

Electrophysiological evidence of altered facial expressions recognition in Alzheimer's disease: A comprehensive ERP study



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HIGHLIGHTS

- ERPs can be used as a valuable tool to investigate emotional face processing in AD.
- The categorization of emotional facial expressions was intact in individuals with AD.
- P100, N170, and VPP to emotional expressions were altered in AD compared to controls.

ABSTRACT

Objectives: The present study aims to evaluate the amplitude and latency of event-related potentials (ERPs) P100, N170, VPP and N230 in individuals with Alzheimer's disease (AD) compared to healthy elderly controls, using a passive viewing task of emotional facial expressions.

Methods: Twenty-four individuals with mild to moderate AD and 23 demographically matched healthy elderly controls were included in the study. ERP P100, N170, VPP and N230 amplitude and latency values were compared between groups.

Results: The categorization of emotional facial expressions was intact; yet, increased P100 amplitude and latency, decreased N170 amplitude, and increased VPP amplitude were observed in AD compared to controls. Increased N230 amplitude and latency were observed in response to angry expressions, while neutral expressions elicited decreased amplitude and latency.

Conclusions: Increased P100 amplitude and latency may reflect reduced amygdala volume and disruptions in the visual system, while decreased N170 and increased VPP amplitudes may reflect impaired perceptual processing, mitigated by a greater involvement of prefrontal areas for task performance in AD.

Significance: This study is the first to report a complex pattern of ERPs to emotional facial expressions in individuals with AD.

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1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by episodic memory impairment, which is related to the atrophy in entorhinal cortex, hippocampus and external temporal associative regions (Braak and Braak, 1996; Bediou et al., 2009). A gradual decline in executive functions,

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language and visuospatial skills develops with the progression of cortical pathology.

Many studies report that social cognitive deficits may accompany cognitive impairment in individuals with AD, as shown by poorer performance on theory of mind tasks (Cuerva et al., 2001; Verdon et al., 2007) and recognizing facial expressions (Hargrave et al., 2002; Spoletini et al., 2008; Bediou et al., 2009; Henry et al., 2009; Satler et al., 2010; Hot et al., 2013; Maki et al., 2013; Torres et al., 2015; Virtanen et al., 2017) compared with healthy elderly controls. These studies found impaired categorization of angry, fearful, happy and sad face expressions in individuals with AD. However, there is a debate in the literature regarding whether the impaired emotional processing in AD is a separate entity (Bediou et al., 2009; Klein-Koerkamp et al., 2012) or a by-product of global cognitive decline (Albert et al., 1991; Cadieux and Greve, 1997; Koff et al., 1999; Bucks and Radford, 2004; Garcia-Rodriguez et al., 2009).

Early automatic processing of emotional facial expressions involves amygdala, thalamus, striate cortex and superior colliculus (Adolphs, 2002a), while a detailed decoding of the emotions extends toward the superior temporal sulcus (STS), fusiform face area (FFA), orbitofrontal cortex (OFC), occipital face area (OFA), basal ganglia and insula (Adolphs, 2002b; Vuilleumier and Pourtois, 2007; Mende-Siedlecki et al., 2013; Sapey-Triomphe et al., 2015; see for a meta-analysis, Sabatinelli et al., 2011). The amygdala is especially important for the recognition of fear (LeDoux, 2003) and happiness (Phan et al., 2002), the OFC for anger (Blair et al., 1999) and the insula for disgust (Wicker et al., 2003). The amygdala (Horinek et al., 2007; Wright et al., 2007; Cavado et al., 2011) and prefrontal cortex (Braak and Braak, 1991; Salat et al., 2001; Bakkour et al., 2013), two brain areas involved in emotional processing, are found to be affected by AD pathology (Klein-Koerkamp et al., 2012).

The accurate interpretation of emotional facial expressions is essential for non-verbal communication, understanding of the emotional states of others and the continuation of social interactions. Impaired emotion recognition is associated with reduced quality of life and increased caregiver burden in AD (Phillips et al., 2010; McCade et al., 2013; Elferink et al., 2015), therefore deserves further investigation.

Event-related potentials (ERPs) are considered as an ideal tool to investigate synaptic neurotransmission and neural correlates of perceptual and cognitive processes with high temporal resolution (Cook and Leuchter, 1996; Horvath et al., 2018). Affective ERP studies using emotional faces as stimuli mainly focused on P100, N170 and vertex positive potential (VPP).

ERP P100 is a positive peak, generated in the extrastriate visual cortex as an early response to visual stimuli and is thought to reflect the early automatic encoding of emotional facial expressions (Di Russo et al., 2002; Woldorff et al., 2002; Batty and Taylor, 2003; Müller-Bardorff et al., 2018). Intracranial EEG studies showed differential amygdala responses in the P100 time window, suggesting an association between P100 and amygdala activation (Krolak-Salmon et al., 2004; Mendez-Bertolo et al., 2016; Müller-Bardorff et al., 2018). Several studies found increased P100 amplitudes in response to facial stimuli compared to scrambled faces and non-face stimuli (i.e., flowers, buildings) (Halit et al., 2000; Itier and Taylor, 2002, 2004; Herrmann et al., 2005; Holmes et al., 2008; Mueller et al., 2009; Mühlberger et al., 2009). Batty and Taylor (2003) showed larger P100 amplitudes to neutral and surprised faces compared to happy, sad, angry, disgusted and fearful faces in healthy young individuals.

ERP N170, a negative peak over parieto-occipital regions, is dominant for faces and reflects the face specific structural encoding (Bötzel et al., 1995; Bentin et al., 1996; George et al., 1996; Miyoshi et al., 2004; Eimer, 2011; Schweinberger and Neumann,

2016). Generally, N170 amplitudes are larger in the right hemisphere for faces compared to objects (Rossion, et al., 2003). VPP is a positive peak over fronto-central regions, within the similar N170 time frame (Bötzel and Grüssel, 1989; Jeffreys and Tukmachi, 1992; Jeffreys, 1996; Joyce and Rossion, 2005). N170 and VPP are thought to be generated by the same neural structures, the middle fusiform gyrus, the inferior occipital cortex, and the STS (Jeffreys, 1989, 1996; Joyce and Rossion, 2005). While both N170 and VPP are associated with bottom-up perceptual processing of faces in the occipito-temporal cortex, VPP was found to reflect an integration of top-down and bottom-up visual processing (Lu et al., 2017). There is increasing evidence that both N170 and VPP components are modulated by emotional faces (Pizzagali et al., 2000; Caharel et al., 2005, 2006; Ashley et al., 2004; Blau et al., 2007; Wild-Wall et al., 2008; Brenner et al., 2014; Yang et al., 2015; see for a meta-analysis, Hinojosa et al., 2015). Accordingly, Tottenham et al. (2009) stated that happy, fearful and angry faces elicited larger VPP responses than sad and neutral faces in healthy adults. Additionally, studies showed enhanced N170 amplitude in response to angry faces (Batty and Taylor, 2003; Blau et al., 2007; Scheffer et al., 2013).

ERP N230 is a negative peak larger for emotional faces (Balconi and Pozzoli, 2003; 2008) over midline electrodes (Streit et al., 2000). Balconi and Pozzoli (2003, 2008) reported that neutral faces elicited reduced N230 amplitude than surprised, happy, sad, fearful and angry faces in healthy young adults. Moreover, larger N230 amplitudes were showed for angry, fearful and surprised faces compared to happy and sad (Balconi and Pozzoli, 2003).

There is a gap in the literature regarding ERP correlates of emotional face processing in AD. N230 is the least examined affective ERP component and there is no previous evidence regarding how N230 amplitude and/or latency alter between individuals with AD and healthy controls in response to emotional facial expressions. To the best of our knowledge, there has only been two studies reporting P100 changes in response to facial stimuli in individuals with cognitive impairment (Chen and Pai, 2010; Saavedra et al., 2012a). Cheng and Pai (2010) compared individuals with very mild AD and healthy elderly controls using a familiarity decision task and found shorter P100 latency in the AD group, of which the reason was stated to be unclear, yet there was no significant difference in P100 amplitude. Saavedra et al. (2012a) reported increased P100 amplitude elicited by unknown faces and enhanced prefrontal activation in the P100 time window in individuals with mild cognitive impairment (MCI)/AD compared to controls. These studies also showed reduced N170 amplitudes in individuals with AD compared to controls (Cheng and Pai, 2010; Saavedra et al., 2012a). In Saavedra et al.'s (2012b) study, enhanced VPP amplitudes in addition to decreased N170 were found in MCI/AD compared with controls.

Previous studies of affective ERPs have some limitations. First, the emotional processing tasks used in above-mentioned studies involved cognitive demands (i.e., familiarity judgment task, emotion judgment task), which impede the differentiation between emotional and cognitive task performances in individuals with AD by taxing cognitive resources. Second, studies by Saavedra et al. (2012a,b) had relatively small sample sizes (i.e., 12 and 8 individuals with cognitive impairment, respectively), which limit the generalizability of study findings. Third, although Cheng and Pai (2010) reported altered P100 latency in AD, this finding seemed to be rather unexpected and was not discussed by the authors. Hence, further studies are needed to understand the neural underpinnings of emotional facial processing in AD.

The present study aims to investigate the amplitude and latency modulations of P100, N170, VPP and N230 by passive viewing of emotional facial expressions in individuals with AD compared to healthy elderly controls. Based on the literature, we hypothesized

that the individuals with AD will exhibit decreased N170 and increased P100 and VPP amplitudes compared to healthy controls. We also hypothesized that emotional facial expressions will elicit higher N230 amplitudes than neutral faces.

2. Materials and Methods

2.1. Participants

Twenty-three individuals with AD and age-, gender-, education- and handedness-matched 24 healthy controls were included to the study. The study recruited seventeen individuals with mild AD (Clinical Dementia Rating Scale, CDR = 1, Morris, 1993) and six with moderate AD (CDR = 2) in accordance with the NIA-AA diagnostic criteria (McKhann et al., 2011) from the outpatient memory clinics of Dokuz Eylul University (n = 22) and Istanbul Medipol University (n = 2). The AD diagnosis was determined by neurologists. Some of the participants in the present study were included in our previous report (Güntekin, Hanoğlu, Aktürk, Fide, Emek-Savaş, Ruşen, Yıldırım, Yener, in preparation). At the time of the study, participants with AD were within the first two years of diagnosis and received ongoing donepezil or rivastigmine therapy or a combined therapy with memantine.

Demographically matched healthy controls were recruited from various community sources. Neuropsychological assessments and EEG recordings of healthy controls were carried out in Dokuz Eylul University (n = 20) and in Istanbul Medipol University (n = 3) using the same protocol. All participants underwent complete neurological, structural magnetic resonance imaging (MRI) and laboratory examinations.

The exclusion criteria for individuals with AD included scoring more than 24 in the Mini-Mental State Examination (MMSE, Folstein et al., 1975), presence of severe dementia, treatment with antipsychotics, and having comorbidities that reduce their life expectancy significantly. The exclusion criteria for the voluntary healthy elderly controls included neurological abnormality or global cognitive impairment (MMSE score < 27; CDR > 0, Morris, 1993); history of neurological, psychiatric, or systemic disorders; and history of severe head injury and alcohol or drug abuse. Participants with deficits in face discrimination (Benton Face Recognition Test, BFRT < 40, Benton et al., 1994) were excluded from the study, based on previous literature (Tranel et al., 2009) indicating a dissociation between visuo-perceptual discrimination of faces and recognition of emotional face expressions. Individuals with AD who have a face discrimination deficit may exhibit poorer performance in recognition of emotional face expressions (Allender and Kaszniak, 1989; Cadieux and Greve, 1997; Hargrave et al., 2002). Thus, we wanted to control for deficits in face discrimination as a potential confounder. Participants with depressive conditions (Geriatric Depression Scale, GDS > 14, Yesavage et al., 1983) were also excluded, as depression was reported to interfere with the ability to process emotional information (Roberts et al., 1996) and older adults with a mood disorder were found to be mildly impaired in recognition of emotional expressions compared to healthy older adults (Philips et al., 2010). In addition, participants who had less than 40 artifact-free EEG epochs were excluded from the study. Participants were not compensated for their participation in the study. The study conformed to the principles of the Declaration of Helsinki. The experimental protocols were approved by the local ethical committee, and all participants and/or their relatives provided written informed consent.

There were no statistical differences in gender, age, education, handedness or Geriatric Depression Scale (GDS) score between groups. Although there was a trend for group difference in education; due to lack of significant correlations between education and

the amplitude and latency values of ERPs, analyses were not adjusted for education. Demographic and clinical characteristics of participants are presented in Table 1. All participants reported normal or corrected-to-normal eyesight.

2.2. Neuropsychological measures

The MMSE was used to measure general cognitive status, and the CDR was used to determine disease severity. A comprehensive neuropsychological test battery covering the cognitive domains of episodic memory, attention, executive functions, visuospatial skills and language was administered to all participants. Verbal episodic memory was evaluated with Oktem Verbal Memory Processes Test (OVMPPT), which includes a 15-item word list to measure immediate recall, total learning and delayed recall (Oktem, 1992). Visual episodic memory was assessed by WMS-R Visual Reproduction Subtest (Wechsler, 1987). Attention was evaluated with WMS-R Digit Span Test Forward (Wechsler, 1981) and Trail Making Test Part A (Reitan, 1955). Executive functions were assessed with WMS-R Digit Span Test Backward, Trail Making Test Part B and verbal fluency tasks (i.e., animal and F-A-S) and Stroop Test (Stroop, 1935). Visuospatial skills were evaluated with Benton Line Orientation Test (Benton et al., 1978) and BFRT (Benton et al., 1994), which assesses perceptual discrimination and matching of non-emotional/neutral faces. Language was assessed with the 15-item version of the Boston Naming Test (Kaplan et al., 2001).

The raw neuropsychological test scores were first converted into z-scores, which were then combined to derive composite scores (i.e., domains). The mean composite scores of study groups are presented in Table 1. As expected, individuals with AD showed lower composite z-scores in episodic memory ($p < .001$), attention ($p < .01$), executive functions ($p < .01$) and visuospatial skills ($p < .001$) domains in comparison to healthy controls.

2.3. Electrophysiological recording, paradigm and analysis

EEGs were recorded from 30 Ag/AgCl electrodes positioned on an elastic cap (Easy-Cap) (Brain Products GmbH; Gilching, Germany) according to the international 10–20 system and were referenced to linked earlobe electrodes (A1 + A2). The ground electrode was located over the right earlobe. EOGs from medial upper and lateral orbital rim of the right eye were registered. All electrode impedances were kept less than 10 kΩ. EEG and EOG were amplified by means of a Brain Amp 32-channel DC system machine with 0.1–70 Hz band-pass filter and were digitized online with a sampling rate of 500 Hz (Brain Products GmbH; Gilching, Germany).

Table 1
Demographic, clinical and neuropsychological characteristics of participants.

	Healthy Controls (n = 24)	Individuals with AD (n = 23)	p
Age	71.71 ± 8.52	72.96 ± 4.73	.54 ^a
Gender (M/F)	13/11	13/10	.87 ^b
Education	11.83 ± 4.56	9.52 ± 3.46	.06 ^a
Handedness (Right/Left/Both)	21/2/1	20/1/2	.67 ^b
MMSE	29.00 ± 1.47	21.48 ± 3.45	.00 ^a
GDS	5.25 ± 6.46	5.43 ± 4.27	.91 ^a
BFRT	46.92 ± 3.77	43.56 ± 3.50	<.01 ^a
Episodic Memory	0.77	−0.81	.00 ^a
Attention	0.38	−0.37	<.01 ^a
Executive Functions	0.45	−0.35	<.01 ^a
Visuospatial Skills	0.48	−0.54	.00 ^a
Language	0.00	0.00	1.00 ^a

The letter “a” indicates statistical analysis of independent samples t-test, “b” indicates statistical analysis of chi-square, MMSE: Mini-Mental State Examination, GDS: Yesavage Geriatric Depression Scale, BFRT: Benton Face Recognition Test. Demographical and clinical data are presented as mean ± standard deviation. Neuropsychological data are presented as z scores.

Pictures of five facial expressions (angry, happy, fearful, neutral and sad; respectively) of three different females from the Ekman and Friesen (1976) Pictures of Facial Affect were shown in five consecutive sessions during EEG recording. Each session contained 60 black and white photos 17 × 17 cm in size which were displayed for 1 sec with the inter-stimulus interval varied randomly from 3 to 7 sec, and stimuli were presented on a computer screen 120 cm in front of the participants. The pictures of the same valence were presented in a random order within each session, but the order of sessions (i.e., angry, happy, fear, neutral and sad) was fixed for all participants.

Following each recording session, participants were asked to label the facial expression on each photograph (i.e., three different females), and the participants who could not identify the facial expression were presented a written card and prompted to choose the relevant facial expression. After each labeling or recognition phase of the task, participants were asked to rate the degree of valence (positivity/negativity) and arousal (excited/calm) using a Self-Assessment Manikin (SAM) scale (Lang and Bradley, 1994). For valence, the ratings between 1 and 4 points (1 point = the most positive) represented positive mood, 5 represented neutral mood, and 6–9 points (9 points = the most negative) represented negative mood. For arousal, 1 point indicated the highest arousal and 9 points indicated the lowest arousal. Participants were given 2 points for each correctly labeled facial expression and 1 point for the correct recognition.

Offline data analysis was performed with Brain Vision Analyzer 2.1 (Brain Products GmbH; Gilching, Germany). ERPs were examined in five separate sessions that the angry, happy, fearful, neutral and sad facial expressions were presented. A band-pass filter at 0.5–30 Hz with a 12 dB/octave slope and a 50 Hz notch filter were applied to the continuous EEG data from each session. Filtered EEG data were segmented into 1000 ms epochs, with 200 ms pre-stimulus and baseline corrected in the time domain using the pre-stimulus interval.

Artifacts were automatically rejected based on the following criteria: (1) maximum amplitude in an epoch was $\pm 100 \mu\text{V}$; (2) maximum allowed voltage step was $50 \mu\text{V}/\text{ms}$; (3) maximum allowed difference in a 200 ms interval was $100 \mu\text{V}$ and (4) lowest activity in a 100 ms interval was $0.5 \mu\text{V}$. One healthy control and three individuals with AD were excluded at the beginning of the study due to insufficient epoch numbers ($N < 40$) in any of the five conditions. The remaining 24 healthy controls and 23 individuals with AD were included in further analysis. EEG data with at least 40 artifact-free epochs were averaged to obtain ERPs. Groups' grand average ERP waveforms were computed for each condition. A repeated measures ANOVA for number of epochs revealed no reliable differences for CONDITION [$F_{2,813,1628,301} = 1.571$; $p = .20$], GROUP [$F_{1,45} = 1.342$; $p = .25$], or their interaction [$F_{2,813,1628,301} = 2.507$; $p = .07$].

The amplitude and latency values of ERP components were measured using automatic peak detection at the electrodes where they were most prominent. P100 was measured as the maximum positive peak in the 30–150 ms time interval from the occipital electrodes (O_1 , O_z and O_2). Peak amplitude and latency of N170 and VPP were measured in the 120–220 ms time window. For N170, bilateral posterior temporal and occipital electrodes (P_7 , P_8 , O_1 and O_2); for VPP, midline fronto-central electrodes (F_z , FC_z and C_z) were examined. N230 was measured at frontal and central electrode locations (F_3 , F_z , F_4 , C_3 , C_z and C_4) in the 200–370 ms time window.

2.4. Statistical analysis

Statistical analyses were carried out with IBM SPSS Statistics 24.0 software. Comparison of demographic and clinical informa-

tion (i.e., MMSE and CDR), visuo-perceptual abilities (BFRT), cognitive composite scores and behavioral data (i.e., categorization of facial expressions and valence/arousal ratings) between groups were carried out with independent samples t-test.

Separate repeated measures ANOVAs were performed for the peak amplitude and latency values of ERP P100, N170, VPP and N230 components. In repeated measures ANOVA, LATERALITY (for P100 and N230) or HEMISPHERE (for N170) was taken as a between-subjects factor, consistent with the previously defined electrode locations for each component. LATERALITY indicates left, mid and right electrode distribution and HEMISPHERE, left and right sided electrodes. For the P100 amplitude and latency values, the repeated measures ANOVA included 2-levels GROUP [controls, AD] as a between-subjects factor and 5-levels CONDITION [angry, happy, fear, neutral, sad] and 3-levels LATERALITY [left, mid, right] as within-subject factors. For the N170 amplitude and latency values, the repeated measures ANOVA included 2-levels GROUP [controls, AD] as a between-subjects factor and 5-levels CONDITION [angry, happy, fear, neutral, sad], 2-levels LOCATION [posterior temporal, occipital] and 2-levels HEMISPHERE [left, right] as within-subject factors. For the VPP amplitude and latency, repeated measures ANOVA included 2-levels GROUP [controls, AD] as a between-subjects factor and 5-levels CONDITION [angry, happy, fear, neutral, sad] and 3-levels LOCATION [frontal, fronto-central, central] as within-subject factors. For the N230 amplitude and latency, repeated measures ANOVA included 2-levels GROUP [controls, AD] as a between-subjects factor and 5-levels CONDITION [angry, happy, fear, neutral, sad] and 3-levels LOCATION [frontal, central] and 3-levels LATERALITY [left, mid, right] as within-subject factors.

When the Mauchly's test indicated that the assumption of sphericity had been violated, the Greenhouse-Geisser correction was applied where $\epsilon < 0.75$, and the Huynh-Feldt correction was applied where $\epsilon > 0.75$. Post-hoc analyses were performed using either independent samples t-test or paired sample t-test, which were adjusted using a Bonferroni correction. Levels of $p < .05$ were considered as significant for all statistical analyses.

In addition, correlations between ERP measures and general cognitive status, face discrimination performance and behavioral data were sought. The correlation findings are reported in the [Supplementary Material and Supplementary Table 1](#).

3. Results

3.1. Behavioral data

Group performances on the categorization of facial expressions are shown in [Fig. 1](#). Individuals with AD performed worse than healthy controls on labeling neutral expressions ($p < .01$). The correct categorization rate for neutral expressions was 50.72% in the AD group and 76.39% in the control group. The neutral expressions were mistaken for sad (AD: 20.30%, controls: 11.11%), angry (AD: 14.49%, controls: 8.33%), happy (AD: 10.14%, controls: 1.39%) and fear (AD: 4.35%, controls: 2.78%). The AD group showed significantly higher valence ratings for angry expressions than the control group ($p = .03$), indicating that the individuals with AD rated angry faces as more unpleasant. The arousal ratings did not differ between groups.

As the order of sessions was fixed for all participants, we examined whether a possible habituation and/or order effect occurred in the sample, as task fatigue could have accounted for poorer performance on later sessions. We did not find any difference in the amplitude and latency measures of P100, N170, VPP and N230 between the angry condition (i.e., first session) and the sad condition (i.e., last session), for individuals with AD or healthy controls ($p > .05$).

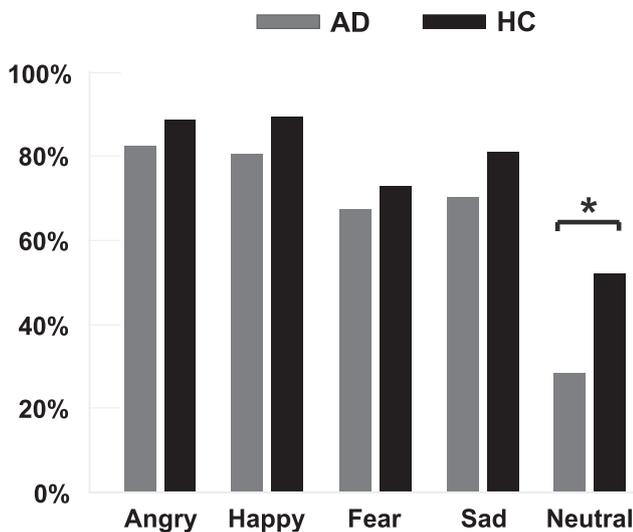


Fig. 1. Percentages of correct facial expression categorization across groups. The asterisk indicates significant difference between groups.

3.2. Responses of ERP components to experimental conditions

3.2.1. P100

There was a main GROUP effect [$F_{1,45} = 4.547$; $p = .04$] on P100 amplitude; indicating significantly larger P100 amplitudes in individuals with AD compared with healthy controls (Fig. 2).

A GROUP \times LATERALITY interaction effect was observed [$F_{2,90} = 4.544$; $p = .02$]. Post-hoc analysis revealed that individuals with AD had higher latencies in the left ($p < .01$) and mid ($p = .01$) occipital electrodes in comparison with healthy controls. There was also a main LATERALITY effect [$F_{2,90} = 3.705$; $p = .03$], indicating delayed P100 latencies on the left and mid electrodes than the right (all, $p < .02$).

3.2.2. N170

A main GROUP effect [$F_{1,45} = 8.475$; $p = .01$] was found on N170 amplitude values; indicating significantly lower N170 amplitudes in individuals with AD compared to healthy controls. There was also a main LOCATION effect [$F_{1,45} = 15.139$; $p < .001$], showing larger N170 amplitudes on posterior temporal electrodes than occipital electrode sites (Fig. 3B).

There was a main LOCATION effect on N170 latency [$F_{1,45} = 47.247$; $p < .001$]; demonstrating increased N170 latency on posterior temporal electrodes compared to occipital electrodes. A main HEMISPHERE effect was observed on N170 latency [$F_{1,45} = 12.226$; $p < .01$], indicating increased N170 latency in the right compared to the left. An interaction effect of LOCATION \times HEMISPHERE [$F_{1,45} = 10.268$; $p < .01$] was also found. Post-hoc comparisons showed that at the posterior temporal electrodes, N170 latencies were longer in the right electrode sites compared to the left ($p < .001$).

3.2.3. VPP

An interaction effect of GROUP \times CONDITION \times LOCATION was found [$F_{4,360} = 3.207$; $p = .01$]; however, post-hoc analysis revealed non-significant results. An interaction effect of GROUP \times CONDITION was observed [$F_{4,180} = 4.919$; $p < .01$]. Post-hoc analysis revealed that VPP amplitudes were significantly enhanced in individuals with AD compared to healthy controls in response to fearful ($p = .02$) and neutral ($p = .02$) expressions (Fig. 4A). A main CONDITION effect was also observed [$F_{4,180} = 5.509$; $p < .001$]; indicating higher VPP amplitudes in response to angry, happy and fear expressions than sad and neutral expressions (all, $p < .001$).

Mauchly's Test of Sphericity indicated that the assumption of sphericity had been violated for the CONDITION \times LOCATION interaction effect [$\chi^2_{35} = 200.916$; $p < .001$]. Therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\epsilon = 0.54$). There was a CONDITION \times LOCATION [$F_{4,29,192.91} = 6.182$; $p < .001$] interaction effect; demonstrating increased amplitudes on angry, happy and fear conditions [frontal and fronto-central electrodes (all, $p < .05$)], and on happy and fear conditions [central electrodes (all, $p < .03$)] than the neutral and sad conditions (Fig. 4B).

Mauchly's Test of Sphericity indicated that the assumption of sphericity had been violated for the LOCATION effect [$\chi^2_2 = 54.072$; $p < .001$]. Therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\epsilon = 0.59$). A main LOCATION effect on VPP latency [$F_{1,23,55.55} = 5.091$; $p = .02$] was found, indicating shortened latency values on frontal electrodes compared to fronto-central ($p = .07$) and central ($p < .01$) electrode sites. No other main effect or interaction was significant.

3.2.4. N230

Mauchly's Test of Sphericity indicated that the assumption of sphericity had been violated for the CONDITION effect [$\chi^2_9 = 32.554$; $p < .001$]. Therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\epsilon = 0.69$). A main CONDITION effect was found [$F_{2,78,125.11} = 3.110$; $p = .03$]; indicating larger N230 amplitudes for angry expressions compared to happy, fear, neutral and sad expressions (all, $p < .001$); for happy expressions compared to fearful expressions ($p = .03$), and for sad expressions compared to fearful and neutral expressions (all, $p = .01$) (Fig. 5A).

Mauchly's test indicated that the assumption of sphericity had been violated for the CONDITION \times LOCATION \times LATERALITY interaction effect [$\chi^2_{35} = 64.370$; $p < .01$], therefore degrees of freedom were corrected using Huynh-Feldt estimates of sphericity ($\epsilon = 0.76$). There was a CONDITION \times LOCATION \times LATERALITY interaction effect [$F_{7,27,32.12} = 2.333$; $p = .02$]. Post-hoc comparison indicated that the angry expressions elicited larger amplitudes than the fearful [left and right frontal (all, $p < .03$) and all central electrodes (all, $p < .01$)], happy [mid and right frontal and central electrodes (all, $p < .04$)], sad [mid ($p = .01$) and right ($p = .03$) central electrodes], and neutral [left ($p = .03$) and mid ($p < .01$) central electrodes] expressions (Fig. 5B).

There was a LOCATION \times LATERALITY interaction effect on N230 amplitude [$F_{2,90} = 3.966$; $p = .02$]. Post-hoc comparison indicated that larger amplitudes were measured at mid-frontal and -central electrode locations than left and right frontal and central electrodes (all, $p < .001$). Moreover, N230 amplitude was higher over the right central electrode compared to right frontal ($p = .01$) and left central electrodes ($p = .01$).

A main CONDITION effect was found on N230 latency [$F_{4,180} = 2.839$; $p = .03$]. Post-hoc comparisons showed that N230 latencies were delayed in response to angry facial expressions compared to fearful ($p = .02$), sad ($p = .02$) and neutral ($p = .03$) expressions.

Table 2 presents a summary of the ANOVA results in tabular form.

4. Discussion

The present study aimed to investigate ERP responses to happy, angry, fearful, sad and neutral face stimuli in individuals with mild to moderate AD in comparison with demographically-matched healthy controls. To the best of our knowledge, this is the first study investigating ERP P100, N170, VPP and N230 responses in individuals with AD using a passive viewing task of emotional

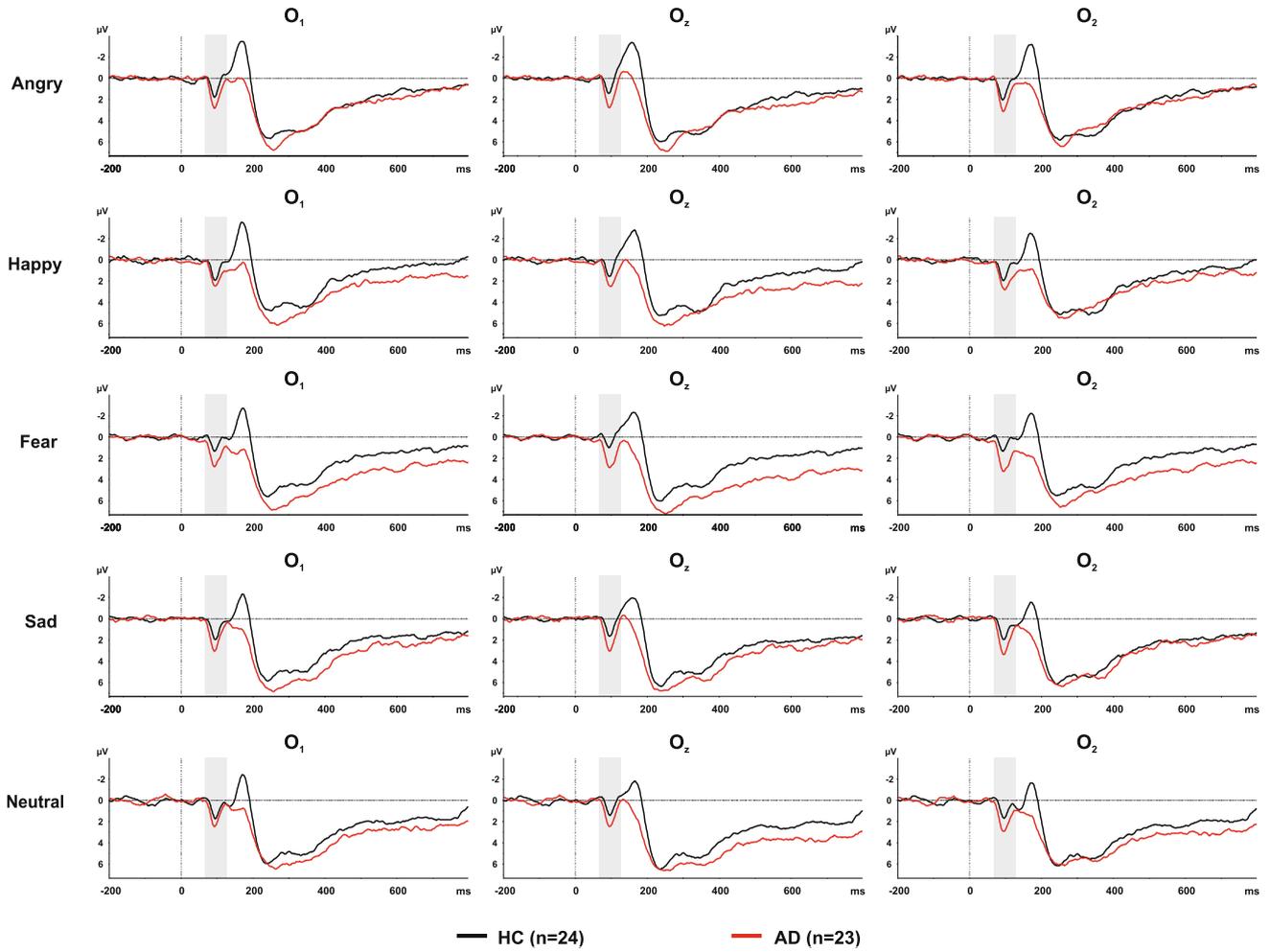


Fig. 2. Grand averaged ERP waveforms of healthy controls and individuals with AD demonstrating P100 component at occipital electrode locations for study conditions.

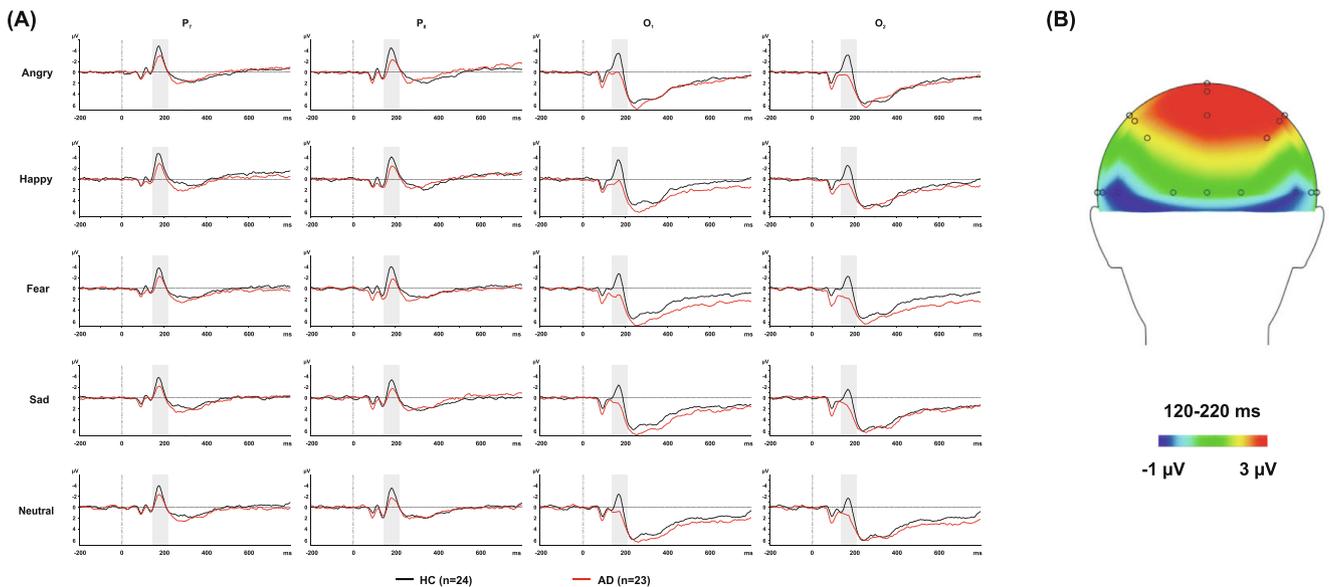


Fig. 3. (A) Grand averaged ERP waveforms of healthy controls and individuals with AD demonstrating N170 component on posterior temporal and occipital locations for study conditions. (B) Topographical map of N170 time window showing larger N170 amplitudes on posterior temporal electrodes than occipital electrode sites.

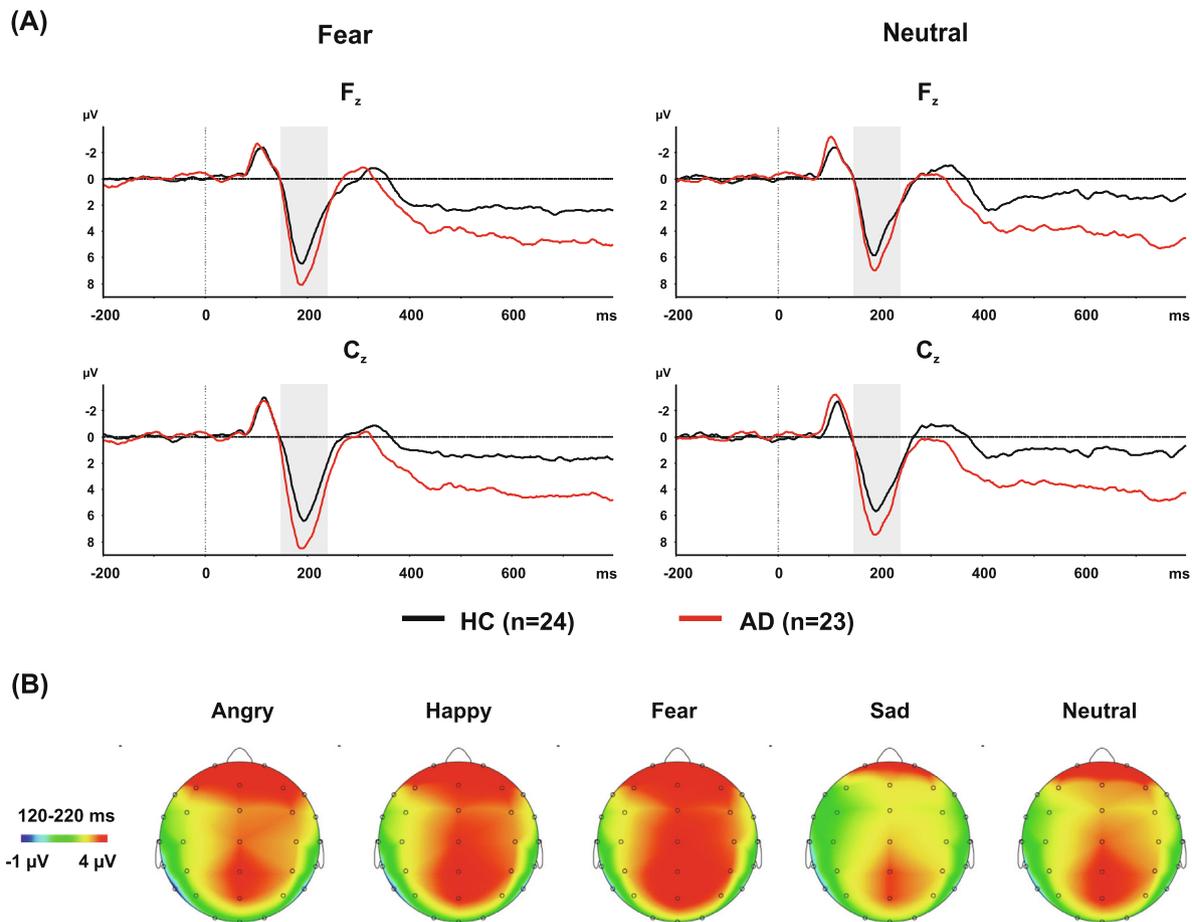


Fig. 4. (A) Grand averaged ERP waveforms of healthy controls and individuals with AD demonstrating VPP component on frontal and central locations for fear and neutral conditions. (B) Topographical maps of VPP time window across study conditions.

facial expressions. Our main findings can be summarized as increased P100 amplitude and latency, decreased N170 amplitude, and increased VPP amplitude in individuals with AD compared to healthy controls, with similar performance on categorization of emotional facial expressions between groups.

4.1. Behavioral data

Although previous studies reported impaired emotion labeling performances in AD (Hargrave et al., 2002; Spoletini et al., 2008; Bediou et al., 2009; Henry et al., 2009; Satler et al., 2010; Hot et al., 2013; Maki et al., 2013; Torres et al., 2015; Virtanen et al., 2017), the present study found no significant differences between groups, except for the labeling of neutral expressions.

Earlier studies indicated that impairment in emotion discrimination is associated with deficits in language and visuo-perceptual processes (Albert et al., 1991; Cadieux and Greve, 1997; Roudier et al., 1998; Koff et al., 1999; Ogrocki et al., 2000; Bucks and Radford, 2004; Burnham and Hogervorst, 2004; Guaita et al., 2009). The current study included only individuals with intact visuo-perceptual abilities as assessed by BFRT to eliminate a possible confounding effect and the language abilities were similar between groups. Therefore, it is possible that the lack of difference in categorization of emotional facial expressions between groups was due to intact visuo-perceptual and language abilities in participants with AD.

The present study also indicates that individuals with AD tend to categorize neutral faces as negative emotional face expressions (i.e., angry, sad or fear) and rate angry faces as more

unpleasant compared to healthy elderly controls. One possible explanation may be an overgeneralization of negative emotions in AD, which was previously shown in various disorders that affect emotional processing [i.e., depression (Leppänen et al., 2004), anxiety (Lundh and Öst, 1996; Yoon and Zinbarg, 2008), schizophrenia (Holt et al., 2006), and autism spectrum disorder (Mathersul et al., 2013; Eack et al., 2015)]. Another explanation may be an amplification of negative emotional expressions in AD. In line with this, Smith (1995) showed increased responsiveness to negative stimuli in AD, suggesting difficulties with suppression.

On the other hand, the misinterpretation of neutral expressions as more negative may have also been caused by an underrepresentation of positive emotions in the current study (Eack et al., 2015). That is, there were more negatively valenced faces (i.e., sad, fear, angry) compared to positive ones (i.e., happy). Normative data for the Ekman and Friesen (1976) Pictures of Facial Affect showed that neutral facial expressions were perceived as more ambiguous than other expressions (Yoon and Zinbarg, 2008), indicating that neutral faces were the most difficult to categorize. Previous studies revealed that individuals with MCI performed poorly compared to healthy controls in response to subtle emotional expressions (Spoletini et al., 2008; Bediou et al., 2009). This is consistent with research by Torres et al. (2015), who reported a progressive impairment of the ability to comprehend complex emotional situations in individuals with mild AD. Taken together, neutral expressions being more ambiguous and negative valenced faces being more frequent in this study, may have facilitated a negative response bias in individuals with AD.

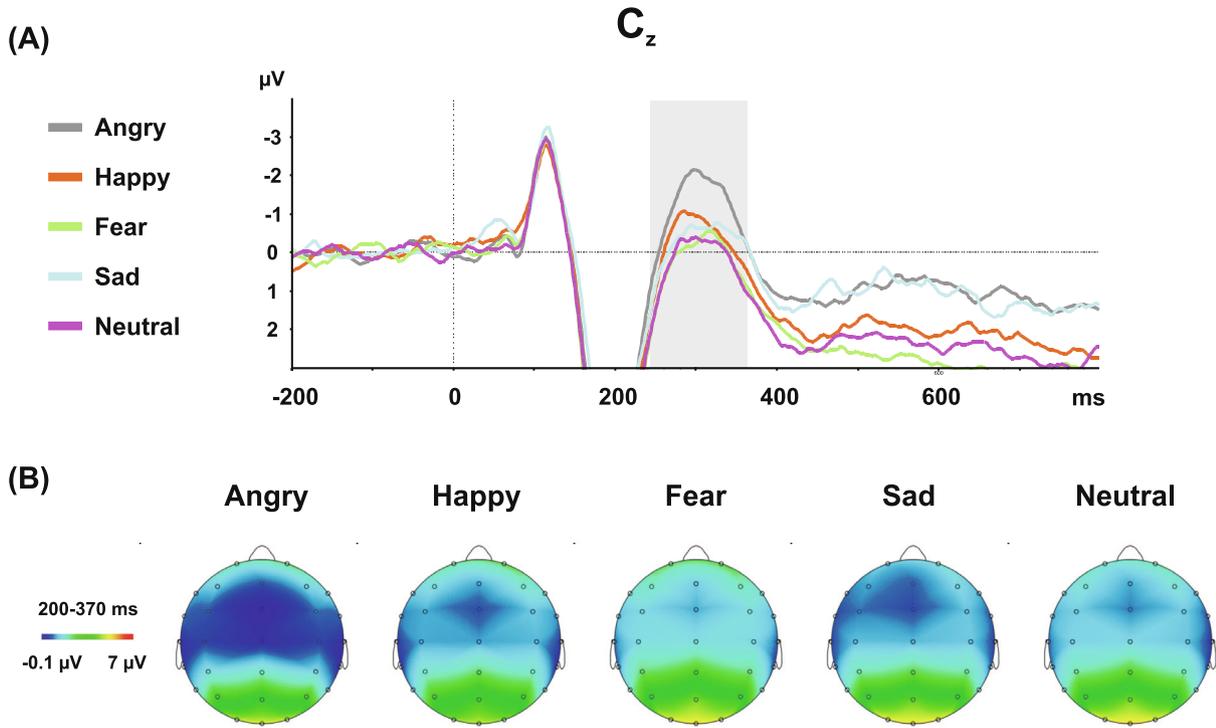


Fig. 5. (A) Grand averaged ERP waveforms demonstrating the condition differences on N230 component. (B) Topographical maps of N230 time window across study conditions.

Table 2
The ANOVA summary table.

	Amplitude (µV)				Latency (ms)			
	P100	N170	VPP	N230	P100	N170	VPP	N230
GROUP	.	.	***	.				.
CONDITION								
LOCATION	N/A	***			N/A	***	.	
HEMISPHERE/LATERALITY						**		
GROUP × CONDITION								
GROUP × LOCATION	N/A				N/A			
GROUP × HEMISPHERE/LATERALITY			N/A				N/A	
CONDITION × LOCATION	N/A		***		N/A			
CONDITION × HEMISPHERE/LATERALITY			N/A					N/A
LOCATION × HEMISPHERE/LATERALITY	N/A		N/A	.	N/A	**		N/A
GROUP × CONDITION × LOCATION	N/A				N/A			
CONDITION × LOCATION × HEMISPHERE/LATERALITY	N/A		N/A	.	N/A			N/A
GROUP × CONDITION × LOCATION × HEMISPHERE/LATERALITY	N/A		N/A		N/A			N/A

Hemisphere/laterality are combined to simplify the table since a given design could contain either hemisphere or laterality as a variable. N/A means that this particular effect was not part of the design for this component. N/S results were left blank in the table.

. $p < .05$.
 ** $p < .01$.
 *** $p < .001$.

Nonetheless, misinterpretation of facial expressions of emotion may be an aspect of behavioral symptoms and/or poor social judgement in AD, which could result in increased caregiver burden and decreased quality of life (Hargrave et al., 2002; McLellan et al., 2008; Torres et al., 2015). Hence, behavioral interventions aimed to improve social-cognitive deficits in individuals with AD may need to address this negative response bias.

4.2. P100

Based on previous literature, we hypothesized that individuals with AD would have increased P100 amplitudes in response to

facial expressions compared with healthy controls and our results sustained the hypothesis. Saavedra et al. (2012a) reported increased P100 amplitude and enhanced prefrontal activation in the P100 latency window elicited by facial stimuli in elderly adults with cognitive impairment compared to controls. The authors suggested that increased P100 amplitudes could be due to deficits in early perceptual processing and enhanced prefrontal activation in the P100 latency could be related to compensatory processes, underlying the intact behavioral task performances in MCI/AD (Saavedra et al., 2012a).

P100 has been associated with early global processing of facial stimuli (Batty and Taylor, 2003) and with the initial discrimination

of emotions at the level of extrastriate visual cortices (Di Russo et al., 2002; Woldorff et al., 2002; Müller-Bardorff et al., 2018). The amygdala is thought to act as a rapid relevance detector in response to emotionally significant stimuli (Phelps and LeDoux, 2005; Müller-Bardorff et al., 2018), and modulate emotional face processing in extrastriate visual cortices (Rotshtein et al., 2001, 2010; Vuilleumier et al., 2004; Noesselt et al., 2005; Pessoa and Adolphs, 2010). In this vein, Müller-Bardorff et al. (2018) showed that blood oxygenation level dependent (BOLD) responses of amygdala and lateral posterior occipital cortex were associated with P100 amplitude and were involved in the early differential responses to emotional versus neutral facial expressions.

Structural MRI studies have demonstrated prominent volumetric reductions in amygdala in individuals with AD (Keane et al., 2002; Rosen et al., 2002, 2006; Basso et al., 2006; Horinek et al., 2006, 2007). Moreover, AD pathology (i.e., amyloid plaques and neurofibrillary tangles) has been consistently shown in both cortical and subcortical regions associated with visual processing (Braak and Braak, 1991; Tzekov and Mullan, 2014; Albers et al., 2015; Kusne et al., 2017; Kaufman et al., 2018; Braak and Tredici, 2018). Therefore, we speculate that the amygdala atrophy and disruptions in the visual system may underlie increased P100 amplitude and latency in individuals with AD.

4.3. N170 and VPP

Our findings supported the hypothesis, indicating significantly decreased N170 and increased VPP amplitudes in individuals with AD compared to healthy controls. The present results corroborate the findings of Saavedra et al.'s (2012b) study, which involved a longitudinal design and compared a small sample of participants at baseline (16 young adults, 15 elderly adults and 12 individuals with MCI/AD), 8-months follow-up (11 elderly adults, 8 individuals with MCI/AD) and 2-years follow-up (8 elderly adults, 4 individuals with MCI/AD), using a familiarity task. The authors reported decreased N170 and enhanced VPP amplitudes in individuals with MCI/AD compared to young adults at baseline and compared to elderly adults at follow-up evaluations (Saavedra et al., 2012b).

An explanation for the increased VPP amplitude could be a potential compensatory mechanism involving a greater recruitment of prefrontal regions for task performance in AD. In line with this, previous neuroimaging studies showed increased prefrontal activity and/or connectivity in AD either in task conditions or in the resting-state compared to elderly controls (Horwitz et al., 1995; Grady et al., 2001, 2003; Pariente et al., 2005; Wang et al., 2007). A positron emission tomography (PET) study by Horwitz et al. (1995) reported that the distributed cortical network involved in face processing were not functioning in individuals with AD. During a face matching task, the AD group showed a greater use of frontal regions compared to healthy elderly controls, while the two groups did not differ significantly in their task performance (Horwitz et al., 1995). The increased activity and/or functional connectivity associated with the prefrontal regions have been interpreted as a possible compensatory mechanism, allowing individuals to maintain task performance despite brain pathology by recruiting more cognitive resources.

A possible explanation for the discrepancy between N170 and VPP amplitudes is a disconnection between the face processing related posterior regions and the prefrontal areas in AD (Marinkovic et al., 2000). Several studies suggest that AD may be regarded as a disconnection syndrome (Supekar et al., 2008; Canuet et al., 2012; Reis and Evans, 2013; Nimmrich et al., 2015; Ishii et al., 2017; Horvath et al., 2018), based on the findings of default mode network (DMN) changes (Buckner et al., 2008; Mevel et al., 2011) and the anterior-posterior disconnection phenomenon (Marinkovic et al., 2000; Wang et al., 2007; Buckner

et al., 2008; Yener et al., 2009; Başar et al., 2010; Yener and Başar, 2010). Moreover, previous neuroimaging studies showed structural and/or functional changes in areas related to facial expression recognition such as STS (Gómez-Isla et al., 1997) and middle FFA (Bokde et al., 2010) in individuals with AD. As mentioned in the Introduction, while N170 was found to be only related to bottom-up perceptual processing of faces, VPP was associated with the integration of top-down processing from the prefrontal cortex and the bottom-up processing from the occipital cortex (Lu et al., 2017). The decreased N170 and increased VPP amplitudes in AD may reflect impaired perceptual processing, mitigated by a greater involvement of prefrontal areas during task performance. These findings suggest that examining N170 and VPP together could indicate AD related neurophysiological changes better.

The current study also showed that happy, angry and fearful expressions elicited increased VPP amplitudes compared to the sad and neutral faces in the whole study sample. In earlier studies, Tottenham et al. (2009) and Luo et al. (2010) reported that VPP was modulated by emotional face stimuli in healthy participants; to our knowledge, this is the first study to show this effect in the healthy elderly and individuals with AD.

4.4. N230

Based on previous literature (Balconi and Pozzoli, 2003; 2008), we hypothesized that neutral expressions would elicit lower N230 amplitudes compared to emotional facial expressions. Our results are parallel with previous studies, which reported increased amplitude and latency of N230 to angry faces in comparison with neutral faces. The categorization of happy expressions was associated with N230 amplitudes in the whole sample, which was driven by healthy controls.

4.5. Limitations and future directions

As the current study only included face stimuli, and not examined ERPs to non-face stimuli or non-emotion recognition tasks, we cannot conclude whether the ERP changes observed in AD are specific to face processing. Future studies involving both face and non-face social/emotional stimuli are required to differentiate the alterations in emotion recognition and face processing in individuals with AD.

The current study used face stimuli from the Pictures of Facial Affect (Ekman and Friesen, 1976), which are not identical in emotion intensity. Previous studies reported that the intensity of facial expressions may affect the task performance of individuals with MCI or AD (Spoletini et al., 2008; Bediou et al., 2009; Elferink et al., 2015). Individuals with MCI performed poorly compared to healthy controls when subtle emotional expressions (i.e., low-intensity faces) were presented (Spoletini et al., 2008; Bediou et al., 2009). The available research is limited and is not on AD; however, we cannot exclude a possible confounding effect of emotion intensity on task performances. Further studies using both low- and high-intensity faces are needed. Moreover, the present study only included stationary pictures, which may not reflect the difficulties experienced in real-life social interactions by individuals with AD. Future studies comparing stationary and dynamic expressions could provide more insight into the different aspects of emotion recognition deficits and their clinical implications in AD.

Among the six basic facial expressions, we did not include disgust and surprise as stimuli. Previous studies reported contradictory results on the recognition of disgust (Hargrave et al., 2002; Burnham and Hogervorst, 2004; Henry et al., 2008) and impaired recognition of surprise in individuals with AD (Hargrave et al., 2002; Henry et al., 2008). The underrepresentation of positive

emotions in the current study may have caused a negative response bias in individuals with AD; hence, future studies including all six basic facial expressions are needed.

Lastly, in the present study, all participants received blocks of emotional face stimuli, which were presented in a fixed order. Amplitude and latency values of ERPs did not differ between the first and last session, and previous studies indicated that the N170 and N2 components are resistant to habituation (Olofsson et al., 2008). Yet, future research should use a randomized design.

5. Conclusion

To our knowledge, this is the first study examining the amplitude and latency modulations of P100, N170, VPP and N230 by passive viewing of emotional facial expressions in individuals with AD compared to healthy elderly controls. Our results indicate altered early electrophysiological responses in AD, possibly due to amygdala atrophy, visual system dysfunction and the so called anterior-posterior disconnection phenomenon. Individuals with AD performed similarly to healthy controls on categorization of emotional facial expressions; however, they labeled neutral expressions as more negative and rated angry expressions as more unpleasant, suggesting a possible overgeneralization of negative emotions. The clinical implications and significance of these results are yet to be established; but we believe these findings may inform future research to clarify the behavioral and neural underpinnings of emotional facial processing in AD.

Declaration of Competing Interest

None of the authors has potential conflicts of interest to be disclosed.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clinph.2019.06.229>.

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