Pre-attentive processing of Alzheimer's disease: an event-related potential study

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Research

Keywords: Alzheimer's disease, pre-attentive processing, visual processing, vMMN, P3a, P3b

Posted Date: December 16th, 2019

DOI: https://doi.org/10.21203/rs.2.19010/v1

Abstract

Background: While identifying Alzheimer's Disease (AD) in its early stages is crucial, traditional neuropsychological tests tend to lack sensitivity and specificity for its diagnosis. Based on the early visual attention deficits of adults with AD, which are apparent before cognitive deficits emerge, this study aimed to investigate visual attentional characteristics of adults with AD, from pre-attentive to attentive processing, using a visual oddball task and event-related potentials (ERPs).

Methods: Cognitively normal elderly controls (NC, *n*=27) and patients with probable AD (AD, *n*=10) were recruited. Participants performed a three-stimulus visual oddball task and were asked to press a designated button in response to the target stimuli. The amplitudes of 4 ERPs were analyzed. Visual mismatch-negativity (vMMN) was analyzed around the parieto-occipital and temporo-occipital regions. P3a was analyzed around the fronto-central regions, whereas P3b was analyzed around the centro-parietal regions.

Results: Late vMMN amplitudes of the AD group were significantly smaller than those of the NC group, while early vMMN amplitudes were comparable. Compared to the NC group, P3a amplitudes of the AD group were significantly smaller for the infrequent deviant stimuli but the amplitudes for the standard stimuli were comparable. Lastly, the AD group had significantly smaller P3b amplitudes than the NC group.

Conclusion: Our findings imply that AD patients exhibit pre-attentive visual processing deficits, known to affect later higher-order brain functions. In a clinical setting, the visual oddball paradigm could be used to provide helpful diagnostic information since pre-attentive ERPs can be induced by passive exposure to infrequent stimuli.

Background

Cognitive impairment is an essential diagnostic feature of dementia or mild cognitive impairment due to Alzheimer's disease (AD) (1). However, a growing number of studies have suggested that deficits in bottom-up sensory processing due to AD may precede and influence the later deficits in top-down cognitive functions in AD (2–8). Supporting this hypothesis, previous studies reported that AD patients showed reduced perfusion in the regions involved in visual processing and maintaining and shifting attention (9, 10), and they had deficits in visual processing (2, 8, 11–13), visual attention (3–7, 14, 15), and activation of the attention network (16) before they began to show cognitive deficits. These results implied that adults with AD may have deficits in attention, including pre-attentive processing, in its early stage (17).

Vision is pre-attentively processed, without conscious action, before selective attention occurs (18, 19). Pre-attentive processing aids the visual system in detecting changes quickly and effectively in the absence of attention (20, 21). Three event-related potential (ERPs) components reflect different stages of visual information processing: mismatch-negativity (MMN), P3a, and P3b (22–24). MMN is a negative

deflection within the parieto-occipital and parieto-temporal areas peaking at around 150–200 ms after presentation of an infrequent deviant stimuli within a sequence of frequent standard stimuli (25). Recently, an integrative approach using an equiprobable sequence proposed two sub-components of MMN. An early MMN occurs at around 100 to 250 ms after stimuli presenting in the parieto-occipital areas (25–27) and a late MMN occurs at around 250 to 400 ms after stimuli presentation in temporo-occipital areas (28). The early MMN reflects lower refractoriness with a greater activation level in response to the deviant stimuli compared to the standard stimuli, while late MMN reflects the neural activity of memory-comparison-based deviance detection (28). P3a is a positive deflection observed in fronto-central areas peaking at around 250 to 300 ms after the presentation of infrequent deviant stimuli (29). In contrast, P3b is a positive deflection observed in parietal areas peaking at around 300 to 700 ms after the presentation of task-relevant stimuli. P3a is known to reflect automatic reorienting or attention shifting (30–32) whereas P3b is known to reflect allotment of attentional resources and working memory (24, 33, 34). In addition, simply being exposed to deviant auditory stimuli without paying deliberate attention has evoked MMN and P3a successfully in younger adults (35, 36).

Since ERPs do not require active behavioral response (35, 36) and deficits in pre-attentive processing precede cognitive deficits in AD, ERP components may provide earlier and more sensitive diagnostic information for AD. Supporting this hypothesis, AD patients exhibited abnormally late MMNs to visual stimuli (17, 37). Most previous studies on P3 characteristics in patients with AD used auditory stimuli of P3b only and reported conflicting results (38–41). However, the limited number of studies on visual processing in adults with AD have reported reduced P3b amplitudes (24) and delta power reduction, which is known as one of the major components of P3 (42, 43).

This study aimed to compare visual processing of AD patients and cognitively normal controls by measuring ERPs while they were performing active visual oddball tasks. We employed the active visual oddball tasks to measure both the pre-attentive (vMMN and P3a) and attentive (P3b) visual processes.

Methods

Participants

The aim of this study was to compare visual processing of AD patients and cognitively normal controls by measuring ERPs while they were performing active visual oddball tasks. We enrolled 27 community-dwelling elderly individuals with normal cognition (NC) who were volunteers from the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD) (44). We compared our NC participants to 10 patients with probable AD (AD) according to the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association diagnostic criteria (45) who were visitors to the Dementia Clinic of the Seoul National University Bundang Hospital (SNUBH). The KLOSCAD is a nationwide, population-based, prospective, elderly cohort study on cognitive aging and dementia. In the KLOSCAD, a total of 6,818 community-dwelling Koreans aged 60 years or older were randomly sampled from 30 villages and towns across South Korea using residential

rosters. All participants were fully informed with the protocol of this study and provided written informed consent signed by themselves or their legal guardians. This study was approved by the Institutional Review Board of the SNUBH. (IRB, No. B-1312/231-002).

Experimental design

We administered 2 sessions of visual oddball detection tasks to each participant (Figure 1). Each session consisted of 240 trials. In each session, we instructed participants to look at the fixation point presented at the center of the screen and to press a response button as quickly as possible when a target stimulus appeared on the screen. We displayed three types of stimuli: standard (a cross-shaped array of white squares, 83.3% occurrence rate), target (a white square, 8.3% occurrence rate), and deviant (a X-shaped array of white squares, 8.3% occurrence rate). We displayed each stimulus on the screen for 200 ms followed by a 2.5 ± 0.5 second inter-stimulus interval (ISI). Between sessions, we checked-in with participants to assess their fatigue and encouraged participants if necessary.

See Figure 1.

Electroencephalography (EEG) recording

EEG signals were sampled at 1000 Hz on 64 channels using a 64-channel quick-cap with a Neuroscan SynAmp2 amplifier (Compumedics, Victoria, Australia). The recorded signals were then referenced to the mean value of M1 and M2 using MATLAB-based EEGLAB (46) to remove baseline activity. Filtering was performed using a band-pass filter of 0.1-30 Hz and artifacts and noise were removed by independent component analysis (ICA). Using ERPLAB (47), the timepoints 200 ms prior to stimulus presentation and 800 ms after stimuli presentation were used to generate a bin and epoch for each stimulus. Epochs with extreme values were rejected (lower limit: -70 μ , upper limit: 70 μ). The remaining epochs were used to calculate ERP components for each subject.

ERP analysis

Preprocessed EEG data from multiple electrodes were averaged based on pre-defined regions of interest. By averaging electrodes that exhibit consistent and comparable responses, it was possible to obtain more reliable results than using single electrodes separately. The mean amplitude was obtained by calculating the average value of the peak between 200 ms before the stimulus onset to 800 ms after the stimulus. Early vMMN was analyzed around the parieto-occipital regions (electrodes PO3, PO4, PO5, PO6, PO7, and PO8) and was defined as a mean difference between standard and deviant stimuli with the time range of 130 to 250 ms after the stimuli presentation. Late vMMN was analyzed around temporo-occipital regions (electrodes T5 and T6) and was defined as a mean difference between standard and deviant stimuli with the time range of 250 to 400 ms after the stimuli. P3a was analyzed around the fronto-central area (electrodes FC1, FC2, FC3, FC4, and FCz) and was defined as the mean amplitude around 350 to 550 ms after stimuli presentation in standard and deviant conditions. Lastly, P3b was analyzed around the centro-parietal region (electrodes CP1, CP2, CP3, CP4, CP5, CP6, and CPz) and parietal area (electrode P1,

P2, P3, P4, P5, P6, and Pz), and was defined as the mean amplitude around 350 to 550 ms after the stimuli in standard and target conditions.

Statistical analysis

We compared demographic information between groups using Student t tests (age) and chi square tests (sex).

We compared the response time to the target condition between participant groups using a Student t-test. We analyzed the accuracy of the visual oddball detection task using a repeated measures analysis of variance (rmANOVA) that computed the type of stimuli (standard, deviant, or target) as a within-subject factor and the diagnosis of the participants (NC or AD) as a between-subject factor.

We compared the amplitudes of early and late vMMN between participant groups using a one-way ANOVA. We compared the P3a amplitude between participant groups using an rmANOVA that computed the type of stimuli (standard or deviant) as a within-subject factor and the diagnostic group (NC or AD) as a between-subject factor. We compared the P3b amplitude using an rmANOVA that computed the type of stimuli (standard or target) and the position of electrodes (centro-parietal or parietal) as within-subject factors and the diagnostic group (NC or AD) as a between-subject factor. We used Greenhouse-Geisser corrections when sphericity was violated and reported corrected *p*-values. We considered a *p*-value <.05 as statistically significant.

Results

The AD group was less educated than the NC group (t_{35} = 3.76, p = 0.001) but comparable to the NC group in age and sex (Table 1).

As summarized in Table 2, the AD group performed the visual oddball detection tasks more slowly than did the NC group (t_{35} = -2.14, p = 0.392). In the rmANOVA, the main effects of diagnostic group ($F_{1,35}$ = 102.52, p < 0.001), type of stimuli ($F_{2,70}$ = 38.68, p < 0.001), and their interaction ($F_{2,70}$ = 35.34, p < 0.001) were significant for the accuracy of visual oddball detection tasks. Overall, the AD group performed the visual oddball detection tasks less accurately than did the NC group. The AD group performed the standard stimuli more accurately than the deviant stimuli (p < 0.001) and target stimuli (p < 0.001) while the NC group performed the deviant stimuli and the target stimuli as accurately as the standard stimuli.

Figure 2 displays the overall mean amplitude of ERPs elicited at parieto-occipital (mean of PO3, PO4, PO5, PO6, PO7, and PO8), temporo-occipital (mean of T5 and T6), fronto-central (FCz), centro-parietal (CPz) and parietal (Pz) areas from both participant groups. The amplitude of early vMMN was comparable between the AD and NC groups ($F_{1,35}$ = 1.91, p = 0.176), while that of late vMMN was smaller in the AD group compared to the NC group ($F_{1,35}$ = 5.51, p = 0.025). The amplitudes of early and late vMMN are displayed in Figure 3.

See Figures 2 and 3.

The main effects of the participant group ($F_{1,35}$ = 4.7, p = 0.037), the type of stimuli ($F_{1,35}$ = 6.49, p = 0.015), and their interaction ($F_{1,35}$ = 5.05, p = 0.031) on P3a amplitude were significant. Post-hoc analyses revealed that, compared to the NC group, the AD group had smaller amplitudes of P3a in response to deviant stimuli ($F_{1,35}$ = 6.5, p = 0.015) but comparable amplitudes of P3a in response to standard stimuli ($F_{1,35}$ = 1.57, p = 0.219).

The main effects of the participant group ($F_{1,35}$ = 7.65, p = 0.009), the type of stimuli ($F_{1,35}$ = 25.61, p < 0.001), and the interaction between the type of stimuli and the electrode site ($F_{1,35}$ = 24.12, p < 0.001) on P3b amplitude were significant. However, the main effect of the electrode site ($F_{1,35}$ = 0.48, p = 0.44), the interaction of the participant group with the type of stimuli ($F_{1,35}$ = 1.93, p = 0.174), and the electrode sites ($F_{1,35}$ = 0.18, p = 0.639) were not significant. Both AD and NC groups exhibited larger P3b amplitudes in response to target stimuli compared to the standard stimuli, with the AD group showing smaller P3b amplitudes than those of the NC group. Post-hoc analysis revealed that P3b amplitudes were largest in the centro-parietal region in response to standard stimuli, while they were largest in the parietal region in response to target stimuli. The amplitudes of the ERP components from both groups are summarized in Table 3.

Discussion

Pre-attentive sensory processing analyzed by MMN and P3a brain responses was associated with cognitive and psychosocial functioning in healthy adults (48). The early vMMN is known to reflect a refractory effect, with a decrease in refractoriness observed from neurons in response to deviant stimuli. In contrast, the late vMMN is suggested to reflect a memory-based deviance detection process (28). This study found that AD patients exhibited smaller amplitudes of the late vMMN and P3a in response to deviant visual stimuli than did cognitively normal controls. However, the early vMMN was comparable between the AD patients and the cognitively normal controls.

A study on vMMN amplitude of adults with AD reported no significant difference in the early vMMN amplitudes during an epoch from 147–213 ms post stimuli (49). This finding is consistent with our results of intact early vMMN amplitudes during a similar epoch of 130–250 ms post stimuli. In contrast, Tales et al., (37) found that AD patients showed larger late vMMN amplitudes (epoched from 250 to 400 ms) compared with the control group, suggesting inefficient hyper-activation in response to deviant stimuli in AD patients. In their later study, AD patients receiving acetylcholinesterase inhibitor therapy exhibited significantly larger vMMN amplitudes in the early stage (epoched from 140 to 250 ms) but not in the late stage (epoched from 250 to 400 ms). This type of therapy is known to affect visual attention-related functions (50) and MMN (51). These results are not consistent with our results of reduced late vMMN amplitudes (from 250 to 400 ms post stimuli), which may be due to an inter-stimulus effect. Tales et al. applied a short inter-stimulus interval (ISI) of less than 1 second, whereas the ISI of our study was

between 2 and 2.5 seconds. ISI is known to affect ERP amplitudes with larger negative ERP amplitudes at longer ISIs in normal controls (52). However, a study on auditory MMN and AD reported decreased MMN amplitudes at longer ISIs compared with the control group, implying the memory trace decays faster in the AD patients (53).The authors suggested that a longer ISI forces participants to maintain the memory trace longer to recognize deviant stimuli from standard stimuli. Taking these results together, the application of long ISI may be more sensitive for detecting the memory-based deviance detection process of adults with AD.

Previous research reported that a smaller vMMN amplitude was associated with lower cognitive function in both healthy elderly individuals (48) and AD patients (17, 37, 49, 54). According to the hierarchical prediction coding framework, the vMMN reflects prediction error signals to deviant stimuli at lower levels of information processing, which assists the central nervous system in updating an internal model of probability for detecting deviant stimuli (28, 55). Reduced vMMN amplitudes in other clinical studies have been interpreted as deficits in pre-attentive prediction error and deviance processing (56). Previous studies on AD and visual processing using cognitive tasks and functional magnetic resonance imaging (fMRI) analysis reported visual processing deficits in adults with AD which were associated with the integrity of the temporo-occipital cortex (8, 12). These results imply that AD patients may have deficits in detecting and processing deviant stimuli while maintaining their refractory neural responses to repetitive stimuli.

In our study, the AD group exhibited significantly reduced P3a amplitudes in response to deviant stimuli compared to NC. Most previous studies analyzing P3a in adults with AD have used an auditory modality (57–61). In these studies on auditory P3a of adults with AD, some reported an extended latency (60) or reduced amplitude (59), while others reported no difference at all (61). For example, Cecchi and colleagues (59) used an auditory oddball paradigm with white noise as deviant stimuli and observed reduced P3a amplitudes from adults with AD. In contrast, Yamaguchi and colleagues (61) used 60 unique sounds as deviant stimuli and observed no difference in P3a amplitude between the adults with AD and healthy controls. When evoking a P3a that reflects an attentional switch, using more task-relevant stimuli as deviant stimuli is encouraged as using unique random noises only distracts participants and may interact with other ongoing neural processes (62, 63). Therefore, the task design of Cecchi and colleagues (59), using white noise as deviant stimuli, would be more sensitive to P3a activity. Based on these results, we designed the deviant stimuli in our study to be different from both standard and target stimuli, but not unique to each deviant stimulus, thus providing coherent task-relevant cues instead of random distractions. The P3a is known to reflect pre-attentive processing of novel information and has been reported to be related to cognitive functioning (48, 64). Our results are consistent with deficits in attention and executive function tasks of adults with AD in neuropsychological tests (64) and imply that AD patients have deficits in pre-attentive visual processing.

The AD group exhibited overall reduced P3b amplitudes with no overall significant P3b effect. These results were consistent with previous studies (24, 38, 65). For examples, in a study using a geometric figure discrimination task, AD patients exhibited reduced P3b amplitude (24). P3b is known to reflect the

allotment of working memory resources, and these results imply that the AD group have deficits in allotting attentional resources for information processing (24, 33, 34). Reduced P3b amplitude has been reported for various neurological and psychological diseases and is not disease-specific; hence, it is difficult to use P3b alone as a marker for AD (66–70). However, ERP components of pre-attentive processing along with P3b would help provide more extensive information on the visual processing deficits of adults with AD. It should be taken into consideration that P3b reflects late information processing and that an earlier N2 component may affect late P3b amplitudes (71). Therefore, it is possible that the early pre-attentive processing deficits observed in the late vMMN and P3a may have affected the reduced P3b amplitudes. Further study is needed to isolate late visual information processing specifically.

This study has several limitations. First, the number of AD patients that participated in the study was small. Securing a large enough cohort of comparable participants is important to properly compare ERP components (72). However, AD patients did not exhibit larger amplitudes in any component compared to healthy controls, a result that is usually predicted when there are a small number of participants (72). Second, medication regimens and treatment effects of AD patients were not controlled. In the study by Tales and colleagues (17), it was suggested that acetylcholinesterase inhibitor medication may affect vMMN amplitudes. In our study, patients' individual medications were not controlled; therefore, it was impossible to control the effect of acetylcholinesterase inhibitor on ERP components.

Conclusions

In conclusion, the AD group exhibited significantly reduced amplitudes of the late vMMN, P3a, and P3b amplitudes, while exhibiting early vMMN amplitudes comparable to those of healthy controls. These results imply that AD patients have deficits in pre-attentive deviant stimuli detection and processing while maintaining their refractory neural responses to repetitive stimuli and that these deficits may affect later cognitive functions.

Declarations

Ethical approval and consent to participate

This study involving human participants was reviewed and approved by the Institutional Review Board of the SNUBH (IRB, No. B-1312/231-002). All participants provided written informed consent to participate in this study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by a grant from the SNUBH Research Fund (grant number 03-2013-009) and by a grant from the Korean Health Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (grant number HI09C1379(A092077)).

Author Contribution

EN, KL, JH, and KK designed the study. KL, JB, SS, and SB acquired the data. EN, KL, and EK analyzed the data and wrote the article with KK. The article was reviewed by KL, JH, and KK. All authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

Acknowledgements

Not applicable.

Abbreviations

AD: Alzheimer’s disease; ANOVA: Analysis of variance; ERP: Event-related potential; fMRI: Functional magnetic resonance imaging; ISI: Inter-stimulus interval; KLOSCAD: Korean Longitudinal Study on Cognitive Aging and Dementia; MMN: Mismatch negativity; rmANOVA: Repeated measures analysis of variance; SNUBH: Seoul National University Bundang Hospital; vMMN: Visual mismatch negativity.

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Tables

Table 1. Demographic characteristics of the participants.

	NC	AD	*Statistics*	
	(n=27)	(n=10)	t *or* X^2	p
Sex (female, %)	48.1	70	1.40	.2362
Age (years)	70.81 (4.39)	73.5 (7.15)	-1.11	.2887
Education (years)	13.93 (3.00)	9.30 (4.11)	3.76	.0006

Group means are listed with standard deviation

Table 2. Behavioral performance of the visual oddball detection task in the NC and AD groups.

	NC (n=27)	AD (n=10)
	Mean	Mean
Standard Stimuli Accuracy (%)	99.91 (0.16)	94.78 (6.64)
Deviant Stimuli Accuracy (%)	97.66 (4.78)	42.80 (39.76)
Target Stimuli Accuracy (%)	66.72 (0.86)	41.74 (31.68)
Total Response Time (ms)	490.71 (117.82)	588.02 (135.92)

Group means are listed with standard deviation

Table 3. Mean amplitudes of the early vMMN, late vMMN, P3a, and P3b induced during the visual oddball detection task for the NC and AD groups.

	NC (n=27)	AD (n=10)	*Statistics* t or F	p
vMMN				
Early vMMN	-0.93 (2.09)	-2.55 (5.15)	1.38	0.18
Late vMMN	-0.69 (1.15)	0.47 (1.80)	-2.35	0.02
P3a				
Standard	4.06 (2.72)	2.86 (2.17)	1.57	0.22
Deviant	6.32 (3.94)	3.00 (1.77)	6.50	0.02
P3b				
Standard (CPz)	3.24 (2.61)	1.65 (2.83)	2.20	0.15
Standard (Pz)	2.50 (2.62)	1.08 (3.49)		
Target (CPz)	7.43 (3.56)	4.06 (4.38)	7.14	0.01
Target (Pz)	8.06 (3.44)	4.22 (4.05)		

Group means are listed with standard deviation

Figures

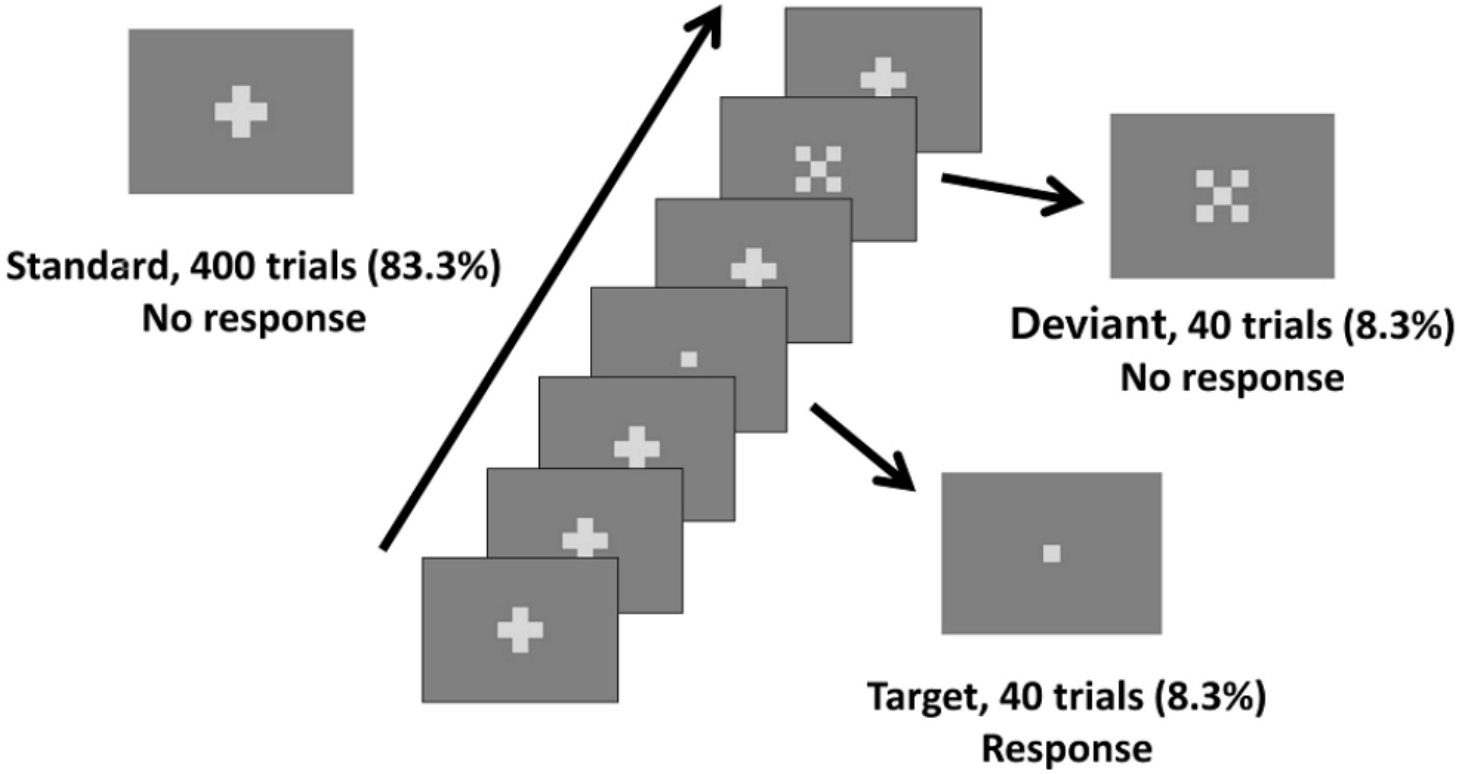

Figure 1

The visual oddball detection task. Three types of stimulus were displayed on screen: standard (83.3% occurrence rate), target (8.3% occurrence rate) and deviant (8.3% occurrence rate). Participants were requested to press a button in response to the target stimuli. Stimulus would be displayed for 200 ms with an interstimulus interval of 2.5±0.5 s.

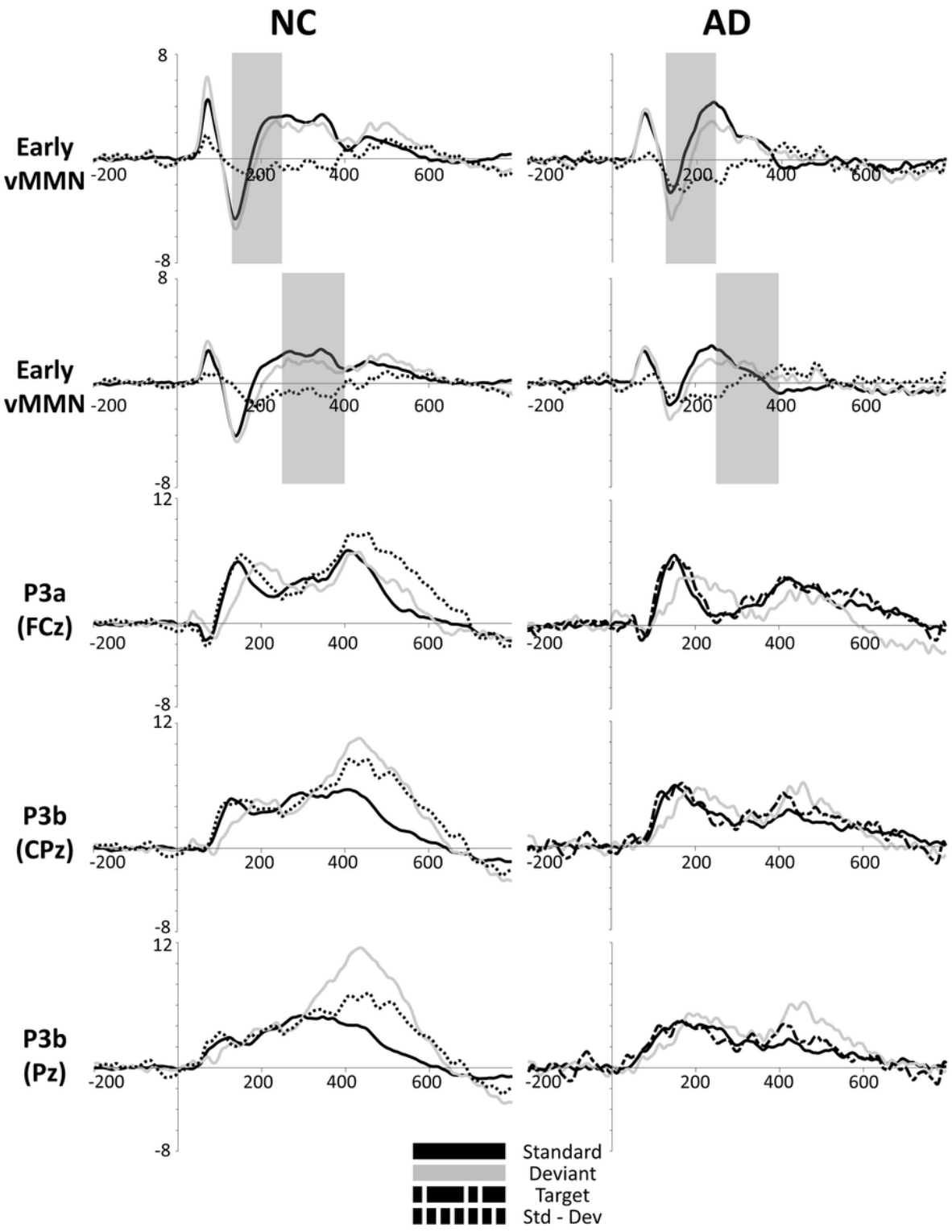

Figure 2

Overall mean ERP. The overall mean amplitudes (μV) of early vMMN (1st row, mean of PO3, PO4, PO5, PO6, PO7, and PO8 electrodes), late vMMN (2nd row, mean of T5 and T6 electrodes), P3a (3rd row, FCz), P3b (4th–5th row, CPz and Pz electrodes) elicited by standard (black solid), deviant (grey solid), and target (black dash-dot) stimuli and the difference wave between standard and deviant condition (black dotted) for the NC (left) and AD (right) groups.

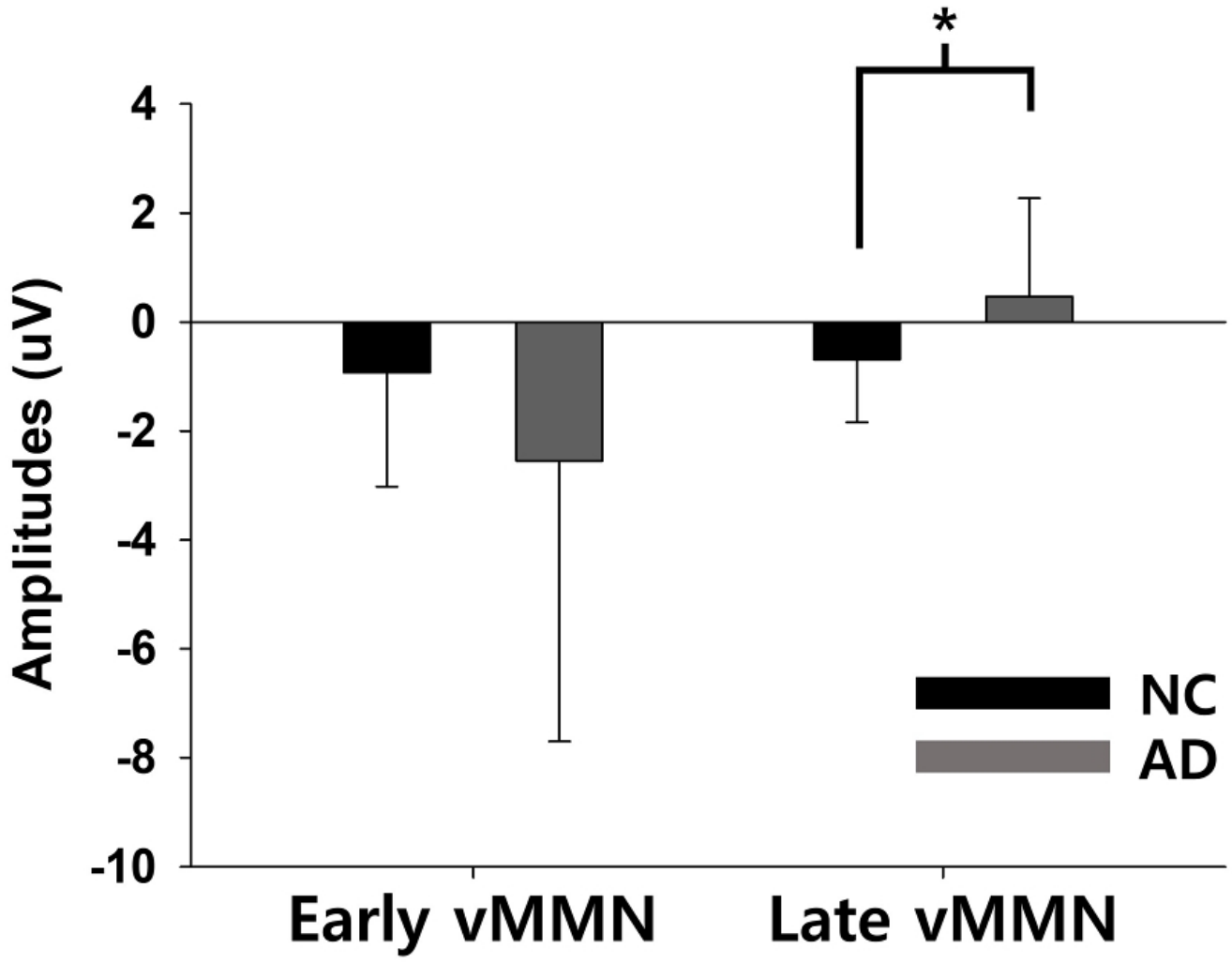

Figure 3

Bar graph of vMMN amplitudes (μV). Mean amplitudes of early vMMN (left) and late vMMN (right) for the NC (black) and AD (grey) groups.