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Behavioral and Electrophysiological Correlates of Memory Binding Deficits in Patients at Different Risk Levels for Alzheimer's Disease

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Abstract. Deficits in visual short-term memory (VSTM) binding have been proposed as an early and specific marker for Alzheimer's disease (AD). However, no studies have explored the neural correlates of this domain in clinical categories involving prodromal stages with different risk levels of conversion to AD. We assessed underlying electrophysiological modulations in patients with mild cognitive impairment (MCI), patients in the MCI stages of familial AD carrying the mutation E280A of the presenilin-1 gene (MCI-FAD), and healthy controls. Moreover, we compared the behavioral performance and neural correlates of both patient groups. Participants completed a change-detection VSTM task assessing recognition of changes between shapes or shape-color bindings, presented in two consecutive arrays (i.e., study and test) while event related potentials (ERPs) were recorded. Changes always occurred in the test array and consisted of new features replacing

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studied features (shape only) or features swapping across items (shape-color binding). Both MCI and MCI-FAD patients performed worse than controls in the shape-color binding condition. Early electrophysiological activity (100–250 ms) was significantly reduced in both clinical groups, particularly over fronto-central and parieto-occipital regions. However, shape-color binding performance and their reduced neural correlates were similar between MCI and MCI-FAD. Our results support the validity of the VSTM binding test and their neural correlates in the early detection of AD and highlight the importance of studies comparing samples at different risk for AD conversion. The combined analysis of behavioral and ERP data gleaned with the VSTM binding task can offer a valuable memory biomarker for AD.

Keywords: Electroencephalogram (EEG), event related potentials (ERPs), familial Alzheimer's disease, memory binding, mild cognitive impairment, short-term memory

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INTRODUCTION

The temporary and integrated retention of perceptual features relevant to an object (e.g., shapes and colors) relies on short-term memory binding [1]. A subdomain of this function, called visual short-term memory (VSTM) binding, is impaired in patients with early-onset familial [2] and late-onset sporadic [3, 4] Alzheimer's disease (AD). Moreover, these deficits also emerge in asymptomatic and neuropsychologically normal carriers of the single mutation E280A in the presenilin-1 gene (E280A-PSEN1) [2], which leads to familial AD in 100% of cases [5]. Such difficulties are observed throughout an otherwise asymptomatic period, presumably starting around 12 years before disease onset [2]. Crucially, VSTM binding remains uncompromised throughout normal aging [6–8] and in other types of non-AD dementia [9].

Therefore, VSTM binding deficits seem to constitute an early and specific marker for AD [2–4], appearing in familial and sporadic variants long before other disturbances tapped by classical neuropsychological tasks. In this sense, further research is needed to assess whether the VSTM binding task can validly and reliably detect subtle deficits in patients at risk for AD, such as those with mild cognitive impairment (MCI) [10, 11]. To date, only one study has reported behavioral VSTM binding deficits in this population [12], and none has explored their underlying electrophysiological correlates. The latter gap needs to be bridged, especially since electrophysiological methods are robust, non-invasive, low-cost tools [13] to trace neurocognitive changes throughout both the asymptomatic and symptomatic stages of AD [14].

To this end, we explored whether VSTM binding impairments are associated with electrophysiological changes in two clinical groups at different risk levels for AD: patients who may develop late-onset sporadic AD such as those with MCI (most of them amnestic MCI, single or multi-domain) and patients in the prodromal stages of familial AD carrying the mutation E280A of the presenilin-1 gene (MCI-FAD). Specifically, we compared behavioral and event-related potential (ERP) measures between these samples and healthy controls. Building on previous findings, we hypothesized that both patient samples would show behavioral and electrophysiological abnormalities in the VSTM task, particularly in the memory binding condition. Moreover, since the risk of conversion to AD is 100% for MCI-FAD and much lesser for MCI, we predicted different behavioral and electrophysiological profiles in each group. In particular, we expected that MCI-FAD would show more restricted behavioral and electrophysiological abnormalities in the binding relative to shape only condition of the VSTM task. More generally, this study seeks to test the sensitivity of this memory biomarker as a potential contribution to the early identification of AD pathology.

MATERIALS AND METHODS

Participants

Thirteen patients with MCI were recruited from the Institute of Cognitive Neurology (INECO) in Buenos Aires, Argentina. Diagnosis was based on criteria by Pertersen [15] and Winblad et al. [16] (for further details, see Supplementary Data S1). All the patients underwent neurological, neuropsychiatric, and neuropsychological evaluations. Most of the patients ($n = 9$) were impaired in memory functions (amnestic MCI single domain or amnestic MCI multi-domain) while three patients were classified as non-amnestic MCI multi-domain. Both amnestic MCI single and multi-domain patients were included since these two clinical phenotypes have been shown high risk for AD conversion [17].

The MCI-FAD sample comprised 10 patients recruited from the Colombian province of Antioquia.

All of them carried the mutation E280A of the presenilin-1 gene, which leads to early-onset familial AD in 100% of carriers [5]. These patients also completed formal neurological and neuropsychological assessments.

Two separate groups of healthy participants were formed as controls for the MCI and MCI-FAD groups. These samples, which comprised 14 and 10 individuals, respectively, were matched for age and education with their respective patient samples and recruited from their corresponding geographical area. For further details about the control groups, see Tables 1 and 2, as well as Supplementary Data S1.

Neither the patients nor the controls had a history of psychiatric or neurological diseases. All participants provided written informed consent in agreement with the Helsinki declaration. The Ethics Committees of the University of Antioquia and INECO approved this study.

Neuropsychological assessment

The general cognitive status of MCI patients was assessed with the Mini-Mental State Examination (MMSE) [18] and the Addenbrooke's cognitive examination–revised (ACE-R) [19]. Their premorbid intellectual level was examined with the word accentuation test [20]. Memory was assessed with the Rey auditory verbal learning test (RAVLT) [21] and the recall of the complex Rey figure [21]. Attention and executive functions were evaluated via a digit span task [22], the two parts of the trail-Making test (TMT-A and TMT-B) [21], and a verbal fluency task [21, 23]. Visuospatial and constructional abilities were assessed with the copy task of the complex Rey figure [21]. Additional data were garnered through the instrumental activities of daily living scale (IADL) [24] and the geriatric depression scale (GDS) [25].

MCI-FAD patients were evaluated with the MMSE, the verbal fluency task, the TMT-A, the copy and recall task of the complex Rey figure, and the IADL. Demographic and neuropsychological data of these patients were compared to those of the control group or to the local norms [26, 27] via independent sample and one sample *t*-tests, respectively.

The Visual Short-Term Memory Task

The VSTM task taps change-detection skills to assess memory for single or combined features [4]. It is sensitive to impairments of integrative memory functions in both late-onset sporadic and familial AD [2–4, 28]. The task consists of visual arrays of stimuli sequentially presented on a computer screen. An example of a trial is shown in Fig. 1. Each trial features a study array followed by a test array. In 50% of the trials, the two arrays show identical items. In the remaining half, two items in the test array are replaced by new items. The to-be-remembered items change location from study to test, rendering location an uninformative feature (i.e., it cannot be used as a memory cue). Participants are asked to remember the items shown during the study and decide whether the items that follow in the test display are the same or different (see more details in Supplementary Data S2).

The stimuli consisted of either single shapes (i.e., VSTM for single features) or shapes combined with colors (i.e., VSTM binding). Each type of stimulus was presented in a separate condition. During the shape-only condition, participants viewed three black shapes for study. In the test array for "different trials", two of the previously studied items were replaced by new shapes. In the shape-color binding condition, participants were presented with three shapes, each in a different color. Detection of changes across displays now required remembering the combinations of shape and color presented in the study array. In the test display for "different trials", the color of two shapes swapped relative to the ones they had in the study phase. No shape or color was repeated within a given array. Previous research has shown that healthy memory for binding is consistently defined by memory for the more challenging feature [29–31]. It is therefore revealing when this relationship between memory for binding and memory shapes is lost in AD. However, color has not showed to constrain consistently memory for binding as shape did it. Thus, the shape-binding comparison presents a conservative and reliable indicator of an impairment that is unrelated to task difficulty [30].

Each condition consisted of a brief practice session followed by 100 test trials per experimental condition (200 trials in total). Trials were fully randomized across participants and conditions were delivered in a counterbalanced order.

Electroencephalogram (EEG) recording

MCI patients and controls

MCI patients and their controls sat comfortably at a desk with a computer, set up in an electrically shielded, dimly lit room. As they performed

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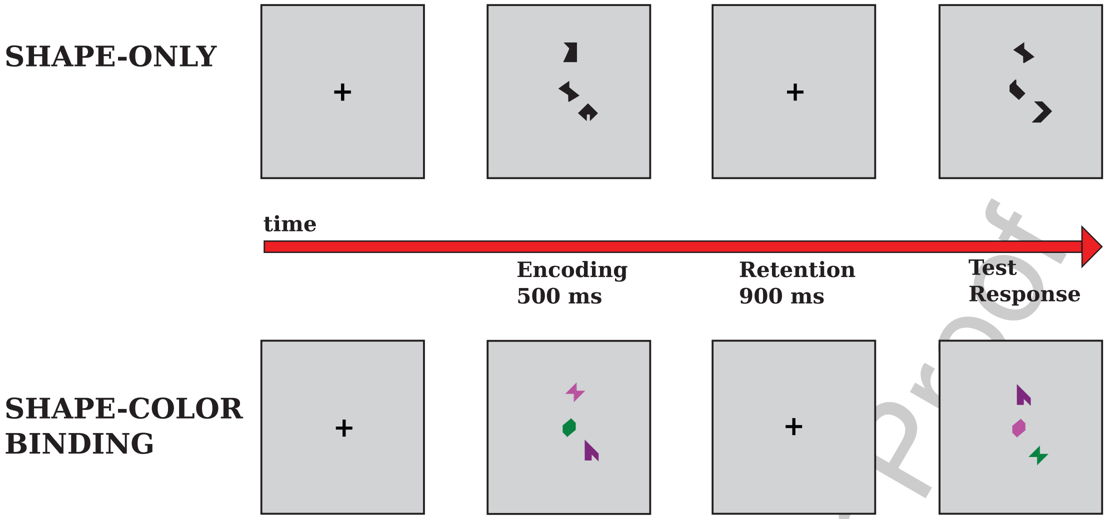

Fig. 1. Examples of “different trials” in each condition of the VSTM task.

the VSTM task, EEG recordings were obtained with a Biosemi 128-channel Active Two system (Amsterdam, NLD). The sampling rate was set at 512 Hz, and signals were bandpass filtered between 1 Hz (high pass) and 100 Hz (low pass).

MCI-FAD patients and controls

MCI-FAD patients and their controls completed the task in a room offering similar conditions as the one described above. EEG activity was collected using 64-channel SynAmps 2.5 system from Neuroscan. In order to eliminate oculomotor artifacts, the EOG signal was collected with 4 electrodes (HEOR, HEOL, VEOL, and VEOU). Impedances were kept below 10 KΩ. The sampling rate was set at 500 Hz, and signals were bandpass filtered between 1 Hz (high pass) and 100 Hz (low pass).

Data analyses

Behavioral data

Comparisons of demographic and neuropsychological data between each patient sample and its corresponding control group were performed via parametric *t*-tests. As in previous studies [2, 12], corrected recognition in the VSTM task was calculated by subtracting the proportion of false alarms from the hits. We followed the same procedure for each sample (MCI versus controls and MCI-FAD versus controls) and condition (shape only and shape-color binding)—see Supplementary Data S4. These indexes were compared through non-parametric Mann-Whitney U tests with Bonferroni correction.

Considering that MCI and MCI-FAD groups were different in terms of age, for this calculation we used control-group-derived parameters of the variables revealing significant between-group differences (i.e., patients versus their respective controls). For each MCI and MCI-FAD patient, we calculated normalized z scores using parameters (mean and SD) derived of the respective control group. *Z*-scores were then compared across the two groups through a non-parametric Mann-Whitney U test. In addition, the effect size for all pairwise comparisons was calculated following the Cohen’s method.

ERPs

MCI and MCI-FAD data were analyzed offline following the same procedures. Analyses were performed with EEGLAB (version 13.1.1b) and MATLAB (version R2012a). Data were filtered between 0.5 Hz (high-pass) and 30 Hz (low-pass) and were down-sampled to 256 Hz. EEG activity was re-referenced to the grand average. Visual inspection of the data was followed by independent component analysis (ICA) to further remove oculomotor artifacts. Continuous EEG data were segmented in epochs of –200 to 1000 ms locked to stimulus onset. Epochs containing artifacts which exceeded a threshold of +/– 100 μV were manually removed. Separate average waveforms were computed for each individual in each condition of the VSTM task (i.e., shape

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only and shape-color binding). Only correct trials were considered for analysis.

First, to identify significant between-group differences across the two conditions, we used a combination of the Monte Carlo test and non-parametric bootstrapping running 4,000 permutations. The data were later analyzed by applying 4,000 permutation draws to generate a histogram called the Monte-Carlo approximation of the permutation distribution. To calculate the differences between our data and this distribution, we used the Monte-Carlo estimation of the permutation *p*-value, which is the proportion of random partitions in which the observed test statistic is larger than the value drawn from the permutation distribution. If this *p*-value is smaller than the critical alpha-level, then it is concluded that the data between the two groups are significantly different. This method offers a straightforward solution for multiple comparison problems and does not depend on multiple comparisons correction or Gaussian assumptions about the probability distribution of the data [32, 33]. This approach has been used in recent ERPs reports of our group [33–35]. Permutations were calculated following a component-free approach across the entire array of electrodes for every millisecond. Electrodes with significant results ($p < 0.01$) were placed into regions of interest (ROIs), and the activity within such regions was averaged out. We considered 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). For each ROI we assigned seven and fourteen electrodes in the MCI and MCI-FAD samples respectively (see Supplementary Figure 1).

Then, we compared the average activity from the six ROIs using 4,000 bootstrapping permutations ($p < 0.05$). Such contrasts were independently carried out in three time-windows (early: 100–250 ms; intermediate: 250–500 ms; late: 500–900 ms) for each condition (shape only and shape-color binding), memory phase (encoding and test), and group—see Supplementary Data S4. This activity was also compared across groups: (a) MCI versus controls, (b) MCI-FAD versus controls, and (c) MCI versus MCI-FAD. These analyses were focused on four different components: N1, P2, P3, and LPP. The N1 is a parieto-occipital negative component [36], peaking around 170 ms post-stimulus onset, which reflects early stages of visual processing and is sensitive to different types of attention [37, 38]. The P2 is a positive component with fronto-central distribution, peaking around 150–300 ms [39]. This component has been associated with attentional control processes, such as stimulus evaluation [39] and feature detection of task-relevant stimuli [40]. The P3 is a positive centro-parietal component, which peaks between 300 and 600 ms post-stimulus-onset, and is considered to reflect activity in a distributed network associated with attention and working memory [41, 42], including context updating and attentional resource allocation [43]. The LPP is a slow positive modulation with an onset around 400–1000 ms after stimulus presentation. The enhancement of this component has been related to memory encoding and storage processes [44, 45]. Moreover, it has been associated with post-retrieval stages, such as decisional monitoring [46] and evaluation [47–50] processes. All the functions indexed by these components are called upon by the VSTM task.

RESULTS

MCI Patients versus healthy controls

Behavioral data

Neuropsychological assessment. The results of the neuropsychological assessment are shown in Table 1. Relative to controls, MCI patients had poorer cognitive performance on both screening tests and on the majority of standard neuropsychological measures (memory, language, and attention)—see details in Supplementary Data S4.

VSTM task. There were no significant within-group differences in response accuracy between task conditions in controls (Mann-Whitney U: 66.5, $Z = 1.42$, $p = 0.16$, $d = 0.60$) or MCI patients (Mann-Whitney U: 54, $Z = 1.54$, $p = 0.12$, $d = 0.64$). MCI patients performed significantly worse than controls in both the shape-only (Mann-Whitney U: 42.5, $Z = 2.33$, $p < 0.05$, $d = 0.91$) and the shape-color binding (Mann-Whitney U: 42.0, $Z = 2.35$, $p < 0.05$, $d = 0.92$) conditions (see Fig. 2D).

ERP results

MCI versus controls. Shape-only condition. Significant differences in P2 amplitude during the encoding phase emerged during the early time-window (100–250 ms) over the bilateral FC region (left: $t = 3.16$, $p < 0.01$, $d = 1.22$; right: $t = 3.16$–, $p < 0.01$, $d = 1.21$). The same was true of the LPP amplitude during the late time-window (500–900 ms) over the

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Table 1
Demographic and neuropsychological data of MCI patients and controls, with results from statistical comparisons

	MCI ($n=13$)		controls ($n=14$)		t-test		Effect size
	Mean	*SD*	Mean	*SD*	t	p	Cohen's d
Age	73.08	9.01	67.21	10.14	–1.58	NS	–0.61
Education	14.08	4.44	16.50	1.99	1.85	NS	0.70
GDS	6.00	3.74	4.93	2.95	–0.83	NS	–0.32
IADL (Fam)	6.38	1.06					
WAT	41.46	8.42	45.98	4.32	1.77	NS	0.67
ACE-III	81.15	12.49	95.07	4.30	3.87	0.0007	1.47
MMSE	26.46	2.47	29.50	0.52	4.50	0.0001	1.70
RAVLT-Total Recall	28.77	9.49	43.93	9.22	4.214.13	0.0003	1.62
RAVLT-Delayed Recall	4.46	3.71	11.09	10.06	2.24	0.03	0.87
RAVLT-List Recognition (corrected)	0.67	0.15	0.95	0.32	2.88	0.008	1.12
Rey Figure - Copy	30.42	4.58	32.16	5.80	0.86	NS	0.33
Rey Figure - Recall	11.04	6.36	16.49	6.55	2.19	0.04	0.84
Rey Figure - Recognition	17.62	2.53	21.69	3.65	3.34	0.003	1.29
Digit Span	5.54	1.13	7.22	3.23	1.77	0.09	0.69
TMT-A	59.23	24.37	42.63	25.87	–1.71	NS	-0.66
TMT-B	183.38	119.47	87.81	46.52	–2.78	0.01	–1.05
Verbal Fluency F	12.08	5.20	17.50	9.30	1.85	NS	0.71
Verbal Fluency A	11.54	4.41	21.74	22.41	1.61	NS	0.63
Verbal Fluency S	11.23	3.17	15.14	2.91	3.35	0.003	1.29

NS, non-significant; RAVLT, Rey Auditory Verbal Learning Test; IADL, Instrumental Activities of Daily Living Scale; WAT, Word Accentuation Test; TMT-A, Trail-Making Test (part A); TMT-B, Trail-Making Test (part B); ACE, Addenbrooke's Cognitive Examination; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale.

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right CP region ($t=2.20$, $p<0.05$, $d=0.84$). In the test phase, we found differences in N1 amplitude during the early time-window (100–250 ms) over the right PO region ($t=–2.40$, $p<0.05$, $d=–0.92$) (see Fig. 2A-C).

Shape-color binding condition. There were significant differences in the encoding phase during the early time-window (100–250 ms). These concerned the P2 component over the bilateral FC region (left: $t=2.37$, $p<0.05$, $d=0.91$; right: $t=2.43$, $p<0.05$, $d=0.93$) and the N1 component over the right PO region ($t=–2.33$, $p<0.05$, $d=–0.90$). In the test phase, significant differences in N1 amplitude emerged during the early time-window (100–250 ms) over the PO region bilaterally (left: t: –2.53, $p<0.01$, $d=–0.97$; right: $t=–3.15$, $p=0.01$, $d=–1.20$), and in the LPP during the late time-window (500–900 ms) over the right FC ($t=2.57$, $p=0.02$, $d=1.00$) and the CP ($t=2.69$, $p=0.01$, $d=0.05$) regions (see Fig. 2A-C).

MCI-FAD patients versus healthy controls

Behavioral data

Neuropsychological assessment. Demographic data and general cognitive state results are shown in Table 2. Statistical comparisons revealed that MCI-FAD patients had poorer general cognitive abilities and memory performance than healthy controls. However, the IADL scale revealed that they were highly functional, confirming the pre-dementia stage of this sample.

VSTM task. Response accuracy to the two VSTM task conditions was similar in both controls (Mann-Whitney U: 34, $Z=1.17$, $p=0.24$, $d=0.64$) and MCI-FAD patients (Mann-Whitney U: 28, $Z=1.63$, $p=0.10$, $d=0.77$). Between-group comparisons revealed higher accuracy for controls in the shape-color binding condition (Mann-Whitney U: 22.5, $Z=–2.08$, $p<0.05$, $d=0.93$), but no differences were observed in the shape-only condition (Mann-Whitney U: 25.0, $Z=–1.89$, $p=0.063$, $d=1.02$)—see Fig. 3D.

ERPs results

MCI-FAD versus controls Shape-only condition. Significant differences during the encoding phase were observed for the P3 component in the intermediate time-window (250–500 ms) over the left PO region ($t=–2.17$, $p<0.05$, $d=0.75$)—see Fig. 3A-C.

Shape-color binding condition. We found significant between-group differences in the amplitude of two components during the encoding phase: P2, over the right FC region ($t=2.57$, $p<0.05$, $d=1.08$); and N1, over the left PO region ($t=–2.91$, $p<0.01$, $d=–1.14$); both patterns emerged during the early time-window (100–250 ms)—see Fig. 3A-C.

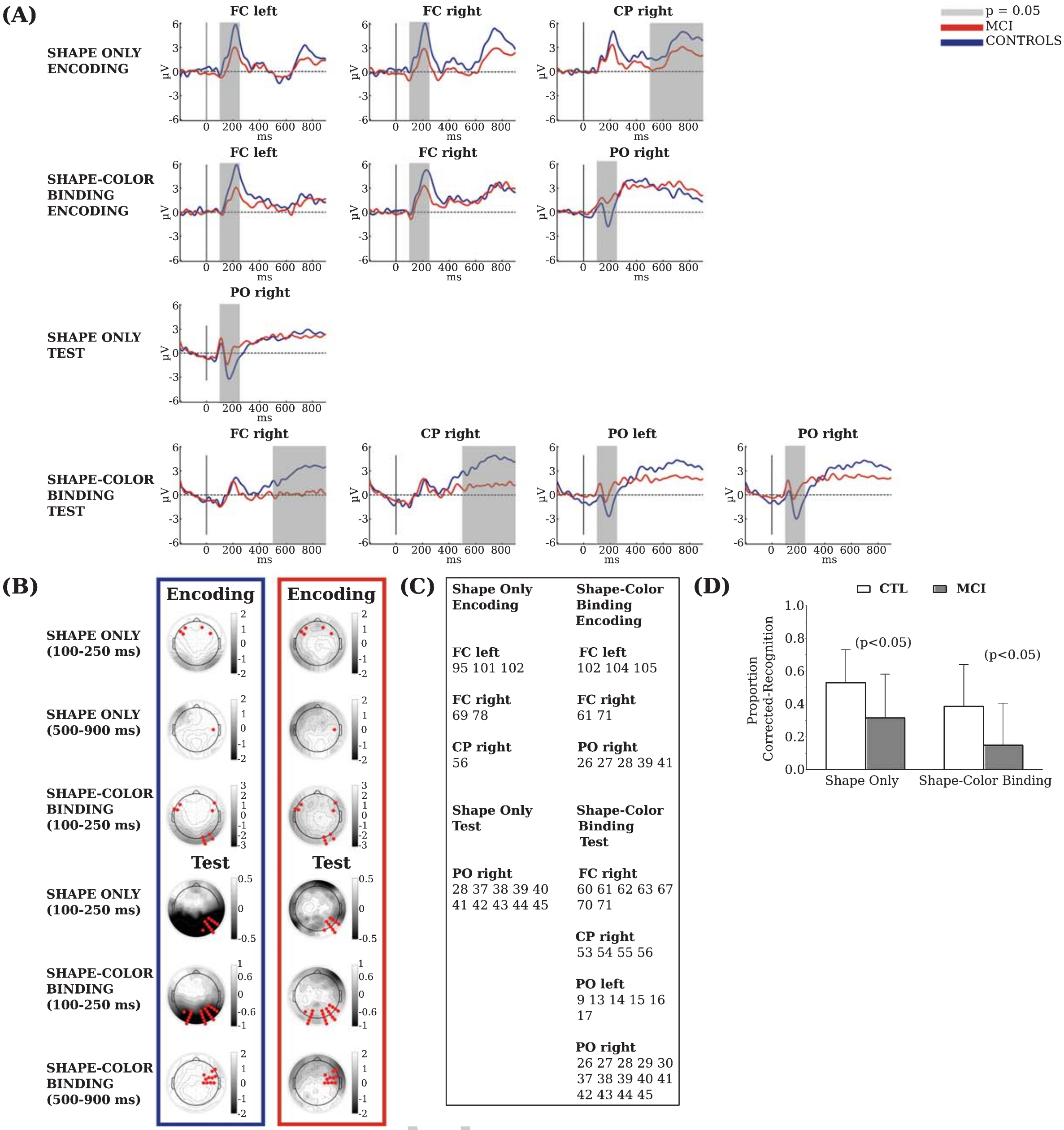

Fig. 2. A) ERP activity from significant ROIs comparing MCI patients and controls in the shape-only (encoding and test) and shape-color binding (encoding and test) conditions. B) Electrodes by numbers comprising the ROIs. Red points indicate significant electrodes. C) Scalp distribution of activity during the early (100–250 ms) and late (500–900 ms) time-windows across conditions and groups. D) Mean performance during the VSTM task in the shape-only and shape-color binding conditions. Error bars represent standard deviations from the mean.

MCI versus MCI-FAD

VSTM task

No significant differences emerged between groups upon comparing their *Z*-scores (see details in data analyses) from performance on the shape-color binding condition of the VSTM task (Mann-Whitney U: 63, $Z = -0.09$, $p = 0.93$, $d = 0.02$)—see Supplementary Fig. 4.

ERPs results

We also compared the patients' *Z*-scores drawn from the electrophysiological data that indicated significant between-group differences over specific

Table 2
Demographic and neuropsychological data of MCI-FAD patients and healthy controls, with results from statistical comparisons

	MCI-FAD ($n = 10$)		Controls ($n = 10$)		t-test		Effect size
	Mean	*SD*	Mean	*SD*	t	p	Cohen's d
Age	44.40	3.20	44.30	5.60	–0.05	NS	–0.02
Education	7.30	4.10	11.30	13.90	0.87	NS	0.38
MMSE	25.20	4.50	29.10	1.10	2.75	0.023	0.86
IADL (Fam)	7.2	1.0					
Verbal Fluency	15.3	5.0	21.4	4.8	3.66	0.006	1.02
TMT-A	87.75	38.30	73.67	26.44	1.04	NS	–0.33
Rey Figure – Copy	21.89	5.03	26.38	4.99	2.68,	.028	0.73
Rey Figure – Recall	7.33	4.89	14.32	5.18	4.29	.003	1.14

NS, non-significant; IADL, Instrumental Activities of Daily Living Scale (IADL); MMSE, Mini-Mental State Examination; TMT-A, Trail-Making Test (part A).

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ROIs and time-windows. Only the ERP activity elicited during the shape-color binding condition met these criteria (FC right, during the encoding phase, in the early time-window). However, contrasts between MCI and MCI-FAD including this activity revealed no significant differences (see Supplementary Fig. 4).

Summary of findings

Behavioral performance on the shape-color binding condition was significantly worse in MCI and MCI-FAD than in their respective control groups. No differences between MCI and MCI-FAD were observed in the shape-color binding condition. Also, comparisons between each patient group and its respective controls showed that performance on the shape-only condition was impaired for MCI but not for MCI-FAD patients.

ERP activity underlying VSTM performance was significantly reduced in MCI and MCI-FAD patients compared to their corresponding control groups (Table 3). This was observed in all ROIs, with most conspicuous activation decreases appearing over FC and PO regions during the early time-window (N1 and P2). MCI patients exhibited reduced amplitude across both conditions and memory phases, whereas MCI-FAD patients showed reduced amplitude in both conditions but only during the encoding phase. Differences in behavioral performance were associated to measurable differences in the underlying ERPs in MCI patients. For MCI-FAD patients, differences observed in the ERPs elicited during the shape-only condition were not accompanied by significant differences in behavioral performance. However, such an association was present for the shape-color binding condition. Finally, analysis of electrophysiological data from MCI and MCI-FAD patients showed no differences in the shape-color binding condition between groups, although both exhibited significant deficits in this function.

DISCUSSION

To our knowledge, this is the first study comparing the behavioral and electrophysiological correlates of VSTM binding deficits in patients in the prodromal stages (i.e., MCI) of sporadic and familial AD. The two samples shared a common phenotype characterized by behavioral and electrophysiological deficits during the shape-color binding condition of the VSTM task. These results lend further support to the validity of the VSTM binding test in the early detection of dementia. By comparing a sample of MCI patients with 100% probability of conversion to AD with a sample of MCI patients with a less certain conversion probability, we have identified a VSTM binding deficits as marker common to both populations. Below we discuss the theoretical implications of our findings.

Behavioral performance on the VSTM task

MCI patients performed significantly worse than healthy controls in both the shape-only and shape-color binding conditions of the VSTM task. These findings are consistent with those reported in a recent study [12] using the same task. However, previous studies in patients with early-onset familial [2] and late-onset sporadic AD [3, 4] have found a selective deficit in the shape-color binding condition. The discrepancy across these studies may be due to methodological differences. Previous studies have equated performance on the baseline condition (i.e., shape only) across patients and controls by assessing the former with smaller set sizes (i.e., patients

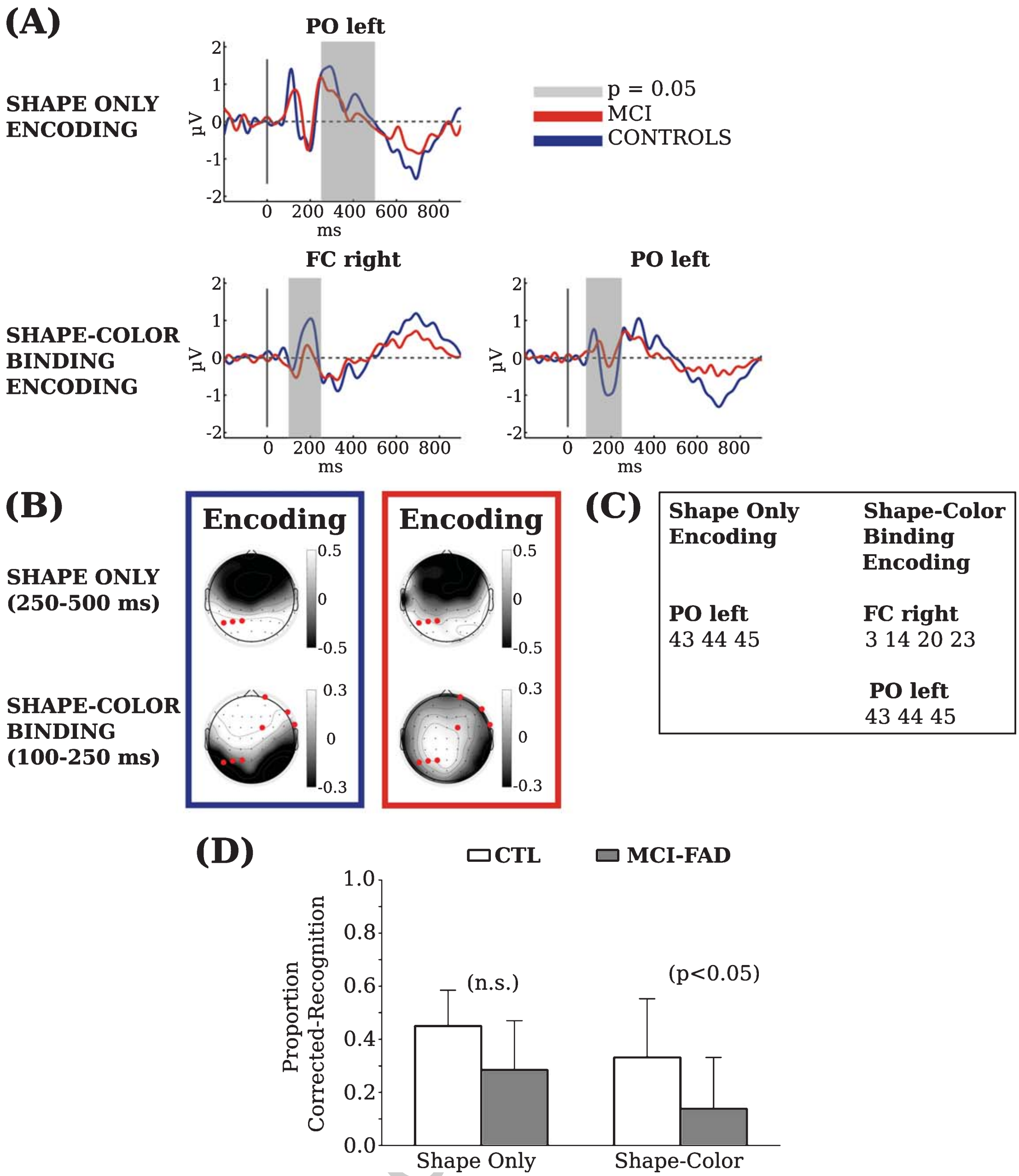

Fig. 3. A) ERP activity from significant ROIs comparing MCI-FAD and controls in the shape-only (encoding) and shape-color binding (encoding) conditions. B) Electrodes by numbers comprising the ROIs. Red points indicate significant electrodes. C) Scalp distribution of activity during the early (100–250 ms) and intermediate (250–500 ms) time-windows across conditions and groups. D) Mean performance during the VSTM task in the shape-only and shape-color binding conditions. Error bars represent standard deviations from the mean.

saw arrays of two items and controls saw arrays of three items). In the present study, as in the one conducted by [12], patients were assessed with the same set size. We followed the logic of earlier studies involving pre-symptomatic mutation carriers [2]. That is, patients who did not meet criteria for dementia and controls were evaluated under the same testing conditions (i.e., same memory load). Although this approach proved valid for the preclinical stages of AD, it does not seem to hold for the clinical stages (i.e., MCI). Nevertheless, shape-only is just a baseline condition that does not hold sensitivity and specificity for AD. It is the shape-color binding condition of the task that has proved clinically relevant. Future

Table 3
Summary of significant results ($p < 0.05$) drawn from the ERP analyses

Between-group contrasts (patients versus controls)							
100–250	N1	MCI versus CTR	TB	TS EB TB			
		FAD versus CTR	EB				
	P2	MCI versus CTR				ES EB	ES EB
		FAD versus CTR					EB
250–500	P3	MCI versus CTR					
		FAD versus CTR					
500–900	LPP	MCI versus CTR			ES TB		TB
		FAD versus CTR					

E, encoding; T, test; S, shape only; B, shape-color binding.

studies interested in the previously reported dissociation (i.e., shape-only versus shape-color binding) may want consider this methodological caveat. In fact, our results show that impairments in shape-color binding are systematically observed across the two populations and were the only deficits found in those with the highest risk for AD (MCI-FAD).

MCI-FAD patients were outperformed by controls, but the difference only reached significance in the shape-color binding condition. This finding aligns with previous reports of VSTM binding deficits in asymptomatic carriers of the mutation E280A in the presenilin-1 gene [2, 3]. Although mutation carriers in the present study were in more advanced stages of the disease process, our results corroborate that VSTM binding deficits may emerge well before the onset of full-blown AD. Note that mean scores for the shape-only condition also evinced a drop in MCI-FAD patients. However, unlike what was observed in MCI, this difference did not reach significance. This discrepancy could partially reflect age differences between the samples, as MCI patients were older than MCI-FAD patients. Although age does not differentially affect short-term memory binding abilities [6, 8, 51], it has an overall impact on short-term memory. This may account for the slightly greater difference between conditions in each group. However, performance on the shape-color binding condition was similar between patient groups. Accordingly, VSTM binding seems to be selectively compromised by AD, above and beyond the effects of age. As suggested in previous research then, this memory function may well constitute a sensitive marker for AD [3, 4, 6, 9]. Note that although Argentinean controls were older and had more years of education than those from Colombia, the behavioral performance of these samples was indistinguishable—see also Parra et al. [3], who reported similar findings in samples of sporadic and familiar AD. Therefore, demographic variables could be ruled out as a factor behind the key findings reported here and in previous studies.

Electrophysiological correlates of the VSTM task

Compared to controls, MCI patients exhibited reduced amplitudes in all ERP components associated with the VSTM task. The cognitive mechanisms supporting this memory function seem to be attenuated along relevant processing stages. Specifically, the amplitude of the N1 component was reduced in both memory phases of the shape-color binding condition, and in the test phase of the shape-only condition. Notably, the scalp distribution (and similar source space [36]) of the diminished N1 was detected over parieto-occipital regions. Enhancements of N1 modulations have been associated to facilitatory mechanisms of spatial attention and orientation towards task-relevant stimuli [37, 38], which subserve discrimination processes [52]. Moreover, N1 modulations may be sensitive to variations in the visual parameters of stimulus configuration [53], reflecting early information processing prior activation of abstract feature representations of the perceived objects. Also, during the encoding phase of both task conditions, P2 modulations were less positive-going in MCI patients than in controls. These differences were observed over bilateral fronto-central regions, in line with the previously reported source of this component [39]. The P2 seems to index stimulus evaluation [39] and detection of features in task-relevant stimuli [40]. Thus, diminished amplitudes of the N1 and P2 components in MCI patients may reflect abnormalities in the early visual integration stages of memory binding. These findings suggest impairments in processing of stimulus features and detection of relevant features, mechanisms related to visual and orbitofrontal association cortices, respectively.

These findings could be interpreted at the neural network level. Recent findings have shown a structural and functional default-model network disruption in AD, which is related to components of the disease pathology such as amyloid and tau

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deposition [54]. In the earliest stages of disease, functional disruption in default-mode network regions involves affectation of medial temporal lobe structures that are implicated in the declarative memory system. In line with this evidence, it has been proposed that neurofibrillary tangles develop initially in the anterior subhippocampal (perirhinal/entorhinal) cortex before the hippocampus [55]. The anterior subhippocampal area forms part of the anterior mesiotemporal network which has been associated with "object-based context-free memory" [55]. These areas would receive perceptual and semantic [56] information to perform higher-level inter-items associations [57].

MCI patients also exhibited reduced amplitudes in the LPP component. This occurred first over centro-parietal regions during the encoding phase of shape-only condition, which may reflect a general encoding deficit. Consistent with this interpretation, it has been suggested that LPP enhancement reflects additional involvement of memory encoding and storage processes [44, 45]. A more elaborate encoding is associated with larger LPP amplitude over parietal scalp sites [58, 59]. Thus, relative to MCI patients, control subjects may have deployed more successful encoding strategies during perceptual input.

Furthermore, reduced LPP amplitude was also observed in MCI patients during the test phase of shape-color binding over centro-parietal and fronto-central electrodes. This abnormal pattern may be related to better control mechanisms during retrieval and post-retrieval processes, reflecting differences in monitoring and evaluation processes required to decide whether a change across study and test arrays. In line with this view, the LPP has been implicated in post-retrieval processes, such as decisional monitoring [46] and evaluation [47–50]. For instance, Eimer and Mazza [48] showed reduced LPP amplitudes when participants were uncertain about the presence of a change between stimulus displays. Thus, convergent evidence suggests that in MCI patients, impaired evaluation and monitoring processes during the comparison of the two memory arrays may increase uncertainty about feature changes, particularly in the shape-color binding condition. From a behavioral perspective, this is consistent with the view that higher similarity between study- and test-item configurations induces greater error rates during the comparison stages of a change-detection task [60]. Comparison processes between arrays containing multi-feature objects seem to demand more cognitive resources than those required to compare single-feature objects. Such resources would avoid misattribution of features across objects, thus contributing to solve the binding problem. Our results indicate that a fronto-parietal network may subserve these binding operations, and that failures of such a network are crucially related to memory binding impairments in patients at risk for AD.

It is worth mentioning that despite the vast existing literature regarding the deficit in associative memory resulting from damage to the hippocampus which has proved a significant predictor of likelihood of conversion from MCI to AD, the evidence regarding the VSTM task has consistently shown that memory binding functions assessed by this change detection paradigm does not involve the hippocampus [61–63]. Indeed, the change detection task reported here has proved to be performed accurately after hippocampal pathology [62]. Moreover, a recent fMRI study in healthy individuals [5] has been shown that binding function does not involve the hippocampus but it relies on a network that involves the activity of parietal and occipito-temporal areas.

Otherwise, LPP retrieval-related activity has been associated with processes of familiarity and recollection (dual process model of recognition) [64] both of which contribute to performance on change detection tasks. Consistent with our results, a recent ERP study [65] showed that amnestic MCI patients present an attenuation of LPP waveforms during the performance of a recognition memory task when they retrieved memories based on recollection and familiarity processes. Thus, this evidence suggests that in MCI patients, reduced amplitude of LPP in the shape-color binding condition may involve retrieval affectation of recollection and familiarity-based memories, either because fewer items are retrieved, and/or fewer entire item-configurations have been successful retrieved.

In addition to visual electrophysiological markers found in our study, the P50 auditory component has been recently proposed as a candidate ERP biomarker of prodromal AD [66]. MCI patients with amyloid and p-Tau positive showed larger P50 amplitudes relative to the amyloid-negative patients during the performance of an oddball task, which reflects poorer inhibitory control to sensory information. However, despite the amplitude of P50 is larger in MCI relative to older normal controls, it increases with normal aging [67, 68]. Crucially, VSTM binding has been shown to be more specific since it remains uncompromised throughout normal aging [6–8]. Therefore, combining with ERP, the VSTM task may offer a

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unique opportunity to detect early neurocognitive abnormalities associated with risk for AD.

MCI-FAD patients exhibited attenuated electrophysiological responses only in the encoding phase of the VSTM task. Specifically, they showed reduced amplitudes of N1 and P2 components associated to shape-color binding processing over parieto-occipital and fronto-central regions, respectively. As we discussed above, reduced N1 amplitude may reflect difficulties to direct attention to task-relevant stimuli [37, 38] and process attributes of visual configurations [53], all linked to early visual processing. Reduced amplitude of the P2 component seems related to deficits in stimulus evaluation [39] and features detection processes [40]. Limitations to encode feature bindings in MCI may thus originate quite early in the visual processing stream. MCI-FAD patients also showed reduced amplitude of the P3 component over parieto-occipital regions in the shape-only condition. This component is considered to reflect activity in a distributed network subserving attention and working memory [41, 42], including context updating and resource allocation [43]. Specifically, P3 increases when stimulus encoding promotes successful memory storage and facilitates retrieval during recognition tasks [69]. Thus, while behaviorally unimpaired, MCI-FAD patients did show electrophysiological evidence of subthreshold anomalies during the shape-only condition of the VSTM task. These subthreshold impairments support the proposal that the mechanisms responsible for holding combinations of shape and color in VSTM are affected by AD to a far greater extent than those responsible for holding single features, such as shapes. Previous ERP studies assessing memory impairments in E280A-PSEN1 presymptomatic mutation carriers have reported functional disruption of brain regions similar to those reported in our study [70, 71]. Taken together, all these findings highlight the importance of ERP analysis to unveil key neural correlates of cognitive impairments throughout the continuum of AD.

Finally, we compared electrophysiological data from MCI and MCI-FAD considering variables which indicated departure from normality. Specifically, we focused on P2 modulations during the encoding phase of the shape-color binding condition over the right fronto-central ROI. Crucially, no between-group differences were observed. This suggests that both prodromal stages of AD (i.e., sporadic-MCI and familiar-MCI) share a common behavioral and electrophysiological phenotype associated to VSTM binding. Such ERP abnormalities seem to reflect impairments during early sensory processing, which are probably associated with stimulus evaluation [39] and feature detection [40]. When we compared patients to their respective controls, both clinical samples showed decreased N1 activity over parieto-occipital regions, suggesting similar deficits in feature discrimination processes [52]. As recently shown in fMRI studies [29, 72–74], these regions seem to support spatial attentional mechanisms necessary to integrate features in VSTM. Therefore, the reduced amplitudes observed in MCI and MCI-FAD during the encoding of shape-color bindings over fronto-central and parieto-occipital regions could be associated to specific impairments in attentional mechanisms supporting feature conflation in VSTM. We argue that these indexes of activation could to reflect reduced attentional control efficiency in frontoparietal attention circuit required for encoding/consolidation binding in VSTM. In sum, the abnormalities observed during the encoding stages in both patient samples could account for behavioral feature-binding impairments in the VSTM task.

Providing that age is not an influential factor, contrasting performance of MCI patients whose phenotype unequivocally suggests the presence of AD (younger MCI-FAD patients) with those with a less certain phenotype (older MCI patients), enables assessment of whether such VSTM binding deficit are a phenotypic feature of prodromal AD regardless of its clinical variant. In line with previous studies suggesting that is the case for patients with the full-blown disease [2], our results revealed that this also characterizes stages of AD prior to diagnosis. Although these results are appealing, they also pose some challenges as contrary to our MCI-FAD cases, we do not predict that 100% of our MCI cases will progress to AD. Future studies involving larger samples of MCI patients should investigate the specific phenotype of those patients who drive such a group effect reported here.

Neurocognitive processes can be studied appropriately with high-temporal resolution techniques such as EEG. These methods are suited to capture properties of transient cognitive events [75] that may be undetected via high-spatial resolution techniques, such as fMRI. In the context of the VSTM binding task, previous fMRI studies [74] did not identify task-related activation over frontal regions. In the present study, within-group analyses showed significant enhanced fronto-central activity during the test phase of the shape-color binding condition. However,

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we did corroborate the involvement of posterior (viz., parietal) regions in feature binding. Therefore, our results suggest that combining the VSTM task with ERP analysis may offer a unique opportunity to detect early neurocognitive alterations in individuals at risk for AD. Such electrophysiological findings underscore the potential of the VSTM task as a biomarker for AD.

Implications and further assessments

Electrophysiological markers could be considered in daily clinical practice to favor the early detection of AD. Such inexpensive, non-invasive measures are robust, fast to compute, and applicable for large-scale screening. This novel approach can overcome several limitations of available biomarkers for AD [14, 54]. As ERPs have high temporal resolution, they can detect subtle information-processing abnormalities, even in the absence of significant behavioral manifestations. Such methodological attributes have important clinical implications in the context of VSTM research. We have replicated behavioral VSTM binding impairments in AD samples [2, 9, 12], further demonstrating their presence in presymptomatic stages of AD (see also [1]). VSTM binding deficits thus seem to constitute a phenotypic feature of AD, detectable throughout the continuum of the disease. The task used in this study could represent a valuable tool to identify candidates for prevention trials. Previous ERPs studies [76–78] have proposed statistical methods for single-case analyses that can be implemented by future research assessing patients in prodromal stages of AD. Moreover, individual ERPs measures may be useful in follow-up clinical assessment of individuals at risk of developing AD or patients with diagnosis of MCI or AD. Longitudinal ERPs measures may provide further insights on the AD nature and may be potentially useful in predicting the disease progression based on the combination of behavioral and electrophysiological measures. Moreover, although computerized assessments of cognitive functions in the early detection of AD are not commonly used, their validity and reliability as testing tools for the clinical practice is being recognized [79]. Computerized testing tools have a number of complementary advantages. They allow more standardized, precise and objective measures of subject performance, and features such as randomization allow throw out practice effects. Finally, computerized assessment can be self-administered and may provide faster results.

We acknowledge some limitations in the present work. First, the two patient samples are not comparable in terms of their demographic characteristics, and they were recruited from different countries. To control for these factors we standardized VSTM scores and demonstrated that, despite such differences, both samples shared a common phenotype both behaviorally and electrophysiologically. Finally, other important limitation is that our MCI group included different clinical phenotypes. However, our sample is similar to that reported in the only study that had assessed different clinical phenotypes of MCI with the VSTM task, in which most of patients were impaired in memory [12]. Future research may to study how sensitive VSTM binding is to cognitive and neuropathological changes considering larger MCI cohort with different characteristics of clinical phenotypes.

CONCLUSION

The prodromal stages of AD are characterized by VSTM binding deficits cutting across sporadic and familial variants of the disease. Such deficits are accompanied by detectable and measurable electrophysiological abnormalities, which are also shared by MCI patients. The incorporation of ERP analyses can boost the sensitivity of the VSTM task to anticipate probable AD, both physiologically (by unveiling relevant biological mechanisms) and clinically (by detecting impaired individuals earlier). All in all, we advocate the combined analysis of behavioral and ERP data gleaned with the VSTM binding task can offer a valuable tool for assessing memory impairments in individuals at risk for AD.

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SUPPLEMENTARY MATERIAL

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