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

Pietto, Marcos; Parra Rodriguez, Mario; Trujillo, Natalia; Flores, Facundo; García, Adolfo M.; Bustin, Julian; Richly, Pablo; Manes, Facundo; Lopera, Francisco; Ibáñez, Agustín M.; Baez, Sandra

Published in:
Journal of Alzheimer's Disease

DOI:
10.3233/JAD-160056

Publication date:
2016

Document Version
Peer reviewed version

Behavioral and electrophysiological correlates of memory binding deficits in patients at different risk levels for Alzheimer's disease

Running title: Memory binding in the prodromal stages of AD

Marcos Pietto [a,b #], Mario A. Parra [c,d,e,f #], Natalia Trujillo [g,h], Facundo Flores [i], Adolfo M. García[a,j], Julian Bustin [i], Pablo Richly [i], Facundo Manes [a,i,l], Francisco Lopera [h], Agustín Ibáñez [a,f,l,m], Sandra Baez [a,n*]

[a] Instituto de Neurociencia Cognitiva y Traslacional (INCyT), Laboratorio de Psicología Experimental y Neurociencias (LPEN), Fundación INECO, Universidad de Favaloro, Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Buenos Aires, Argentina..
[b] Unidad de Neurobiología Aplicada (UNA), CEMIC, Buenos Aires, Argentina.
[c] School of Life Sciences, Psychology, Heriot-Watt University, UK.
[d] Human Cognitive Neuroscience and Centre for Cognitive Ageing and Cognitive Epidemiology, Department of Psychology, University of Edinburgh, UK.
[e] Alzheimer Scotland Dementia Research Centre and Scottish Dementia Clinical Research Network, UK.
[f] Universidad Autónoma del Caribe, Barranquilla, Colombia
[g] School of Public Health, University of Antioquia (UDEA), Medellın, Colombia.
[h] Neuroscience Group, Faculty of Medicine, University of Antioquia (UDEA), Medellın, Colombia.
[i] Institute of Cognitive Neurology (INECO) & Institute of Neuroscience, Favaloro University, Buenos Aires, Argentina.
[j] Faculty of Elementary and Special Education (FEEyE), National University of Cuyo (UNCuyo), Sobremonte 74, C5500, Mendoza, Argentina.
[l] ACR Centre of Excellence in Cognition and its Disorders, Macquarie University, Sydney, Australia.
[m] Laboratory of Cognitive Neuroscience, Universidad Adolfo Ibanez, Santiago, Chile.
[n] Grupo de Investigación Cerebro y Cognición Social, Bogotá, Colombia.

First authors

* Correspondence concerning this article should be addressed to: Sandra Baez, Ph.D., Laboratory of Experimental Psychology & Neuroscience (LPEN), Institute of Cognitive Neurology (INECO) & CONICET, Pacheco de Melo 1860, Buenos Aires, Argentina, Postal Code 1126. Phone/Fax: +54 (11) 4812-0010. sbaez@ineco.org.ar

Response to Reviewers

Reviewer 1

The authors have addressed most of my concerns, but there are a few outstanding issues.

Comment 1. Following the reviewers' comments, the authors state that they removed the analysis concerning MCI subtypes from the main text, but the introduction still mentions: "Finally, we expected different patterns of performance across MCI subtypes, anticipating greater VSTM binding deficits in the multiple-domain amnestic variant. "

Response 1. We appreciate the Reviewer's comment. In the revised version of the manuscript we have removed all sentences concerning MCI subtypes analyses from the main text.

Comment 2. I am not sure that the supplementary data is necessary, as the number of patients in the subgroups are so small.

Response 2. We appreciate the Reviewer's suggestion. We acknowledge that we have small MCI subgroups sample sizes; however, only for curious readers we have presented the results from MCI subgroups in the supplementary data. Moreover, in the supplementary data we provide additional important information about participants and data analysis, and include relevant results concerning electrophysiological data. Therefore, we decided to preserve the supplementary data.

Comment 3. The authors may want to reconsider the following two sentences in the discussion "Recent findings have shown progressive functional default-model network disruption in AD which is related to the spread of tau pathology. In the earliest stages of disease, functional disruption in default-mode network regions involves the affectation of medial temporal lobe structures that are implicated in declarative memory system." There appears to be more evidence that amyloid, rather than tau pathology, is related to dysfunction of the default network. Also these sentences are not coherent with the text that follows.

Response 3. We thankfully welcome this remark. We acknowledge that our previous version of the manuscript was not provided specification regarding the evidence of topographic correspondence between amyloid deposition and the default-model network. We have now provided a better description in the current version of the manuscript. Moreover, we have corrected the paragraph in order to avoid inconsistencies.

The paragraph has been reformulated as follows:

"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 deposition [1]. 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 befor e the hippocampus [2]. The anterior subhippocampal area forms part of the anterior mesiotemporal network which has been associated with “object-based context-free memory” [2]. These areas would receive perceptual and semantic [3] information to perform higher-level inter-items associations [4]”.

Comment 4. The following statement should be reconsidered:" Finally, computerized assessment can be self-administered and through it can reach faster results". Although there is a certain amount of ambiguity in this sentence, it may suggest that the authors recommend computerized self-administration of diagnostic tests for faster results? As this is not desirable I feel that the authors should remove or re-formulate this sentence.

Response 4. We appreciate the Reviewer’s suggestion and have reformulated the sentence as follows:

Page 24, line 19: “Finally, computerized assessment can be self-administered and can provide faster results”.

Comment 5. Finally, the manuscript should be re-read carefully as there are some grammatical errors.

Response 5. We thank the Reviewer for this comment. We have now examined the manuscript in detail to avoid grammatical errors.

References

[1] Pievani M, de Haan W, Wu T, Seeley WW, Frisoni GB (2011) Functional network disruption in the degenerative dementias. Lancet Neurol 10, 829-843.
[2] Didic M, Barbeau EJ, Felician O, Tramoni E, Guedj E, Poncet M, Ceccaldi M (2011) Which memory system is impaired first in Alzheimer's disease? J Alzheimers Dis 27, 11-22.
[3] Graham KS, Patterson K, Powis J, Drake J, Hodges JR (2002) Multiple inputs to episodic memory: words tell another story. Neuropsychology 16, 380-389.
[4] Mayes A, Montaldi D, Migo E (2007) Associative memory and the medial temporal lobes. Trends Cogn Sci 11, 126-135.

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 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: Mild cognitive impairment, familial Alzheimer's disease, short-term memory, memory binding, EEG, ERPs.

1. 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) [4], 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.

2. Materials and methods

2.1. 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 Alzheimer's disease 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.

2.2. 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.

2.3. 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 Alzheimer's disease [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 Figure 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.

2.4. 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 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).

2.5. 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 vs. controls and MCI-FAD vs. 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 vs. 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 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 [33, 34]. This approach has been used in recent ERPs reports of our group [35-37]. Permutations were calculated following a component-free approach across the entire array of electrodes for every millisecond. Electrodes with significant results ($p < .01$) 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 ($p < .05$). 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 vs. controls, (b) MCI-FAD vs. controls, and (c) MCI vs. MCI-FAD. These analyses were focused on four different components: N1, P2, P3, and LPP. The N1 is a parieto-occipital negative component [38], peaking around 170 ms post-stimulus onset, which reflects early stages of visual processing and is sensitive to different types of attention [39, 40]. The P2 is a positive component with fronto-central distribution, peaking around 150-300 ms [41]. This component has been associated with

attentional control processes, such as stimulus evaluation [41] and feature detection of task-relevant stimuli [42]. 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 [43, 44], including context updating and attentional resource allocation [45]. 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 [46, 47]. Moreover, it has been associated with post-retrieval stages, such as decisional monitoring [48] and evaluation [49-52] processes. All the functions indexed by these components are called upon by the VSTM task.

3. Results

3.1. MCI patients vs. 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 S4.

VSTM task

There were no significant within-group differences in response accuracy between task conditions in controls (Mann-Whitney U: 66.5, $Z = 1.42$, $p = .16$, $d = .60$) or MCI patients (Mann-Whitney U: 54, $Z = 1.54$, $p = .12$, $d = 0.64$). MCI patients performed significantly worse than controls in both the shape-only (Mann-Whitney U: 42.5, $Z = 2.33$, $p < .05$, $d = .91$) and the shape-color

binding (Mann-Whitney U: 42.0, $Z = 2.35$, $p < .05$, $d = .92$) conditions (see Figure 2D).

ERP results

MCI vs. 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: $t = 3.16$, $p < .01$, $d = 1.22$; right: $t = 3.16$-, $p < .01$, $d = 1.21$). The same was true of the LPP amplitude during the late time-window (500-900 ms) over the right CP region ($t = 2.20$, $p < .05$, $d = .84$). In the test phase, we found differences in N1 amplitude during the early time-window (100-250 ms) over the right PO region ($t = -2.40$, $p < .05$, $d = -.92$) (see Figure 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: $t = 2.37$, $p < .05$, $d = 0.91$; right: $t = 2.43$, $p < .05$, $d = .93$) and the N1 component over the right PO region ($t = -2.33$, $p < .05$, $d = -.90$). 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, $p < .01$, $d = -.97$; right: $t = -3.15$, $p = .01$, $d = -1.20$), and in the LPP during the late time-window (500-900 ms) over the right FC ($t = 2.57$, $p = .02$, $d = 1.00$) and the CP ($t = 2.69$, $p = .01$, $d = .05$) regions (see Figure 2A-C).

3.2. MCI-FAD patients vs. 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, $Z = 1.17$, $p = .24$, $d = .64$) and MCI-FAD patients (Mann-Whitney U: 28, $Z = 1.63$, $p = .10$, $d = .77$). Between-group comparisons revealed higher accuracy for controls in the shape-color binding condition (Mann-Whitney U: 22.5, $Z = -2.08$, $p < .05$, $d = .93$), but no differences were observed in the shape-only condition (Mann-Whitney U: 25.0, $Z = -1.89$, $p = .063$, $d = 1.02$) –see Figure 3D.

ERPs results

MCI-FAD vs. 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 ($t = -2.17$, $p < .05$, $d = .75$) –see Figure 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 < .05, d = 1.08); and N1, over the left PO region (t = -2.91, p < .01, d = -1.14); both patterns emerged during the early time-window (100-250 ms) –see Figure 3A-C.

3.3. MCI vs. 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 = -.09, p = .93, d = .02) –see Supplementary Figure 4.

ERPs results

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

4. 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.

4.1. 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 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 which does not hold sensitivity and specificity for AD. It is the shape-color binding condition of the task that has proved clinically relevant. Future studies interested in the previously reported dissociation (i.e., shape-only vs. 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, 53], 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.

4.2. 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 [38]) 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 [39, 40], which subserve discrimination processes [54]. Moreover, N1 modulations may be sensitive to variations in the visual parameters of stimulus configuration [55], 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 [41]. The P2 seems to index stimulus evaluation [41] and detection of features in task-relevant stimuli [42]. 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 deposition [56]. 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 [57]. The anterior subhippocampal area forms part of the anterior mesiotemporal network which has been associated with "object-based context-free memory" [57]. These areas would receive perceptual and semantic [58] information to perform higher-level inter-items associations [59].

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 [46, 47]. A more elaborate encoding is associated with larger LPP amplitude over parietal scalp sites [60, 61]. 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 [48] and evaluation [49-52]. For instance, Eimer and Mazza [50] 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

Eliminado: These findings could be interpreted at the neural network level. Recent findings have shown progressive functional default-model network disruption in AD which is related to the spread of tau pathology [56]. The symptoms at early stages of AD seem to be indicative of a pathology spread throughout interconnected regions within large-scale networks [56]. In the earliest stages of disease, functional disruption in default-mode network regions involves the affectation of medial temporal lobe structures that are implicated in 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 [57]. The anterior subhippocampal area form part of anterior mesiotemporal network which has been associated with "object-based context-free memory" [57]. These areas would receive perceptual and semantic [58] information to perform higher level inter-items associations [59]. Thus, convergent evidence suggests that diminished amplitudes in P2 and N1 at early stages of processing in MCI patients could be associated with functional disruption of attentional recruitment in frontal areas and associative cortical regions required for working memory encoding/consolidation of the integration of features within unified objects.

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 [62]. 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 [63-65]. Indeed, the change detection task reported here has proved to be performed accurately after hippocampal pathology [64]. 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) [66] both of which contribute to performance on change detection tasks. Consistent with our results, a recent ERP study [67] 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 [68]. MCI patients with Amyloid and p-Tau positive showed larger P50 amplitudes relative to the amlyloid-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 [69, 70]. Crucially, VSTM binding has been shown to be more specific since it remains uncompromised throughout normal aging [6, 71, 72]. Therefore, combining with ERP, the VSTM task may offer a 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 [39, 40] and process attributes of visual configurations [55], all linked to early visual processing. Reduced amplitude of the P2 component seems related to deficits in stimulus evaluation [41] and features detection processes

[42]. 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 [43, 44], including context updating and resource allocation [45]. Specifically, P3 increases when stimulus encoding promotes successful memory storage and facilitates retrieval during recognition tasks [73]. 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 [74, 75]. 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 [41] and feature detection [42]. 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 [54]. As recently shown in fMRI studies [29, 76-78], 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 [79] which may be undetected via high-spatial resolution techniques, such as fMRI. In the context of the VSTM binding task, previous fMRI studies [78] 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, 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.

4.3. 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, 80]. 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 [81-83] 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 [84]. 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.

Eliminado: through it can reach

Con formato: Fuente: (Predeterminado) Times, Diseño: Claro (Blanco)

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 [85]. 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.

5. 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.

Acknowledgments

Authors declare no conflict of interests. This work was partially supported by grants from CONICET, CONICYT/FONDECYT Regular (1130920), FONCyT-PICT 2012-0412, 2012-1309, FONDAP 15150012 and the INECO Foundation. MAP work was supported by Alzheimer's Society, Grant # AS-R42303. This study was also supported by the MRC grant # MRC-R42552, awarded to MAP in collaboration with AI and FM. We acknowledge the contribution from CODI, University of Antioquia, whose Sustainability Program 2015-2016 supported the Neuroscience Group of Antioquia led by Professor Francisco Lopera. We also acknowledge the support from the Alzheimer´s Scotland Dementia Research and the Centre for Cognitive Ageing and Cognitive Epidemiology part of the cross council Lifelong Health and Wellbeing Initiative (MR/K026992/1) both from the University of Edinburgh.

References

[1] Luck SJ, Vogel EK (1997) The capacity of visual working memory for features and conjunctions. *Nature* **390**, 279-281.

[2] Parra MA, Abrahams S, Logie RH, Mendez LG, Lopera F, Della Sala S (2010) Visual short-term memory binding deficits in familial Alzheimer's disease. *Brain* **133**, 2702-2713.

[3] Parra MA, Sala SD, Abrahams S, Logie RH, Mendez LG, Lopera F (2011) Specific deficit of colour-colour short-term memory binding in sporadic and familial Alzheimer's disease. *Neuropsychologia* **49**, 1943-1952.

[4] Parra M, Abrahams S, Logie R, Della Sala S (2010) Visual short-term memory binding in Alzheimer's disease and depression. *J Neurol* **257**, 1160-1169.

[5] Lopera F, Ardilla A, Martinez A, Madrigal L, Arango-Viana JC, Lemere CA, Arango-Lasprilla JC, Hincapie L, Arcos-Burgos M, Ossa JE, Behrens IM, Norton J, Lendon C, Goate AM, Ruiz-Linares A, Rosselli M, Kosik KS (1997) Clinical features of early-onset Alzheimer disease in a large kindred with an E280A presenilin-1 mutation. *JAMA* **277**, 793-799.

[6] Parra MA, Abrahams S, Logie RH, Sala SD (2009) Age and binding within-dimension features in visual short-term memory. *Neurosci Lett* **449**, 1-5.

[7] Read CA, Rogers JM, Wilson PH (2015) Working memory binding of visual object features in older adults. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*, 1-19.

[8] Rhodes S, Parra MA, Logie RH (2015) Ageing and feature binding in visual working

memory: The role of presentation time. *Q J Exp Psychol (Hove)*, 1-15.

[9] Della Sala S, Parra MA, Fabi K, Luzzi S, Abrahams S (2012) Short-term memory binding is impaired in AD but not in non-AD dementias. *Neuropsychologia* **50**, 833-840.

[10] Sarazin M, Berr C, De Rotrou J, Fabrigoule C, Pasquier F, Legrain S, Michel B, Puel M, Volteau M, Touchon J, Verny M, Dubois B (2007) Amnestic syndrome of the medial temporal type identifies prodromal AD: a longitudinal study. *Neurology* **69**, 1859-1867.

[11] Fischer P, Jungwirth S, Zehetmayer S, Weissgram S, Hoenigschnabl S, Gelpi E, Krampla W, Tragl KH (2007) Conversion from subtypes of mild cognitive impairment to Alzheimer dementia. *Neurology* **68**, 288-291.

[12] Koppara A, Frommann I, Polcher A, Parra MA, Maier W, Jessen F, Klockgether T, Wagner M (2015) Feature Binding Deficits in Subjective Cognitive Decline and in Mild Cognitive Impairment. *J Alzheimers Dis* **48 Suppl 1**, S161-170.

[13] da Silva FL (2013) EEG and MEG: relevance to neuroscience. *Neuron* **80**, 1112-1128.

[14] Poil SS, de Haan W, van der Flier WM, Mansvelder HD, Scheltens P, Linkenkaer-Hansen K (2013) Integrative EEG biomarkers predict progression to Alzheimer's disease at the MCI stage. *Front Aging Neurosci* **5**, 58.

[15] Petersen RC (2004) Mild cognitive impairment as a diagnostic entity. *J Intern Med* **256**, 183-194.

[16] Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Backman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, de Leon M, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, van Duijn C, Visser P, Petersen RC (2004) Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J*

Intern Med **256**, 240-246.

[17] Mitchell J, Arnold R, Dawson K, Nestor PJ, Hodges JR (2009) Outcome in subgroups of mild cognitive impairment (MCI) is highly predictable using a simple algorithm. *J Neurol* **256**, 1500-1509.

[18] Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.

[19] Torralva T, Roca M, Gleichgerrcht E, Bonifacio A, Raimondi C, Manes F (2011) Validation of the Spanish Version of the Addenbrooke's Cognitive Examination-Revised (ACE-R). *Neurologia* **26**, 351-356.

[20] Burin DI, Jorge RE, Arizaga RA, Paulsen JS (2000) Estimation of premorbid intelligence: the word accentuation test-Buenos Aires version. *Journal of Clinical and Experimental Neuropsychology* **22**, 677-685.

[21] Burin DI, Ramenzoni V, Arizaga RL (2003) Evaluación neuropsicológica del envejecimiento: normas según edad y nivel educacional. *Revista Neurológica Argentina* **28**, 149-152.

[22] Wechsler D (2002) Buenos Aires: Paidós.

[23] Butman J, Allegri RF, Harris P, Drake M (2000) Fluencia verbal en español. Datos normativos en Argentina. *Medicina* **60**, 561-564.

[24] Lawton MP, Brody EM (1969) Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* **9**, 179-186.

[25] Yesavage JA, Brink T, Rose TL, Lum O, Huang V, Adey M, Leirer VO (1983) Development and validation of a geriatric depression screening scale: a preliminary report. *Journal of psychiatric research* **17**, 37-49.

[26] Acosta-Baena N, Sepulveda-Falla D, Lopera-Gomez CM, Jaramillo-Elorza MC, Moreno S, Aguirre-Acevedo DC, Saldarriaga A, Lopera F (2011) Pre-dementia clinical stages in presenilin 1 E280A familial early-onset Alzheimer's disease: a retrospective cohort study. *Lancet Neurol* **10**, 213-220.

[27] Ardila A, Lopera F, Rosselli M, Moreno S, Madrigal L, Arango-Lasprilla JC, Arcos M, Murcia C, Arango-Viana JC, Ossa J, Goate A, Kosik KS (2000) Neuropsychological profile of a large kindred with familial Alzheimer's disease caused by the E280A single presenilin-1 mutation. *Arch Clin Neuropsychol* **15**, 515-528.

[28] Parra MA, Saarimäki H, Bastin ME, Londoño AC, Pettit L, Lopera F, Della Sala S, Abrahams S (2015) Memory binding and white matter integrity in familial Alzheimer's disease. *Brain*, awv048.

[29] Parra MA, Della Sala S, Logie RH, Morcom AM (2014) Neural correlates of shape-color binding in visual working memory. *Neuropsychologia* **52**, 27-36.

[30] Allen RJ, Baddeley AD, Hitch GJ (2006) Is the binding of visual features in working memory resource-demanding? *J Exp Psychol Gen* **135**, 298-313.

[31] Wheeler ME, Treisman AM (2002) Binding in short-term visual memory. *J Exp Psychol Gen* **131**, 48-64.

[32] Mansbach WE, Mace RA, Clark KM (2015) Mild cognitive impairment (MCI) in long-term care patients: subtype classification and occurrence. *Aging Ment Health*, 1-6.

[33] Nichols TE, Holmes AP (2002) Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp* **15**, 1-25.

[34] Hesse E, Mikulan E, Decety J, Sigman M, Garcia Mdel C, Silva W, Ciraolo C, Vaucheret E, Baglivo F, Huepe D, Lopez V, Manes F, Bekinschtein TA, Ibanez A (2016) Early

detection of intentional harm in the human amygdala. *Brain* **139**, 54-61.

[35] Hesse E, Mikulan E, Decety J, Sigman M, Garcia Mdel C, Silva W, Ciraolo C, Vaucheret E, Baglivo F, Huepe D, Lopez V, Manes F, Bekinschtein TA, Ibanez A Early detection of intentional harm in the human amygdala. *Brain* **139**, 54-61.

[36] Chennu S, Noreika V, Gueorguiev D, Blenkmann A, Kochen S, Ibanez A, Owen AM, Bekinschtein TA Expectation and attention in hierarchical auditory prediction. *J Neurosci* **33**, 11194-11205.

[37] Gonzalez-Gadea ML, Chennu S, Bekinschtein TA, Rattazzi A, Beraudi A, Tripicchio P, Moyano B, Soffita Y, Steinberg L, Adolfi F, Sigman M, Marino J, Manes F, Ibanez A Predictive coding in autism spectrum disorder and attention deficit hyperactivity disorder. *J Neurophysiol* **114**, 2625-2636.

[38] Di Russo F, Martinez A, Sereno MI, Pitzalis S, Hillyard SA (2002) Cortical sources of the early components of the visual evoked potential. *Hum Brain Mapp* **15**, 95-111.

[39] Luck SJ, Heinze HJ, Mangun GR, Hillyard SA (1990) Visual event-related potentials index focused attention within bilateral stimulus arrays. II. Functional dissociation of P1 and N1 components. *Electroencephalogr Clin Neurophysiol* **75**, 528-542.

[40] Hillyard SA, Anllo-Vento L (1998) Event-related brain potentials in the study of visual selective attention. *Proc Natl Acad Sci U S A* **95**, 781-787.

[41] Potts GF (2004) An ERP index of task relevance evaluation of visual stimuli. *Brain Cogn* **56**, 5-13.

[42] Luck SJ, Hillyard SA (1994) Electrophysiological correlates of feature analysis during visual search. *Psychophysiology* **31**, 291-308.

[43] Kok A (2001) On the utility of P3 amplitude as a measure of processing capacity.

Psychophysiology **38**, 557-577.

[44] Polich J (2007) Updating P300: an integrative theory of P3a and P3b. *Clin Neurophysiol* **118**, 2128-2148.

[45] Smart CM, Segalowitz SJ, Mulligan BP, MacDonald SW (2014) Attention capacity and self-report of subjective cognitive decline: a P3 ERP study. *Biol Psychol* **103**, 144-151.

[46] Koenig S, Mecklinger A (2008) Electrophysiological correlates of encoding and retrieving emotional events. *Emotion* **8**, 162-173.

[47] Friedman D, Johnson R, Jr. (2000) Event-related potential (ERP) studies of memory encoding and retrieval: a selective review. *Microsc Res Tech* **51**, 6-28.

[48] Trott CT, Friedman D, Ritter W, Fabiani M, Snodgrass JG (1999) Episodic priming and memory for temporal source: event-related potentials reveal age-related differences in prefrontal functioning. *Psychol Aging* **14**, 390-413.

[49] Nessler D, Mecklinger A, Penney TB (2001) Event related brain potentials and illusory memories: the effects of differential encoding. *Brain Res Cogn Brain Res* **10**, 283-301.

[50] Eimer M, Mazza V (2005) Electrophysiological correlates of change detection. *Psychophysiology* **42**, 328-342.

[51] Koivisto M, Revonsuo A Event-related brain potential correlates of visual awareness. *Neurosci Biobehav Rev* **34**, 922-934.

[52] Busch NA (2013) The fate of object memory traces under change detection and change blindness. *Brain Res* **1520**, 107-115.

[53] Brockmole JR, Parra MA, Della Sala S, Logie RH (2008) Do binding deficits account for age-related decline in visual working memory? *Psychon Bull Rev* **15**, 543-547.

[54] Vogel EK, Luck SJ (2000) The visual N1 component as an index of a discrimination

process. *Psychophysiology* **37**, 190-203.

[55] Mazza V, Caramazza A (2015) Multiple object individuation and subitizing in enumeration: a view from electrophysiology. *Front Hum Neurosci* **9**, 162.

[56] Pievani M, de Haan W, Wu T, Seeley WW, Frisoni GB Functional network disruption in the degenerative dementias. *Lancet Neurol* **10**, 829-843.

[57] Didic M, Barbeau EJ, Felician O, Tramoni E, Guedj E, Poncet M, Ceccaldi M Which memory system is impaired first in Alzheimer's disease? *Journal of Alzheimer's Disease* **27**, 11-22.

[58] Graham KS, Patterson K, Powis J, Drake J, Hodges JR (2002) Multiple inputs to episodic memory: words tell another story. *Neuropsychology* **16**, 380-389.

[59] Mayes A, Montaldi D, Migo E (2007) Associative memory and the medial temporal lobes. *Trends Cogn Sci* **11**, 126-135.

[60] Friedman D, Trott C (2000) An event-related potential study of encoding in young and older adults. *Neuropsychologia* **38**, 542-557.

[61] Sanquist TF, Rohrbaugh JW, Syndulko K, Lindsley DB (1980) Electrocortical signs of levels of processing: perceptual analysis and recognition memory. *Psychophysiology* **17**, 568-576.

[62] Awh E, Barton B, Vogel EK (2007) Visual working memory represents a fixed number of items regardless of complexity. *Psychol Sci* **18**, 622-628.

[63] Parra MA, Fabi K, Luzzi S, Cubelli R, Hernandez Valdez M, Della Sala S Relational and conjunctive binding functions dissociate in short-term memory. *Neurocase* **21**, 56-66.

[64] Baddeley A, Allen R, Vargha-Khadem F Is the hippocampus necessary for visual and verbal binding in working memory? *Neuropsychologia* **48**, 1089-1095.

[65] Mayes AR, Holdstock JS, Isaac CL, Montaldi D, Grigor J, Gummer A, Cariga P, Downes JJ, Tsivilis D, Gaffan D, Gong Q, Norman KA (2004) Associative recognition in a patient with selective hippocampal lesions and relatively normal item recognition. *Hippocampus* **14**, 763-784.

[66] Rugg MD, Curran T (2007) Event-related potentials and recognition memory. *Trends Cogn Sci* **11**, 251-257.

[67] Wolk DA, Manning K, Kliot D, Arnold SE Recognition memory in amnestic-mild cognitive impairment: insights from event-related potentials. *Front Aging Neurosci* **5**, 89.

[68] Green DL, Payne L, Polikar R, Moberg PJ, Wolk DA, Kounios J P50: A candidate ERP biomarker of prodromal Alzheimer's disease. *Brain Res* **1624**, 390-397.

[69] Golob EJ, Irimajiri R, Starr A (2007) Auditory cortical activity in amnestic mild cognitive impairment: relationship to subtype and conversion to dementia. *Brain* **130**, 740-752.

[70] Azumi T, Nakashima K, Takahashi K (1995) Aging effects on auditory middle latency responses. *Electromyogr Clin Neurophysiol* **35**, 397-401.

[71] Read CA, Rogers JM, Wilson PH Working memory binding of visual object features in older adults. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* **23**, 263-281.

[72] Rhodes S, Parra MA, Logie RH Ageing and feature binding in visual working memory: The role of presentation time. *Q J Exp Psychol (Hove)* **69**, 654-668.

[73] Azizian A, Polich J (2007) Evidence for attentional gradient in the serial position memory curve from event-related potentials. *J Cogn Neurosci* **19**, 2071-2081.

[74] Quiroz YT, Ally BA, Celone K, McKeever J, Ruiz-Rizzo AL, Lopera F, Stern CE, Budson AE (2011) Event-related potential markers of brain changes in preclinical

familial Alzheimer disease. *Neurology* **77**, 469-475.

[75] Bobes MA, Garcia YF, Lopera F, Quiroz YT, Galan L, Vega M, Trujillo N, Valdes-Sosa M, Valdes-Sosa P (2010) ERP generator anomalies in presymptomatic carriers of the Alzheimer's disease E280A PS-1 mutation. *Hum Brain Mapp* **31**, 247-265.

[76] Xu Y, Chun MM (2006) Dissociable neural mechanisms supporting visual short-term memory for objects. *Nature* **440**, 91-95.

[77] Todd JJ, Marois R (2004) Capacity limit of visual short-term memory in human posterior parietal cortex. *Nature* **428**, 751-754.

[78] Shafritz KM, Gore JC, Marois R (2002) The role of the parietal cortex in visual feature binding. *Proc Natl Acad Sci U S A* **99**, 10917-10922.

[79] Cohen MX *Analyzing neural time series data: theory and practice*, MIT Press.

[80] Pievani M, de Haan W, Wu T, Seeley WW, Frisoni GB (2011) Functional network disruption in the degenerative dementias. *Lancet Neurol* **10**, 829-843.

[81] Peterburs J, Pergola G, Koch B, Schwarz M, Hoffmann KP, Daum I, Bellebaum C (2011) Altered error processing following vascular thalamic damage: evidence from an antisaccade task. *PLoS One* **6**, e21517.

[82] Dalrymple KA, Oruc I, Duchaine B, Pancaroglu R, Fox CJ, Iaria G, Handy TC, Barton JJ (2011) The anatomic basis of the right face-selective N170 IN acquired prosopagnosia: a combined ERP/fMRI study. *Neuropsychologia* **49**, 2553-2563.

[83] Oruc I, Krigolson O, Dalrymple K, Nagamatsu LS, Handy TC, Barton JJ (2011) Bootstrap analysis of the single subject with event related potentials. *Cogn Neuropsychol* **28**, 322-337.

[84] Canini M, Battista P, Della Rosa PA, Catricala E, Salvatore C, Gilardi MC, Castiglioni I

Computerized neuropsychological assessment in aging: testing efficacy and clinical ecology of different interfaces. *Comput Math Methods Med* **2014**, 804723.

[85] Koppara A, Frommann I, Polcher A, Parra MA, Maier W, Jessen F, Klockgether T, Wagner M Feature Binding Deficits in Subjective Cognitive Decline and in Mild Cognitive Impairment. *J Alzheimers Dis* **48 Suppl 1**, S161-170.

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	.0007	1.47
MMSE	26.46	2.47	29.50	0.52	4.50	.0001	1.70
RAVLT-Total Recall	28.77	9.49	43.93	9.22	4.214.13	.0003	1.62
RAVLT-Delayed Recall	4.46	3.71	11.09	10.06	2.24	.03	0.87
RAVLT-List Recognition (corrected)	0.67	0.15	0.95	0.32	2.88	.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	.04	0.84
Rey Figure -	17.62	2.53	21.69	3.65	3.34	.003	1.29

Recognition							
Digit Span	5.54	1.13	7.22	3.23	1.77	.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	.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	.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.

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	.023	0.86
IADL (Fam)	7.2	1.0					
Verbal Fluency	15.3	5.0	21.4	4.8	3.66,	.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).

Table 3. Summary of significant results ($p < .05$) drawn from the ERP analyses.

BETWEEN-GROUP CONTRASTS (PATIENTS VS. CONTROLS)								
100-250	N1	MCI vs. CTR	TB	TS EB TB				
		FAD vs. CTR	EB					
	P2	MCI vs. CTR					ES EB	ES EB
		FAD vs. CTR						EB
250-500	P3	MCI vs. CTR						
		FAD vs. CTR						
500-900	LPP	MCI vs. CTR				ES TB		TB
		FAD vs. CTR						

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

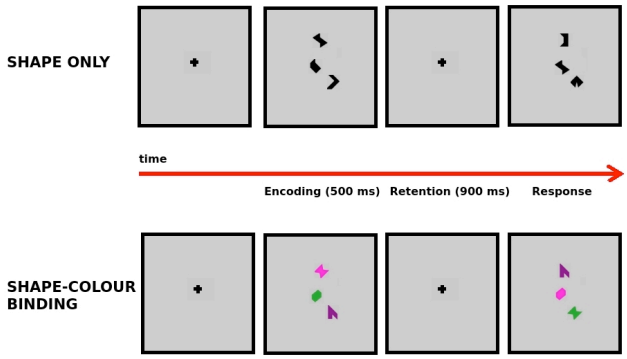

Figure 1. Examples of "different trials" in each condition of the VSTM task.

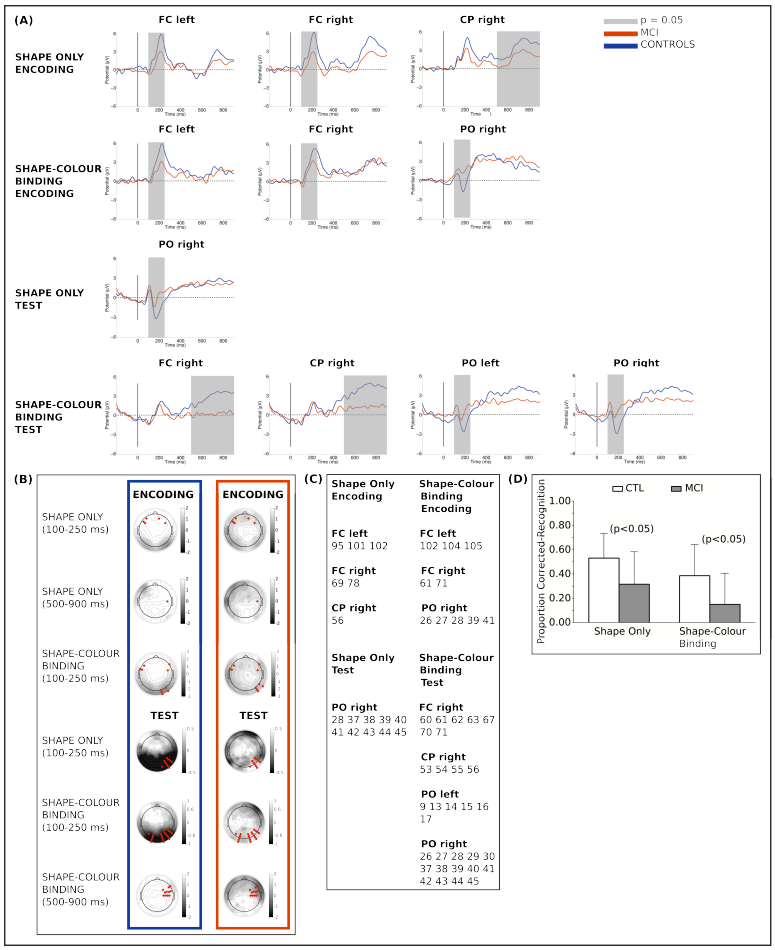

Figure 2. (A) ERP activity from significant ROIs comparing MCI patients and controls in the shape-only (encoding and test) and shape-color binding (encoding and test) conditions. (B) Electrodes by numbers comprising the ROIs. Red points indicate significant electrodes. (C) Scalp distribution of activity 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.

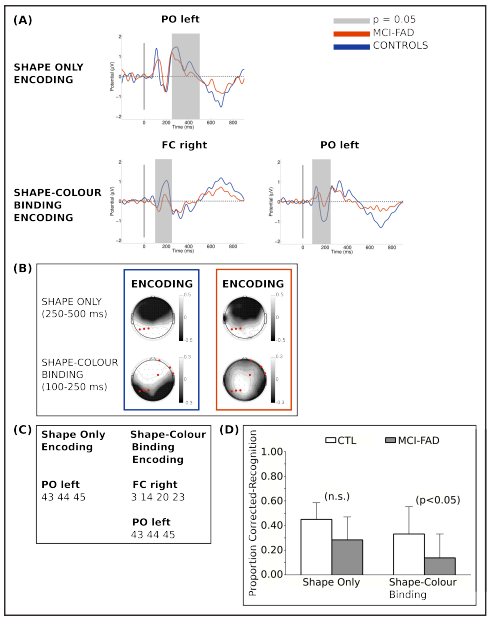

Figure 3. (A) ERP activity from significant ROIs comparing MCI-FAD and controls in the shape-only (encoding) and shape-color binding (encoding) conditions. (B) Electrodes by numbers comprising the ROIs. Red points indicate significant electrodes. (C) Scalp distribution of activity during the early (100-250 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.

Supplementary data

S1. Participants

Mild cognitive impairment patients

MCI patients were diagnosed according to the criteria proposed by Pertersen [1] and Winblad et al. [2], namely: (1) change in cognition recognized by the affected individual and/or a close informant; (2) relatively preserved general cognition for age; (3) objective memory impairment (defined by scores of 1.5 SDs below age norms); (4) independence in functional activities; and (5) absence of dementia [3].

MCI subtypes

Clinical phenotypes of MCI were distinguished based on previously established criteria [2, 4]. MCI patients were classified into three sub-groups according to an impairment threshold set at 1.5 SDs for memory, executive functions, and attention capacity: non-amnestic MCI (in which patients had executive and/or attention impairments), amnestic MCI (in which patients had only memory impairment), and multi-domain MCI (in which patients had memory and executive and/or attention impairments).

MCI-FAD patients

MCI-FAD patients were recruited in a large kindred from the Colombian province of Antioquia. These individuals carried a gene mutation (i.e., E280A in the PSEN-1 gene) that leads to early-onset familial Alzheimer's disease in 100% of cases [5]. At the time of assessment, all the participants led an active working life, proved functionally independent, and were off medication (i.e., anticholinesterase inhibitors). Patients with MCI-FAD met the definition proposed by [6].

All the participants had previously undergone genetic screening and the presence of the mutation, which was unknown both to the participants and the researchers, had been either confirmed or ruled out.

S2. Visual short-term memory task

The trial sequence was as follows: each trial began with a fixation cross visible for 500 ms. This was followed by the study array, which also remained on screen for 500 ms. Then came a blank retention interval of 900 ms, after which the test array appeared and persisted until the participant responded. Participants tested in Argentina used a mouse to indicate recognition of a change (or absence thereof) between the study and the test arrays (left button for "same trial" and right button for "different trial"). Participants tested in Colombia responded orally upon the experimenter's request. This procedure allowed the isolation of the artifact induced by verbal responses. The experimenter then entered participants' responses using the keyboard. The results presented here suggest that these different procedures do not affect response accuracy. The two patient samples were affected and their impairments were indistinguishable.

S3. Data analysis

Behavioral data

Neuropsychological assessment

Comparisons among MCI subtypes

Intra-group analyses within the MCI sample were performed to determine whether these subgroups are comparable in term of demographic (i.e. age, education) and cognitive functioning (ACE III). This analysis was effectuated using a non-parametric Kruskal-Wallis test. A Tukey

correction was applied to each comparison among MCI subtypes.

VSTM task

Comparisons among MCI subtypes

For an intra-group analyses within the MCI sample, patients were pooled into three clinical phenotypes [1, 2, 4]: (a) non-amnestic MCI with deficits in a single domain (nMCI), (b) pure amnestic MCI (aMCI), and (c) multiple-domain amnestic MCI (mMCI) –see S1. To compare the performance of these subgroups on the VSTM task, we used a non-parametric Kruskal-Wallis test. A Tukey correction was applied to each comparison among MCI subtypes. This procedure was not applied to the FAD-MCI patients as they were all in an mMCI stage.

Comparisons between MCI and MCI-FAD

As a confirmatory analysis in order to compare behavioral and ERP data between the MCI and FAD-MCI groups, we converted raw scores to z-scores. For this calculation we used group-derived parameters (common mean and SD of the overall group) of the variables revealing significant between-group differences. *Z*-scores were then compared across the two groups through a non-parametric Mann-Whitney U test. In addition, for all pairwise comparisons the effect size Cohen's method was calculated.

S4. Results

S4.1 MCI patients vs. healthy controls

Behavioral data

Neuropsychological assessment

Statistical comparisons revealed that MCI patients had poorer cognitive performance on both screening tests and on the majority of standard neuropsychological tests. The domains yielding more severe impairments were memory, language, and attention. However, no differences were found between MCI patients and controls in premorbid intelligence, copy of the Rey figure, TMT-A, digit span, and two of the phonological fluency task trials. Finally, MCI patients showed no impairments in daily living functions, which ruled out the presence of dementia (see Table 1 in main text).

Comparisons among MCI subtypes

MCI subgroups were comparable in terms of age (Kruskal-Wallis test H: 0.07, p = .96), years of education (Kruskal-Wallis test H: 1.34, p = .51) and in cognitive functioning (Kruskal-Wallis test H: 6.22, p = .08).

There were significant differences among MCI subtypes in both the shape-only (Kruskal-Wallis test H: 8.6, p = .01) and the shape-color binding (Kruskal-Wallis test H: 6.5 p = .04) conditions. Multiple comparisons showed that nMCI outperformed mMCI on both the shape-only (Z = 2.54, p = .03, d = 2.50) and the shape-color binding (Z = 2.40; p = .05, d = 2.54) conditions. In addition, performance in the shape-only condition was better for aMCI than mMCI (Z = 2.44, p = .04, d = 2.52). No significant differences were found between aMCI and nMCI in any

condition (see Supplementary Table 1).

ERP results

MCI patients

Encoding phase. There were differences between conditions in the right FC region, departing from the P2 ($t = -3.04$, $p < .01$, $d = -0.58$) to the P3 component ($t = -2.80$, $p < .05$, $d = -0.67$), which emerged in the early time-window (100-250 ms) and extended over the intermediate time-window (250-500 ms). Differences were also observed in the amplitude of the P2 component during the early time-window (100-250 ms) over the left ($t = -2.30$, $p < .05$, $d = -0.37$) and the right ($t = -2.41$, $p < .05$, $d = -0.45$) CP regions. Furthermore, there were differences over the right CP region in the P3 ($t = -2.26$, $p < .05$, $d = -0.48$) during the intermediate time-window (250-500 ms) and in the LPP ($t = -2.80$, $p < .01$, $d = -0.47$) in a latency range of 500-900 ms. We also found bilateral differences over the PO region in the N1 (left: $t = -2.35$, $p < .05$, $d = -0.36$; right: $t = -2.98$, $p < .01$, $d = -0.42$) and the LPP (left: $t = -2.27$, $p < .05$, $d = -0.45$; right: $t = -2.82$, $p < .01$, $d = -0.59$) components, in early (100-250 ms) and late (500-900 ms) time-windows, respectively.

Test phase. We found differences in P2 amplitudes over bilateral FC regions (left: $t = -2.48$, $p < .05$, $d = -0.57$; right: $t = 2.46$, $p < .05$, $d = 0.47$) in the early time-window (100-250 ms). Significant differences also emerged in the N1 component over the left CP ($t = -2.66$, $p < .05$, $d = -0.44$) and bilateral PO regions (left: $t = -3.55$, $p < .01$, $d = -0.40$; right: $t = -2.59$, $p < .05$, $d = -0.48$), both in early time-windows (100-250 ms) (see Supplementary Figure 2).

Closer inspection of the waveforms revealed that the above effects were driven by larger amplitudes of all the ERP components, except N1 and P2, during the shape-color binding condition relative to the shape-only condition. The amplitude of N1 during the encoding and test and the amplitude of P2 during the test phase were larger in the shape-only than in the shape-color binding condition (see Supplementary Table 3).

Controls

Encoding phase. No significant differences between conditions were observed.

Test phase. We found differences between conditions over the left FC region in the amplitude of the P2 ($t = -2.53$, $p < .05$, $d = -0.65$), P3 ($t = -3.36$, $p < .05$, $d = -0.70$), and LPP ($t = -3.02$, $p < .05$, $d = -0.77$) components during the early (100-250 ms), intermediate (250-500 ms), and late (500-900 ms) time-windows, respectively. Differences in these time-windows were also observed in the left (early: $t = -2.42$, $p < .05$, $d = -0.47$; intermediate: $t = -3.36$, $p < .01$, $d = -0.64$; late: $t = -4.24$, $p < .01$, $d = -0.98$) and right (early: $t = -2.08$, $p < .05$, $d = -0.42$; intermediate: $t = -3.52$, $p < .01$, $d = -0.46$; late: $t = -3.87$, $p < .01$, $d = -0.78$) CP regions for the P2, P3, and LPP components. In addition, there were differences over the right PO region, departing from the P3 ($t = -1.97$, $p < .05$, $d = -0.29$) to the LPP ($t = -3.45$, $p < .01$, $d = -0.53$), which emerged in the intermediate time-window (250-500 ms) and extended over the late time-window (500-900 ms). Differences were also observed in the LPP component ($t = -2.67$, $p < .05$, $d = -0.56$) over the left PO during the late time-window (500-900 ms) (see Supplementary Figure 2).

Closer inspection of the waveforms revealed that these effects were driven by larger amplitudes of all the ERP components in the shape-color binding condition compared to the shape-only

condition (see Supplementary Table 3).

S.4.2 MCI-FAD patients vs. healthy controls

ERP results

MCI-FAD patients

Encoding phase. There were significant differences between conditions in the P2 amplitude over the left FC ($t = -2.18$, $p < .01$, $d = -1.10$) during the early time-window (100-250 ms). This time-window also yielded differences in the N1 component over the right CP ($t = 3.24$, $p < .05$, $d = 1.26$) and PO ($t = 3.05$, $p < .05$, $d = 1.13$) regions (see supplementary Figure 3).

Test phase. There were differences between conditions in the N1 amplitude over the right PO region ($t = 3.15$, $p < .05$, $d = 0.33$) during the early time-window (100-250 ms) –see supplementary Figure 3.

These within-group analyses showed that all the ERPs exhibited greater amplitude in the shape-color binding than in the shape-only condition (see Supplementary Table 3).

Controls

Encoding phase. We found significant differences between conditions over the left PO region in the amplitude of the N1 ($t = 2.60$, $p < .05$, $d = 0.49$) and P3 ($t = 2.19$, $p < .05$, $d = 0.51$) components during early (100-250 ms) and intermediate (250-500 ms) time-windows, respectively. There were also differences in the amplitude of the N1 ($t = 3.00$, $p < .05$, $d = 0.32$) over the right PO during the early time-window (100-250 ms) –see supplementary Figure 3.

Test phase. We found significant differences between conditions in the P2 component during the early window (100-250 ms) over the left FC ($t = -3.08$, $p < .01$, $d = -0.95$). Amplitude differences during that same time-window also emerged for the N1 component over the right CP ($t = 2.97$, $p < .01$, $d = 0.81$) and PO ($t = 4.35$, $p < .01$, $d = 0.53$) regions (see supplementary Figure 3).

Closer inspection of the waveforms revealed that the above effects were driven by larger amplitudes of all the ERP components in the shape-color binding condition relative to the shape-only condition (see Supplementary Table 3).

S.4.3 MCI vs. 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: 52.0, $Z = .78$, $p = .44$, $d = .52$).

ERP results

We also compared the patients' z-scores drawn from the electrophysiological data which indicated significant between-group differences over specific ROIs and time-windows (see section 3.3 in the main text). However, contrasts between MCI and MCI-FAD including ERP activity revealed no significant differences (Mann-Whitney U: 63.0, $Z = .09$, $p = .93$, $d = .05$).

Supplementary Table 1. VSTM task performance in different MCI's subgroups.

VSTM task conditions	Mean (*SD*) corrected recognition scores			
	nMCI (*n* = 4)	aMCI (*n* = 4)	mMCI (*n* = 5)	Controls
Shape only	0.50 (0.17)	0.47 (0.14)	0.05 (0.19)	0.45 (0.13)
Shape-color binding	0.34 (0.15)	0.25 (0.24)	-0.08 (0.18)	0.33 (0.22)

Supplementary Table 2. Demographic data and general cognitive impairment in different MCI's subgroups.

	Mean (*SD*)		
	nMCI (n = 4)	aMCI (n = 4)	mMCI (n = 5)
Age	73.00 (12.57)	71.50 (11.39)	74.40 (4.83)
Education	14.25 (6.18)	15.75 (0.96)	12.60 (4.93)
ACE III	87.25 (5.50)	88.25 (2.36)	70.60 (14.64)

Table 3. Summary of significant results ($p < .05$) drawn from the ERP analyses.

WITHIN-GROUP CONTRASTS (SHAPE ONLY VS. SHAPE-COLOR BINDING)								
			Parieto-occipital		Centro-parietal		Fronto-central	
Time-window (ms)	**ERP**	**Group-contrast**	**L**	**R**	**L**	**R**	**L**	**R**
100-250	N1	MCI	E T	E T	T			
		MCI-CTR			T	T		
		FAD		E T		E		
		FAD-CTR	E	E T		T		
	P2	MCI			E	E	T	E T
		MCI-CTR					T	
		FAD						
		FAD-CTR					T	
250-500	P3	MCI				E		E
		MCI-CTR		T	T	T	T	
		FAD						
		FAD-CTR	E					
500-900	LPP	MCI	E	E		E		
		MCI-CTR		T	T	T	T	
		FAD						
		FAD-CTR						

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

Supplementary figures

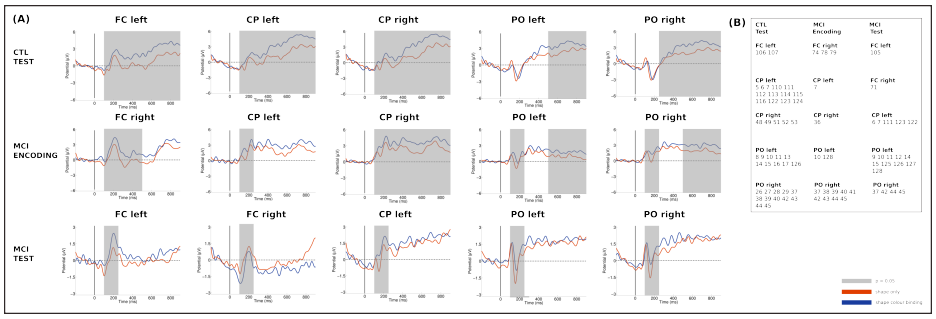

Figure 1. (A) ERP activity from significant ROIs between the shape-only and shape-color binding conditions in each memory phase of the VSTM task, in controls and MCI patients. (B) Electrodes by numbers comprising the ROIs.

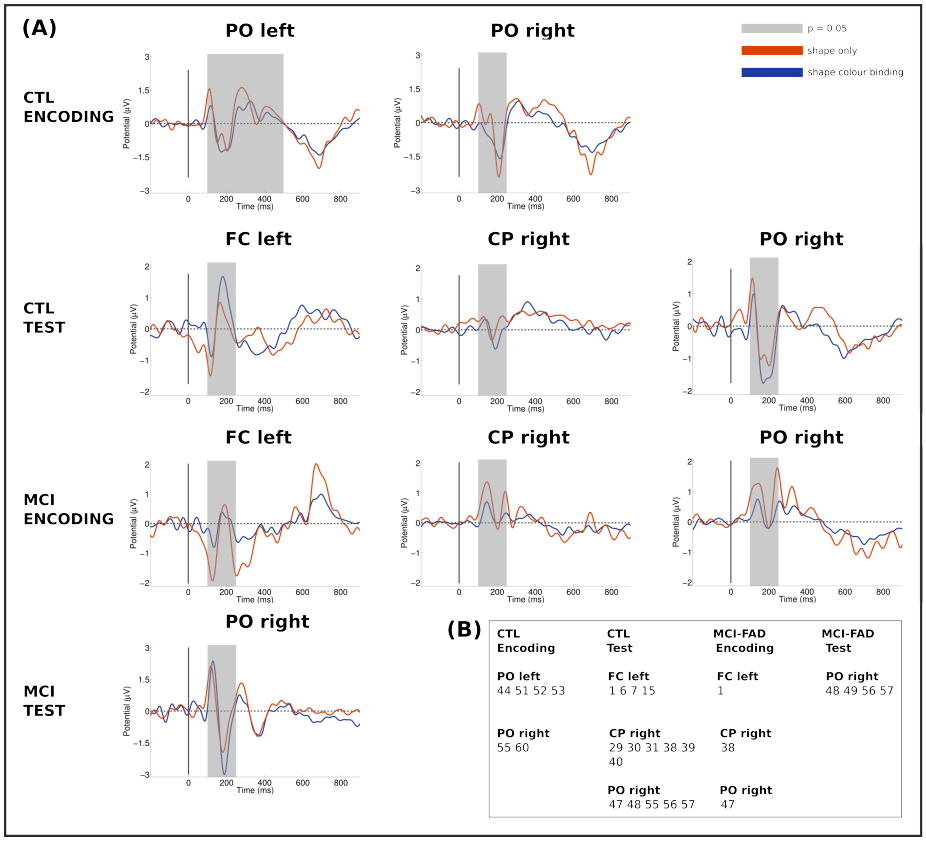

Figure 2. (A) ERP activity from ROIs yielding significant differences between the shape-only and the shape-color binding conditions in each memory phase of the VSTM task, in controls and MCI-FAD patients. (B) Electrodes by numbers comprising the ROIs.

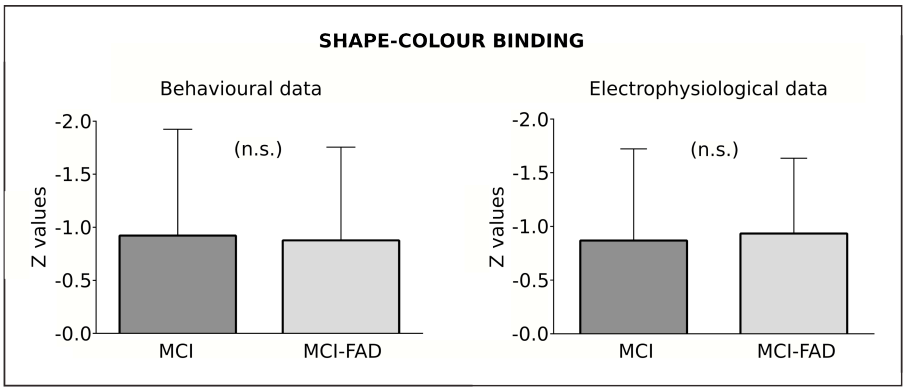

Figure 3. Behavioral and electrophysiological comparisons between MCI and MCI-FAD during the VSTM task. The y-axis shows the means of the distance between patients and controls, as measured with *z*-values. Error bars represent standard deviations from the mean. The mean *z* value of behavioral performance in the shape-color binding condition is depicted on the left side. The mean *z* value of electrophysiological activity in the shape-color binding condition is portrayed on the right (ROI: FC right; memory-phase: encoding; time-window: 100-250 ms).

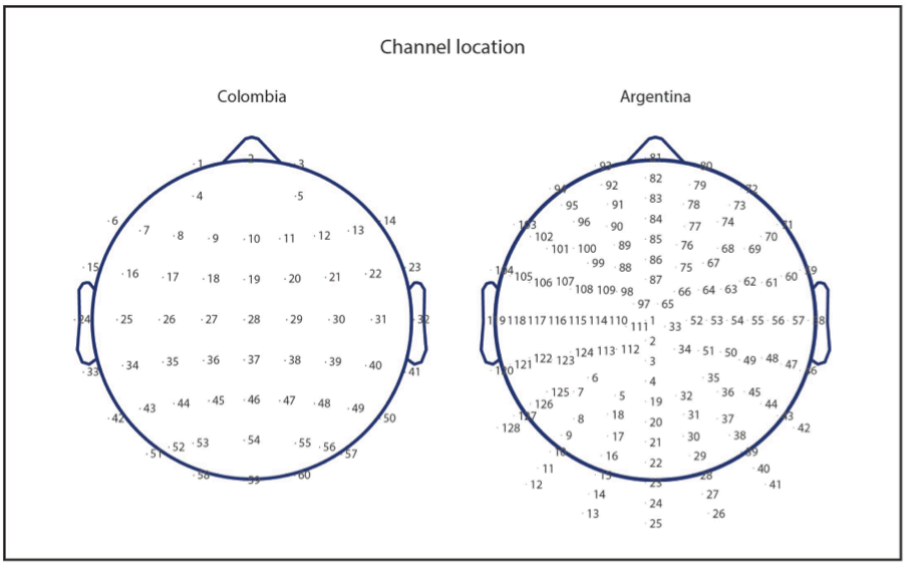

Figure 4. Implemented electrode dispositions by number in Colombia (MCI and controls, left panel) and Argentina (MCI-FAD and controls, right panel).

Supplementary References

[1] Pievani M, de Haan W, Wu T, Seeley WW, Frisoni GB (2011) Functional network disruption in the degenerative dementias. *Lancet Neurol* **10**, 829-843.

[2] Didic M, Barbeau EJ, Felician O, Tramoni E, Guedj E, Poncet M, Ceccaldi M (2011) Which memory system is impaired first in Alzheimer's disease? *J Alzheimers Dis* **27**, 11-22.

[3] Graham KS, Patterson K, Powis J, Drake J, Hodges JR (2002) Multiple inputs to episodic memory: words tell another story. *Neuropsychology* **16**, 380-389.

[4] Mayes A, Montaldi D, Migo E (2007) Associative memory and the medial temporal lobes. *Trends Cogn Sci* **11**, 126-135.

[5] Lopera F, Ardilla A, Martinez A, Madrigal L, Arango-Viana JC, Lemere CA, Arango-Lasprilla JC, Hincapie L, Arcos-Burgos M, Ossa JE, Behrens IM, Norton J, Lendon C, Goate AM, Ruiz-Linares A, Rosselli M, Kosik KS (1997) Clinical features of early-onset Alzheimer disease in a large kindred with an E280A presenilin-1 mutation. *JAMA* **277**, 793-799.

[6] Acosta-Baena N, Sepulveda-Falla D, Lopera-Gomez CM, Jaramillo-Elorza MC, Moreno S, Aguirre-Acevedo DC, Saldarriaga A, Lopera F (2011) Pre-dementia clinical stages in presenilin 1 E280A familial early-onset Alzheimer's disease: a retrospective cohort study. *Lancet Neurol* **10**, 213-220.