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Original Article

Cognitive evidence on EEG-P300 in healthy individuals with High Depression Scores

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ABSTRACT

Background: Depression is common among elderly and middle-aged individuals and is a reason for decreased quality of life. Depression may lead to impairments in cognitive abilities. The P300 potential is one of the most used event-related potentials (ERPs) to evaluate cognition. This study investigated the P300 amplitude differences between individuals with depressive symptoms and nondepressed healthy elderly individuals. **Materials and Methods:** The current study included twenty individuals with high depression scores (high DS, age: 64.80 ± 7.22, 6 M/14 F) and twenty demographically matched participants with low depression scores (low DS, age: 64.20 ± 6.21, 7 M/13 F). The Geriatric Depression Scale (GDS) was used to evaluate whether participants have depressive symptoms. All of the participants were underwent a comprehensive neuropsychological battery. The ERPs were recorded with a visual classical oddball paradigm. The P300 amplitudes were measured in the 250–550 ms time window. **Results:** High DS group had lower P300 amplitudes than low DS individuals regardless of electrode location. Correlation analyses showed that there was a significant correlation between GDS scores and the P300 amplitudes recorded from the F_z electrode. **Conclusion:** The current study showed the reduced P300 amplitudes on individuals with high GDS scores. The P300 potential may be a useful tool to determine possible changes or impairments due to subthreshold depressive symptoms.

KEYWORDS: *Depressive symptoms, event-related potential, healthy individuals, P300*

INTRODUCTION

Depression is a common problem among older adults and one of the most significant causes of emotional dysfunction and medical problems in late life.[1] Depression is not a normal part of aging; thus, its consequences affected the quality of life and cognitive functions negatively. Although it is known that diminished cognitive performance is associated with aging, studies showed that prolonged depressive symptoms lead to memory decline, but memory decline does not necessarily cause depressive symptoms.[2-4] Elderly depression is especially hard to investigate because the nature of aging includes impairments in cognitive functioning and diminished cognitive abilities. A wide range of studies showed that depressive symptoms are risk factors for dementia and mild cognitive impairment.[5,6] The motivational symptoms are thought to be the most associated factors with dementia due to individuals' lack of interest and loss of energy toward daily activities.[7] One of the most used self-administrative scales to evaluate depressive symptoms in individuals above 50 years old is the Geriatric Depression Scale (GDS) which has thirty items.[8] Ertan *et al*. showed that the GDS is a reliable and valid scale for depression in older individuals.[9] The cutoff score was stated as 14 for the depression diagnosis.

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Electroencephalography (EEG) is one of the advantageous methods to evaluate cognitive functioning. EEG is a noninvasive, low-cost, and useful technique which is sensitive to cognitive performance with an advantage of greater temporal resolution. Event-related potentials (ERPs) are electrical potentials that are generated by the brain and reflect the summed activity of excitatory and inhibitory postsynaptic potentials.[10] P300 is the most commonly examined ERP, which had a maximum peak of around 300 ms after the task-related stimulus.[11] P300 is thought to reflect many cognitive functions such as attention, memory, decision-making, and inhibition.[12] Therefore, it is widely used in research related to cognitive impairment and dementia.[13] In addition to its cognitive reflection, P300 amplitudes also positively correlated with gray matter volume and myelination.[14,15] Some studies suggested that P300 amplitude reduction occurs in prefrontal cortex lesions, neurodegenerative disorders involving basal ganglia.[16] Numerous studies had shown that P300 latency is prolonged in individuals with depressive symptoms and major depressive disorder.[17-21] However, P300 amplitude had more inconsistent results. Some studies found reduced P300 amplitudes in major depressive disorder, whereas others found no difference.[17,21-24] The effect of depressive symptoms on P300 amplitudes is still unclear. Therefore, the aim of the current study is to determine possible cognitive impairments in healthy elderly and middle-aged individuals with high depression scores by assessing P300 amplitudes.

Materials and Methods

Participants

The study included a total of forty participants which were divided into two groups each consisting of twenty participants with GDS scores of 14 and above (high DS) and GDS scores under 14 (low DS). The inclusion criteria for all participants are as follows: (1) neuropsychological test scores within the range of demographically adjusted norms,[25-27] (2) no history of neurological or psychiatric conditions, (3) no history of alcohol and drug misuse, (4) no vascular lesions and/or atrophy in magnetic resonance imaging (MRI), (5) no impairment in visual abilities that may affect the EEG recordings, and (6) Mini–Mental State Examination (MMSE) score of ≥27. All participants were examined by a psychiatrist and underwent a detailed psychiatric assessment. None of the participants meet the DSM-V criteria of major depressive disorder. In addition, none of the subjects were under any antidepressant treatments. Table 1 presents the demographic and neuropsychological features of the participants.

Table 1: Demographic and neuropsychological data of the participants

	High DS	Low DS	*P*
N	20	20	
GDS[a]*	2.60±2.95	17.00±3.96	<0.001
Age[a]	64.80±7.22	64.20±6.21	0.708
Education[a]	12.20±3.99	12.10±4.73	0.943
Gender[b] (male/female)	6/14	7/13	0.557
Epoch[a]	36.40±4.43	35.35±5.30	0.501
MMSE[a]	29.30±0.87	29.00±0.97	0.309
OVMPT-total score[a]	122.55±10.04	115.55±13.16	0.076
OVMPT-immediate recall[a]	5.55±1.23	5.20±1.96	0.504
OVMPT-free recall[a]	13.25±1.21	13.10±1.12	0.686
OVMPT-total recall[a]	15.00±0	15.00±0	0.323
Stroop interference[a]	46.85±11.09	42.68±14.71	0.323
Categorical fluency[a]	25.95±5.02	22.95±5.58	0.082
Phonemic fluency[a]*	45.67±11.37	36.32±10.09	0.012
BNT[a]	14.95±0.22	15.00±0	0.324
Digit span-forward[a]	5.90±0.97	5.70±0.80	0.481
Digit span-backward[a]	4.50±0.69	4.25±0.64	0.241
BLOT[a]	24.13±2.93	23.53±3.09	0.589

*Statistical difference across groups as $P<0.05$, [a]Independent samples *t*-test, [b]Chi-square analysis. Data were presented as mean±SD. High DS: High depressive symptoms, Low DS: Low depressive symptoms, GDS: Geriatric Depression Scale, MMSE: Mini–Mental State Examination, OVMPT: Oktem Verbal Memory Processes Test, BNT: Boston Naming Test, BLOT: Benton Line Orientation Test

All participants provided written informed consent according to the Helsinki Declaration. This study is approved by the Local Ethics Committee of Dokuz Eylul University.

Neuropsychological assessment

All participants underwent a comprehensive neuropsychological assessment, neurological examination, and MRI procedures. The neuropsychological tests included Oktem Verbal Memory Processes Test (OVMPT), WMS-R digit span test (forward and backward), Stroop test, verbal fluency tests (categorical and phonemic), Boston Naming Test, Benton Line Orientation Test (BLOT), and MMSE. Four different scores were obtained from OVMPT as a total score, immediate recall, free recall, and total recall [Table 1].

In addition, GDS was applied all of the participants. GDS, which is a self-administrative scale, has a total of thirty items with a maximum score of 30 and a minimum score of 0. The higher scores on GDS indicate increased depressive symptoms, and the cutoff score for depression is 14.

Results of the independent samples *t*-test showed no significant differences in age, education, and

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gender across groups. However, the analysis revealed a significant difference in phonemic fluency scores (t[35] = 2.65, P = 0.012) showing lower scores in participants with high GDS scores (M = 36.32, standard deviation [SD] = 10.09) than low GDS scores (M = 45.67, SD = 11.37).

Electroencephalography recordings, paradigm, and analysis

EEG was recorded from thirty Ag/AgCl electrodes placed on an elastic cap according to the international 10–20 systems, and linked ear electrodes (A1 + A2) were used as references. Electrooculogram was recorded from the medial upper and lateral orbital location of the right eye. All electrode impedances were below 10 kΩ. The EEG was digitized at a rate of 500 Hz with the BrainAmp 32-channel DC amplifier with a 0.03–70-Hz band limit.

A classical visual oddball paradigm was used. A total of 120 stimuli (40 target/80 standard) were presented. The stimuli had a 1-s duration, and the interstimulus interval randomly changed between 3 and 7s. The visual stimuli were presented in random order from a 22" screen with a refresh rate of 60 Hz. The target and standard stimuli had 40 cd/cm^2 and 10 cd/cm^2, respectively. All participants were asked to mentally count the target stimuli and report the number.

Offline analyses were performed using Brain Products Vision Analyzer 2.1 (Brain Products GmbH; Gilching, Germany). The high pass filtered with 0.1 Hz with zero-phase shift Butterworth filter applied to raw EEG data and power-line noise was eliminated by a 50-Hz notch filter. Extended infomax independent component analysis was used to correct eye movements and muscle contractions. The data were further filtered between 0.5 and 30 Hz and segmented into 1000-ms epochs time locked to the target stimuli onset including the 200-ms prestimulus period.

Baseline correction was applied about 200 ms of prestimulus. Automatic artifact rejection was applied to eliminate epochs exceeding ± 70 μV. To obtain ERPs, artifact-free epochs were averaged. Maximum peak P300 amplitudes were measured between 250 and 500 ms time window from F_z, C_z, and P_z electrodes.

EEG recordings were performed during morning hours (approximately between 09.00 and 10.00 am) of typical weekdays.

Statistical analysis

IBM SPSS Statistics 24.0 software (SPSS Inc., Chicago, Illinois, USA) was used for all statistical analyses. Independent samples *t*-test was used to evaluate demographic and neuropsychological data. Repeated measures analysis of variance (ANOVA) with within-subject factor 3 level LOCATION (frontal, central, and parietal) was used to compare P300 amplitudes. The correlation analysis was performed by using Pearson correlation analysis among P300 amplitudes and GDS scores. The Bonferroni correction was applied for correlation analysis.

Results

Peak P300 amplitudes

Repeated measures ANOVA showed that there is a significant main GROUP effect ($F_{(1,38)}$ = 4.460, P = 0.041), indicating that individuals with high GDS scores had lower P300 amplitudes compared to individuals with low GDS scores [Table 2 and Figure 1]. There were no main LOCATION effect and GROUP × LOCATION interaction effect.

Correlations among P300 amplitudes and Geriatric Depression Scale scores

A significant negative moderate correlation was observed between P300 amplitude from the F_z electrode and GDS score [r = −408, P = 0.009, Figure 2].

Discussion

The current study aimed to investigate differences in cognitive functioning between depressed and not depressed cognitively healthy individuals by comparing P300 amplitudes. In our study, it is found that P300 amplitudes are lower in depressed elderly and middle-aged individuals in comparison to not depressed individuals. In addition, GDS scores were found to be correlated with P300 amplitude recorded from the F_z electrode location.

It is known that P300 amplitude is lower in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. Likewise, reduced P300 amplitudes were reported in schizophrenia and bipolar disorder.[28-33] P300 is known to be associated with many cognitive functions as attention and working memory.[33] The lower P300 amplitudes in individuals with high depression scores may indicate that attention and working memory functions are impaired, even

Table 2: The peak P300 amplitudes from F_z, C_z, and P_z electrode locations

	High DS	Low DS
F_z	5.36±2.30	7.04±1.89
C_z	5.49±2.08	6.83±2.30
P_z	5.34±2.27	6.37±2.18

Data were presented as mean±SD. SD: Standard deviation, High DS: High depressive symptoms, Low DS: Low depressive symptoms

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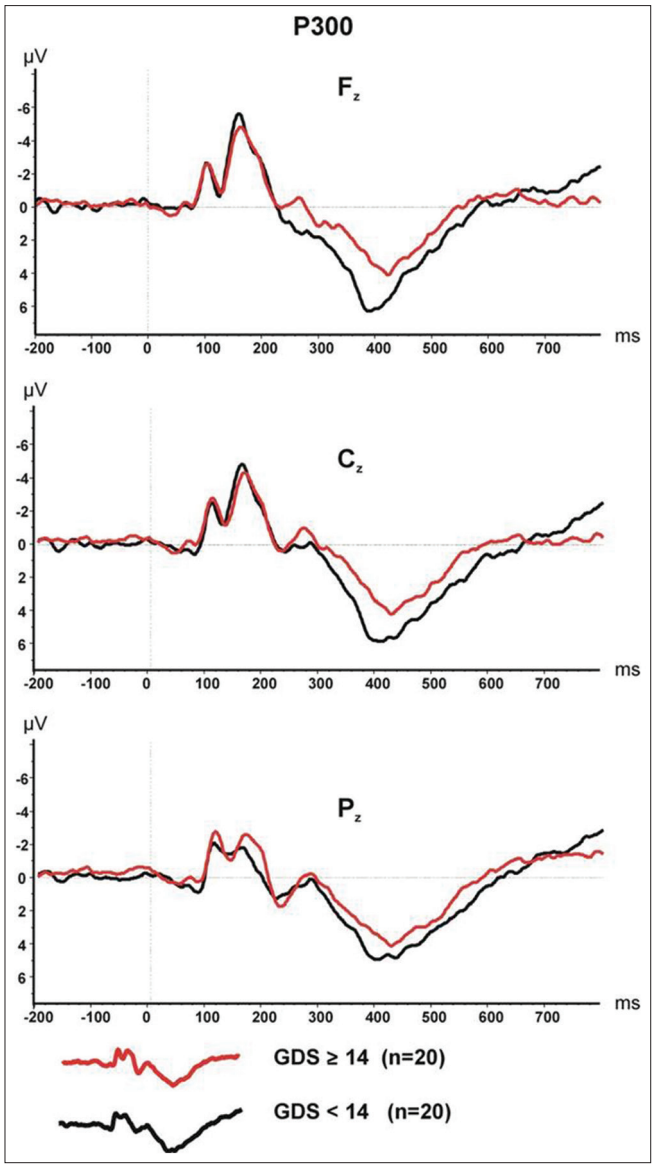


Figure 1: Peak P300 amplitudes in two groups at Fz, Cz, and Pz electrode locations

though it is not yet reflected by the neuropsychological tests.

P300 amplitude is also related to attentional resources devoted during cognitive tasks.[21,33] The diagnostic criteria for the major depressive disorder include cognitive dysfunction described as "diminished ability to think or concentrate."[34,35] The reduction of P300 amplitude may be the reflection of impaired attention or diminished attentional resources. This impairment and/or diminished resources may have derived from a lack of motivation to complete a task or directly from cognitive impairments. Although neuropsychological test scores are within the adjusted norms, depressive symptoms may lead to a reduction in P300 amplitudes because of impaired attention. However, we think there

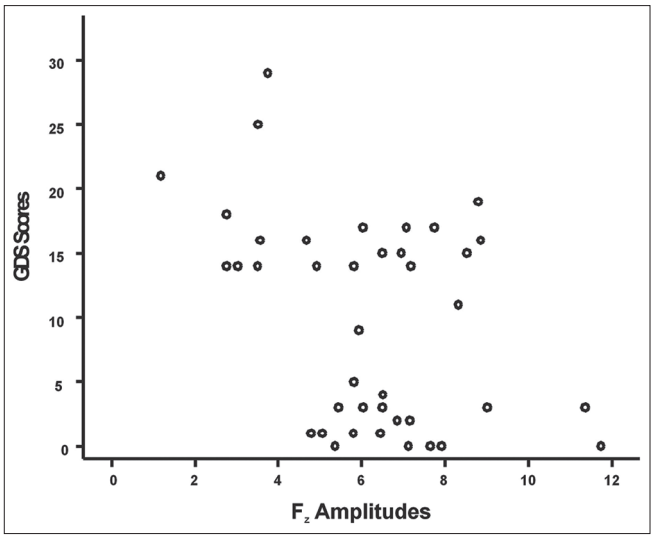


Figure 2: Peak P300 amplitudes from Fz electrode and Geriatric Depression Scale scores

is a higher probability that the lower P300 amplitudes are more likely to be caused by a general cognitive impairment than lack of motivation. Because, it is shown that neuropsychological dysfunction is persistent after treatment of depressive symptoms.[36,37] In addition, Vandoolaeghe *et al*. reported in their longitudinal study that prolonged P300 latencies had not recovered or shortened after Hamilton Depression Rating Scale scores decreased with antidepressant treatment.[17]

The generators P300 are reported to be temporoparietal junction, insula, inferior and right middle frontal gyrus, and frontal midline areas.[38] A meta-analysis showed that anterior cingulate, dorsolateral, medial, and inferior prefrontal cortex, insula, superior temporal gyrus, basal ganglia, and cerebellum regions are related to depression.[39] The overlap between P300 generators and brain regions that are affected by depressive symptoms could be the explanation of alterations in P300 amplitudes. It is reported that frontocentral theta activity reflected the modulation of switching the focus of attention and attention toward task-related stimuli.[40] Since delta and theta oscillations are thought to be components of P300, the impaired attention in individuals with high depressive scores may cause impairment in theta, thus P300.

Unlike the current study, Vandoolaeghe *et al*. and Kalayam and Alexapoulos found no difference in P300 amplitudes between depressed and nondepressed individuals.[17,24] Vandoolaeghe *et al*. did not report the neuropsychological, neurological, or neuroimaging evaluations of the control group.[17] Similar to the aforementioned study, Kalayam and Alexapoulos did not apply neuropsychological tests to control groups, and

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exclusion criteria were set to MMSE <16.[24] Therefore, they did not find a significant difference in P300 amplitude may be due to the possibility that healthy controls had minor cognitive impairments that did not reflect in daily living activities. The negative correlation between P300 amplitude and GDS scores showed that not only P300 amplitude differentiate between depressed and healthy elderly and middle-aged individuals, it is also sensitive to the degree of depressive symptoms. These results lead us to thought that the use of P300 amplitude in depression may help them determine the severity of depressive symptoms, thus the degree of cognitive impairment. Even though depressive symptoms are not sufficient enough for the diagnosis of major depressive disorder, P300 amplitude is a sensitive tool for both depressive symptoms and cognitive impairment due to depressive symptoms.

The current study has some limitations. First, our study consists of cross-sectional data of participants, thus we had limited and participant-reported knowledge of past psychiatric and neurological disorders. Second, this cross-sectional study does not provide information about the effect of antidepressant treatment on cognitive symptoms and/or P300 amplitudes. In addition, we did not take into account the duration of depressive symptoms. One of the limitations is that the current study has a limited number of participants as sample. Future studies should use larger samples with longitudinal designs that may lead to more reliable results on the relationship of P300 amplitudes and depression.

Conclusion

The current study showed reduced P300 amplitude on individuals with high depression scores in comparison to individuals with low depression scores. We concluded that the depressive symptoms showed by GDS were accompanied by a reduction in P300 amplitudes. P300 may be a valuable tool for examining subthreshold depressive symptoms in healthy elderly and middle-aged individuals. As mentioned before, P300 amplitude changes in depressive symptoms are still unclear. Thus, we think that the current study will have an important contribution to the literature due to its cognitively healthy and drug-naive sample.

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Conflicts of interest

There are no conflicts of interest.

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