yisela Cala-Martínez [b,c], Mario Alfredo Parra [d,e,*]

[a] Neurocognition and Psychophysiology Laboratory, Universidad Surcolombiana, Neiva, Colombia
[b] Department of Psychology, Master Programme of Clinical Neuropsychology, Universidad Surcolombiana, Neiva, Colombia
[c] Department of Psychology, Universidad Cooperativa de Colombia, Neiva, Colombia
[d] Department of Psychological Sciences and Health, University of Strathclyde, Glasgow, UK
[e] Associate Researcher, Latin American Brain Health Institute, University Adolfo Ibañez, Chile

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ABSTRACT

Background: Visual Short-Term Memory Binding (VSTMB) is a preclinical marker of Alzheimer's disease (AD). Reduced early event-related potentials (ERPs) (100–250 ms) over fronto-central (FC) and parieto-occipital (PO) regions have been reported in patients with Mild Cognitive Impairment (MCI) seen in the clinic. We investigated such ERPs in a larger sample of community-dwelling older adults who had not sought medical advice.
Methods: Participants (n = 215) were assessed with a neuropsychological battery and the VSTMB Task. The latter assessed the ability to detect changes between two consecutive arrays of shapes or colored shapes (the Binding condition). Time-locked EEG signals were collected during the task.
Results: Those who met the MCI criteria (n = 108) showed binding impairment. ERP analyses revealed significant Group x Time Windows interactions. Early ERP showed reduced neural recruitment (MCI < healthy controls (HC)) over the right FC regions, left PO, and right centro-parietal (CP) regions during Binding encoding, and over PO regions bilaterally and left FC during retrieval. Late ERP showed increased neural recruitment (MCI > HC) on left FC and PO regions during retrieval.
Conclusions: Hyper-recruitment may reflect functional reorganization aimed at behavioral compensation in the early stages of MCI. The role of such amplitude shifts as pointers of transition points in the AD continuum needs further investigation.

1. Introduction

Recent estimates suggest that there will be approximately 152.8 million cases of dementia in the world by 2050 and in Latin American countries, cases will grow up to 310% compared to current figures (Nichols et al., 2022). Alzheimer's disease (AD) is the most common type of dementia (Jack et al., 2018; Sperling et al., 2011). It causes a profound and progressive decline in cognition, emotional regulation, and functional abilities (King et al., 2017) leading to a significant societal impact (Hojman et al., 2015; Kalaria et al., 2008; Maestre, 2012; Quiroz et al., 2022; Slachevsky et al., 2013). Factors associated with dementia risk and normal ageing in Low- and Middle-Income Countries (LMIC) vary considerably from those reported in developed countries (e.g., low education, poor social determinants of health), and Colombia does not escape from such a landscape (Amaya Vargas et al., 2014; Gooding et al., 2006; Larson, 2019; Nichols et al., 2022; Parra et al., 2018; Ribeiro et al., 2021; Santamaria-Garcia et al., 2023). In fact, such non-canonical risk factors have been considered drivers of the abovementioned dementia forecast for Latin American countries (Parra et al., 2018; Parra et al., 2021). Epidemiological studies carried out in southern Colombia have warned about the high prevalence of dementia (Gooding et al., 2006) and Mild Cognitive Impairment (MCI) (Bonilla-Santos et al., 2023) observed in this region. This situation is worsened by the limited access to state-of-the-art diagnostics such as biomarkers for neurodegenerative diseases (Damian et al., 2021; Parra et al., 2023) which widens the inequity gap (Ferrando & Damian, 2021). Hence, we urgently need

* Corresponding authors at: Department of Psychological Sciences & Health, University of Strathclyde, Graham Hills Building, 40 George Street, Glasgow, G1 1QE, UK (A. González-Hernández). Psychology Department, University Surcolombiana, Neiva, Huila, Colombia (M.A. Parra).
E-mail addresses: alfredis.gonzalez@usco.edu.co (A. González-Hernández), mario.parra-rodriguez@strath.ac.uk (M.A. Parra).

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affordable methodologies that can be swiftly implemented and scaled up to aid in the diagnosis of dementia (Parra et al., 2019b).

To that aim, neurophysiological methods, particularly the EEG, are proposed as first-line screening tools to identify high-risk subjects (Rossini et al., 2020). There is growing empirical evidence of multiscale electrophysiological methods capable of detecting the pathophysiological expression of neurodegenerative diseases, including neural signatures of their risk (Loughrey et al., 2023), prodromal (Parra et al., 2017a; Babiloni et al., 2020; Clark et al., 2022; Smith et al., 2022) as well as full-blown dementia stages (Huggins et al., 2021; Moguilner et al., 2022; Prado et al., 2023). Event-related and phase-locked activity has proved informative about differences between clinical stages of the AD continuum (Fide et al., 2023; Smith et al., 2022), in comparison with other dementias (Guntekin et al., 2022) and during multicentric, double-blind, randomized, and placebo-controlled clinical trials (Yener et al., 2022).

An approach to grant sensitivity and specificity to electrophysiological methods is combining them with cognitive assessments (Parra, 2022; Parra et al., 2019b, 2020). For example, memory markers (Parra, Calia, et al., 2022) combined with EEG recordings have yielded biomarker evidence of the AD continuum (Clark et al., 2022; Huggins et al., 2021; Josefsson et al., 2019; Parra et al., 2017a; Pietto et al., 2016; Smith et al., 2022). Particularly, the role of short-term memory has been investigated (Ibanez & Parra, 2014; Pergher et al., 2019; Weissberger et al., 2017), and specifically, short-term memory tasks involving the integration of perceptual information have been shown to discriminate between MCI subtypes and controls (Costa et al., 2017; Della Sala et al., 2018; Martinez-Florez et al., 2021), and to identify AD across various countries (Cecchini et al., 2023; Logie et al., 2015).

Previous studies reported altered patterns of EEG-derived brain connectivity in the prodromal stages of familial AD during a VSTMB Task (VSTMBT). Parra et al. (2017) observed increased information sharing (i.e., connectivity measured via weighted symbolic mutual information) over central regions in 89% of a small sample of carriers of the mutation E280A-PSEN1 who were in the MCI stages. Earlier studies have shown that individuals with MCI exhibit increased synchronization and coherence in EEG frequency bands such as increased power in the theta and alpha bands has been observed (McBride et al., 2013). The authors suggested that such patterns of heightened neural activity reflect compensatory mechanisms as the brain attempts to maintain cognitive functions. As the disease progresses from MCI to AD dementia, there is a noticeable decline in EEG activity. This is characterized by a reduction in alpha activity and an increase in delta activity, indicating a shift towards slower brain wave patterns. This decline in EEG activity corresponds with the loss of cognitive functions and neural degeneration associated with AD (Babiloni et al., 2020, 2021; McBride et al., 2013; Rossini et al., 2020). Longitudinal EEG studies in Aβ positive patients have also revealed a clear pattern of initial increased brain activity followed by a significant decrease as the disease advances (Scheijbeler et al., 2023).

The role of functional connectivity during the VSTMBT in the assessment of sporadic MCI patients was discussed by Smith et al. (2022), who suggested compensatory changes in the binding network seemingly setting boundaries between age-related and pathological neurocognitive decline. Compared to familial AD, sporadic MCI shows notable differences in network topology (Clark et al., 2022). Early event-related potentials (ERP) elicited in occipital and frontal areas (Ortega et al., 2016) appear to provide some neural correlates. Pietto et al. (2016) assessed sporadic and familial MCI patients recruited from the clinic who were presented with the VSTMBT synchronized with the EEG. They showed reduced early electrophysiological activity (100–250 ms) over fronto-central (FC) and parieto-occipital (PO) regions. The evidence reviewed above supports the notion that the EEG can yield new biomarker solutions for the early detection of AD. These methods appear to unveil discernible neural patterns which, in the transition across the early stages, are often characterized by over-expression of brain activity (i.e., hyper-synchronization, increased connectivity, over-recruitment) (Morrison et al., 2019; Paitel et al., 2021; Parra et al., 2017a). As the disease progresses, advanced neurodegeneration causes a significant decrease in brain activity. Therefore, strategies aimed at the early detection of the disease using EEG may focus on the search for both increased and decreased patterns of brain activity, with the former seemingly related to compensatory functional reorganization (i.e., synaptopathology) and the latter to neurodegeneration (Parra et al., 2017a; Pietto et al., 2016).

A feature shared by these earlier studies is that their relatively small samples were recruited primarily from lab or clinical settings. Considering the high prevalence of dementia in LMIC, coupled with issues surrounding limited access to healthcare resources and the frequently observed lower socio-economic status of the affected individuals, the adoption of community-based approaches is highly desirable. Given the accessibility of these techniques and their strengths in identifying individuals at high risk in the early stages, community-based studies would ensure a broader representation of the population and foster a more egalitarian approach to early detection and intervention.

Therefore, the present study aimed to investigate the electrophysiological correlates (EPR) of VSTMB in a more extensive sample of community-dwelling older adults who exhibited a high-risk profile for dementia (i.e., MCI). More specifically, we aimed to explore if the ERP patterns (i.e., components, time-windows, and ROI) that discriminated between healthy controls and patients with sporadic and familial risk of AD reported by Pietto et al. (2016) also characterize cognitively impaired older adults who were screened in the community. As the current investigation focused on older adults who had not sought medical advice at the time of testing, we predicted that their MCI would be in the early stages (i.e., relative to those assessed by Pietto et al., 2016). Considering the evidence above reviewed about prominent EEG changes observed in the early stages of MCI, we hypothesized that differences in the electrophysiological activity during the Shape-Color binding condition of the VSTMBT between MCI patients and HC would be characterized by a combination of hypo- and hyper-recruitment of neural resources (as informed by ERP amplitudes) in the former group relative to the latter group. Based on Pietto et al. (2016), we predicted that increased neural recruitment would be more apparent over anterior regions (e.g., late frontal ERP components), which are more prompted to compensatory strategies developed in older age (Cabeza et al., 2018; Reuter-Lorenz & Park, 2014). The earlier ERP components reported by Pietto et al., (2016) could reveal reduced brain activation, particularly during the encoding stages, thus providing a physiological substrate of the encoding deficit consistently reported in patients with or at risk of AD dementia while they perform the VSTMBT (Parra et al., 2017b; Smith & Escudero, 2017).

2. Methods

This was a cross-sectional case-control study of individuals identified in a community population from southern Colombia. The cases were identified based on standard clinical diagnostic criteria (Petersen, 2004; Winblad et al., 2004). All the participants were assessed with standard neuropsychological tasks and electroencephalographic recordings.

2.1. Participants

The complete protocol describing recruitment is available from Bonilla Santos et al. (2023). Fig. 1 shows a flowchart illustrating the selection of participants. A total sample of 621 community-dwelling older adults who had not sought medical advice was invited to participate. Of these, 283 participants were excluded based on several criteria: active psychiatric illness, alcohol/drug history, score on the GDS > 5 (Yesavage et al., 1982), cerebrovascular disease (Hachinski Ischemic Score > 4; Hachinski et al., 1975), significant underlying medical and/or neurological conditions, visual impairment not corrected, and MMSE $<$

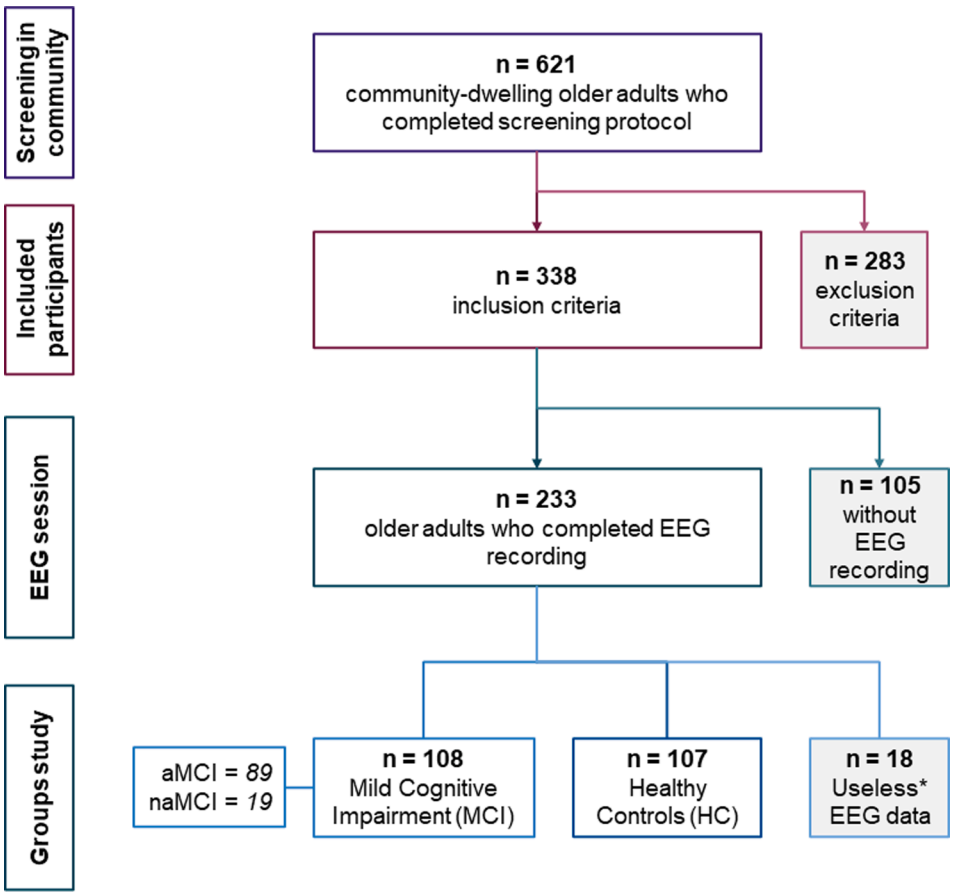

Fig. 1. A flowchart depicts the steps followed to configure the study sample. *Notes*: *aMCI:* amnestic Mild Cognitive Impairment; *naMCI*: non-amnestic Mild Cognitive Impairment; *Useless EEG data corresponds to records without triggers or incomplete due to technical failures.

24. Of the 338 participants who met the inclusion criteria, 233 completed the screening protocol in the laboratories of neurocognition and psychophysiology of Universidad Surcolombiana and Universidad de la Amazonía in Southern Colombia. Among the participants who completed the EEG session, 107 were Healthy Controls (HC), and 108 met the criteria for Mild Cognitive Impairment (MCI). Most of the patients (n = 89) were impaired in their memory functions (amnestic MCI single domain or amnestic MCI multi-domain), while nineteen patients were classified as non-amnestic MCI. Patients with EEG recordings without triggers or incomplete due to technical failures were also excluded (<5%).

The above sample was drawn from a cohort of 823 participants recruited by Bonilla-Santos et al., (2023) in their epidemiological study. According to Naing et al. (2022), the likelihood of encountering cases in a smaller sample is higher when a disease is prevalent. Using Scalex, the tool provided by the authors, we found that for the prevalence of 53.6% (Bonilla-Santos et al., 2023), a sample size of 630 for absolute precision of ±4%, 95% confidence (49.6%-57.6%), and a potential loss of 5% (it was very low in this study) would suffice for a prevalence study. Naing et. al. (2022) acknowledged that a precision of even 5% would be possible for an expected prevalence of 50% or above. Nevertheless, we ran a priori and a posteriori sample size and power calculations considering the various levels of analysis included in our study. To investigate the hypothesis linked to behavioral data drawn from the VSTMBT, we have a mixed model with Group (Controls vs MCI) as the between-subjects factor and Condition (Shape Only vs Shape-Color Binding) as the within-subjects factor. Using G-power, for a medium effect size (0.25), alpha = 0.05, 80% power, 2 Groups, 2 measures and a reliable correlation between repeated measures (0.5), we needed a sample of 34 participants. For the ERP data, we focused on the Shape-Color Binding condition of the VSTMBT for reasons explained in our manuscript. Based on Pietto et al. (2016), who reported significant differences between controls and MCI-FAD over the right FC region ($t = 2.57$, $p < 0.05$, $d = 1.08$) and Sporadic MCI over the left FC region ($t = 3.16$, $p < 0.01$, $d = 1.22$), both showing large effect sizes, we ran a priori sample size calculation aiming at a large effect size (f=0.5), alpha = 0.05, 80% power, 2 Groups, one measure (as we only focused on the VSTM Binding condition) and a reliable correlation between repeated measures (0.5). The result showed that a sample of 102 participants (51 per group) would suffice. Finally, we ran some a posteriori calculations to verify the accuracy of our literature-based estimates. This information (1-β) is reported in our results.

As we were interested in the risk of AD dementia among community-dwellers with MCI, we added some additional criteria to those used by Bonilla-Santos et al. (2023) (i.e., MMSE >=24, no evidence of Cerebrovascular Disease or Depression). Such criteria undoubtedly made this sample less representative of the broader population of older adults at risk of dementia. However, we aimed to include older adults with a risk profile as compatible as possible with that seen in cases of AD dementia. Given our sample size, we needed to rely on a more specific selection framework to address such an aim.

The group of healthy participants was matched for age and education with the MCI group. None of the participants had a history of psychiatric or neurological diseases. All participants provided written informed consent in accordance with the Helsinki declaration. The Ethic Committee of the Hospital Universitario “Hernando Moncaleano Perdomo” approved this study.

2.2. Materials

2.2.1. Neuropsychological assessment

The general cognitive status of MCI patients was assessed with the Addenbrooke's cognitive examination–revised (ACE-R Colombia), which evaluates the following cognitive domains: attention/orientation, memory, fluency, language, and visuospatial skills (Ospina Garcia, 2015; Bonilla-Santos et al., 2024) and with the CERAD to assess the cognitive areas of orientation, fixation, concentration, calculation, memory, and language (Aguirre-Acevedo et al., 2007; Aguirre-Acevedo et al., 2016; Torres et al., 2021). The CERAD includes the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), Boston Naming test (BNT-15), Word List Memory (WLM), Word List Recall (WRL) and Word List Recognition (WRL) task, Praxis Copy (PC) and Recall (EC) task, Semantic Fluency and Phonological Fluency (FAS), Rey-Osterrieth Figure Copy and Recall, and Trail Making Test A/B.

2.2.2. Visual Short-Term memory task (VSTMBT)

The VSTMBT evaluates memory for single or combined features via a change-detection paradigm (Parra et al., 2010b). The task has been extensively used to identify impairments of integrative memory functions in patients with or at risk of Alzheimer's disease (Parra et al., 2010b; Pietto et al., 2016).

Stimuli.

Stimuli consisted of visual arrays of 3 items randomly placed within an imaginary 3x3 square grid on a 21″ size LCD screen which, at a distance of 60 cm from the chin rest, held 10° of visual angle. Task display parameters (refresh rate, etc.) were set to optimal by the stimulation software (see below). Each item within the grid held 1° of visual angle and was separated from the other two items by no less than 1° (see Brockmole et al., 2008; Parra et al., 2010b). Items for the visual arrays were drawn from a set of 8 Colors and a set of 8 shapes. Stimuli luminance was carefully controlled, as reported by Parra et al. (2010a).

The VSTMBT was presented on a monitor (21″, 1920x1080) using E-Prime software (version 3.0, Psychology Software Tools, USA) synchronized with ActiveView software (V. 9.0) for data recording. The task presented visual arrays with three stimuli each. Each trial consisted of a study array and a test array (see Fig. 2). The location of the items changes between the study and test phases, making it an uninformative feature. Detecting changes across displays required remembering either the shapes or the combinations of shape and color presented in the study array. Stimuli included single shapes (Shape Only condition) and shapes with colors (Shape-Color Binding condition). The experimental design included a brief practice session for each condition, followed by a total of 100 test trials per condition. The trials were fully randomized across participants, and the order of the conditions was counterbalanced. On half of the trials, the test array exactly matched the memory array. On the other half of the trials, they differed. Differences were because new shapes which did not appear during the study array were selected from the set of 8 and presented in the test array (Shape Only) or because two studied colored shapes swapped their colors in the test array (Shape-Color Binding).

2.2.3. Electroencephalogram (EEG)

EEG data was recorded using 64 channels ActiveTwo equipment (Biosemi, Amsterdam, The Netherlands). External electrodes for EOG were used (VEOL and HEOR). All signals were recorded at a sampling rate of 1024 Hz. The VSTMBT task was presented using E-Prime software (version 3.0, Psychology Software Tools, USA) synchronized with ActiveView V912 software (Biosemi, Amsterdam, The Netherlands). The setup for EEG recording included a comfortable chair and a chin rest located in a dimmed temperature-controlled room.

2.2.4. Procedures

Participants were recruited following "An Inclusive Approach to Recruitment in Underrepresented Populations" which we present in supplementary material (S.5). The study was conducted at the Neurocognition and Psychophysiology Laboratory of Universidad Surcolombiana, and transportation costs from the participants' residences to the laboratory was covered by the research. Upon arrival, the project was explained, and the informed consent form was signed. Each participant attended three sessions. In the first two sessions, a psychologist with knowledge and training in neuropsychology administered an assessment protocol as reported in Bonilla-Santos et al. (2023). Based on the outcomes from a discussion of a multidisciplinary team (psychologists, neurologists, and psychiatrists), who reviewed cases and applied the study's criteria (i.e., inclusion, exclusion and diagnostic), participants were classified into healthy (i.e., control group – HC) and mild cognitive impairment group (MCI). Those who met the inclusion criteria were scheduled for a third session to conduct the EEG recording both in the morning or in the afternoon (see Supplementary Material S.2, Table 6 for more details about EEG recording times).

The EEG equipment was placed in a quite dimmed room. Although we do not have a Faraday Chamber, the lab is set up in a dedicated room free from other equipment, i.e., the acquisition systems, such as Computers, power connectors, etc., are kept in a separate room. Participants are assessed in individual, sound-attenuated testing cubicles. After setting up the EEG acquisition system, a ten-minute resting state was recorded. Then, the VSTMBT was administered as described in section 2.2.2. Throughout the session, one of the researchers monitored the recording, performing a visual inspection for artefacts and noting any findings in a logbook which were then considered at the preprocessing stages.

2.3. Data analyses

2.3.1. Behavioral data

Demographic and neuropsychological data of the patients were compared to those of the control group via parametric t-tests. As in previous studies, the variable obtained from the VSTMBT was the

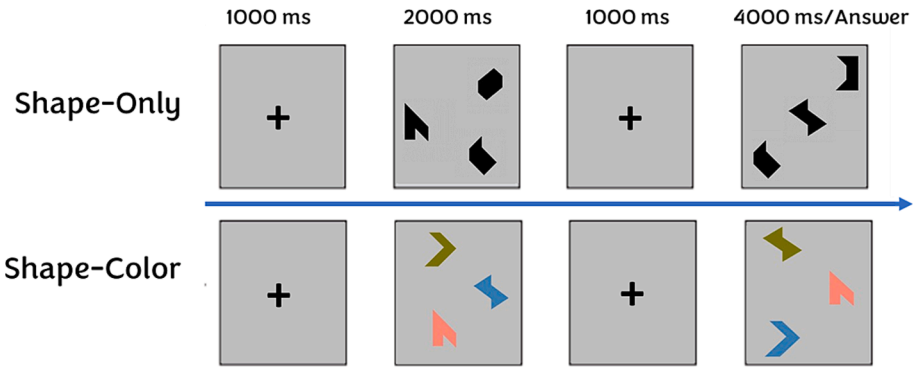

Fig. 2. An example of a trial of the VSTMBT for each condition.

percentage of correct recognition (Cecchini et al., 2023). The VTSMBT data was subjected to a mixed ANOVA model with Group (HC vs MCI) as the between-subjects factor and Condition (Shape-Only vs Shape-Color Binding) as the repeated measure. Post-hoc tests were carried out to explore the main effects and the origin of the interactions. False Discovery Rates (FDRs) were applied to multiple comparisons to correct for Type-I error.

2.3.2. ERPs

All the data were pre-processed offline using FASTER (version 1.2.4; Nolan et al., 2010) in MATLAB (version R2021a) and EEGLAB (version 2022.1). The EEG data was filtered between 1 Hz (high-pass) and 30 Hz (low-pass) and down-sampled to 250 Hz. The EEG activity was re-referenced to the grand average. To eliminate oculomotor artifacts, independent component analysis (ICA) was performed and complemented using ICLabel (V.1) with a threshold in 0.9. All artefacts marked for rejection were confirmed by a visual inspection of the data. The continuous EEG data were epoched from –250 to 1300 ms locked to stimulus onset. The remaining artefactual epochs were manually removed. Average waveforms were computed separately for each individual and for each condition of the VSTMBT (i.e., Shape-Only and Shape-Color Binding). The analysis only considered trials with correct responses.

To identify significant differences between the two conditions, we employed a combination of the Monte Carlo test and non-parametric bootstrapping with 1,000 permutations. This approach, as described by Pietto et al. (2016), provides a simple solution to the problem of multiple comparisons and does not rely on correction for multiple comparisons or Gaussian assumptions about the data distribution. We analysed the entire array of electrodes for every millisecond to calculate the permutations in a component-free approach.

Electrodes and time windows that showed significant results ($p < 0.05$) were assigned to regions of interest (ROIs), and the activity within each ROI was averaged. We defined six ROIs: (1) fronto-central left (FC left), (2) fronto-central right (FC right), (3) centro-parietal left (CP left), (4) centro-parietal right (CP right), (5) parieto-occipital left (PO left), and (6) parieto-occipital right (PO right). The time windows and electrodes used to analyze the EEG data varied across the two conditions of the VSTMBT.

We compared ROIs across Groups using parametric tests. Mixed ANOVA models were used to explore main effects and interactions of the between-subjects factor Group and the within-subjects factor Time Windows over the identified ROI. We were particularly interested in the main effect of Group and its interaction with Time Windows, with the latter informing on ROI where ERP activity may differentially vary across groups. As different time windows would comprise physiological activity which would vary naturally (e.g., ERP components), such a main effect alone was not considered informative. All the ANOVA models controlled for the effects of age and education. Pairwise contrasts were FDR-corrected (Pike, 2011). ERPs with significant differences were plotted, and their corresponding voltage maps were displayed for the relevant ROI and time windows. In the last step, we ran correlations between average ERP activity across ROI and Time windows for memory phases (i.e., encoding and retrieval) that yielded significant between-group differences. Those averages were correlated with behavioral data drawn from the relevant condition of the VSTMBT. Our representative sample size largely drove the choice of parametric tests. With large enough sample sizes (> 30 or 40), the normality assumption should not cause concerns (Ghasemi & Zahediasl, 2012), allowing for the use of parametric procedures (Elliott & Woodward, 2007).

3. Results

3.1. Behavioral data

3.1.1. Neuropsychological assessment

Of the 210 participants, 107 were healthy controls, while 103 met the criteria for MCI. Table 1 shows demographic variables as well as the results of the neuropsychological assessment (see Supplementary S.4, Table 5 for detailed demographic and comorbidity data). MCI patients demonstrated inferior cognitive abilities compared to controls, as evidenced by their lower scores on the screening assessments and standard neuropsychological evaluations for memory, language, and executive functions. Also, relative to HC, MCI patients were older and had fewer years of education. We, therefore, controlled for such factors in the reported analyses.

3.1.2. Behavioral results from the VSTMBT

The mixed model revealed a significant main effect of Group [$F(1,210) = 38.26p < 0.001$, $\eta^2 = 0.154$] whereby performance from HC was higher than that of MCI patients (HC: M=85.24, SD=9.54, MCI: M=68.95, SD=10.62). There was a significant main effect of Condition [$F(1,210) = 436.62$, $p < 0.001$, $\eta^2 = 0.675$] whereby performance on Shape-Only was higher than performance on Shape-Color Binding (Shape-Only: M=77.21, SD=10.38, Shape-Color Binding: M=61.92, SD=10.91). The Group x Condition interaction was non-significant [$F(1,210) = 0.536p = 0.465$, $\eta^2 = 0.003$] (see Fig. 3).

Table 1
Descriptive statistics and group comparisons for neuropsychological data.

Variables	All (n = 210)	HC (n = 107)	MCI (n = 103)	*P value* [a]
Demographic characteristics				
Age, years	60.9 (6.6)	59.5 (6.4)	62.2 (6.5)	0.002
Years of education	10.5 (6)	13 (5.6)	8 (5.4)	0.001
Gender (female)	79 %	82.4 %	75.7 %	0.227[b]
Neuropsychological assessment				
Cognitive Screen				
ACER-Col	86.3 (9.3)	90.6 (5.4)	82.1 (10.7)	0.001
MMSE	27.3 (1.7)	27.8 (1.7)	26.8 (1.7)	0.001
Language				
BNT-15	13 (1.8)	13.8 (1.2)	12.2 (2.1)	0.001
Memory				
Word List Learning	15.6 (4)	17.7 (3.5)	13.5 (3.5)	0.001
Word List Learning Delayed recall	5.3 (2.2)	6.4 (1.7)	4.2 (2)	0.001
Word List Recognition	9.4 (0.8)	9.7 (0.5)	9.1 (1)	0.001
CP Delayed recall	6.6 (2.6)	7.8 (1.9)	5.5 (2.6)	0.001
RCFT Delayed recall.	15.7 (10.9)	17.7 (6.6)	13.6 (13.8)	0.006
Delayed Free recall −FCSRT.	9.5 (3.5)	10.6 (3.1)	8.4 (3.6)	0.001
Delayed Cued recall −FCSRT.	14.1 (2.9)	14.9 (2.6)	13.4 (2.9)	0.001
Visuospatial				
CP Copy	8.8 (1.6)	9.5 (1.1)	8.2 (1.8)	0.001
RCFT Delayed copy.	29.5 (6.7)	32.1 (4.1)	27.2 (7.5)	0.001
Executive functioning				
Phonemic Fluency (FAS)	29.9 (11.7)	34.3 (10.5)	26 (11)	0.001
TMT-A (seconds)	118.4 (55)	104.5 (48)	130.3 (57.1)	0.001
TMT- B (seconds)	193.8 (78.8)	166.5 (69.2)	221.3 (78.6)	0.001

[a] t- student test.
[b] Chi-square test, HC: Healthy Controls, MCI: Mild Cognitive Impairment, ACER-Col: Addenbrooke's cognitive examination–revised, MMSE: Mini-Mental State Examination; BNT: Boston Naming test, FCSRT: Free and Cued Selective Reminding Test, RCFT: Rey-Osterrieth Complex Figure; CP: Constructional Praxis, FAS: Phonemic fluency test; and TMT: Trail Making Test.

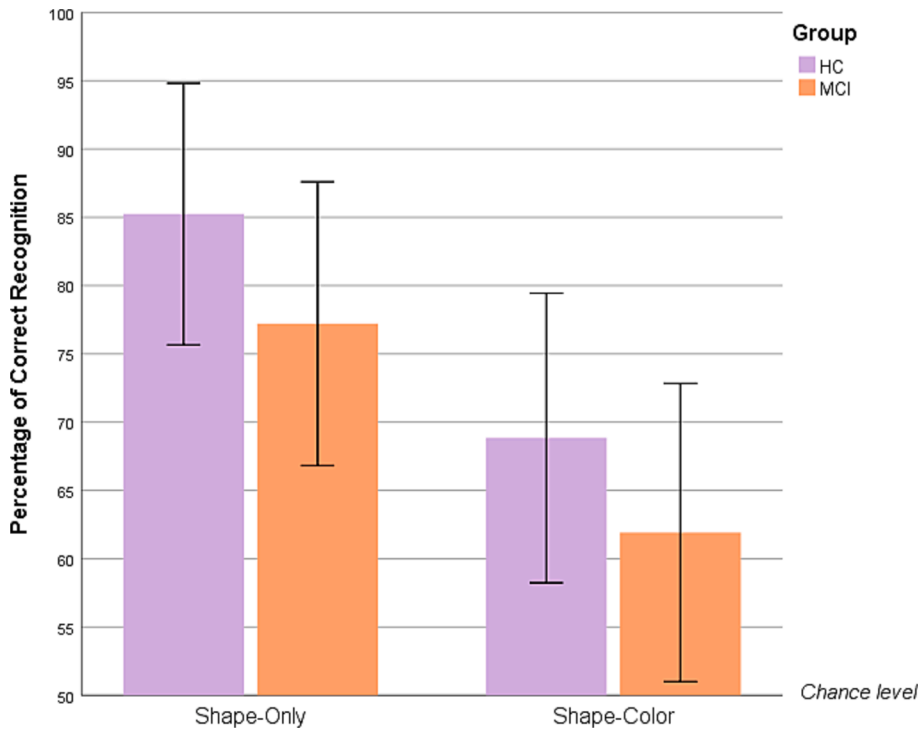

Fig. 3. Percentage of correct recognition across groups and conditions of the VSTMBT. Notes: HC: Healthy Controls, MCI: Mild Cognitive Impairment.

3.2. ERP results

As the number of electrodes per ROI varied across time windows, as informed by our unbiased data-driven method (a combination of the Monte Carlo test and non-parametric bootstrapping), we present a summary of such distribution in supplementary material S.1 (Fig. 1). Following the recommendations by Parra et al. (2019) and Della Sala et al. (2018), and for the sake of brevity, only the ERP results drawn from the analysis of the Shape-Color Binding condition of the VSTMBT are reported in the main manuscript. The results from the analysis of ERP data linked to the Shape-Only condition are presented in supplementary material S.2 (Figs. 2, 3, and 4, and Tables 1 and 2).

Detailed outcomes from the statistical analysis of the data drawn from the Shape-Color Binding condition are shown in supplementary material S.3 (Figs. 5, 6, and 7, and Tables 3 and 4). Here, we report on our main outcomes in line with our model whereby main effects and interactions are reported first, followed by Type-I error corrected pairwise tests. For the encoding phase, the factor Group revealed effects that tended towards significance over right FC regions ($p=0.089$) and reached significance over right CP regions ($p=0.042$). A marginal interaction between Group and Time Window was observed over the right PO regions ($p=0.056$).

The effect over right FC regions emerged from the time window 900-1200ms ($t = 2.13$, $p = 0.034$, $d = 0.29$), driven by a larger activation in HC ($M = 0.151$ μV, $SD = 0.33$) than in MCI patients ($M= 0.055$ μV, $SD = 0.32$) (Fig. 4A). In the right CP regions, activity within the time window 300-500ms revealed significant between-group differences ($t = 2.19$, $p = 0.030$, $d = 0.30$), again driven by a larger activation in HC ($M= 0.131$ μV, $SD = 0.31$) than in MCI patients ($M = -0.047$ μV, $SD = 0.25$) (Fig. 4B). Activation over the right PO regions was also within 300-500ms ($t = 2.20$, $p = 0.028$, $d = 0.30$) showing the same pattern (HC: $M = 0.232$ μV, $SD = 0.44$; MCI patients: 0.103 μV, $SD = 0.42$) (Fig. 4C). In sum, the encoding phase of the Shape-Color Binding condition revealed between-group differences early over posterior brain regions and late over frontal regions.

For the retrieval phase, no main effects of the factor Group were observed. This, however, interacted with Time Windows over FC regions on the right ($p<0.001$) and left ($p<0.001$) hemispheres and over PO regions also over the right ($p<0.001$) and left ($p<0.001$) hemispheres (see Supplementary Material S.3, Fig. 5). Follow-up tests identified three significant differences in the Time Window 150-400ms, which happened to capture the ascending/descending slope from previous activity (we did not follow a component-driven but rather a data-driven approach). Of these, two showed larger activation in MCI patients than in HC (left FC region: MCI > HC, $M = 0.181$ μV, $SD = 0.34$ and $M = 0.091$ μV, $SD = 0.30$ respectively, $t = -2.06$, $p = 0.040$, $d = 0.28$ and left PO region: MCI > HC, $M = -0.269$ μV, $SD = 0.45$ and $M= -0.096$ μV, $SD = 0.49$, respectively, $t = -2.97$, $p = 0.008$, $d = 0.37$), and one (right PO) showed the opposite pattern (HC > MCI, $M = -0.275$ μV, $SD = 0.49$ and $M= -0.123$ μV, $SD = 0.49$, respectively, $t = -2.27$, $p = 0.024$, $d = 0.31$).

Similar differences were observed in the Time Window 850-1200ms over the left FC and right PO regions both showing greater activation in MCI than in HC (left FC: MCI > HC, $M= 0.107$ μV, $SD = 0.32$ and $M = 0.019$ μV, $SD = 0.25$, respectively, $t = -2.23$, $p = 0.027$, $d = 0.30$), and in the right PO (right PO: MCI > HC, $M= -0.185$ μV, $SD = 0.49$, $M = -0.065$ μV, $SD = 0.3$, respectively; $t = 2.09$, $p = 0.038$, $d = 0.28$) (Fig. 5). In sum, while the encoding phase of the Shape-Color Binding condition of the VSTMBT revealed reduced activity in MCI patients relative to HC, the retrieval phase revealed mixed findings with a tendency towards larger activation in MCI than in HC.

Finally, we ran Pearson bivariate correlations between ERP activity drawn from the encoding and retrieval phases of the Shape-Color Binding condition averaged across ROI and Time Windows where significant between-group effects were observed, and behavioral data drawn from that condition. While ERP activity during the encoding phase significantly and positively correlated with behavioral data ($n = 213$, $r = 0.282$, $p < 0.001$) (Fig. 6A), ERP activity during the retrieval phase significantly but negatively correlated with behavioral data ($n = 213$, $r = -0.233$, $p < 0.001$).

4. Discussion

The present study was set out to investigate the hypothesis that different patterns of electrophysiological activity during the Shape-

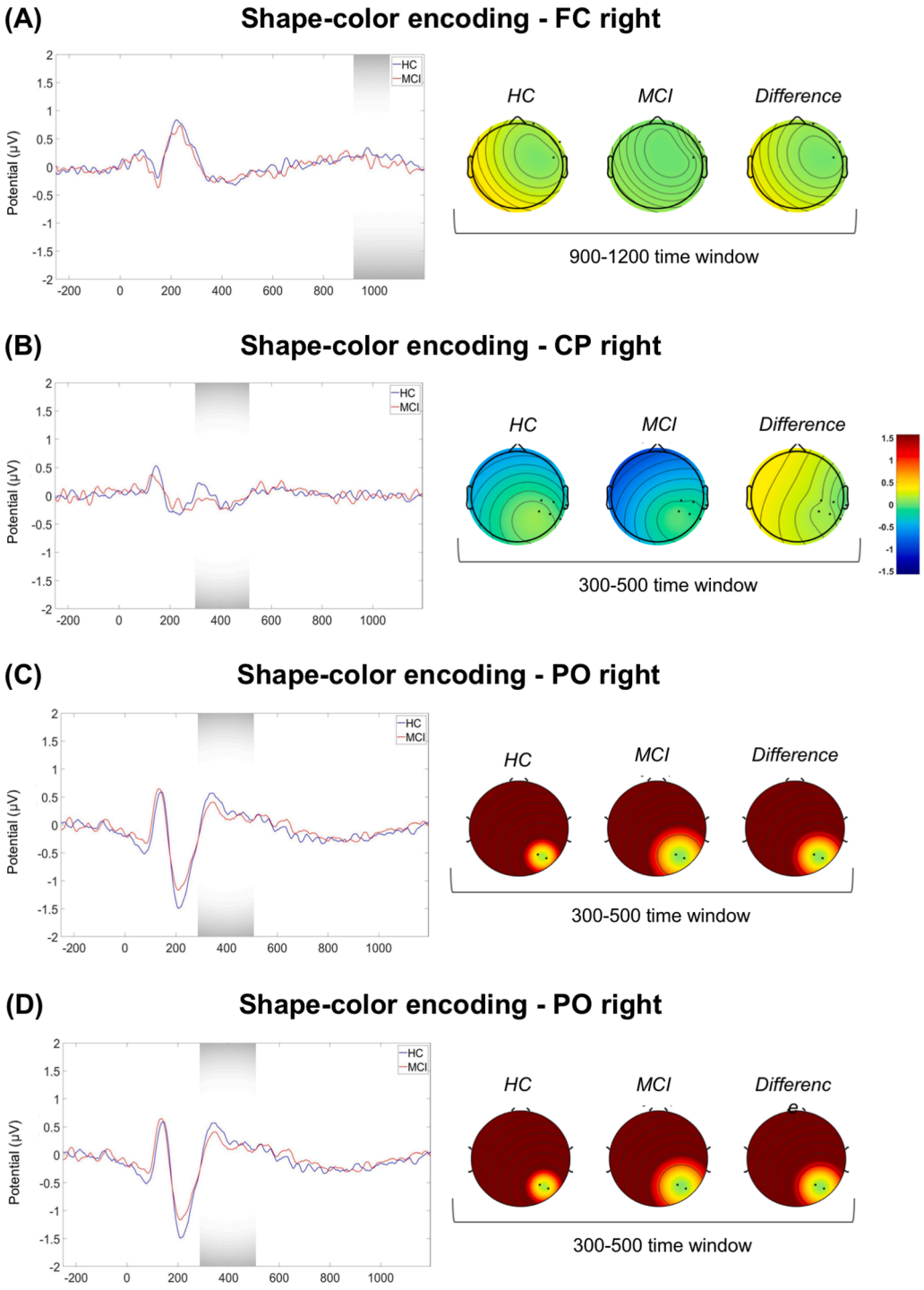

Fig. 4. ERPs and voltage maps for ROI and Time Windows where significant effects were observed during the encoding phase of the Shape-Color Binding condition of the VSTMBT. Notes: HC: Healthy Controls, MCI: Mild Cognitive Impairment, FC: Fronto-Central, CP: Centro-Parietal, PO: Parieto-Occipital.

Color Binding condition of the VSTMBT would help differentiate MCI patients from HC. More specifically, we predicted that hypo and hyper-recruitment of neural resources could be observed in the former group, given the relatively early stages of their MCI. This hypothesis proved valid. Key findings from this study worth discussing are, first, neuropsychologically, our patient group displayed significant impairments in a rather extensive test battery despite such individuals having neither received a formal diagnosis prior to the study nor had they sought advice from health care providers. Second, the encoding phase of the Shape-Color Binding task revealed significant abnormalities in the form of hypo-activation in MCI patients relative to controls over brain regions previously found to be impaired (i.e., decreased neural responsiveness) in MCI patients recruited from the clinic. Third, the retrieval phase of the Shape-Color Binding task also revealed significant abnormalities in the form of hypo and hyper-activation in MCI patients relative to controls. Hyper-activation was found over brain regions that previously showed decreased activity in clinic-based MCI patients who were in relatively more advanced stages. Finally, whereas encoding-related increases in ERP activity predicted better behavioral outcomes, retrieval-related increases were associated with poorer performance. We now discuss these findings in turn.

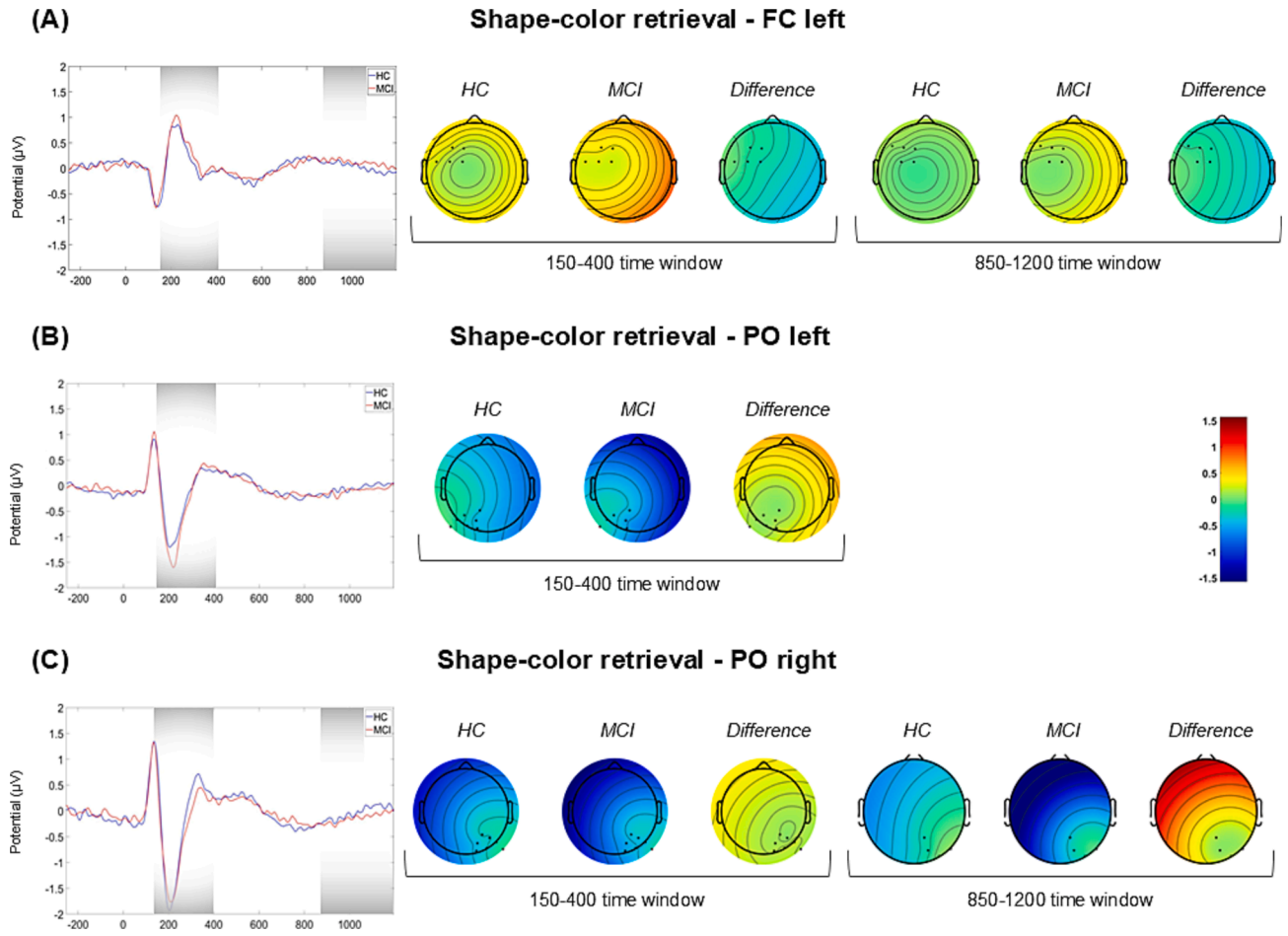

Fig. 5. ERPs and maps activity for ROIs and time windows with significant interactions between groups in retrieval Shape-Color condition. Notes: HC: Healthy Controls, MCI: Mild Cognitive Impairment, FC: Fronto-Central, CP: Centro-Parietal, PO: Parieto-Occipital.

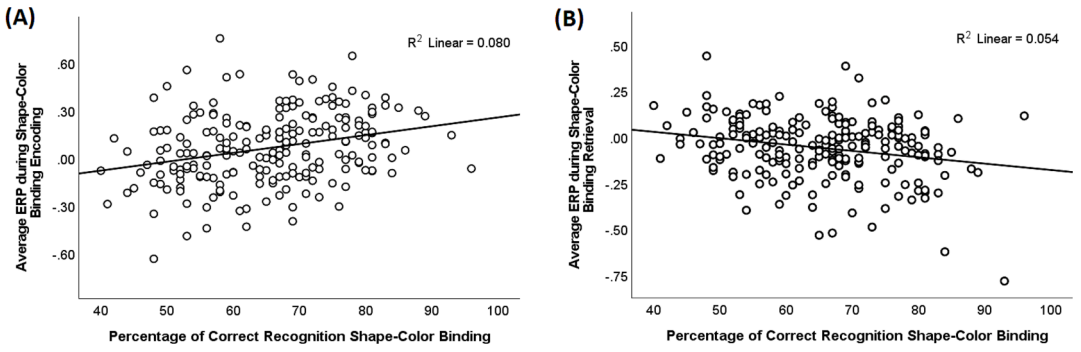

Fig. 6. Correlations between ERPs during memory phases of the Shape-Colour Binding condition of the VSTMBT and behavioral responses from such a test.

4.1. Neuropsychological abnormalities in underdiagnosed older adults

The electrophysiological correlates of VSTMB have been previously investigated in older adults at risk of dementia (i.e., MCI). Pietto et al. (2016) reported reduced early activity (100–250 ms) over fronto-central (FC) and parieto-occipital (PO) regions in MCI patients recruited from the clinic. We investigated if such an electrophysiological pattern is also observed in a larger sample of community-dwelling older adults with MCI who had not sought medical advice. A critical ongoing debate in the literature on cognitive ageing is how we define normality and allocate participants to control groups (Bos et al., 2018; Parra, 2022; Parra et al., 2023). Recent evidence from CSF/PET Amyloid findings in asymptomatic adults suggests that preclinical and prodromal AD may be more prevalent than previously estimated (Jansen et al., 2022).

In Latin American countries, this situation is worsened by the lack of culturally valid assessment tools, which has traditionally represented a significant barrier to early diagnosis (Custodio et al., 2020; Custodio et al., 2017; Parra, 2014; Parra et al., 2018, 2019b, 2021, 2022a). Our current results lend further support to this ongoing debate, confirming that if properly assessed (i.e., by carefully applying strict clinical criteria), a significant number of older adults who have not approached health services would likely receive a diagnosis of MCI. This is a challenge not only faced by Latin American countries. In a longitudinal study of MCI by Parra et al. (2022a) in the UK, the authors initially recruited

70 older adults who self-reported as healthy and enrolled as control volunteers. After applying the diagnostic criteria, the authors found that 28 of those did not meet the criteria for cognitive normality and were, therefore, reallocated to other clinical groups. Even though extensive campaigns are carried out worldwide to raise awareness about dementia and the importance of early diagnosis, many people are still driven by stereotypes, stigmas, and prejudices and do not seek help early enough (Parra et al., 2018, 2021). Another barrier is the lack of proper screening tools available to individuals from low-resource settings (Custodio et al., 2020). Our proposed EEG/ERP biomarkers hold the potential to increase trust, thus encouraging people to come forward earlier and, in so doing, allowing for an earlier diagnosis. We next discuss the roles of such biomarkers.

4.2. Abnormal EEG/ERP biomarkers in early MCI

Despite the accrued evidence suggesting the strengths of the EEG in the characterization and detection of dementia (Babiloni et al., 2020), the tool has received neither enough attention nor sufficient support. Rossini et al. (2020) presented a report from the International Federation of Clinical Neurophysiology highlighting the role of advanced EEG signal analysis in the pathophysiological characterization of dementing diseases. Our results lend support to such recommendations and further endorse their potential use along the disease continuum. We have contributed evidence backing up the proposal that brain signal fluctuations differ between healthy older and cognitively impaired older adults.

An aspect that supports the clinical relevance of the study's findings is the fact that our reported effects are from task-related EEG. The EEG and dementia literature to date has mainly focused on resting state EEG (see Babiloni, Barry, et al., 2020; Babiloni, Blinowska, et al., 2020; Babiloni et al., 2021, 2023; Rossini et al., 2020 for a few very recent examples). A potential rationale is that these are more commonly recorded in clinical settings and are easier to acquire and harmonize across centers and to analyze. However, a shortcoming of resting EEG metrics is their limited specificity. For instance, Rossini et al. (2020) argued that using the EEG alongside cognitive tests sensitive and specific to AD can help address this shortcoming. Others have collected and analyzed EEG data during performance on such tests (such as the current study). In an earlier study by Parra et al. (2017), the authors reported that resting EEG connectivity detected 100% of MCI patients while task-related connectivity achieved 89% classification accuracy. Similar findings were reported by McBride et al. (2013), who found that resting-state EEG accurately distinguished between MCI and HC while task-related EEG (i.e., counting backward condition) was better at discriminating AD from HC. An account to explain these observations is that brain signals elicited by AD cognitive makers will discriminate well the patients with or at risk of this type of dementia but will face challenges with MCI patients. MCI is a heterogeneous and uncertain diagnostic category. By simultaneously collecting EEG data during performance on cognitive tests sensitive and specific to AD we could separate abnormal ageing trajectories, thus granting this neuroscience method more diagnostic specificity at the individual level, which will support its validity as a biomarker. For example, we conducted an exploratory ROC analysis of EPR and cognitive tests recommended by a European consensus group, including the VSTMB task (Costa et al., 2017; see Supplementary S.2, Fig. 8 and Table 7). The results show that the classification accuracy of these assessments was similar.

Another recommendation emerging from the present study's findings is what to look out for when we draw biomarker evidence from EEG data. Based on our results and those from earlier studies, we argue that in the early preclinical stages of AD, the brain undergoes massive functional reorganizations to compensate for the spread of pathology. Such functional reorganization will trigger excessive recruitment expressed as hyperexcitability (Parra et al., 2013) or hyperconnectivity (Parra et al., 2017b). Next, we discuss the shift from hyper- to hypo-excitability as a signature of brain compensation. Parra et al. (2017) observed in MCI patients due to familial AD (Acosta-Baena et al., 2011; Lopera et al., 1997) that hyper-connectivity within the VSTMB network characterized almost 90% of the patients. In our community-dwelling older adults with MCI, we found abnormal electrophysiological responses over brain regions previously reported by Pietto et al. (2016). Some important distinctions between these samples are worth highlighting. For example, Pietto et al. (2016)'s patients and controls had a higher education than ours, which could explain why the MMSE of their controls was higher. The fact that our MCI patients had more than 6 years of less education than Pietto's patients, even though the MMSE of our and Pietto's cases was similar, suggests that our patients were in less advanced stages of MCI. In support of this notion is the observation of increased neural recruitment over brain regions where Pietto et al. reported reduced activity. Our observation of reduced task-related EEG activity during the encoding stages of the VSTMBT (early ERPs) is in line with previous studies using EEG (Parra et al., 2017a) and eye-tracking (Parra et al., 2022b) combined with the VSTMBT. The observation that it was during the retrieval stage that over-recruitment of brain activity became apparent is an interesting finding. Poorly encoded visual information may trigger more exhaustive search mechanisms which might need to engage extra resources in individuals undergoing neurodegeneration. Rhodes et al. (2015) demonstrated that the capacity of visual working memory for features and bindings varies depending on how its contents are retrieved, thus suggesting that the retrieval stages may inform additional mechanisms that may be differently affected by the disease. Our results suggest that such compensatory over-recruitment observed during retrieval with reduced brain activity evidenced at encoding may be neural signatures of impaired cognitive function in patients with MCI at risk of AD. We will discuss brain compensation and neurodegeneration further in the next section.

4.3. Compensatory neural changes as an early indication of dementia risk

We found reduced neural recruitment in MCI patients during early ERP components, particularly over the left PO and right CP regions during the Shape-Color encoding phase, as well as over bilateral PO and left FC regions during retrieval. Hyper-recruitment was observed during late ERP components, with MCI patients exhibiting increased neural recruitment over right FC regions during Shape-Color encoding and over left FC and PO regions during retrieval. Using an incidental emotional memory task performed within the fMRI scanner, Parra et al. (2013) showed that for MCI patients to achieve a level of performance like that observed in controls, they had to recruit more medial temporal lobe resources. It seems that the continuum of neuropathological changes that are triggered by ageing and accelerated by neurodegenerative diseases are characterized by a sequence of compensatory (i.e., increased brain activity underpinning normal behaviors) followed by non-compensatory functional reorganization (i.e., increased brain activity no longer supporting adaptive behaviors), which ends in a massive functional loss (decreased brain activity reflecting significant neurodegeneration). Compensatory changes in ageing have been widely reported (Cabeza et al., 2018; Reuter-Lorenz & Park, 2014; Stern, 2021). Our data fully supports this notion. Significant positive correlations were found between brain activity and behaviors (compensatory hyper-activations during encoding) coexisting with significant negative correlations (non-compensatory hyper-activations during retrieval), with the latter appearing over regions where earlier studies found significantly decreased activity. Although the literature reporting on non-compensatory functional reorganization is growing fast (Cassandra et al., 2019; Gaubert et al., 2019; Smith et al., 2022; Wang et al., 2015), discrepancies remain.

Published studies have been biased towards evidence indicating reduced physiological responses in those affected by dementia or at risk of developing it, not paying enough attention to evidence indicating increased activity in the early stages of dementia or the transition from

normal ageing to the prodromal stages of the disease. Emerging evidence suggests that a reduction of neural responses may be a feature of the advanced stages of the disease, with the early stages often revealing increased neural responses, which could be either compensatory or non-compensatory. The number of studies supporting the latter is growing. Our study aims to contribute to this emerging view. Cassandra et al. (2019) reviewed ERP studies in MCI and AD patients and found that those exploring late ERP components (from P300 onwards) reported mixed findings (i.e., decreased ERP activity coexisting with increased ERP activity, with the latter often exceeding the former), especially in the prodromal stages of AD. They discussed the work by Liddell et al. (2007), who observed increased amplitude of P300 in MCI but decreased amplitudes in AD. Later components, which are drawn from differences between tasks or task conditions and index working memory capacity (the PNwm, Deiber et al., 2015, and the CDA, Bagattini et al., 2017) also revealed mixed findings. The PNwm showed decreased responses in MCI, and the CDA revealed increased responses. Potential sources of such discrepancies can be methodological (i.e., tasks used to derive EPRs), physiological (cognitive and brain reserve Celone et al., 2006), or individual differences (strategy utilization, Riby & Orme, 2013). Beuzeron-Mangina and Mangina (2009) explored the P450 during a Memory Workload Paradigm (i.e., a word list learning task) in very early AD (MMSE: 26.5±2.3), mild vascular dementia (MVD), and controls. The authors found consistent hyper-recruitment only in the very early AD group. They interpret this as compensatory brain responses to meet the task's demands, which they argued may reflect dysfunction of cholinergic systems. Olichney et al. (2006) found an atypical (larger) frontal N400 and P600 during word repetition, which they interpreted as mechanisms recruiting additional brain regions to compensate for performance. Future studies will need to investigate the mapping of these functional neural stages along the continuum from normal ageing to AD dementia to explore whether ERPs can be used as markers of critical transition points throughout such a continuum.

This hyper-recruitment phenomenon may reflect compensatory changes in the early stages of MCI, as individuals strive to maintain cognitive functioning. These results are in line with the idea that the brain undergoes adaptive reorganization in response to cognitive decline (Pietto et al., 2016), and they emphasize the potential utility of EEG-based cognitive biomarkers for screening community-dwelling older adults at risk of dementia. This study represents a significant contribution as it is the first community-based ERP study in this region of Colombia and Latin America, to the best of our knowledge. The correspondence between our findings and those reported by previous research carried out within clinical settings adds to the robustness of the observed electrophysiological patterns associated with VSTMB deficits in individuals at risk of dementia, such as those with MCI. Furthermore, the identification of hyper-recruitment in MCI patients underscores the complexity of neural adaptations in response to cognitive impairment.

The above arguments can be used to make some recommendations to encourage the clinical community to endorse the EEG as a tool to address the mechanistic and diagnostic aspects of AD.

1) Increased neural recruitment in cognitively unimpaired older adults or those with subjective cognitive complaints during performance on cognitive tests sensitive and specific to AD, which leads to improved behaviors, can be seen as an indication of the early preclinical stages of the disease.
2) Increased neural recruitment in cognitively impaired older adults (e.g., MCI) during performance on cognitive tests sensitive and specific to AD, which fails to compensate for behavioral responses, can be seen as an indication of the prodromal stages of the disease.
3) Decreased neural recruitment in cognitively impaired older adults who could still engage with cognitive tests sensitive and specific to AD, and who show significant behavioral impairments can be seen as an indication of the early stages of dementia.

Future studies will be needed to investigate the mapping of these functional neural stages along the AD continuum and their relation to behaviors and clinical symptoms. Our results suggest that such compensatory over-recruitment observed during retrieval with reduced brain activity evidenced at encoding may be neural signatures of impaired cognitive function in patients with MCI at risk of AD.

While this study provides valuable insights into the neurophysiological correlates of VSTMB deficits in a community-dwelling population, some limitations should be considered. For example, we did not have available biomarker evidence as informed by the A/T/N framework (Jack et al., 2018), so we relied on the syndromic approach by applying classical clinical criteria. This is relevant because our group recently reported one of the highest prevalences of MCI observed to date in Latin America in this region of Colombia (Bonilla-Santos et al., 2023). Of note, non-canonical risk factors were identified in the region (i.e., environmental pollutants), which may be associated with non-AD dementia. Our analyses were based on average amplitude measures. The evidence delivered to date using the VSTMB paradigm suggests that latency is not an informative variable when discriminating between groups. Amplitude has proved to be the most informative outcome. This could be explained, at least in part, by the populations in which such cognitive function has been investigated using ERP. Pietto et al. (2016) investigated MCI patients in the course of familial or sporadic AD, who were in early prodromal stages. In this current study, MCI were in stages even earlier than those studied by Pietto et al. Accrued evidence suggests that network-level dysfunction (Parra et al., 2017b; Smith et al., 2022), loss of white matter integrity (Parra et al., 2015), grey matter loss (Valdés Hernández et al., 2020), and Amyloid-β accumulation (Parra et al., 2024) can all account for VSTMB deficits in individuals at risk of AD. Future studies will be needed to explore the association between the neural correlates of EPR amplitude and latency across the different stages of the disease continuum. Furthermore, the present study did not include IQ, socioeconomic status, ethnicity, or lifestyle factors measures. These are important factors not only in predicting the risk of or protection against dementia (Livingston et al., 2020) but also in unveiling the variability of ageing trajectories across different sociocultural contexts (Baez et al., 2023; Ibanez et al., 2020, 2021; Ibanez & Eyre, 2023). Future EEG studies with even larger sample sizes will be needed to explore the potential contributions of such factors (see, for example, Moguilner et al., 2024) to the task-related EEG patterns observed in this study. Although we recruited a representative sample of the targeted population, such representativeness was limited by the strict inclusion criteria used to investigate our hypotheses. Future studies with larger sample sizes should explore the influence of the confounding factors here excluded, not only to generalize these results to the broader population but also to explore their contributions to trajectories of risk profiles (i.e., different types of dementia and related diseases).

In conclusion, this study highlights the importance of EEG-based cognitive biomarkers in detecting early neurophysiological changes associated with cognitive decline in community-dwelling older adults at risk of dementia. The evidence presented here supports electrophysiological assessments as a valuable tool for identifying individuals in the early stages of cognitive impairment. Future follow-up studies are recommended to track changes in VSTMB functions over time to establish their predictive value, as suggested by Cecchini et al. (2023).

Author contribution statement.

Alfredis Gonzalez-Hernandez and Jasmin Bonilla-Santos directed the study. Mario A Parra, Alfredis Gonzalez-Hernandez, Jasmin Bonilla-Santos, Rodrigo Gonzalez-Montealegre and Dorian Cala-Martinez designed the study, wrote the protocol and revised the paper. Rodrigo Gonzalez-Montealegre and Mario A Parra managed the literature research, analyses and wrote the first draft of the manuscript. collected experimental data. All authors contributed to and have approved the final manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2025.01.009.

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