Demonstration of Early Cognitive Impairment in Parkinson's Disease with Visual P300 Responses

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ABSTRACT

Introduction: Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease. Cognitive changes in PD are less observable than motor symptoms; thus, research on cognitive processes, which are known to be impaired from the early stages of PD, is minimal. The purpose of this study is to research the brain dynamics of cognitively normal PD patients and healthy elderly controls using event-related potentials (ERPs) and to evaluate their relationships with neuropsychological tests.

Methods: Eighteen cognitively normal PD patients and 18 age-, gender-, and education-matched healthy controls were included in the study. Detailed neuropsychological tests were applied to all participants. Electroencephalography (EEG) was performed according to the international 10-20 system, and a classical visual oddball paradigm was used in the experiments. ERP responses in the 0.5 to 25 Hz frequency range were examined. P300 amplitude and latency values were measured from the F₃, F_z, F₄, C₃, C_z, C₄, P₃, P_z, P₄, O₁, O₂, and O_z electrode sites. In addition, the correlations between P300 responses and neuropsychological test scores were analyzed.

Results: Significant differences were found between the P300 amplitudes of cognitively normal PD patients and healthy elderly controls [$F_{(1,31)}=9.265$; $p=0.005$]. P300 amplitudes were significantly lower for PD patients at the F₃, F_z, C₃, C_z, P₃, and P_z electrode sites than for healthy elderly controls. Moderate correlations were found between Stroop test score and P₄ amplitude, digit span forward and C₃ and P_z amplitude, and digit span backward and O₁ amplitude.

Conclusion: The major finding of this study was the detection of cognitive changes by electrophysiological methods in PD patients who were indicated to be cognitively normal by neuropsychological tests. These findings suggest that cognitive changes in PD patients, which are not yet reflected in neuropsychological tests, may be detected by electrophysiological methods in earlier stages.

Keywords: Parkinson's disease, event-related potentials, visual, P300

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease (AD). Idiopathic Parkinson's disease (IPD) is the most common cause of parkinsonism; its prevalence in the later stages of life is reported to be 2% to 3% in people age 65 and over and 10% in people age 80 and over (1).

Physical symptoms are severe in PD; as a result, non-physical changes may be overlooked. Cognitive changes are difficult to diagnose in PD patients because they retain their mental acuity and continue their daily living activities. Cognitive impairment is a primary symptom of AD; however, because of the severity of motor symptoms, cognitive changes in PD have remained unrecognized for years (2).

Traditionally, cognitive impairment is expected to be observed during the later stages of PD; however, cognitive impairment in the early stages is reported in approximately 30% to 35% of patients (3,4).

Parkinson's disease mild cognitive impairment (PD-MCI) is similar to mild cognitive impairment (MCI) which is currently considered to be prodromal AD (5). However, unlike MCI, cognitive changes in PD-MCI do not primarily affect memory; instead, they affect the patient's attention, language, visuospatial skills, and executive functions (6). It has been found that 75% to 80% of PD patients develop dementia during disease progression (4). Further progression of cognitive impairment and deterioration in daily living activities were defined as the dementia stage of Parkinson's disease (PD-D) (2).

Event-related potentials (ERPs) represent the synchronous activity of large neuron groups that fire together during an electroencephalogram (EEG) recording upon application of cognitive load. ERPs can be obtained using different paradigms. The classical oddball paradigm is the most frequently used method to elicit ERPs.

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P300 is the most investigated component of ERPs; it is a large positive wave that occurs approximately 300 ms after the target stimuli is presented (7). The P300 component reflects cognitive processes during complex memory tasks and is related to focused attention, working memory, signal detection, and decision-making processes (8,9,10,11). It is known that P300 responses may vary depending on neurotransmitter changes in specific diseases. Particularly, dopaminergic deficiencies in frontal areas are reported to affect electrophysiological responses (12).

In the present study, we aimed to investigate changes in the brain dynamics of PD using P300 responses together with neuropsychological tests in cognitively normal PD patients and healthy controls. The intent of this study is to further the understanding of cognitive changes in PD, which progress concurrently with motor symptoms without being detected.

METHODS

Subjects

The sample of this study consisted of PD patients who were being followed up at the movement disorders clinic of the Department of Neurology at Dokuz Eylül University (DEU) Hospital, as well as healthy controls recruited via bulletin board announcements at DEU Hospital. The local ethics committee (05.03.2014–1476-GOA) approved the study, and all participants provided written informed consent.

All participants underwent neurological examination and magnetic resonance imaging (MRI) prior to the study. Eighteen patients with PD [mean age: 65.30 (± 6.67)] who were confirmed to be cognitively normal after detailed neuropsychological assessment and 18 age-, gender-, and handedness-matched healthy controls [mean age: 69.10 (± 8.44)] participated in the study. Neuropsychological test scores did not differ between the PD patients and the healthy controls ($p > 0.05$). The clinical and demographic characteristics of the groups are shown in Table 1.

Patients were diagnosed with IPD according to the Unified Parkinson Disease Rating Scale (UPDRS) motor scale, which was administered by neurologists (13,14). Patients between stages I and III on the Hoehn and Yahr scale were included (15). The EEG recordings and neuropsychological assessments of the PD patients were performed during their "on" periods.

In this study, PD-MCI patients were excluded according to the level 2 criteria provided by the Movement Disorder Society (MDS) (16). According to these criteria, patients should be evaluated in detail in five cognitive domains (attention/working memory, executive functions, language, episodic memory, and visuospatial functions). To be diagnosed with PD-MCI, patients must demonstrate impairments in at least two cognitive domains or in two tests that examine the same domain. Test scores that have a standard deviation of 1.5 below normal values are accepted as abnormal. Patients who had impairment in two or more cognitive domains and in their activities of daily living were considered to have PD-D and were excluded from the study (2). The PD patients included in this study had no subjective complaints about their cognitive functions, and their daily living activities were preserved. Patients with prominent cerebral atrophy or vascular lesions were excluded.

Two volunteers with cognitive impairment detected by neuropsychological tests and two PD patients with inadequate numbers of epochs in their EEG analyzes were excluded from the study. Three PD patients were also excluded due to their motor disabilities. The Geriatric Depression Scale

Table 1. Clinical and demographic characteristics of healthy controls and PD patients

	Healthy controls (n=18) Mean (SD)	PD patients (n=18) Mean (SD)	p
Age	69.10 (8.44)	65.30 (6.67)	0.053 ^a
Education	9.83 (4.97)	8.64 (4.35)	0.398 ^a
Gender (M/F)	15/3	15/3	1.000 ^b
Handedness (right/left)	16/2	18/0	0.146 ^a
Hoehn and Yahr score	-	2.2 (0.67)	-
UPDRS motor score	-	19 (8.81)	-
Disease duration (year)	-	4.08 (3.18)	-
Age of disease onset	-	61.42 (7.85)	-
Behavioral score (/40)	39/40	39/40	0.510 ^a
MMSE	28.94 (1.11)	28.83 (1.30)	0.784 ^a
PD: Parkinson's disease; MMSE: mini mental state examination; SD: standard deviation; M: male; F: female; ^a independent sample t-test, ^b chi-square test			

was administered to all subjects; participants who had total scores of 11 or more out of 30 were excluded (Table 1).

Neuropsychological Assessment

A detailed neuropsychological test battery was applied to all participants by neuropsychologists. The following tests were administered: the Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) to assess global cognitive status; the Wechsler Memory Scale-Revised (WMS-R) visual reproduction subtest to assess visual memory; the Öktem Verbal Memory Processes Test (ÖVMPT) to assess verbal memory; the WMS-R digit span forward and backward tests to assess attention; the Stroop test, categorical and lexical verbal fluency tests, the The Wechsler Adult Intelligence Scale–fourth edition (WAIS-IV) similarities subtest, proverb interpretation, and the Wisconsin Card Sorting Test to assess executive functions; the Boston naming test to assess language; and simple copying tests, the clock drawing test, and the Benton Line Orientation Test to assess visuospatial skills (17,18,19,20,21,22,23,24,25,26,27,29).

Electrophysiological Recordings

All EEG recordings were performed in a sound-attenuated, isolated room in the morning (when the PD patients were in their "on" periods). The EEGs were recorded from 30 Ag/AgCl electrodes over an elastic cap (EasyCap; Brain Products GmbH, Gilching, Germany) according to the international 10-20 system. Linked earlobe electrodes (A1+A2) were used as references. The electrooculogram (EOG) was recorded from the medial upper and lateral orbitals of the right eye. Impedance was maintained below 10 k Ω for all electrodes. Each EEG was digitalized with a 500 Hz sampling rate using a 32-channel amplifier (BrainAmp DC; Brain Products GmbH, Gilching, Germany) with band limits of 0.01 to 250 Hz.

A classical oddball paradigm was used in the experiments. In the oddball paradigm, the visual stimulus has a time of 10 ms r/f and a duration of 1 sec. The luminance of the standard stimulus was 10 cd/cm² (probability: 80/120) and that of the target stimulus was 40 cd/cm² (probability: 40/120). The participants were asked to mentally count the target stimuli. The target stimuli were segmented offline as 500 ms pre-stimulus and 1000 ms post-stimulus (BrainVision Analyzer; Brain Products GmbH,

Gilching, Germany). Epochs containing artifacts (such as eye movement or blinking) were manually removed.

Subject averages and grand averages were calculated for all electrode sites. The obtained epochs were filtered between 0.5 and 25 Hz for ERPs after averaging, and the peak amplitudes and latency values of P300 in the 250 to 600 ms time window were measured from the F_3 , F_z , F_4 , C_3 , C_z , C_4 , P_3 , P_z , P_4 , O_1 , O_z , and O_2 electrode sites (30).

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences Statistics (SPSS) 17 (IBM; Armonk, NY, USA). The neuropsychological test scores of the healthy controls and PD patients were compared by independent sample t-test. The P300 amplitude and latency values were analyzed with repeated measures ANOVA. In this analysis, anterior-posterior (frontal, central, parietal, occipital) $\times$ sagittal (left, middle, right) values were examined. The corrected Greenhouse-Geisser p values were taken into consideration. Post-hoc analyzes were performed by independent sample t-test.

The relationships between the neuropsychological test scores and the visual P300 amplitude and latency values of the groups were analyzed with partial correlations in which age, gender, and education were taken as covariates. The relationships between the visual P300 amplitude and latency values and the Hoehn and Yahr score, disease duration, age of disease onset, and UPDRS motor scores of the PD patients were analyzed with partial correlations in which age, gender, and education were again taken as covariates. The significance value was accepted as $p < 0.05$ in all analyzes.

RESULTS

Visual Event-Related P300 Amplitude Values

Repeated measures ANOVA revealed a significant difference between the visual P300 amplitude values of the healthy control group and the cognitively normal PD patient group [$F_{(1,31)} = 9.265$; $p = 0.005$]. According to the independent sample t-test, the visual P300 amplitude values of the PD patients were lower than those of the healthy controls over the electrode sites F_3 , F_z , C_z , C_4 , P_z , and P_4 (Table 2, Figure 1).

Visual Event-Related P300 Latency Values

The visual P300 latency values of the cognitively normal PD patients and healthy controls did not differ between the groups [$F_{(1,31)} = 3.294$; $p = 0.079$] (Table 3).

Correlations Between Neuropsychological Test Scores and Visual Event-Related P300 Amplitude and Latency Values

According to the partial correlation analysis, a moderate negative correlation was observed between Stroop test score and P_4 amplitude value ($r = -0.384$; $p = 0.035$). The digit span forward test score demonstrated moderate positive correlations with the C_3 and P_z amplitude values ($r = 0.482$ and $r = 0.366$, respectively; $p < 0.05$). A moderate positive correlation was found between digit span backward test score and O_1 amplitude value ($r = 0.359$; $p = 0.040$). Lexical verbal fluency test score showed moderate positive correlations with the amplitude values from the F_4 , C_3 , C_z , C_4 , P_3 , P_z , P_4 , and O_z electrode sites (respectively; $r = 0.553$, $p = 0.017$; $r = 0.538$, $p = 0.021$; $r = 0.634$, $p = 0.005$; $r = 0.583$, $p = 0.011$; $r = 0.598$, $p = 0.009$; $r = 0.632$, $p = 0.005$; $r = 0.549$, $p = 0.018$; $r = 0.473$, $p = 0.047$). The correlation results are shown in Table 4.

Table 2. Visual P300 amplitude values in healthy controls and PD patients

Electrode site	Healthy controls (n=18) (Mean μV (SD))	PH Olguları (n=18) (Mean μV (SD))	p
F_3	6.85 (1.95)	5.69 (1.14)	0.038*
F_z	7.63 (2.68)	5.39 (1.45)	0.004*
F_4	6.76 (2.61)	5.30 (1.79)	0.058
C_3	6.25 (2.28)	5.01 (1.48)	0.061
C_z	7.39 (3.04)	5.06 (1.69)	0.007*
C_4	6.83 (3.01)	4.97 (1.89)	0.033*
P_3	5.74 (2.74)	4.49 (2.74)	0.123
P_z	6.99 (3.38)	4.72 (1.74)	0.016*
P_4	6.40 (3.43)	4.36 (1.92)	0.035*
O_1	4.71 (2.47)	3.34 (1.89)	0.070
O_z	4.77 (2.97)	3.26 (1.99)	0.081
O_2	4.82 (3.01)	3.40 (1.95)	0.102

PD: Parkinson's disease; μV : microvolt; SD: standard deviation; * $p < 0.05$

Correlations between Visual P300 Amplitude and Latency Values and Clinical Scales, Disease Duration, and Age of Disease Onset

In this study, no correlation between the visual P300 amplitude values and Hoehn and Yahr scores of the PD patients were found. UPDRS motor score had a moderate positive correlation with F_4 amplitude ($r = 0.533$; $p = 0.041$). Furthermore, age of disease onset and C_3 amplitude had a moderate negative correlation ($r = -0.521$; $p = 0.046$) (Table 4). There were no correlations between visual P300 latency value and disease duration, age of disease onset, UPDRS motor score, or Hoehn and Yahr score.

DISCUSSION

In the present study, the P300 amplitude responses of cognitively normal PD patients were significantly lower than those of healthy controls in the frontal (left-middle), central (right-middle), and parietal (right-middle) regions. This difference was especially prominent in midline locations.

Previous studies demonstrated reduced P300 amplitudes in non-demented PD patients compared to healthy controls (31,32,33,34,35,36). Electrophysiological findings in PD have been reported to be influenced by variables such as age, age of disease onset, and disease duration (34). In this study, the P300 amplitudes of cognitively normal PD patients were lower than those of healthy controls, in accordance with previous research. However, the diagnostic criteria for PD-MCI were defined in 2011 by Litvan et al. (16); studies before this date may have included both cognitively normal PD and PD-MCI patients in the often-used definition of "non-demented PD patients." Due to the lack of clear distinction between the definitions of PD and PD-MCI in studies prior to this date, it is not known whether the P300 responses differed between these two groups. Therefore, this is the first study that investigates P300 response in cognitively normal PD patients.

It is well known that the loss of dopaminergic neurons in the basal ganglia in the early stages of PD results in disruption of the fronto-striatal circuits (37,38,39). Moreover, prominent hypoactivity has been reported in cholinergic pathways in PD (40). Tessitore et al. (41) reported that cognitively normal PD patients had decreased connectivity in the resting state in the right medial temporal lobe and the bilateral inferior parietal cortex. Decreased connectivity was found to be correlated with cognitive indicators; however, it was not correlated with disease duration, motor impairment,

Figure 1. The grand averages of visual event-related potentials (0.5 to 25 Hz) in healthy controls and PD patients

* $p < 0.05$

Table 3. Visual P300 latency values in healthy controls and PD patients

Electrode site	Healthy controls (n=18) P300 latency Mean ms (SD)	PD patients (n=18) P300 latency Mean ms (SD)	p
F ₃	374 (62.70)	348 (67.86)	N.S.
F _z	380 (59.24)	367 (72.93)	N.S.
F ₄	367 (65.14)	378 (71.88)	N.S.
C ₃	422 (47.48)	379 (70.08)	N.S.
C _z	399 (39.78)	398 (107.01)	N.S.
C ₄	398 (40.99)	385 (88.10)	N.S.
P ₃	455 (62.45)	389 (74.76)	N.S.
P _z	410 (36.22)	383 (91.79)	N.S.
P ₄	434 (64.51)	383 (92.47)	N.S.
O ₁	469 (70.57)	394 (112.93)	N.S.
O _z	464 (84.11)	402 (113.95)	N.S.
O ₂	467 (88.65)	400 (110.69)	N.S.

PD: Parkinson's disease; ms: milliseconds; SD: standard deviation; N.S: not significant

or dopaminergic treatment. Considering the P300 component is associated with attention, signal detection, and working memory, the decreased amplitudes in PD patients appear to be consistent with the pathophysiological changes that are visible from the early stages of the disease.

In this study, the differences that distinguish PD patients from healthy controls were observed primarily in the frontal, central, and parietal locations. In structural MRI studies, cortical thinning was reported in non-demented PD patients, particularly in the frontal, parietal, and temporal areas (42,43,44). The differences found in the present study are believed to be associated with the cortical thinning observed in PD. The validity of these electrophysiological findings could be confirmed in future studies by using both EEG and MRI methods to investigate the relationships between EEG data and the structural/functional changes that occur during the course of the disease.

Deficits in visuospatial functions in PD are reported to be associated with the parietal, occipital, and temporal areas and to originate from lesions of the basal ganglia (45,46,47). Grey matter atrophy involving the primary visual cortex, visual association cortex, limbic cortex, and cholinergic structures is believed to cause impairments in visuospatial perception, attention control, and memory functions (48). These structural brain changes in PD eventually lead to dementia. However, we believe that the decline in brain responsiveness due to neuronal loss begins in the early stages of PD, before structural deterioration.

In this study, there were no significant differences between the latency values of cognitively normal PD patients and healthy controls. Furthermore, no relations between P300 latency values and neuropsychological test scores were found. P300 latency is known to reflect the information processing speed of individuals regarding stimulus detection and evaluation; it increases with normal aging as well as with the progression of dementia (49,50,51,52,53). In previous studies, non-demented PD patients demonstrated similar P300 latencies to healthy controls, while

Table 4. Correlations between P300 amplitude values and neuropsychological test scores and clinical scales

Electrode site	Stroop Test	Digit span forward test	Digit span backward test	Lexical fluency	UPDRS motor score	Age of disease onset
F ₄				r=0.553, p=0.017	r= 0.533, p=0.041	
C ₃		r=0.482, p=0.005		r=0.538, p=0.021		r=-0.521, p=0.046
C _Z				r=0.634, p=0.005		
C ₄				r=0.583, p=0.011		
P ₃				r=0.598, p=0.009		
P _Z		r=0.366, p=0.036		r=0.632, p=0.005		
P ₄	r=-0.384, p=0.035			r=0.549, p=0.018		
O ₁			r=0.359, p=0.040			
O _Z				r=0.473, p=0.047		

Parkinson's disease; UPDRS: unified parkinson disease rating scale

PD-D patients showed prolonged P300 latencies compared to both groups (32,54,55).

The effect of dopaminergic treatment on P300 latency is unclear in the literature. Some studies report prolonged P300 latencies in *de novo* PD patients in comparison to levodopa-treated patients as well as healthy controls; these studies showed that levodopa therapy significantly shortened P300 latency (56,57). However, other studies found prolonged P300 latencies in treated patients or found no significant differences (31,58,59,54,55,60) compared with healthy controls.

Ebmeier et al. (60) interpreted the non-differentiation of latencies between treated PD patients and healthy controls as an improving effect of dopaminergic treatment on cognition. The patients included in our study were all receiving dopaminergic treatment. In the present study, the non-significant difference in P300 latency between groups was interpreted in a similar way. Considering this information, future studies with *de novo* PD patients may monitor longitudinal changes in P300 responses and may investigate the effects of dopaminergic medication on electrophysiological parameters.

In addition to dopaminergic treatment, disease duration has also been found to affect P300 latency. Studies with PD patients with disease durations of over five years reported prolonged P300 latencies (31,55). In the present study, the relatively shorter disease duration (mean: 4.08 years) of PD patients may be another reason for the lack of difference in latency between the groups.

Neuropsychological tests are commonly used in PD studies. However, most neuropsychological tests are affected by speed factors. These test scores are particularly affected by motor impairment in PD patients. Electrophysiological methods may alleviate the confounding effects of motor impairment (61).

In a study that investigated the cognitive status and motor symptoms of PD patients, the importance of taking both examinations into account during clinical assessments was emphasized (39). While neuropsychological assessments can be readily affected by motor symptoms, electrophysiological methods are known to give objective results independent from motor conditions (38). In the present study, various correlations were observed between neuropsychological test scores and P300 amplitude values. Stroop test score and P300 amplitude in the right parietal location,

digit span forward score and P300 amplitude in the left central and middle parietal locations, and digit span backward score and P300 amplitude in the left occipital area were found to be positively correlated. Moreover, positive correlations were found between verbal fluency test score and P300 amplitude in the right frontal area, all central and parietal locations, and the middle occipital area. We believe that EEG methods that reflect neuronal functionality without being affected by motor impairments may detect cognitive changes which may not yet be captured by neuropsychological assessments.

Previous studies from our laboratory investigated different patient groups with the ERP method using auditory and visual oddball paradigms; these studies showed that the P300 amplitudes and latencies of AD and MCI patients were different from those of healthy controls (62,63). Moreover, positive correlations were found between P300 amplitude and MMSE, ÖVMPT, digit span, and categorical verbal fluency test scores. The similar findings for cognitively normal PD patients in this study may be due to the electrophysiological manifestations of subclinical cognitive changes.

In this study, the UPDRS motor scores of PD patients were positively correlated with P300 amplitude in the right frontal region; also, age of disease onset was negatively correlated with P300 amplitude in the right central region. These findings indicate that disease duration, disease severity, and the age of disease onset may be reflected in these electrophysiological parameters.

Aging is known to be the biggest risk factor for developing PD. The present study compared cognitively normal PD patients and age-matched healthy controls to eliminate the effects of age. Mild extrapyramidal symptoms may be a part of the normal aging process; however, more serious symptoms generally appear in PD (64). PD pathology involves a characteristic loss of dopaminergic neurons. However, postmortem studies of elderly subjects without PD also reported reduced dopaminergic neurons in the basal ganglia (65). Furthermore, decreased dopamine receptors have been shown to affect cognitive and motor functions (66).

Although similar dopaminergic changes are observed in normal aging and PD, biochemical, motor, and cognitive degeneration is known to be much more severe in PD. Some imaging studies demonstrated that dopaminergic degeneration occurs more rapidly in PD than in normal aging (67). In our study, the neuropsychological profiles of PD patients and healthy

controls were similar; however, more prominent neurochemical and neurophysiological changes were observed in PD patients.

Motor and cognitive impairments in PD were reported to be associated in some studies, but not in others (39,59). In the present study, P300 amplitude was found to be associated with age of disease onset and UPDRS motor score. In light of these findings, electrophysiological analyzes demonstrated possible early cognitive impairment in PD patients with an earlier disease onset, a longer disease duration, and more severe motor disabilities.

The present study demonstrated electrophysiological changes in cognitively normal PD patients, which may aid the diagnosis and treatment of PD and may provide objective findings with minimal involvement of motor functions.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Noninvasive Research Ethics Board of Dokuz Eylül University (05.03.2014 – 1476-GOA).

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