

Cognitive decline effects at an early stage: Evidence from N170 and VPP

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HIGHLIGHTS

- ▶ N170 was reduced in patients with cognitive impairment and elderly compared to young adults.
- ▶ VPP was enhanced in patients with cognitive impairment compared to elderly and young adults.
- ▶ Cognitive decline modulated the perceptual processing of faces.

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ABSTRACT

The perceptual processing of faces was studied using event-related potentials (ERPs) in 12 elderly patients with cognitive impairment, 15 elderly adults and 16 young adults in order to explore the sensitivity of N170/VPP to the cognitive decline associated to Alzheimer's disease. Famous and unknown faces were presented in a familiarity categorization task. Eight patients and 11 elderly adults repeated this task to obtain longitudinal data. Topographical effects were analyzed using PCA. The posterior N170 showed reduced amplitude in patients with cognitive impairment and elderly adults, compared to young adults, which could indicate perceptual impairment in configural face-encoding processing. The anterior VPP showed enhanced amplitude in patients with cognitive impairment, compared to young and elderly adults, which might relate to the prefrontal dysfunction associated to mild dementia. These preliminary findings suggest that N170/VPP could be modulated by the decline related to pathological cognitive aging.

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1. Introduction

Faces convey relevant information on identity of other persons which is crucial for the adaptive control of social behavior. Aging affects the configural face-encoding processing involved in face recognition [3], and amnestic mild cognitive impairment (aMCI) and mild Alzheimer's disease (AD) further compromise the semantic system underlying the recognition of familiar faces [27]. Functional neuroimaging studies utilizing face matching tasks revealed the neural basis of these changes, in which a consistent pattern of over-recruitment of activity in prefrontal areas was associated to aging [16,17], whereas mild AD and aMCI patients additionally showed activity not only in areas along the ventral visual stream, but also in the dorsal, and another alternative neural networks [1,13]. Several studies focused on the timing of aging effects on face recognition through event-related potential (ERPs) recordings [7,12,23]. Regarding face ERPs in aMCI and mild AD

patients, to our knowledge, one study did not report effects [5], whereas another one did [25]. Both studies used a similar familiarity categorization task, but showed a number of differences in stimuli presentation that could explain the discrepancy in the results. Cheng and Pai [5] used 12 complete faces (repeating 10 times) that remained on the screen until the participant made a judgment, whereas Saavedra et al. [25] used 24 faces without contour (repeating 7 times) that appeared 600 ms on the screen. The present study was partially based in the aforementioned article [25] in which a robust effect on early components related to face processing was elicited in aMCI and mild AD patients. Here, our aim was to further investigate the timing and topography of this effect using cross-sectional and longitudinal data.

N170, the earliest and most studied face ERP, is a visual evoked component that is widely regarded as face-sensitive because its amplitude at occipitotemporal electrodes, between 140 and 200 ms after stimulus onset, is virtually always larger in response to faces than in response to non-face objects [10]. The lateral posterior negativity termed N170 appears jointly with a centrally distributed positivity called Vertex Positive Potential (VPP). Response properties of N170 and VPP are closely associated across a range of stimulus and task manipulations, which suggests that they represent the same underlying brain processes [15]. N170 is typically

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Table 1
Mean (and SD) age and Mini-Mental State Examination (MMSE) score for cross-sectional and longitudinal data. Longitudinal data are provided for the first, second and third sequential evaluations.

Cross-sectional data	Young	Elderly adults	Patients
Age	25 (4.6)	83.5 (8.1)	81.8 (9.2)
MMSE	–	27.2 (3.1)	20.8 (4.3)
Longitudinal data	First	Second	Third
Elderly adults			
Age	81.8 (9.4)	82.1 (9.3)	83.9 (8.8)
MMSE	26.9 (3.5)	27.4 (2.5)	26.8 (3.7)
Patients			
Age	80.4 (10.2)	81 (10.3)	87.5 (3.4)
MMSE	21.9 (4.3)	20.6 (5.7)	18.3 (4.6)

regarded as a marker for the categorization of a stimulus as a face, and the structural encoding of faces that precede individual face identification, as in most studies it was not affected by familiarity [26]. Furthermore, N170 is considered to reflect the coding of the configuration of faces, as it is modulated by manipulations that affect the configural processing (such as face inversion, facial features scrambling). In particular, one study reported that cropped faces (without contour) increased N170 amplitude [8]. Remarkably, this “cropping effect” was found for other stimulus categories and interpreted as an amplification subsequent to deletion of features important for face (or object) recognition. In contrast, one study reported a reduction of N170 amplitude for cropped faces in healthy elderly, regarded as an impairment to integrate face features into global structures [7]. The focus of the present study was to investigate whether the N170/VPP component is modulated by cognitive decline in a familiarity categorization task using cropped faces.

2. Materials and methods

Participants in the cross-sectional study were 16 young adults, 15 elderly adults and 12 patients with cognitive impairment (5 with aMCI and 7 with mild AD). In the longitudinal study, 11 elderly adults and 8 patients with cognitive impairment (3 with aMCI and 5 with mild AD) from the initial groups repeated the experiment eight months later. And finally, two years later, 8 elderly adults and 4 patients with cognitive impairment (2 with aMCI and 2 with mild AD) repeated it again. All participants had normal or corrected-to-normal vision. Data on age for all participants and on Mini-Mental State Examination (MMSE) [11] scores for elderly participants are shown in Table 1. Elderly participants were from the day center “Asociación de Familiares de Enfermos de Alzheimer de Tres Cantos” and from the retirement home “Residencia Asistida San Camilo de Tres Cantos”. The inclusion criteria for the group of patients with cognitive impairment were: diagnosis of probable or possible AD according to the criteria developed by the National Institute of Neurological and Communicative Disorders, Stroke, Alzheimer’s Disease and Related Disorders Association [19] or diagnosis of aMCI, fulfilling the criteria for memory impairment and excluding dementia [22]. Except half of patients with mild AD taking cholinesterase inhibitors, the elderly participants used a similar medication, which is not considered to have significant CNS side effects. Caregivers of the patients were informed and gave their consent, but all participants, including the AD and aMCI patients, were able to give their own consent to participate in the study.

All participants completed a familiarity task, in which they were asked to indicate whether faces presented were either famous or unknown, under similar experimental and recording conditions. Stimuli were selected from previous pilot studies in which separate groups of similar aged persons rated a broader set of pictures.

Stimuli consisted of 40 pictures of famous faces (from Hollywood actors) and 40 pictures of unknown faces for young participants; and 24 pictures of famous faces (from famous Spanish persons from the seventies) and 24 pictures of unknown faces for elderly participants. All stimuli were digitized greyscale photographs in which the faces were framed with a black circle (see Fig. 1A). The size of stimuli on the computer screen was 18 cm high and 10 cm wide, occupying a visual angle of about $12.8^\circ \times 7.2^\circ$. Further description of the stimuli is available in Saavedra et al. [24,25]. EEG was recorded with Ag/AgCl disk electrodes from 20 recording sites: Fp1–2, F3–4, C3–4, P3–4, O1–2, F7–8, T3–4, T5–6, Fz, Cz, Pz (10/20 International System) and Oz. The tip of the nose was used as the reference site. Impedance was below 5 k Ω . EOG was recorded from electrodes placed just above the right supraorbital ridge (vertical EOG) and on the right outer cantus (horizontal EOG). EEG and EOG signals were filtered on-line between 0.05 and 30 Hz. A notch filter for 50 Hz was also used. ERPs were derived for each subject by averaging segments of 850 ms (including a pre-stimulus interval of 148 ms for baseline correction) of digitized EEG (12-bit A/D converter, sampled at 250 Hz), from trials with correct responses in the familiarity task, separately for famous and unknown faces (see Fig. 1A). Before averaging, EEG was visually inspected and those segments with excessive EOG and larger 50 μ V artifacts were eliminated. In the cross-sectional analysis, the average number of segments included after rejecting incorrect responses and artifacts, regarding famous (*F*) and unknown (*U*) faces, for the group of young adults were: *F*: 89.33 (63.81%), *U*: 106.65 (76.16%); for the group of elderly adults were: *F*: 44 (52.38%), *U*: 49.83 (59.32%), and for the group of patients with cognitive impairment were: *F*: 38.67 (46.03%), *U*: 35.83 (42.66%). In the longitudinal analysis, the average number of segments included, regarding also the sequential evaluations (1, 2 and 3), for the group of elderly adults were: 1*F*: 47.56 (56.61%), 1*U*: 47.5 (56.54%), 2*F*: 56 (66.67%), 2*U*: 53.33 (63.48%), 3*F*: 46 (54.76%), 3*U*: 46.5 (55.35%); and for the group of patients with cognitive impairment were: 1*F*: 39.43 (46.94%), 1*U*: 36.57 (43.53%), 2*F*: 43.67 (51.98%), 2*U*: 40 (47.62%), 3*F*: 45.5 (54.16%), 3*U*: 42.5 (50.59%).

Data from this set of different groups were submitted, separately for cross-sectional and longitudinal data, to Principal Component Analysis (PCA). The inclusion of a wide variety of individuals to develop ERP component solutions would enhance the generalization of the created components [4]. Detection and quantification of the ERP components was achieved through a covariance-matrix-based two-step PCA, generating spatial factors (using sPCA) from the temporal PCA (tPCA) factor scores. This procedure has been recommended to avoid misinterpretations from the exclusive use of visual inspection and mergence of different ERP components, with similar time courses, derived from a straight tPCA [9]. To compute the PCA matrix the 176 digitized time points (corresponding to the post-stimulus onset interval of 702 ms) were reduced by averaging each five adjacent digitized points (five points representing 20 ms). The decision on the number of components to select was based on the scree test [6] and extracted components were submitted to varimax rotation. To assess experimental effects, linear mixed ANOVAs were performed on sPCA-derived factor scores. In the cross-sectional analysis the inter-subjects factor was GROUP (young, elderly and patients) and the intra-subjects factor (repeated measures) was FACE (famous vs. unknown). In the longitudinal analysis the inter-subjects factor was GROUP (elderly and patients) and the intra-subjects factors (repeated measures) were ASSESSMENT (first, second, third) and FACE (famous vs. unknown). Linear mixed ANOVAs are useful to analyze complex data in a more flexible way than traditional linear general ANOVAs, especially regarding the assumptions of independence and homoscedasticity, and allow the comparison of different sized groups [2].

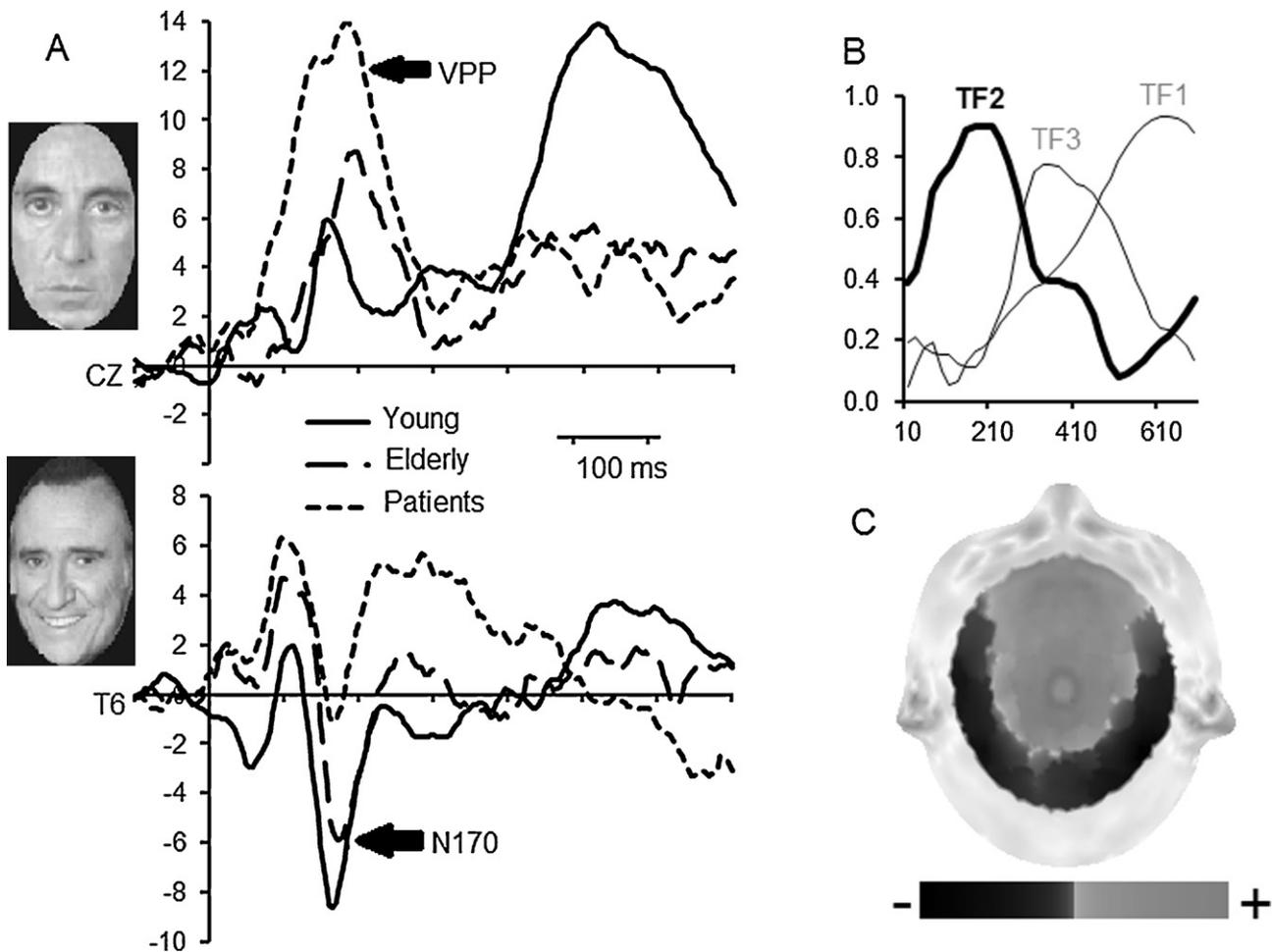


Fig. 1. (A) Examples of famous faces (top for young participants, bottom for elderly participants) and ERP waveforms elicited in response to famous faces in the familiarity task for young, elderly and patients with cognitive impairment, in anterior (CZ) and posterior (T6) locations. The peaks of the effects described in the text are indicated. (B) Temporal PCA factor loadings after varimax rotation. Temporal factor 2 (TF2), related to N170/VPP, is drawn in black. Vertical axis represents factor loadings and horizontal axis represents time in ms. (C) Topographical depicting of the factor scores of temporal factor 2 obtained from the tPCA. Positive values are shown in gray and negative values in black.

3. Results

Linear mixed ANOVAs were also applied to accuracy data, yielding in the cross-sectional analysis an effect of GROUP [$F(2, 40) = 4.21, p = 0.022$]. Young adults (81.56%) were more accurate than patients with cognitive impairment (69.82%) [$t(40) = 2.54, p = 0.045$]. Elderly adults (71.14%) showed no difference with the other two groups, and no other effects or interactions were observed. The longitudinal analysis yielded no effect of GROUP [$F(1, 12) = 0.719, p = 0.413$] between elderly adults (77.3%) and patients with cognitive impairment (74.3%), neither other effects or interactions. Regarding the general cognitive functioning of elderly participants, MMSE scores showed a main effect for GROUP [$F(1, 23) = 26.44, p < 0.001$], but no effects for ASSESSMENT [$F(2, 11) = 2.62, p = 0.115$] or the interaction [$F(2, 11) = 2.92, p = 0.094$] were found.

In the cross-sectional analysis, three components accounting for 90% of the variance were retained from the tPCA (see Fig. 1B). As indicated by the factor loadings, maximal between 160 and 240 ms, the temporal factor 2 was related to N170 and VPP. In order to group in regions the activity recorded through the 20 channels, sPCA were applied to the factor scores of temporal factor 2 (N170/VPP). The sPCA extracted two spatial factors accounting for 92% of the variance. As indicated by the factor loadings, spatial factor 1 was related to anterior regions (F3, F4, Fz and Cz) and thus to VPP, while

spatial factor 2 was related to posterior regions (O1, O2, Oz, T5 and T6) and thus to N170. Linear mixed ANOVAs were applied to the factor scores of both spatial factors: VPP and N170. VPP showed a main effect for GROUP [$F(2, 40) = 4.99, p = 0.012$] explained by the more positive activity for the patients with cognitive impairment in comparison with the young adults [$t(26) = -2.98, p = 0.006$]. N170 showed a main effect for GROUP [$F(2, 40) = 10.27, p < 0.001$] explained by the more negative activity for the young adults compared to elderly adults [$t(29) = -3.13, p = 0.004$] and to patients with cognitive impairment [$t(26) = -4.65, p < 0.001$].

In the longitudinal analysis, three components accounting for 94% of the variance were retained from the tPCA (see Fig. 2B). Temporal factor 2 was related to N170/VPP (maximal factor loadings between 160 and 220 ms). From the sPCA two spatial factors accounting for 88% of the variance were extracted, being factor 1 related to VPP (F3, F4, Fz and Cz) and factor 2 related to N170 (O1, O2, Oz, T5 and T6). Regarding spatial factor VPP, linear mixed ANOVAs revealed a main effect for GROUP [$F(1, 41) = 6.42, p = 0.015$], explained by the more positive activity showed by the patients with cognitive impairment.

4. Discussion

The present study demonstrated that N170/VPP, when elicited by facial processing in a familiarity task, showed differences among

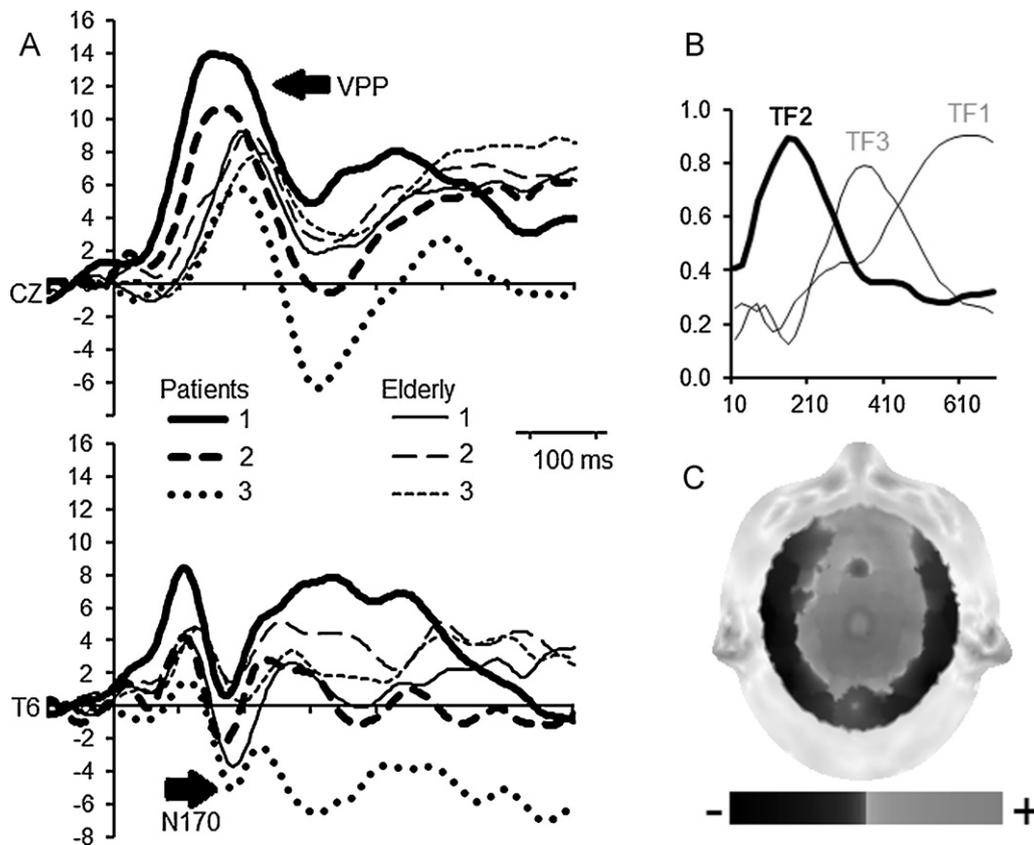


Fig. 2. (A) ERP waveforms elicited in response to famous faces in the familiarity task for patients with cognitive impairment and elderly adults in the first (1), second (2) and third (3) recordings, in anterior (CZ) and posterior (T6) locations. (B) Temporal PCA factor loadings after varimax rotation. Temporal factor 2 (TF2), related to N170/VPP, is drawn in black. Vertical axis represents factor loadings and horizontal axis represents time in ms. (C) Topographical depicting of the factor scores of temporal factor 2 obtained from the tPCA. Positive values are shown in gray and negative values in black.

young adults, elderly adults and elderly patients with cognitive impairment, corroborating previous evidences of changes on facial encoding in aging [3,7]. The present results suggest that these changes could extend in pathological cognitive aging and modulate face processing at an early stage.

Remarkably, we found different modulations for N170 and VPP. Whereas N170 showed enhanced amplitude in young adults compared to elderly adults and patients with cognitive impairment, VPP showed enhanced amplitude in patients with cognitive impairment compared to young adults in the cross-sectional analysis and elderly adults in the longitudinal analysis. Previous studies reported two functional differences between N170 and VPP. First, N170 appears relatively early in the developmental course (6–12 month-old infants) while VPP is not observed in children until age 12. Second, peripheral presentations of faces elicit an N170 but not VPP. The absence of VPP in both cases, rather than attributed to different dipolar sources, could be explained in young children as due to modifications of the cortex folding with age and brain development, while in the second case could be explained by eccentricity and reference-dependent modulations. In the present study, the different modulations on N170 and VPP may reflect the recruitment of additional processes (unrelated to face processing per se) that are active at about the same time as the N170/VPP but whose contributions differ by scalp position [15].

The effects on N170 are congruent with previous reports of a reduction of the N170 amplitude in elderly adults when the contour of the face is eliminated [7], and our results indicate that this reduction also appears in patients with cognitive impairment. The N170 amplitude reduction revealed that these groups are impaired in processing faces when the physiognomic value

of the stimuli is revealed only by components in the absence of the global face structure, reflecting the perceptual impairment in configural face-encoding processing reported in previous studies [3]. An alternative explanation proposed for this reduction in that study [7] was that N170 amplitude negatively correlated with task difficulty, as negative correlations were observed in young and elderly adults between accuracy/RTs and N170 amplitude in gender and familiarity categorization tasks. Our results are also congruent with this interpretation and VPP amplitude appeared to be positively correlated with task difficulty. Young adults showed significant increased accuracy only compared to patients with cognitive impairment, and VPP significant amplitude differences were only observed between these two groups in the cross-sectional analysis, with enhanced VPP amplitude for the patients. The inverse pattern of modulations in N170/VPP in patients with cognitive impairment (enhanced VPP and reduced N170) compared to young adults may relate to marked differences in brain activity patterns as well as in functional connectivity in the patients [1,13]. Specially, the enhanced VPP amplitude may relate to the disrupted interaction between posterior face processing regions and the prefrontal cortex in mild dementia. Prefrontal regions participate in the distributed cortical network involved in face processing, and it has been suggested that posterior areas may lead the more anterior areas at short latencies [18]. In an early neuroimaging study using a face matching task [14], a region of the right prefrontal cortex was highly correlated with activity in occipitotemporal regions in young and elderly adults whereas in Alzheimer's disease patients this region was only correlated with other prefrontal regions, suggesting an alteration of frontally mediated processing during perception.

We failed to find differences between elderly adults and patients with cognitive impairment in the cross-sectional analysis. The differences between these groups only emerged in the longitudinal study, although no differential effects for the sequential evaluations were found. This could be due to a lack of statistical power to detect the differences between the groups, as a result of low sample size. Besides, we also failed to find the positive correlation between VPP and the accuracy in the longitudinal study, where VPP showed increased amplitude but no behavioral differences were observed. The increased VPP amplitude in the patients could be explained by the aforementioned anterior–posterior disruption in AD and the alteration of prefrontal mediated function [14]. From animal models, it is well known that molecular and synaptic alterations can affect the function of networks and, in turn, alteration in network functions can affect individual synapses and molecules. In recent years, it has been suggested that AD may be primarily a disorder of the synapse and synaptic plasticity. Speculatively, the increased VPP in the present study could be related with the evidences showing, on the one hand, that tau and A β -induced synaptic dysfunctions can elicit aberrant excitatory activity at the network level [21] and, on the other hand, that prefrontal synapses are especially vulnerable and their loss is related to cognitive decline [20].

In conclusion, our results suggest that N170/VPP is modulated by the decline associated to pathological cognitive aging, particularly to the processes related to Alzheimer's disease. These results should be considered as preliminary due to both the low sample size in the present study and the usual inter-individual variability of ERP cortical responses. Future studies using other configural modifications of faces and separating AD and aMCI patients are necessary to analyze whether these ERPs allow for the differentiation of stages of cognitive decline and following the course of these clinical disorders.

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