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

3
4 **Running title: Memory binding in the prodromal stages of AD**

5
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39

1 **Response to Reviewers**

2
3 **Reviewer 1**

4
5 The authors have addressed most of my concerns, but there are a few outstanding issues.

6
7 Comment 1. Following the reviewers' comments, the authors state that they removed the analysis
8 concerning MCI subtypes from the main text, but the introduction still mentions: "Finally, we
9 expected different patterns of performance across MCI subtypes, anticipating greater VSTM
10 binding deficits in the multiple-domain amnesic variant. "

11
12 **Response 1. We appreciate the Reviewer's comment. In the revised version of the manuscript we
13 have removed all sentences concerning MCI subtypes analyses from the main text.**

14
15 Comment 2. I am not sure that the supplementary data is necessary, as the number of patients in
16 the subgroups are so small.

17
18 **Response 2. We appreciate the Reviewer's suggestion. We acknowledge that we have small MCI
19 subgroups sample sizes; however, only for curious readers we have presented the results from
20 MCI subgroups in the supplementary data. Moreover, in the supplementary data we provide
21 additional important information about participants and data analysis, and include relevant
22 results concerning electrophysiological data. Therefore, we decided to preserve the
23 supplementary data.**

24
25 Comment 3. The authors may want to reconsider the following two sentences in the discussion
26 "Recent findings have shown progressive functional default-model network disruption in AD
27 which is related to the spread of tau pathology. In the earliest stages of disease, functional
28 disruption in default-mode network regions involves the affection of medial temporal lobe
29 structures that are implicated in declarative memory system." There appears to be more evidence
30 that amyloid, rather than tau pathology, is related to dysfunction of the default network. Also
31 these sentences are not coherent with the text that follows.

32
33 **Response 3. We thankfully welcome this remark. We acknowledge that our previous version of
34 the manuscript was not provided specification regarding the evidence of topographic
35 correspondence between amyloid deposition and the default-model network. We have now
36 provided a better description in the current version of the manuscript. Moreover, we have
37 corrected the paragraph in order to avoid inconsistencies.**

38
39 **The paragraph has been reformulated as follows:**

40
41 **"These findings could be interpreted at the neural network level. Recent findings have shown a
42 structural and functional default-model network disruption in AD, which is related to
43 components of the disease pathology such as amyloid and tau deposition [1]. In the earliest
44 stages of disease, functional disruption in default-mode network regions involves affection of
45 medial temporal lobe structures that are implicated in the declarative memory system. In line
46 with this evidence, it has been proposed that neurofibrillary tangles develop initially in the**

1 anterior subhippocampal (perirhinal/entorhinal) cortex before the hippocampus [2]. The anterior
2 subhippocampal area forms part of the anterior mesiotemporal network which has been
3 associated with "object-based context-free memory" [2]. These areas would receive perceptual
4 and semantic [3] information to perform higher-level inter-items associations [4]".
5

6 Comment 4. The following statement should be reconsidered: " Finally, computerized assessment
7 can be self-administered and through it can reach faster results". Although there is a certain
8 amount of ambiguity in this sentence, it may suggest that the authors recommend computerized
9 self-administration of diagnostic tests for faster results? As this is not desirable I feel that the
10 authors should remove or re-formulate this sentence.
11

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

14
15 Page 24, line 19: "Finally, computerized assessment can be self-administered and can provide
16 faster results".
17

18
19 Comment 5. Finally, the manuscript should be re-read carefully as there are some grammatical
20 errors.
21

22 Response 5. We thank the Reviewer for this comment. We have now examined the manuscript in
23 detail to avoid grammatical errors.
24

25 26 **References**

- 27
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43

1 **Abstract**

2

3 Deficits in visual short-term memory (VSTM) binding have been proposed as an early and
4 specific marker for Alzheimer’s disease (AD). However, no studies have explored the neural
5 correlates of this domain in clinical categories involving prodromal stages with different risk
6 levels of conversion to AD. We assessed underlying electrophysiological modulations in patients
7 with mild cognitive impairment (MCI), patients in the MCI stages of familial AD carrying the
8 mutation E280A of the presenilin-1 gene (MCI-FAD), and healthy controls. Moreover, we
9 compared the behavioral performance and neural correlates of both patient groups. Participants
10 completed a change-detection VSTM task assessing recognition of changes between shapes or
11 shape-color bindings, presented in two consecutive arrays (i.e., study and test) while event
12 related potentials (ERPs) were recorded. Changes always occurred in the test array and consisted
13 of new features replacing studied features (shape only) or features swapping across items (shape-
14 color binding). Both MCI and MCI-FAD patients performed worse than controls in the shape-
15 color binding condition. Early electrophysiological activity (100-250 ms) was significantly
16 reduced in both clinical groups, particularly over fronto-central and parieto-occipital regions.
17 However, shape-color binding performance and their reduced neural correlates were similar
18 between MCI and MCI-FAD. Our results support the validity of the VSTM binding test and their
19 neural correlates in the early detection of AD and highlight the importance of studies comparing
20 samples at different risk for AD conversion. The combined analysis of behavioral and ERP data
21 gleaned with the VSTM binding task can offer a valuable memory biomarker for AD.

22 **Keywords:** Mild cognitive impairment, familial Alzheimer’s disease, short-term memory,
23 memory binding, EEG, ERPs.

1 **1. Introduction**

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

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

21
22 To this end, we explored whether VSTM binding impairments are associated with
23 electrophysiological changes in two clinical groups at different risk levels for AD: patients who

1 may develop late-onset sporadic AD such as those with MCI (most of them amnesic MCI, single
2 or multi-domain) and patients in the prodromal stages of familial AD carrying the mutation
3 E280A of the presenilin-1 gene (MCI-FAD). Specifically, we compared behavioral and event-
4 related potential (ERP) measures between these samples and healthy controls. Building on
5 previous findings, we hypothesized that both patient samples would show behavioral and
6 electrophysiological abnormalities in the VSTM task, particularly in the memory binding
7 condition. Moreover, since the risk of conversion to AD is 100% for MCI-FAD and much lesser
8 for MCI, we predicted different behavioral and electrophysiological profiles in each group. In
9 particular, we expected that MCI-FAD would show more restricted behavioral and
10 electrophysiological abnormalities in the binding relative to shape only condition of the VSTM
11 task. More generally, this study seeks to test the sensitivity of this memory biomarker as a
12 potential contribution to the early identification of AD pathology.

13

14 **2. Materials and methods**

15

16 **2.1. Participants**

17 Thirteen patients with MCI were recruited from the Institute of Cognitive Neurology (INECO) in
18 Buenos Aires, Argentina. Diagnosis was based on criteria by Pertersen [15] and Winblad et al.
19 [16] (for further details, see Supplementary Data S1). All the patients underwent neurological,
20 neuropsychiatric, and neuropsychological evaluations. Most of the patients (n = 9) were impaired
21 in memory functions (amnesic MCI single domain or amnesic MCI multi-domain) while three
22 patients were classified as non-amnesic MCI multi-domain. Both amnesic MCI single and
23 multi-domain patients were included since these two clinical phenotypes have been shown high

1 risk for AD conversion [17].

2

3 The MCI-FAD sample comprised 10 patients recruited from the Colombian province of
4 Antioquia. All of them carried the mutation E280A of the presenilin-1 gene, which leads to
5 early-onset familial Alzheimer's disease in 100% of carriers [5]. These patients also completed
6 formal neurological and neuropsychological assessments.

7

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

13

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

17

18 **2.2. Neuropsychological assessment**

19 The general cognitive status of MCI patients was assessed with the mini mental state
20 examination (MMSE) [18] and the Addenbrooke's cognitive examination-revised (ACE-R) [19].

21 Their premorbid intellectual level was examined with the word accentuation test [20]. Memory
22 was assessed with the Rey auditory verbal learning test (RAVLT) [21] and the recall of the
23 complex Rey figure [21]. Attention and executive functions were evaluated via a digit span task

1 [22], the two parts of the trail-Making test (TMT-A and TMT-B) [21], and a verbal fluency task
2 [21, 23]. Visuospatial and constructional abilities were assessed with the copy task of the
3 complex Rey figure [21]. Additional data were garnered through the instrumental activities of
4 daily living scale (IADL) [24] and the geriatric depression scale (GDS) [25].

5

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

10

11 **2.3. The visual short-term memory task**

12 The VSTM task taps change-detection skills to assess memory for single or combined features
13 [4]. It is sensitive to impairments of integrative memory functions in both late-onset sporadic and
14 familial Alzheimer's disease [2-4, 28]. The task consists of visual arrays of stimuli sequentially
15 presented on a computer screen. An example of a trial is shown in Figure 1. Each trial features a
16 study array followed by a test array. In 50% of the trials, the two arrays show identical items. In
17 the remaining half, two items in the test array are replaced by new items. The to-be-remembered
18 items change location from study to test, rendering location an uninformative feature (i.e., it
19 cannot be used as a memory cue). Participants are asked to remember the items shown during the
20 study and decide whether the items that follow in the test display are the same or different (see
21 more details in Supplementary Data S2).

22

23 The stimuli consisted of either single shapes (i.e., VSTM for single features) or shapes combined

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

14
15 Each condition consisted of a brief practice session followed by 100 test trials per experimental
16 condition (200 trials in total). Trials were fully randomized across participants and conditions
17 were delivered in a counterbalanced order.

18

19 **2.4. EEG recording**

20 *MCI patients and controls*

21 MCI patients and their controls sat comfortably at a desk with a computer, set up in an
22 electrically shielded, dimly lit room. As they performed the VSTM task, EEG recordings were
23 obtained with a Biosemi 128-channel Active Two system (Amsterdam, NLD). The sampling rate
24 was set at 512 Hz, and signals were bandpass filtered between 1 Hz (high pass) and 100 Hz (low

1 pass).

2

3 ***MCI-FAD patients and controls***

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

10

11 **2.5. Data analyses**

12 ***Behavioral data***

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

20

21 Considering that MCI and MCI-FAD groups were different in terms of age, for this calculation
22 we used control-group-derived parameters of the variables revealing significant between-group
23 differences (i.e., patients vs. their respective controls). For each MCI and MCI-FAD patient, we

1 calculated normalized z scores using parameters (mean and SD) derived of the respective control
2 group. Z-scores were then compared across the two groups through a non-parametric Mann-
3 Whitney U test. In addition, the effect size for all pairwise comparisons was calculated following
4 the Cohen's method.

5

6 ***ERPs***

7 MCI and MCI-FAD data were analyzed offline following the same procedures. Analyses were
8 performed with EEGLAB (version 13.1.1b) and MATLAB (version R2012a). Data were filtered
9 between 0.5 Hz (high-pass) and 30 Hz (low-pass) and were down-sampled to 256 Hz. EEG
10 activity was re-referenced to the grand average. Visual inspection of the data was followed by
11 independent component analysis (ICA) to further remove oculomotor artifacts. Continuous EEG
12 data were segmented in epochs of -200 to 1000 ms locked to stimulus onset. Epochs containing
13 artifacts which exceeded a threshold of $\pm 100 \mu\text{V}$ were manually removed. Separate average
14 waveforms were computed for each individual in each condition of the VSTM task (i.e., shape
15 only and shape-color binding). Only correct trials were considered for analysis.

16

17 First, to identify significant between-group differences across the two conditions, we used a
18 combination of the Monte Carlo test and non-parametric bootstrapping running 4.000
19 permutations. The data were later analyzed by applying 4.000 permutation draws to generate a
20 histogram called the Monte-Carlo approximation of the permutation distribution. To calculate the
21 differences between our data and this distribution, we used the Monte-Carlo estimation of the
22 permutation p-value, which is the proportion of random partitions in which the observed test
23 statistic is larger than the value drawn from the permutation distribution. If this p-value is smaller

1 than the critical alpha-level, then it is concluded that the data between the two groups are
2 significantly different. This method offers a straightforward solution for multiple comparison
3 problems and does not depend on multiple comparisons correction or Gaussian assumptions
4 about the probability distribution of the data [33, 34]. This approach has been used in recent
5 ERPs reports of our group [35-37]. Permutations were calculated following a component-free
6 approach across the entire array of electrodes for every millisecond. Electrodes with significant
7 results ($p < .01$) were placed into regions of interest (ROIs), and the activity within such regions
8 was averaged out. We considered six ROIs: (1) fronto-central left (FC left), (2) fronto-central
9 right (FC right), (3) centro-parietal left (CP left), (4) centro-parietal right (CP right), (5) parieto-
10 occipital left (PO left), and (6) parieto-occipital right (PO right). For each ROI we assigned
11 seven and fourteen electrodes in the MCI and MCI-FAD samples respectively (see
12 Supplementary Figure 1).

13

14 Then, we compared the average activity from the six ROIs using 4.000 bootstrapping
15 permutations ($p < .05$). Such contrasts were independently carried out in three time-windows
16 (early: 100-250 ms; intermediate: 250-500 ms; late: 500-900 ms) for each condition (shape only
17 and shape-color binding), memory phase (encoding and test), and group – see Supplementary
18 Data S4. This activity was also compared across groups: (a) MCI vs. controls, (b) MCI-FAD vs.
19 controls, and (c) MCI vs. MCI-FAD. These analyses were focused on four different components:
20 N1, P2, P3, and LPP. The N1 is a parieto-occipital negative component [38], peaking around 170
21 ms post-stimulus onset, which reflects early stages of visual processing and is sensitive to
22 different types of attention [39, 40]. The P2 is a positive component with fronto-central
23 distribution, peaking around 150-300 ms [41]. This component has been associated with

1 attentional control processes, such as stimulus evaluation [41] and feature detection of task-
2 relevant stimuli [42]. The P3 is a positive centro-parietal component, which peaks between 300
3 and 600 ms post-stimulus-onset, and is considered to reflect activity in a distributed network
4 associated with attention and working memory [43, 44], including context updating and
5 attentional resource allocation [45]. The LPP is a slow positive modulation with an onset around
6 400-1000 ms after stimulus presentation. The enhancement of this component has been related to
7 memory encoding and storage processes [46, 47]. Moreover, it has been associated with post-
8 retrieval stages, such as decisional monitoring [48] and evaluation [49-52] processes. All the
9 functions indexed by these components are called upon by the VSTM task.

10

11 **3. Results**

12 **3.1. MCI patients vs. healthy controls**

13 *Behavioral data*

14 Neuropsychological assessment

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

18

19 VSTM task

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

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

2

3 **ERP results**

4 MCI vs. controls

5 *Shape-only condition.* Significant differences in P2 amplitude during the encoding phase
6 emerged during the early time-window (100-250 ms) over the bilateral FC region (left: $t = 3.16$,
7 $p < .01$, $d = 1.22$; right: $t = 3.16$, $p < .01$, $d = 1.21$). The same was true of the LPP amplitude
8 during the late time-window (500-900 ms) over the right CP region ($t = 2.20$, $p < .05$, $d = .84$).

9 In the test phase, we found differences in N1 amplitude during the early time-window (100-250
10 ms) over the right PO region ($t = -2.40$, $p < .05$, $d = -.92$) (see Figure 2A-C).

11

12 *Shape-color binding condition.* There were significant differences in the encoding phase during
13 the early time-window (100-250 ms). These concerned the P2 component over the bilateral FC
14 region (left: $t = 2.37$, $p < .05$, $d = 0.91$; right: $t = 2.43$, $p < .05$, $d = .93$) and the N1 component
15 over the right PO region ($t = -2.33$, $p < .05$, $d = -.90$). In the test phase, significant differences in
16 N1 amplitude emerged during the early time-window (100-250 ms) over the PO region
17 bilaterally (left: $t = -2.53$, $p < .01$, $d = -.97$; right: $t = -3.15$, $p = .01$, $d = -1.20$), and in the LPP
18 during the late time-window (500-900 ms) over the right FC ($t = 2.57$, $p = .02$, $d = 1.00$) and the
19 CP ($t = 2.69$, $p = .01$, $d = .05$) regions (see Figure 2A-C).

20

21

22

23

1 **3.2. MCI-FAD patients vs. healthy controls**

2 ***Behavioral data***

3 Neuropsychological assessment

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

8

9 VSTM task

10 Response accuracy to the two VSTM task conditions was similar in both controls (Mann-
11 Whitney U: 34, $Z = 1.17$, $p = .24$, $d = .64$) and MCI-FAD patients (Mann-Whitney U: 28, $Z =$
12 1.63 , $p = .10$, $d = .77$). Between-group comparisons revealed higher accuracy for controls in the
13 shape-color binding condition (Mann-Whitney U: 22.5, $Z = -2.08$, $p < .05$, $d = .93$), but no
14 differences were observed in the shape-only condition (Mann-Whitney U: 25.0, $Z = -1.89$, p
15 $= .063$, $d = 1.02$) –see Figure 3D.

16

17 ***ERPs results***

18 MCI-FAD vs. controls

19 *Shape-only condition.* Significant differences during the encoding phase were observed for the
20 P3 component in the intermediate time-window (250-500 ms) over the left PO region ($t = -2.17$,
21 $p < .05$, $d = .75$) –see Figure 3A-C.

22

23 *Shape-color binding condition.* We found significant between-group differences in the amplitude

1 of two components during the encoding phase: P2, over the right FC region ($t = 2.57, p < .05, d$
2 $= 1.08$); and N1, over the left PO region ($t = -2.91, p < .01, d = -1.14$); both patterns emerged
3 during the early time-window (100-250 ms) –see Figure 3A-C.

4

5 **3.3. MCI vs. MCI-FAD**

6 *VSTM task*

7 No significant differences emerged between groups upon comparing their Z -scores (see details in
8 data analyses) from performance on the shape-color binding condition of the VSTM task (Mann-
9 Whitney $U: 63, Z = -.09, p = .93, d = .02$) –see Supplementary Figure 4.

10

11 *ERPs results*

12 We also compared the patients' Z -scores drawn from the electrophysiological data that indicated
13 significant between-group differences over specific ROIs and time-windows. Only the ERP
14 activity elicited during the shape-color binding condition met these criteria (FC right, during the
15 encoding phase, in the early time-window). However, contrasts between MCI and MCI-FAD
16 including this activity revealed no significant differences (see supplementary Figure 4).

17

18 *Summary of findings*

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

1
2 ERP activity underlying VSTM performance was significantly reduced in MCI and MCI-FAD
3 patients compared to their corresponding control groups (Table 3). This was observed in all ROIs,
4 with most conspicuous activation decreases appearing over FC and PO regions during the early
5 time-window (N1 and P2). MCI patients exhibited reduced amplitude across both conditions and
6 memory phases, whereas MCI-FAD patients showed reduced amplitude in both conditions but
7 only during the encoding phase. Differences in behavioral performance were associated to
8 measurable differences in the underlying ERPs in MCI patients. For MCI-FAD patients,
9 differences observed in the ERPs elicited during the shape-only condition were not accompanied
10 by significant differences in behavioral performance. However, such an association was present
11 for the shape-color binding condition. Finally, analysis of electrophysiological data from MCI
12 and MCI-FAD patients showed no differences in the shape-color binding condition between
13 groups, although both exhibited significant deficits in this function.

14

15 **4. Discussion**

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

1 implications of our findings.

2

3 **4.1. Behavioral performance on the VSTM task**

4 MCI patients performed significantly worse than healthy controls in both the shape-only and
5 shape-color binding conditions of the VSTM task. These findings are consistent with those
6 reported in a recent study [12] using the same task. However, previous studies in patients with
7 early-onset familial [2] and late-onset sporadic AD [3, 4] have found a selective deficit in the
8 shape-color binding condition. The discrepancy across these studies may be due to
9 methodological differences. Previous studies have equated performance on the baseline
10 condition (i.e., shape only) across patients and controls by assessing the former with smaller set
11 sizes (i.e., patients saw arrays of two items and controls saw arrays of three items). In the present
12 study, as in the one conducted by [12], patients were assessed with the same set size. We
13 followed the logic of earlier studies involving pre-symptomatic mutation carriers [2]. That is,
14 patients who did not meet criteria for dementia and controls were evaluated under the same
15 testing conditions (i.e., same memory load). Although this approach proved valid for the
16 preclinical stages of AD, it does not seem to hold for the clinical stages (i.e., MCI). Nevertheless,
17 shape-only is just a baseline condition which does not hold sensitivity and specificity for AD. It
18 is the shape-color binding condition of the task that has proved clinically relevant. Future studies
19 interested in the previously reported dissociation (i.e., shape-only vs. shape-color binding) may
20 want consider this methodological caveat. In fact, our results show that impairments in shape-
21 color binding are systematically observed across the two populations and were the only deficits
22 found in those with the highest risk for AD (MCI-FAD).

23

1 MCI-FAD patients were outperformed by controls, but the difference only reached significance
2 in the shape-color binding condition. This finding aligns with previous reports of VSTM binding
3 deficits in asymptomatic carriers of the mutation E280A in the presenilin-1 gene [2, 3]. Although
4 mutation carriers in the present study were in more advanced stages of the disease process, our
5 results corroborate that VSTM binding deficits may emerge well before the onset of full-blown
6 AD. Note that mean scores for the shape-only condition also evinced a drop in MCI-FAD
7 patients. However, unlike what was observed in MCI, this difference did not reach significance.
8 This discrepancy could partially reflect age differences between the samples, as MCI patients
9 were older than MCI-FAD patients. Although age does not differentially affect short-term
10 memory binding abilities [6, 8, 53], it has an overall impact on short-term memory. This may
11 account for the slightly greater difference between conditions in each group. However,
12 performance on the shape-color binding condition was similar between patient groups.
13 Accordingly, VSTM binding seems to be selectively compromised by AD, above and beyond the
14 effects of age. As suggested in previous research then, this memory function may well constitute
15 a sensitive marker for AD [3, 4, 6, 9]. Note that although Argentinean controls were older and
16 had more years of education than those from Colombia, the behavioral performance of these
17 samples was indistinguishable –see also Parra, et al. [3], who reported similar findings in
18 samples of sporadic and familiar AD. Therefore, demographic variables could be ruled out as a
19 factor behind the key findings reported here and in previous studies.

20

21 **4.2. Electrophysiological correlates of the VSTM task**

22 Compared to controls, MCI patients exhibited reduced amplitudes in all ERP components
23 associated with the VSTM task. The cognitive mechanisms supporting this memory function

1 seem to be attenuated along relevant processing stages. Specifically, the amplitude of the N1
2 component was reduced in both memory phases of the shape-color binding condition, and in the
3 test phase of the shape-only condition. Notably, the scalp distribution (and similar source space
4 [38]) of the diminished N1 was detected over parieto-occipital regions. Enhancements of N1
5 modulations have been associated to facilitatory mechanisms of spatial attention and orientation
6 towards task-relevant stimuli [39, 40], which subservise discrimination processes [54]. Moreover,
7 N1 modulations may be sensitive to variations in the visual parameters of stimulus configuration
8 [55], reflecting early information processing prior activation of abstract feature representations of
9 the perceived objects. Also, during the encoding phase of both task conditions, P2 modulations
10 were less positive-going in MCI patients than in controls. These differences were observed over
11 bilateral fronto-central regions, in line with the previously reported source of this component
12 [41]. The P2 seems to index stimulus evaluation [41] and detection of features in task-relevant
13 stimuli [42]. Thus, diminished amplitudes of the N1 and P2 components in MCI patients may
14 reflect abnormalities in the early visual integration stages of memory binding. These findings
15 suggest impairments in processing of stimulus features and detection of relevant features,
16 mechanisms related to visual and orbitofrontal association cortices, respectively.

17

18 These findings could be interpreted at the neural network level. Recent findings have shown a
19 structural and functional default-model network disruption in AD, which is related to
20 components of the disease pathology such as amyloid and tau deposition [56]. In the earliest
21 stages of disease, functional disruption in default-mode network regions involves affectation of
22 medial temporal lobe structures that are implicated in the declarative memory system. In line
23 with this evidence, it has been proposed that neurofibrillary tangles develop initially in the

1 anterior subhippocampal (perirhinal/entorhinal) cortex before the hippocampus [57]. The anterior
2 subhippocampal area forms part of the anterior mesiotemporal network which has been
3 associated with “object-based context-free memory” [57]. These areas would receive perceptual
4 and semantic [58] information to perform higher-level inter-items associations [59].

5
6 MCI patients also exhibited reduced amplitudes in the LPP component. This occurred first over
7 centro-parietal regions during the encoding phase of shape-only condition, which may reflect a
8 general encoding deficit. Consistent with this interpretation, it has been suggested that LPP
9 enhancement reflects additional involvement of memory encoding and storage processes [46, 47].
10 A more elaborate encoding is associated with larger LPP amplitude over parietal scalp sites [60,
11 61]. Thus, relative to MCI patients, control subjects may have deployed more successful
12 encoding strategies during perceptual input.

13
14 Furthermore, reduced LPP amplitude was also observed in MCI patients during the test phase of
15 shape-color binding over centro-parietal and fronto-central electrodes. This abnormal pattern
16 may be related to better control mechanisms during retrieval and post-retrieval processes,
17 reflecting differences in monitoring and evaluation processes required to decide whether a
18 change across study and test arrays. In line with this view, the LPP has been implicated in post-
19 retrieval processes, such as decisional monitoring [48] and evaluation [49-52]. For instance,
20 Eimer and Mazza [50] showed reduced LPP amplitudes when participants were uncertain about
21 the presence of a change between stimulus displays. Thus, convergent evidence suggests that in
22 MCI patients, impaired evaluation and monitoring processes during the comparison of the two
23 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 affection 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. -

1 binding condition. From a behavioral perspective, this is consistent with the view that higher
2 similarity between study- and test-item configurations induces greater error rates during the
3 comparison stages of a change-detection task [62]. Comparison processes between arrays
4 containing multi-feature objects seem to demand more cognitive resources than those required to
5 compare single-feature objects. Such resources would avoid misattribution of features across
6 objects, thus contributing to solve the binding problem. Our results indicate that a fronto-parietal
7 network may subserve these binding operations, and that failures of such a network are crucially
8 related to memory binding impairments in patients at risk for AD.

9

10 It is worth mentioning that despite the vast existing literature regarding the deficit in associative
11 memory resulting from damage to the hippocampus which has proved a significant predictor of
12 likelihood of conversion from MCI to AD, the evidence regarding the VSTM task has
13 consistently shown that memory binding functions assessed by this change detection paradigm
14 does not involve the hippocampus [63-65]. Indeed, the change detection task reported here has
15 proved to be performed accurately after hippocampal pathology [64]. Moreover, a recent fMRI
16 study in healthy individuals [5] has been shown that binding function does not involve the
17 hippocampus but it relies on a network that involves the activity of parietal and occipito-
18 temporal areas.

19

20 Otherwise, LPP retrieval-related activity has been associated with processes of familiarity and
21 recollection (dual process model of recognition) [66] both of which contribute to performance on
22 change detection tasks. Consistent with our results, a recent ERP study [67] showed that
23 amnesic MCI patients present an attenuation of LPP waveforms during the performance of a

1 recognition memory task when they retrieved memories based on recollection and familiarity
2 processes. Thus, this evidence suggests that in MCI patients, reduced amplitude of LPP in the
3 shape-color binding condition may involve retrieval affectation of recollection and familiarity-
4 based memories, either because fewer items are retrieved, and/or fewer entire item-
5 configurations have been successful retrieved.

6

7 In addition to visual electrophysiological markers found in our study, the P50 auditory
8 component has been recently proposed as a candidate ERP biomarker of prodromal AD [68].
9 MCI patients with Amyloid and p-Tau positive showed larger P50 amplitudes relative to the
10 amyloid-negative patients during the performance of an oddball task, which reflects poorer
11 inhibitory control to sensory information. However, despite the amplitude of P50 is larger in
12 MCI relative to older normal controls, it increases with normal aging [69, 70]. Crucially, VSTM
13 binding has been shown to be more specific since it remains uncompromised throughout normal
14 aging [6, 71, 72]. Therefore, combining with ERP, the VSTM task may offer a unique
15 opportunity to detect early neurocognitive abnormalities associated with risk for AD.

16

17 MCI-FAD patients exhibited attenuated electrophysiological responses only in the encoding
18 phase of the VSTM task. Specifically, they showed reduced amplitudes of N1 and P2
19 components associated to shape-color binding processing over parieto-occipital and fronto-
20 central regions, respectively. As we discussed above, reduced N1 amplitude may reflect
21 difficulties to direct attention to task-relevant stimuli [39, 40] and process attributes of visual
22 configurations [55], all linked to early visual processing. Reduced amplitude of the P2
23 component seems related to deficits in stimulus evaluation [41] and features detection processes

1 [42]. Limitations to encode feature bindings in MCI may thus originate quite early in the visual
2 processing stream. MCI-FAD patients also showed reduced amplitude of the P3 component over
3 parieto-occipital regions in the shape-only condition. This component is considered to reflect
4 activity in a distributed network subserving attention and working memory [43, 44], including
5 context updating and resource allocation [45]. Specifically, P3 increases when stimulus encoding
6 promotes successful memory storage and facilitates retrieval during recognition tasks [73]. Thus,
7 while behaviorally unimpaired, MCI-FAD patients did show electrophysiological evidence of
8 subthreshold anomalies during the shape-only condition of the VSTM task. These subthreshold
9 impairments support the proposal that the mechanisms responsible for holding combinations of
10 shape and color in VSTM are affected by AD to a far greater extent than those responsible for
11 holding single features, such as shapes. Previous ERP studies assessing memory impairments in
12 E280A-PSEN1 presymptomatic mutation carriers have reported functional disruption of brain
13 regions similar to those reported in our study [74, 75]. Taken together, all these findings
14 highlight the importance of ERP analysis to unveil key neural correlates of cognitive
15 impairments throughout the continuum of AD.

16

17 Finally, we compared electrophysiological data from MCI and MCI-FAD considering variables
18 which indicated departure from normality. Specifically, we focused on P2 modulations during
19 the encoding phase of the shape-color binding condition over the right fronto-central ROI.
20 Crucially, no between-group differences were observed. This suggests that both prodromal
21 stages of AD (i.e., sporadic-MCI and familiar-MCI) share a common behavioral and
22 electrophysiological phenotype associated to VSTM binding. Such ERP abnormalities seem to
23 reflect impairments during early sensory processing, which are probably associated with stimulus

1 evaluation [41] and feature detection [42]. When we compared patients to their respective
2 controls, both clinical samples showed decreased N1 activity over parieto-occipital regions,
3 suggesting similar deficits in feature discrimination processes [54]. As recently shown in fMRI
4 studies [29, 76-78], these regions seem to support spatial attentional mechanisms necessary to
5 integrate features in VSTM. Therefore, the reduced amplitudes observed in MCI and MCI-FAD
6 during the encoding of shape-color bindings over fronto-central and parieto-occipital regions
7 could be associated to specific impairments in attentional mechanisms supporting feature
8 conflation in VSTM. We argue that these indexes of activation could to reflect reduced
9 attentional control efficiency in frontoparietal attention circuit required for
10 encoding/consolidation binding in VSTM. In sum, the abnormalities observed during the
11 encoding stages in both patient samples could account for behavioral feature-binding
12 impairments in the VSTM task.

13

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

1

2 Neurocognitive processes can be studied appropriately with high-temporal resolution techniques
3 such as EEG. These methods are suited to capture properties of transient cognitive events [79]
4 which may be undetected via high-spatial resolution techniques, such as fMRI. In the context of
5 the VSTM binding task, previous fMRI studies [78] did not identify task-related activation over
6 frontal regions. In the present study, within-group analyses showed significant enhanced fronto-
7 central activity during the test phase of the shape-color binding condition. However, we did
8 corroborate the involvement of posterior (viz., parietal) regions in feature binding. Therefore, our
9 results suggest that combining the VSTM task with ERP analysis may offer a unique opportunity
10 to detect early neurocognitive alterations in individuals at risk for AD. Such electrophysiological
11 findings underscore the potential of the VSTM task as a biomarker for AD.

12

13 **4.3. Implications and further assessments**

14 Electrophysiological markers could be considered in daily clinical practice to favor the early
15 detection of AD. Such inexpensive, non-invasive measures are robust, fast to compute, and
16 applicable for large-scale screening. This novel approach can overcome several limitations of
17 available biomarkers for AD [14, 80]. As ERPs have high temporal resolution, they can detect
18 subtle information-processing abnormalities, even in the absence of significant behavioral
19 manifestations. Such methodological attributes have important clinical implications in the
20 context of VSTM research. We have replicated behavioral VSTM binding impairments in AD
21 samples [2, 9, 12], further demonstrating their presence in presymptomatic stages of AD (see
22 also [1]). VSTM binding deficits thus seem to constitute a phenotypic feature of AD, detectable
23 throughout the continuum of the disease. The task used in this study could represent a valuable

1 tool to identify candidates for prevention trials. Previous ERPs studies [81-83] have proposed
2 statistical methods for single-case analyses that can be implemented by future research assessing
3 patients in prodromal stages of AD. Moreover, individual ERPs measures may be useful in
4 follow-up clinical assessment of individuals at risk of developing AD or patients with diagnosis
5 of MCI or AD. Longitudinal ERPs measures may provide further insights on the AD nature and
6 may be potentially useful in predicting the disease progression based on the combination of
7 behavioral and electrophysiological measures. Moreover, although computerized assessments of
8 cognitive functions in the early detection of AD are not commonly used, their validity and
9 reliability as testing tools for the clinical practice is being recognized [84]. Computerized testing
10 tools have a number of complementary advantages. They allow more standardized, precise and
11 objective measures of subject performance, and features such as randomization allow throw out
12 practice effects. Finally, computerized assessment can be self-administered and may provide
13 faster results.

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Times, Diseño: Claro (Blanco)

14
15 We acknowledge some limitations in the present work. First, the two patient samples are not
16 comparable in terms of their demographic characteristics, and they were recruited from different
17 countries. To control for these factors we standardized VSTM scores and demonstrated that,
18 despite such differences, both samples shared a common phenotype both behaviorally and
19 electrophysiologically. Finally, other important limitation is that our MCI group included
20 different clinical phenotypes. However, our sample is similar to that reported in the only study
21 that had assessed different clinical phenotypes of MCI with the VSTM task, in which most of
22 patients were impaired in memory [85]. Future research may to study how sensitive VSTM
23 binding is to cognitive and neuropathological changes considering larger MCI cohort with

1 different characteristics of clinical phenotypes.

2 **5. Conclusion**

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

11

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23

1

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

	MCI (<i>n</i> = 13)		controls (<i>n</i> = 14)		<i>t</i> -test		Effect size
	Mean	<i>SD</i>	Mean	<i>SD</i>	<i>t</i>	<i>P</i>	Cohen's <i>d</i>
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

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

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

	MCI-FAD (<i>n</i> = 10)		Controls (<i>n</i> = 10)		<i>t</i> -test		Effect size
	Mean	<i>SD</i>	Mean	<i>SD</i>	<i>t</i>	<i>p</i>	Cohen's <i>d</i>
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).

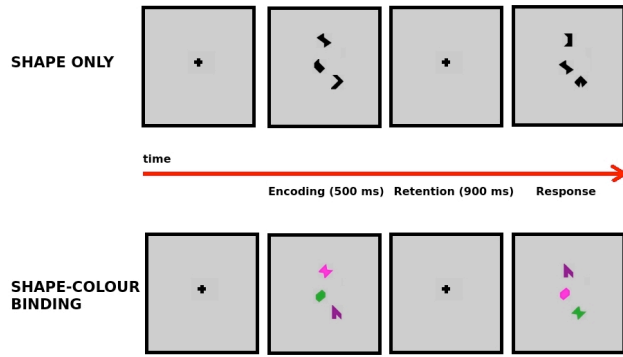
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Table 3. Summary of significant results ($p < .05$) drawn from the ERP analyses.

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

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

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4 **Figure 1.** Examples of “different trials” in each condition of the VSTM task.

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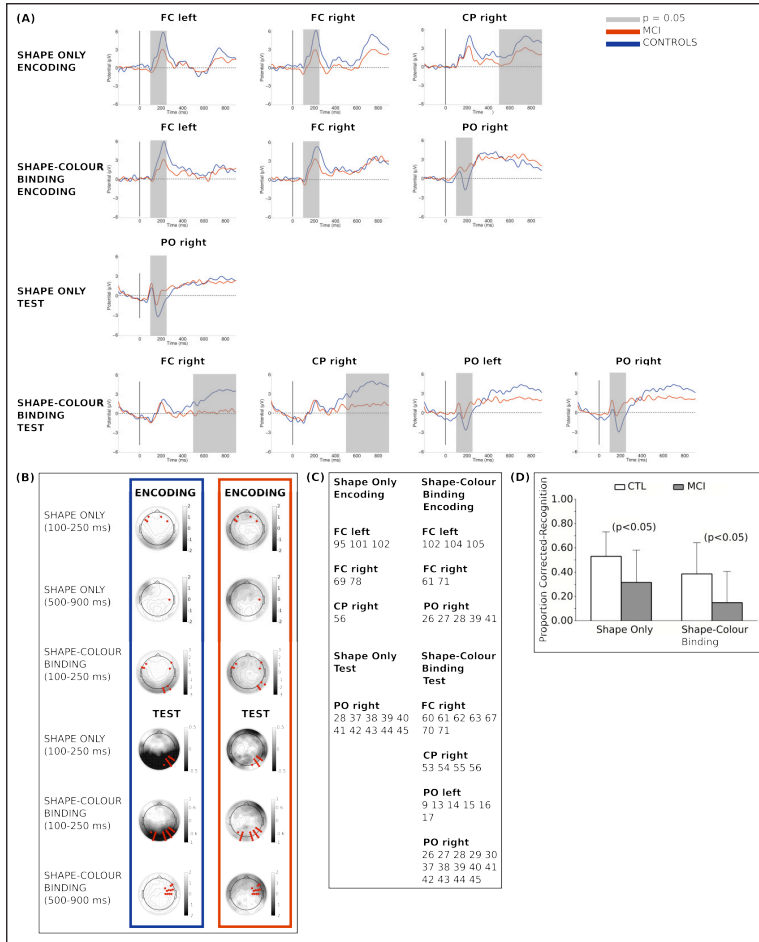
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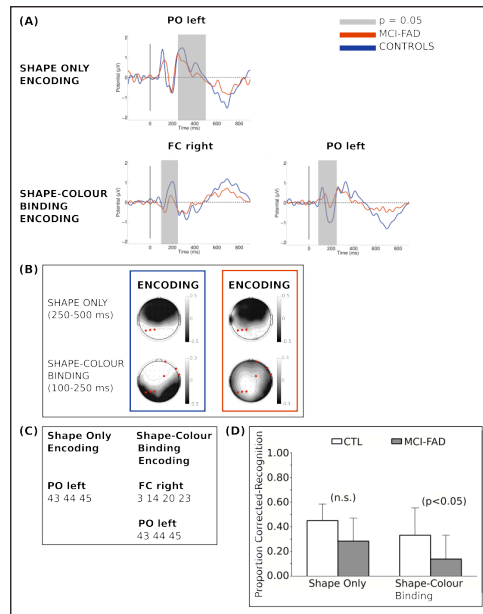
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3 **Figure 2.** (A) ERP activity from significant ROIs comparing MCI patients and controls in the
 4 shape-only (encoding and test) and shape-color binding (encoding and test) conditions. (B)
 5 Electrodes by numbers comprising the ROIs. Red points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



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

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Supplementary data

1

2 **S1. Participants**

3 *Mild cognitive impairment patients*

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

9

10 *MCI subtypes*

11 Clinical phenotypes of MCI were distinguished based on previously established criteria [2, 4].

12 MCI patients were classified into three sub-groups according to an impairment threshold set at
13 1.5 SDs for memory, executive functions, and attention capacity: non-amnesic MCI (in which
14 patients had executive and/or attention impairments), amnesic MCI (in which patients had only
15 memory impairment), and multi-domain MCI (in which patients had memory and executive
16 and/or attention impairments).

17

18 *MCI-FAD patients*

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

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

4

5 **S2. Visual short-term memory task**

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

16

17 **S3. Data analysis**

18 *Behavioral data*

19 *Neuropsychological assessment*

20 Comparisons among MCI subtypes

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

1 correction was applied to each comparison among MCI subtypes.

2

3 *VSTM task*

4 Comparisons among MCI subtypes

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

11

12 Comparisons between MCI and MCI-FAD

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

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1 **S4. Results**

2 **S4.1 MCI patients vs. healthy controls**

3 *Behavioral data*

4 Neuropsychological assessment

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

12

13 **Comparisons among MCI subtypes**

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

17

18 There were significant differences among MCI subtypes in both the shape-only (Kruskal-Wallis
19 test H: 8.6, $p = .01$) and the shape-color binding (Kruskal-Wallis test H: 6.5 $p = .04$) conditions.
20 Multiple comparisons showed that nMCI outperformed mMCI on both the shape-only ($Z = 2.54$,
21 $p = .03$, $d = 2.50$) and the shape-color binding ($Z = 2.40$; $p = .05$, $d = 2.54$) conditions. In
22 addition, performance in the shape-only condition was better for aMCI than mMCI ($Z = 2.44$, p
23 $= .04$, $d = 2.52$). No significant differences were found between aMCI and nMCI in any

1 condition (see Supplementary Table 1).

2

3 ***ERP results***

4 MCI patients

5 Encoding phase. There were differences between conditions in the right FC region, departing
6 from the P2 ($t = -3.04$, $p < .01$, $d = -0.58$) to the P3 component ($t = -2.80$, $p < .05$, $d = -0.67$),
7 which emerged in the early time-window (100-250 ms) and extended over the intermediate time-
8 window (250-500 ms). Differences were also observed in the amplitude of the P2 component
9 during the early time-window (100-250 ms) over the left ($t = -2.30$, $p < .05$, $d = -0.37$) and the
10 right ($t = -2.41$, $p < .05$, $d = -0.45$) CP regions. Furthermore, there were differences over the right
11 CP region in the P3 ($t = -2.26$, $p < .05$, $d = -0.48$) during the intermediate time-window (250-500
12 ms) and in the LPP ($t = -2.80$, $p < .01$, $d = -0.47$) in a latency range of 500-900 ms. We also
13 found bilateral differences over the PO region in the N1 (left: $t = -2.35$, $p < .05$, $d = -0.36$; right: t
14 $= -2.98$, $p < .01$, $d = -0.42$) and the LPP (left: $t = -2.27$, $p < .05$, $d = -0.45$; right: $t = -2.82$, p
15 $< .01$, $d = -0.59$) components, in early (100-250 ms) and late (500-900 ms) time-windows,
16 respectively.

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18 Test phase. We found differences in P2 amplitudes over bilateral FC regions (left: $t = -2.48$, p
19 $< .05$, $d = -0.57$; right: $t = 2.46$, $p < .05$, $d = 0.47$) in the early time-window (100-250 ms).
20 Significant differences also emerged in the N1 component over the left CP ($t = -2.66$, $p < .05$, $d =$
21 -0.44) and bilateral PO regions (left: $t = -3.55$, $p < .01$, $d = -0.40$; right: $t = -2.59$, $p < .05$, $d = -$
22 0.48), both in early time-windows (100-250 ms) (see Supplementary Figure 2).

23

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

6

7 Controls

8 Encoding phase. No significant differences between conditions were observed.

9 Test phase. We found differences between conditions over the left FC region in the amplitude of
10 the P2 ($t = -2.53$, $p < .05$, $d = -0.65$), P3 ($t = -3.36$, $p < .05$, $d = -0.70$), and LPP ($t = -3.02$, $p < .05$,
11 $d = -0.77$) components during the early (100-250 ms), intermediate (250-500 ms), and late (500-
12 900 ms) time-windows, respectively. Differences in these time-windows were also observed in
13 the left (early: $t = -2.42$, $p < .05$, $d = -0.47$; intermediate: $t = -3.36$, $p < .01$, $d = -0.64$; late: $t = -$
14 4.24 , $p < .01$, $d = -0.98$) and right (early: $t = -2.08$, $p < .05$, $d = -0.42$; intermediate: $t = -3.52$, p
15 $< .01$, $d = -0.46$; late: $t = -3.87$, $p < .01$, $d = -0.78$) CP regions for the P2, P3, and LPP
16 components. In addition, there were differences over the right PO region, departing from the P3
17 ($t = -1.97$, $p < .05$, $d = -0.29$) to the LPP ($t = -3.45$, $p < .01$, $d = -0.53$), which emerged in the
18 intermediate time-window (250-500 ms) and extended over the late time-window (500-900 ms).
19 Differences were also observed in the LPP component ($t = -2.67$, $p < .05$, $d = -0.56$) over the left
20 PO during the late time-window (500-900 ms) (see Supplementary Figure 2).

21

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

1 condition (see Supplementary Table 3).

2

3 **S.4.2 MCI-FAD patients vs. healthy controls**

4 *ERP results*

5 MCI-FAD patients

6 Encoding phase. There were significant differences between conditions in the P2 amplitude over
7 the left FC ($t = -2.18$, $p < .01$, $d = -1.10$) during the early time-window (100-250 ms). This time-
8 window also yielded differences in the N1 component over the right CP ($t = 3.24$, $p < .05$, $d =$
9 1.26) and PO ($t = 3.05$, $p < .05$, $d = 1.13$) regions (see supplementary Figure 3).

10

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

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

16

17 Controls

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

23

1 Test phase. We found significant differences between conditions in the P2 component during the
2 early window (100-250 ms) over the left FC ($t = -3.08$, $p < .01$, $d = -0.95$). Amplitude differences
3 during that same time-window also emerged for the N1 component over the right CP ($t = 2.97$, p
4 $< .01$, $d = 0.81$) and PO ($t = 4.35$, $p < .01$, $d = 0.53$) regions (see supplementary Figure 3).

5
6 Closer inspection of the waveforms revealed that the above effects were driven by larger
7 amplitudes of all the ERP components in the shape-color binding condition relative to the shape-
8 only condition (see Supplementary Table 3).

9

10 **S.4.3 MCI vs. MCI-FAD**

11 *VSTM task*

12 No significant differences emerged between groups upon comparing their z-scores (see details in
13 data analyses) from performance on the shape-color binding condition of the VSTM task (Mann-
14 Whitney U: 52.0, $Z = .78$, $p = .44$, $d = .52$).

15

16 *ERP results*

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

21

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

2

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

3

4

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

	Mean (<i>SD</i>)		
	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)

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

WITHIN-GROUP CONTRASTS (SHAPE ONLY VS. SHAPE-COLOR BINDING)								
Time-window (ms)	ERP	Group-contrast	Parieto-occipital		Centro-parietal		Fronto-central	
			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						

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

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Supplementary figures

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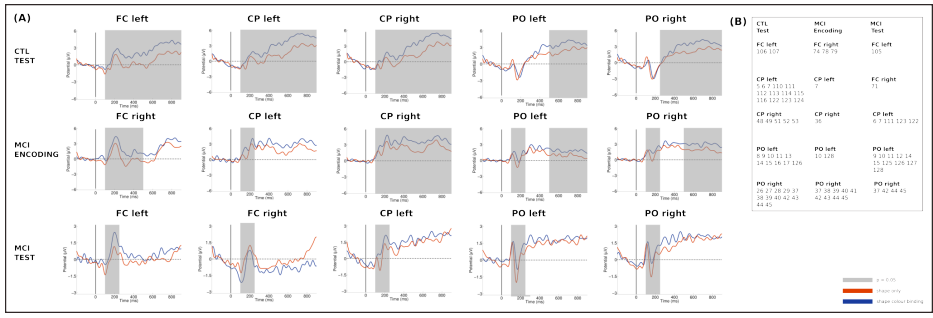
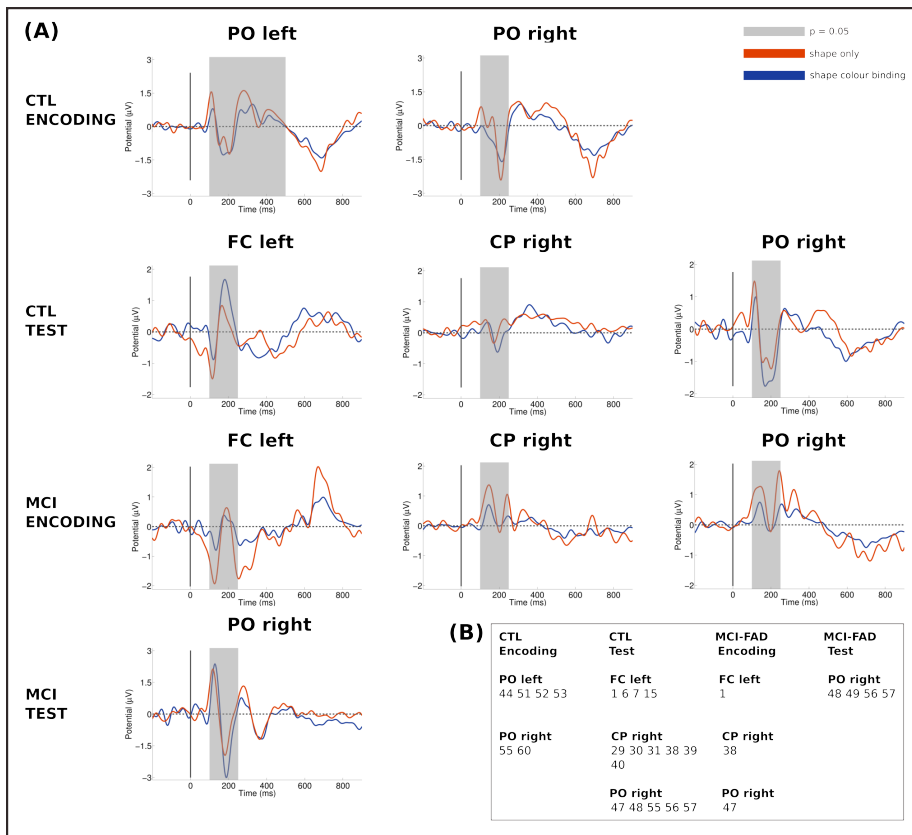


Figure 1. (A) ERP activity from significant ROIs between the shape-only and shape-color binding conditions in each memory phase of the VSTM task, in controls and MCI patients. (B) Electrodes by numbers comprising the ROIs.

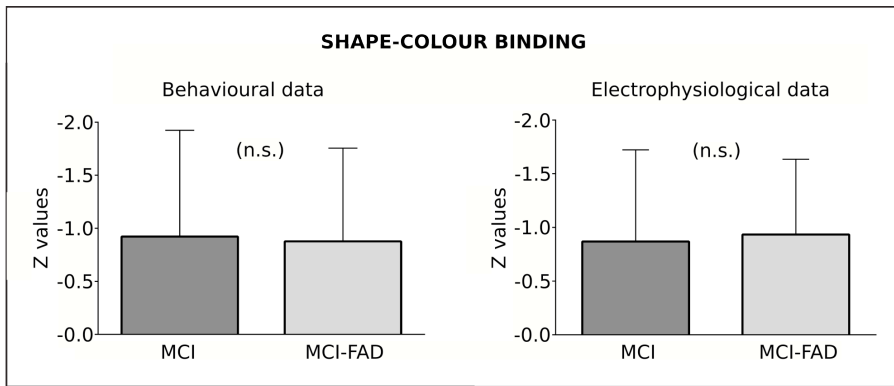


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2 **Figure 2.** (A) ERP activity from ROIs yielding significant differences between the shape-only
 3 and the shape-color binding conditions in each memory phase of the VSTM task, in controls and
 4 MCI-FAD patients. (B) Electrodes by numbers comprising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

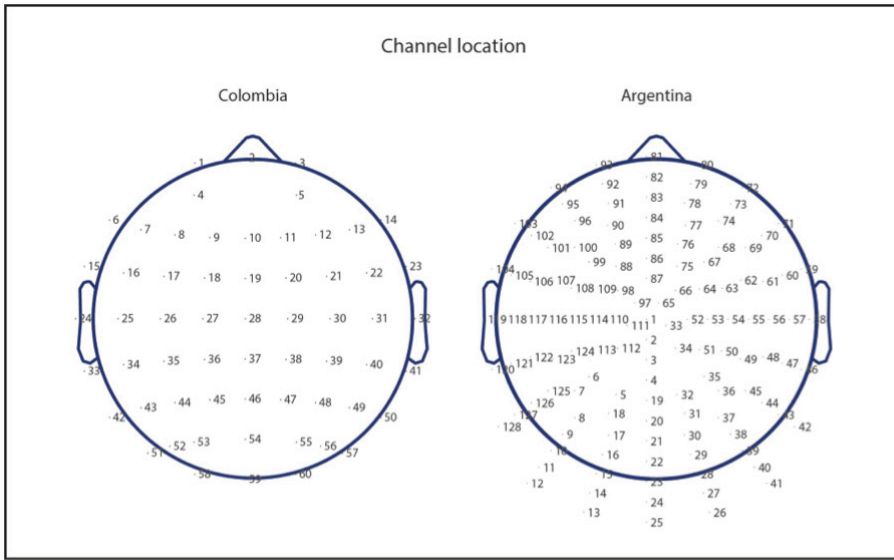
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2 **Figure 3.** Behavioral and electrophysiological comparisons between MCI and MCI-FAD during
3 the VSTM task. The y-axis shows the means of the distance between patients and controls, as
4 measured with z -values. Error bars represent standard deviations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

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

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1 **Supplementary References**

2

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