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

CURRENT STATUS: UNDER REVIEW

Alzheimer's Research & Therapy  BMC

Eunchan Na
Korea Advanced Institute of Science and Technology

Kanghee Lee
Seoul National University Bundang Hospital

Eun Ji Kim
Seoul National University Bundang Hospital

Jong Bin Bae
Seoul National University Bundang Hospital

Seung Wan Suh
Seoul National University Bundang Hospital

Seonjeong Byun
Seoul National University Bundang Hospital

Ji Won Han
Seoul National University Bundang Hospital

Ki Woong Kim  kwkimmd@snu.ac.kr
Seoul National University Bundang Hospital; Seoul National University College of Natural Sciences; Seoul National University College of Medicine
Corresponding Author
ORCiD: 0000-0002-1103-3858

DOI: 10.21203/rs.2.19010/v1

SUBJECT AREAS  Cognitive Neuroscience
KEYWORDS

Alzheimer’s disease, pre-attentive processing, visual processing, vMMN, P3a, P3b
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 tempororo-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.

References

1. American Psychiatric Association., American Psychiatric Association. Task Force on DSM-IV. Diagnostic and statistical manual of mental disorders : DSM-5. 5th ed. Washington, DC: American Psychiatric Association; 2013.

2. Mosimann UP, Felblinger J, Ballinari P, Hess CW, Muri RM. Visual exploration behaviour during clock reading in Alzheimer's disease. Brain : a journal of neurology. 2004;127(Pt 2):431-8. Available from: https://doi.org/10.1093/brain/awh051

3. Perry RJ, Hodges JR. Attention and executive deficits in Alzheimer's disease: A critical review. Brain : a journal of neurology. 1999;122(3):383-404.

4. Tales A, Haworth J, Nelson S, Snowden RJ, Wilcock G. Abnormal visual search in mild cognitive impairment and Alzheimer's disease. Neurocase. 2005;11(1):80-4. Available from: https://doi.org/10.1080/13554790490896974

5. Tales A, Muir JL, Bayer A, Jones R, Snowden RJ. Phasic visual alertness in Alzheimer's disease and ageing. Neuroreport. 2002;13(18):2557-60. Available from: https://doi.org/10.1097/01.wnr.0000047985.70540.9d

6. Tales A, Muir JL, Bayer A, Snowden RJ. Spatial shifts in visual attention in normal ageing and dementia of the Alzheimer type. Neuropsychologia. 2002;40(12):2000-12. Available from: https://doi.org/10.1016/S0028-3932(02)00057-X
7. Tales A, Snowden RJ, Haworth J, Wilcock G. Abnormal spatial and non-spatial cueing effects in mild cognitive impairment and Alzheimer's disease. Neurocase. 2005;11(1):85-92. Available from: https://doi.org/10.1080/13554790490896983

8. van Rhijn SJ, Glosser G, de Vries JJ, Clark CM, Newberg AB, Alavi A. Visual processing impairments and decrements in regional brain activity in Alzheimer's disease. Journal of clinical and experimental neuropsychology. 2004;26(1):11-23. Available from: https://doi.org/10.1076/jcen.26.1.11.23931

9. Kumar A, Schapiro MB, Grady CL, Haxby JV, Wagner E, Salerno J, et al. High-resolution PET studies in Alzheimer's disease. Neuropsychopharmacology. 1991.

10. Waldemar G, Bruhn P, Kristensen M, Johnsen A, Paulson OB, Lassen NA. Heterogeneity of neocortical cerebral blood flow deficits in dementia of the Alzheimer type: a [99mTc]-d, l-HMPAO SPECT study. Journal of Neurology, Neurosurgery & Psychiatry. 1994;57(3):285-95.

11. Alescio-Lautier B, Michel BF, Herrera C, Elahmadi A, Chambon C, Touzet C, et al. Visual and visuospatial short-term memory in mild cognitive impairment and Alzheimer disease: role of attention. Neuropsychologia. 2007;45(8):1948-60. Available from: https://doi.org/10.1016/j.neuropsychologia.2006.04.033

12. Jefferson AL, Barakat LP, Giovannetti T, Paul RH, Glosser G. Object perception impairments predict instrumental activities of daily living dependence in Alzheimer's disease. Journal of clinical and experimental neuropsychology. 2006;28(6):884-97. Available from: https://doi.org/10.1080/13803390591001034

13. Rizzo M. Anderson SD, J. Myers, R. Ball, K. Visual attention impairments in
14. Chau SA, Herrmann N, Sherman C, Chung J, Eizenman M, Kiss A, et al. Visual Selective Attention Toward Novel Stimuli Predicts Cognitive Decline in Alzheimer's Disease Patients. J Alzheimers Dis. 2017;55(4):1339-49. Available from: https://doi.org/10.3233/jad-160641

15. Vasquez BP, Buck BH, Black SE, Leibovitch FS, Lobaugh NJ, Caldwell CB, et al. Visual attention deficits in Alzheimer's disease: relationship to HMPAO SPECT cortical hypoperfusion. Neuropsychologia. 2011;49(7):1741-50. Available from: https://doi.org/10.1016/j.neuropsychologia.2011.02.052

16. Finke K, Myers N, Bublak P, Sorg C. A biased competition account of attention and memory in Alzheimer's disease. Philos Trans R Soc Lond B Biol Sci. 2013;368(1628):20130062. Available from: https://doi.org/10.1098/rstb.2013.0062

17. Tales A, Haworth J, Wilcock G, Newton P, Butler S. Visual mismatch negativity highlights abnormal pre-attentive visual processing in mild cognitive impairment and Alzheimer's disease. Neuropsychologia. 2008;46(5):1224-32. Available from: https://doi.org/10.1016/j.neuropsychologia.2007.11.017

18. Treisman A. Preattentive processing in vision. Computer vision, graphics, and image processing. 1985;31(2):156-77.

19. Wolfe JM, Utochkin IS. What is a preattentive feature? Curr Opin Psychol. 2018;29:19-26. Available from: https://doi.org/10.1016/j.copsyc.2018.11.005

20. Kuldkepp N, Kreegipuu K, Raidvee A, Naatanen R, Allik J. Unattended and attended visual change detection of motion as indexed by event-related potentials and its behavioral correlates. Front Hum Neurosci. 2013;7:476.
21. Seri S, Pisani F, Thai JN, Cerquiglini A. Pre-attentive auditory sensory processing in autistic spectrum disorder. Are electromagnetic measurements telling us a coherent story? International journal of psychophysiology : official journal of the International Organization of Psychophysiology. 2007;63(2):159-63. Available from: https://doi.org/10.1016/j.ijpsycho.2006.03.013

22. Naatanen R, Todd J, Schall U. Mismatch negativity (MMN) as biomarker predicting psychosis in clinically at-risk individuals. Biological psychology. 2016;116:36-40. Available from: https://doi.org/10.1016/j.biopsycho.2015.10.010

23. Rinne T, Sarkka A, Degerman A, Schroger E, Alho K. Two separate mechanisms underlie auditory change detection and involuntary control of attention. Brain research. 2006;1077(1):135-43. Available from: https://doi.org/10.1016/j.brainres.2006.01.043

24. Saito H, Yamazaki H, Matsuoka H, Matsumoto K, Numachi Y, Yoshida S, et al. Visual event-related potential in mild dementia of the Alzheimer's type. Psychiatry and Clinical Neurosciences. 2001;55(4):365-71. Available from: https://doi.org/10.1046/j.1440-1819.2001.00876.x

25. Naatanen R, Gaillard AW, Mantysalo S. Early selective-attention effect on evoked potential reinterpreted. Acta psychologica. 1978;42(4):313-29.

26. Kimura M, Katayama J, Murohashi H. Probability-independent and -dependent ERPs reflecting visual change detection. Psychophysiology. 2006;43(2):180-9. Available from: https://doi.org/10.1111/j.1469-8986.2006.00388.x

27. Mazza V, Turatto M, Sarlo M. Rare stimuli or rare changes: what really matters for the brain? Neuroreport. 2005;16(10):1061-4.
28. Kimura M, Katayama J, Ohira H, Schroger E. Visual mismatch negativity: new evidence from the equiprobable paradigm. Psychophysiology. 2009;46(2):402-9. Available from: https://doi.org/10.1111/j.1469-8986.2008.00767.x

29. Escera C, Alho K, Winkler I, Naatanen R. Neural mechanisms of involuntary attention to acoustic novelty and change. Journal of cognitive neuroscience. 1998;10(5):590-604.

30. Kok A. On the utility of P3 amplitude as a measure of processing capacity. Psychophysiology. 2001;38(3):557-77. Available from: https://doi.org/10.1017/S0048577201990559

31. Pontifex MB, Hillman CH, Polich J. Age, physical fitness, and attention: P3a and P3b. Psychophysiology. 2009;46(2):379-87. Available from: https://doi.org/10.1111/j.1469-8986.2008.00782.x

32. Rushby JA, Barry RJ, Doherty RJ. Separation of the components of the late positive complex in an ERP dishabituation paradigm. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2005;116(10):2363-80. Available from: https://doi.org/10.1016/j.clinph.2005.06.008

33. Goodin DS. Clinical utility of long latency ‘cognitive’event-related potentials (P3): the pros. Electroencephalography and clinical Neurophysiology. 1990;76(1):2-5.

34. Portin R, Kovala T, Polo-Kantola P, Revonsuo A, Müller K, Matikainen E. Does P3 reflect attentional or memory performances, or cognition more generally? Scandinavian Journal of Psychology. 2000;41(1):31-40. Available from: https://doi.org/10.1111/1467-9450.00168

35. Näätänen R. Mismatch negativity (MMN): perspectives for application.
36. Jeon YW, Polich J. P3a from a passive visual stimulus task. Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology. 2001;112(12):2202-8. Available from: https://doi.org/10.1016/S1388-2457(01)00663-0

37. Tales A, Butler S. Visual mismatch negativity highlights abnormal preattentive visual processing in Alzheimer's disease. Neuroreport. 2006;17(9):887-90. Available from: https://doi.org/10.1097/01.wnr.0000223383.42295.fa

38. Polich J, Ladish C, Bloom FE. P300 assessment of early Alzheimer's disease. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section. 1990;77(3):179-89.

39. Kraiuhin C, Gordon E, Coyle S, Sara G, Rennie C, Howson A, et al. Normal latency of the P300 event-related potential in mild-to-moderate Alzheimer's disease and depression. Biological psychiatry. 1990;28(5):372-86.

40. Maurer K, Riederer P, Heinsen H, Beckmann H. Altered P300 topography due to functional and structural disturbances in the limbic system in dementia and psychoses and the pharmacological conditions. Psychiatry research. 1989.

41. Alonso TO, Loeches MM, Miguel F, Abbad EV, Puente AE. P300 latency and amplitude in the diagnosis of dementia. Journal of clinical psychology. 1994;50(3):381-8.

42. Güntekin B, Saatçi E, Yener G. Decrease of evoked delta, theta and alpha coherences in Alzheimer patients during a visual oddball paradigm. Brain research. 2008;1235:109-16. Available from: https://doi.org/10.1016/j.brainres.2008.06.028
43. Demiralp T, Ademoglu A, Schürmann M, Basar-Eroglu C, Basar E. Detection of P300 waves in single trials by the wavelet transform (WT). Brain and language. 1999;66(1):108-28.

44. Han JW, Kim TH, Kwak KP, Kim K, Kim BJ, Kim SG, et al. Overview of the Korean Longitudinal Study on Cognitive Aging and Dementia. Psychiatry Investig. 2018;15(8):767-74. Available from: https://doi.org/10.30773/pi.2018.06.02

45. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984;34(7):939-44. Available from: https://doi.org/10.1212/WNL.34.7.939

46. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods. 2004;134(1):9-21. Available from: https://doi.org/10.1016/j.jneumeth.2003.10.009

47. Lopez-Calderon J, Luck SJ. ERPLAB: an open-source toolbox for the analysis of event-related potentials. Frontiers in human neuroscience. 2014;8:213. Available from: https://doi.org/10.3389/fnhum.2014.00213

48. Light GA, Swerdlow NR, Braff DL. Preattentive sensory processing as indexed by the MMN and P3a brain responses is associated with cognitive and psychosocial functioning in healthy adults. Journal of cognitive neuroscience. 2007;19(10):1624-32. Available from: https://doi.org/10.1162/jocn.2007.19.10.1624

49. Stothart G, Kazanina N, Näätänen R, Haworth J, Tales A. Early visual evoked potentials and mismatch negativity in Alzheimer's disease and mild cognitive
50. Bentley P, Husain M, Dolan RJ. Effects of cholinergic enhancement on visual stimulation, spatial attention, and spatial working memory. Neuron. 2004;41(6):969-82. Available from: https://doi.org/10.1016/S0896-6273(04)00145-X

51. Engeland C, Mahoney C, Mohr E, Illivitsky V, Knott VJ. Acute nicotine effects on auditory sensory memory in tacrine-treated and nontreated patients with Alzheimer's disease: an event-related potential study. Pharmacology Biochemistry and Behavior. 2002;72(1-2):457-64. Available from: https://doi.org/10.1016/S0091-3057(02)00711-6

52. Andrade GN, Butler JS, Mercier MR, Molholm S, Foxe JJ. Spatio-temporal dynamics of adaptation in the human visual system: a high-density electrical mapping study. European journal of neuroscience. 2015;41(7):925-39. Available from: https://doi.org/10.1111/ejn.12849

53. Pekkonen E, Jousmäki V, Könönen M, Reinikainen K, Partanen J. Auditory sensory memory impairment in Alzheimer's disease: an event-related potential study. Neuroreport: An International Journal for the Rapid Communication of Research in Neuroscience. 1994.

54. Kremlacek J, Kreegipuu K, Tales A, Astikainen P, Poldver N, Naatanen R, et al. Visual mismatch negativity (vMMN): A review and meta-analysis of studies in psychiatric and neurological disorders. Cortex; a journal devoted to the study of the nervous system and behavior. 2016;80:76-112. Available from: https://doi.org/10.1016/j.cortex.2016.03.017

55. Stefanics G, Kremláček J, Czigler I. Visual mismatch negativity: a predictive
coding view. Frontiers in Human Neuroscience. 2014;8(666). Available from: https://doi.org/10.3389/fnhum.2014.00666

56. Farkas K, Stefanics G, Marosi C, Csukly G. Elementary sensory deficits in schizophrenia indexed by impaired visual mismatch negativity. Schizophrenia research. 2015;166(1-3):164-70. Available from: https://doi.org/10.1016/j.schres.2015.05.011

57. Juckel G, Clotz F, Frodl T, Kawohl W, Hampel H, Pogarell O, et al. Diagnostic usefulness of cognitive auditory event-related p300 subcomponents in patients with Alzheimer's disease? Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society. 2008;25(3):147-52. Available from: https://doi.org/10.1097/WNP.0b013e31817272c95

58. Howe AS, Bani-Fatemi A, De Luca V. The clinical utility of the auditory P300 latency subcomponent event-related potential in preclinical diagnosis of patients with mild cognitive impairment and Alzheimer's disease. Brain and cognition. 2014;86:64-74. Available from: https://doi.org/10.1016/j.bandc.2014.01.015

59. Cecchi M, Moore DK, Sadowsky CH, Solomon PR, Doraiswamy PM, Smith CD, et al. A clinical trial to validate event-related potential markers of Alzheimer's disease in outpatient settings. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2015;1(4):387-94. Available from: https://doi.org/10.1016/j.dadm.2015.08.004

60. Frodl T, Hampel H, Juckel G, Burger K, Padberg F, Engel RR, et al. Value of event-related P300 subcomponents in the clinical diagnosis of mild cognitive impairment and Alzheimer's Disease. Psychophysiology. 2002;39(2):175-81. Available from: https://doi.org/10.1017/s0048577202010260
61. Yamaguchi S, Tsuchiya H, Yamagata S, Toyoda G, Kobayashi S. Event-related brain potentials in response to novel sounds in dementia. Clinical Neurophysiology. 2000;111(2):195-203. Available from: https://doi.org/10.1016/S1388-2457(99)00228-X

62. Frank DW, Yee RB, Polich J. P3a from white noise. International Journal of Psychophysiology. 2012;85(2):236-41. Available from: https://doi.org/10.1016/j.ijpsycho.2012.04.005

63. Hölig C, Berti S. To switch or not to switch: Brain potential indices of attentional control after task-relevant and task-irrelevant changes of stimulus features. Brain research. 2010;1345:164-75. Available from: https://doi.org/10.1016/j.brainres.2010.05.047

64. Baudic S, Barba GD, Thibaudet MC, Smagghe A, Remy P, Traykov L. Executive function deficits in early Alzheimer's disease and their relations with episodic memory. Archives of clinical neuropsychology: the official journal of the National Academy of Neuropsychologists. 2006;21(1):15-21. Available from: https://doi.org/10.1016/j.acn.2005.07.002

65. Pokryszko-Dragan A, Słotwiński K, Podemski R. Modality-specific changes in P300 parameters in patients with dementia of the Alzheimer type. Medical Science Monitor. 2003;9(4):CR130-CR4.

66. Tzovara A, Rossetti AO, Spierer L, Grivel J, Murray MM, Oddo M, et al. Progression of auditory discrimination based on neural decoding predicts awakening from coma. Brain: a journal of neurology. 2012;136(1):81-9. Available from: https://doi.org/10.1093/brain/aws264

67. Vafaii P, Mazhari S, Pourrahimi AM, Nakhaee N. Hemispheric differences for visual P3 amplitude in patients with schizophrenia. Neuropsychiatry.
68. Hamilton HK, Woods SW, Roach BJ, Llerena K, McGlashan TH, Srihari VH, et al. Auditory and Visual Oddball Stimulus Processing Deficits in Schizophrenia and the Psychosis Risk Syndrome: Forecasting Psychosis Risk With P300. Schizophrenia bulletin. 2019;45(5):1068-80. Available from: https://doi.org/10.1093/schbul/sby167

69. Seer C, Lange F, Georgiev D, Jahanshahi M, Kopp B. Event-related potentials and cognition in Parkinson’s disease: An integrative review. Neuroscience & Biobehavioral Reviews. 2016;71:691-714. Available from: https://doi.org/10.1016/j.neubiorev.2016.08.003

70. Nan C, Wang G, Wang H, Wang X, Liu Z, Xiao L, et al. The P300 component decreases in a bimodal oddball task in individuals with depression: An event-related potentials study. Clinical Neurophysiology. 2018;129(12):2525-33. Available from: https://doi.org/10.1016/j.clinph.2018.09.012

71. Matsuoka H, Saito H, Ueno T, Sato M. Altered endogenous negativities of the visual event-related potential in remitted schizophrenia. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section. 1996;100(1):18-24. Available from: https://doi.org/10.1016/0168-5597(95)00212-X

72. Luck SJ. An introduction to the event-related potential technique. Second edition ed: MIT press; 2014

Tables

Table 1. Demographic characteristics of the participants.
|                                | NC \(n=27\) | AD \(n=10\) | Statistic |
|--------------------------------|-------------|-------------|-----------|
| Sex (female, %)                | 48.1        | 70          | 1.40      |
| Age (years)                    | 70.81 (4.39)| 73.5 (7.15)| -1.11     |
| Education (years)              | 13.93 (3.00)| 9.30 (4.11)| 3.76      |

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

Group means are listed with standard deviation.

**Figures**

![Figure 1](image)

The visual oddball detection task. Three types of stimulus were displayed on screen.
Overall mean ERP. The overall mean amplitudes (μV) of early vMMN (1st row, me
Bar graph of vMMN amplitudes (μV). Mean amplitudes of early vMMN (left) and late vMMN (right) for the NC (black) and AD (grey) groups.