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Mild cognitive impairment in Parkinson's disease is associated with decreased P300 amplitude and reduced putamen volume

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HIGHLIGHTS

- Reduced frontal P300 may precede cognitive and structural changes in cognitively normal Parkinson's disease (PD).
- The reduction in P300 amplitude further spreads to centro-parietal areas in PD with mild cognitive impairment (PD-MCI).
- PD-MCI demonstrated reduced putamen volume, which was associated with impaired executive function.

ABSTRACT

Objective: Functional and structural brain alterations of cognitively normal Parkinson's disease (PD-CN) and Parkinson's disease mild cognitive impairment (PD-MCI) patients were investigated using event-related potentials (ERP) P300 and volumetric magnetic resonance imaging (MRI) parameters.
Methods: Twenty three patients with PD-CN, 21 with PD-MCI, and 23 demographically-matched healthy controls were included. EEGs were recorded using a visual oddball task and mean amplitude and peak latency values of P300 were measured. Gray matter volumes (GMV) of thalamus, caudate, putamen, globus pallidus, hippocampus, amygdala and nucleus accumbens were obtained using FMRIB Integrated Registration and Segmentation Tool. Correlations among P300, subcortical GMV and cognitive performances were assessed.
Results: PD-CN patients demonstrated reduced P300 amplitudes compared to healthy controls. PD-MCI patients had lower P300 amplitudes than both PD-CN patients and controls and reduced volumes of the putamen compared to controls. Both putamen volumes and P300 amplitudes showed moderate associations with executive functions.
Conclusions: Our findings support that P300 amplitude may be a useful marker for the detection of preclinical changes before the appearance of cognitive and structural deterioration in PD, as shown by decreased frontal P300 amplitudes in PD-CN. The reduction further spread to centro-parietal areas in PD-MCI patients, which was accompanied by lower putamen volumes.
Significance: This study is the first to report on changes in ERP P300 amplitude and subcortical volume in well-matched samples of PD-CN, PD-MCI and healthy controls.

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1. Introduction

Parkinson's disease (PD) is a common progressive neurodegenerative disorder which was traditionally characterized by motor clinical manifestations, however, non-motor features also give crucial cues regarding the prognosis of the disease. The Movement Disorders Society (MDS) Task Force reported that a mean of 27% of non-demented patients with PD have cognitive deficits (Litvan et al., 2011). Cognitive impairments in PD with not meeting the criteria for dementia (Emre et al., 2007) has been defined as mild cognitive impairment (PD-MCI; Caviness et al., 2007), and is considered to be a crucial risk factor in the progression of PD dementia (PDD) compared with cognitively normal PD (PD-CN) (Janvin et al., 2005, 2006). A wide spectrum of cognitive deficits on neuropsychological measures involving episodic memory, executive functions, attention, visuospatial skills, and less frequently language develop in the majority of the cases (Caviness et al., 2007; Sollinger et al., 2010). In a recent study, 91% of the PD-MCI cohort was found to progress to PDD within 16 years in a recent study (Hobson and Meara, 2015). Definitions of MCI in PD had been proposed in the literature (Janvin et al., 2006; Caviness et al., 2007); however, the diagnostic criteria for PD-MCI had not existed until 2012 (Litvan et al., 2012). The lack of uniform diagnostic criteria for PD-MCI has hindered the interpretation of previous studies on MCI due to an inclusion of PD-CN and PD-MCI patients into non-demented PD samples.

Electrophysiological methods provide a useful non-invasive tool for disease-related changes in brain functioning (Johnson and Donchin, 1978; Mecklinger et al., 1992; Verleger, 2003; Duncan et al., 2009). Event-related potentials (ERPs) are alterations of brain electrical activity in temporal coincidences with an application of a task, mostly with a cognitive load (Luck and Kappenman, 2012; Verleger and Śmigasiewicz, 2016). The P300 is typically elicited by a classical oddball paradigm (Donchin and Cohen, 1969) and is one of the most frequently studied cognitive ERP component in patients with PD. It reflects context-updating (Donchin, 1981) and has been related to focused attention, encoding into memory and decision making processes (Johnson et al., 1978; Mecklinger et al., 1992; Polich, 2007). Delayed P300 latency has been associated with increasing age (van Dinteren et al., 2014) and has been considered as a promising tool to quantify cognitive impairments associated with PD (Hansch et al., 1982; Seer et al., 2016). P300 measures may change in response to neurotransmitter alterations in specific diseases. Dopaminergic deficiency was specifically described to have an effect on electrophysiological responses (Polich, 2007). Previous electrophysiological studies in PD mainly focused on non-demented PD samples and reported reduced P300 amplitudes in patients compared to healthy controls (Antal et al., 1996; Philipova et al., 1997; Jiang et al., 2000; Tsuchiya et al., 2000; Li et al., 2005). Our groups' earlier work demonstrated decreased P300 amplitudes in PD-CN patients in comparison with healthy controls (Özmüş et al., 2017). However, limited data are available on P300 differences between PD-CN and PD-MCI patients. As PD-MCI constitutes a risk factor for PDD, understanding the neurophysiological basis is critical for identifying novel approaches to diagnosis.

In the literature, P300 is reported to be elicited from sources over cortical along with subcortical structures, including thalamic and basal ganglia regions (Kropotov and Ponomarev, 1991; Rektor et al., 2003, 2004, 2005). In a recent study, involvement of subcortical structures in task-related events was evaluated using simultaneous recordings of cortical and subcortical ERPs in patients with deep brain stimulation (Beck et al., 2018). Not only thalamic regions, but also two regions of basal ganglia, the subthalamic nucleus and the globus pallidus internus, were found to be involved in task-relevant information processing. Accordingly, P300 is proposed to be generated through several temporally overlapping and spatially distributed neural networks (Beck et al., 2018). Moreover, the circuits connecting the basal ganglia to non-motor regions in frontal lobes are associated with a variety of cognitive functions (Alexander et al., 1986; Middleton and Strick, 2000). In this sense, subcortical gray matter (GM) structures may make important contributions to our understanding of neural dynamics and structural changes in PD patients.

Structural magnetic resonance imaging (MRI) has been adopted as a marker of neurodegeneration for Alzheimer's disease and amnestic MCI; however, its utility for PD remains unclear. The main pathological characteristics of PD are arising from the basal ganglia affecting up to 70% of the dopamine secreting neurons in the substantia nigra pars compacta (Janvin et al., 2005). The basal ganglia include a set of connected subcortical structures that are comprised of the caudate and lentiform nuclei (putamen and globus pallidus), the substantia nigra, and the subthalamic nucleus (Kandel et al., 2000). Studies exploring subcortical GMV in PDD reported reductions in volumes of caudate nucleus and thalamus (Burton et al., 2004; Nagano-Saito et al., 2005) and the involvement of hippocampus and parieto-temporal regions was stated as predictors of cognitive decline and progression of PD-MCI to PDD (Weintraub et al., 2012). However, neuroanatomical changes in early PD stages with and without cognitive impairment have not been well described yet.

Previous studies including a sample of non-demented PD reported GMV reductions and alterations in subcortical regions such as caudate nucleus, thalamus, putamen and hippocampus in comparison with healthy controls (Weintraub et al., 2011; Hanganu et al., 2014; Lee et al., 2014; Mak et al., 2014). However, significant subcortical GMV reduction has not always been found in non-demented PD (Tinaz et al.,2011; Zarei et al., 2013; Koshimori et al., 2015), or in PD-CN patients (Menke et al., 2014; Hanganu and Monchi, 2016) compared to healthy controls. Cross-sectional and longitudinal studies demonstrated lower volumes of thalamus (Mak et al., 2014; Foo et al., 2017), nucleus accumbens (Mak et al., 2014, 2015; Hanganu et al., 2014) and amygdala (Hanganu et al., 2014) in PD-MCI patients compared with PD-CN, while a recent study did not find any subcortical GMV differences (Chen et al., 2017). These discrepancies in the literature are possibly related to variations in sample characteristics. Thus, further studies including demographically- and clinically-matched PD-CN and PD-MCI patients are needed to investigate subcortical GMV differences.

In this study, functional and structural brain differences of patients with PD-CN and PD-MCI were investigated by means of ERP P300 and subcortical GMV in comparison to healthy controls. One of our aims was to evaluate the hypothesis that P300 amplitudes would be gradually reduced in PD-CN and PD-MCI patients compared with healthy controls. Secondly, based on the previous literature, we posed the hypothesis that patients with PD-CN would not differ from healthy controls in terms of subcortical GMV. On the other hand, PD-MCI would be characterized by significant subcortical GMV atrophy in comparison with PD-CN patients. As a third interest, correlations of P300 measures with cognitive functions and subcortical GMV were sought, considering previous findings on the role of subcortical structures as generators for P300 and their involvement in cognition. To the best of our knowledge, this is the first study investigating the changes in ERP P300 and volumetric MRI measures of PD-CN, and PD-MCI patients compared to healthy controls using the criteria for PD-MCI classification (Litvan et al., 2012).

2. Materials and method

2.1. Participants

The present study included 23 PD-CN patients (age range: 50–84 years; mean age: 67.30 years) and 21 PD-MCI patients (age range: 61–78 years; mean age: 69.86 years) who were recruited from a movement disorders outpatient clinic in the Department of Neurology at Dokuz Eylül University Hospital and 23 age-, gender- and education-matched healthy controls (age range: 55–84 years; mean age: 66.74 years) who were recruited from various community sources. There were no statistical differences in terms of gender, age, education, and handedness among groups. The PD groups did not differ in terms of duration of disease, UPDRS motor score, and Hoehn &Yahr stage (Table 1). PD groups were clinically diagnosed on the basis of the criteria of UK Parkinson's Disease Society Brain Bank (Hughes et al., 1992). The Unified Parkinson's Disease Rating Scale (UPDRS) Part III (Fahn and Elton, 1987) was used to assess motor disability, and disease severity with using Hoehn & Yahr (1967) scale. The demographic and clinical characteristics of participants are presented in Table 1.

Inclusion criteria of PD-CN and PD-MCI patients were as follows: (1) clinical diagnosis of idiopathic PD, (2) control of motor symptoms with stable dopaminergic treatment, (3) Hoehn & Yahr stage III or less, and (4) scoring below 14 on Yesavage Geriatric Depression Scale (Yesavage et al., 1982; Gürvit and Baran, 2007).

Exclusion criteria of PD-CN and PD-MCI patients were as follows: (1) presence of PD dementia according to the criteria of MDS (Emre et al., 2007), (2) history of visual hallucinations, (3) history of psychiatric disorders, (4) use of medications affecting cognition (e.g. antidepressants, anxiolytics, anti-psychotics), (5) other causes of cognitive impairment (e.g. head trauma, seizures, strokes, drug abuse or chronic alcoholism), (6) presence of vascular brain lesions, cortical atrophy, (7) severe tremors preventing EEG recordings and/or MRI scans and (8) treatment with deep brain stimulation, jejunal levodopa or subcutaneous apomorphine. Exclusion criteria of healthy controls were as follows: (1) neurological abnormalities and/or cognitive impairment (MMSE score $\leq$27), (2) history of neurological and psychiatric disorders, and (3) history of head injury, alcohol or drug abuse.

PD-CN and PD-MCI patients were on the following anti-Parkinsonian treatment at the time of evaluation: L-dopa monotherapy (n = 24), dopamine agonist monotherapy (n = 5), MAO-B inhibitor (n = 2) or a combination of L-dopa and dopamine agonist (n = 13). Levodopa equivalent daily doses (LED) were calculated using a standardized formula for all the dopamine replacement therapies that PD patients were taking (Tomlinson et al., 2010), see Table 1.

Neuropsychological assessments of PD patients were performed during their "on" periods, at 60 to 90 minutes after their morning dose of medication and EEG was recorded on the same day at 60 to 90 minutes after their midday dose of medication. Structural MRI scans of PD patients were done at 60 to 90 minutes after their morning dose of medication in ±15 days. Two PD-CN patients, one PD-MCI patient, and one healthy control did not participate in the MRI phase of the study.

A total of 51 participants with PD were enrolled at the beginning of the study. However, four participants were excluded due to having parkinsonism with Alzheimer's disease. From the remaining participants, 25 of them were classified as PD-CN and 22 of them were detected as having PD-MCI according to the MDS Task Force Level II criteria (Litvan et al., 2012). However, two patients with PD-CN, one with PD-MCI and two healthy controls were excluded due to insufficient artifact-free EEG epochs (<25) at the beginning of the study. The remaining 23 healthy controls, 23 PD-CN, and 21 PD-MCI patients were included in further analysis. All participants had intact visual functions in terms of visual acuity, pupil function, visual field, and color vision. All participants provided written informed consent prior to voluntary participation in the study, and the study protocol was approved by the Ethics Committee of Dokuz Eylul University.

2.2. Neuropsychological assessment and PD-MCI classification

Cognitive performance was assessed by trained neuropsychologists using a comprehensive neuropsychological test battery. According to the recommendations of the MDS Task Force Level II criteria, five cognitive domains including memory, executive functions, attention/working memory, language and visuospatial skills were evaluated (Litvan et al., 2012). The following tests were

Table 1
Demographic, clinical and cognitive characteristics of study groups.

Demographic characteristics	HC (n = 23)	PD-CN (n = 23)	PD-MCI (n = 21)	*p*	PD-CN vs HC	PD-MCI vs HC	PD-CN vs PD-MCI
Age (years)	66.74 ± 6.96	67.30 ± 8.91	69.86 ± 5.78	0.339[a]	NS	NS	NS
Education (years)	12.04 ± 3.99	9.65 ± 3.94	10.24 ± 4.78	0.147[a]	NS	NS	NS
Gender (M/F)	17/6	19/4	16/5	0.765[b]	NS	NS	NS
Hand Dominance (R/L)	21/2	22/1	20/1	0.792[b]	NS	NS	NS
Hoehn & Yahr Score	–	2.02 ± 0.53	2.10 ± 0.44	0.621[c]	NS	NS	NS
UPDRS Motor Score	–	20.09 ± 9.08	21.48 ± 8.58	0.605[c]	NS	NS	NS
Disease Duration (years)	–	4.09 ± 2.61	4.81 ± 2.80	0.381[c]	NS	NS	NS
Daily LED (mg)	–	560.78 ± 305.74	597.43 ± 357.26	0.716[c]	–	–	NS
Global Cognitive Status							
MMSE	29.09 ± 1.12	28.61 ± 1.47	26.67 ± 3.44	**0.001**	1.000	**0.002**	**0.015**
MoCA[a]	–	25.30 ± 3.24	21.95 ± 4.86	–	–	–	**0.010**
Cognitive Domains							
Memory	0.65 ± 0.37	0.35 ± 0.34	−1.09 ± 0.65	**<0.001**	0.095	**<0.001**	**<0.001**
Attention	0.53 ± 0.61	0.25 ± 0.59	−0.79 ± 0.81	**<0.001**	0.534	**<0.001**	**<0.001**
Executive Functions	0.59 ± 0.41	0.36 ± 0.25	−0.39 ± 0.44	**<0.001**	0.065	**<0.001**	**<0.001**
Visuospatial	0.26 ± 1.07	−0.02 ± 0.77	−0.68 ± 1.18	0.102	NS	NS	NS
Language	0.24 ± 0.57	0.07 ± 0.76	−0.34 ± 1.45	0.147	NS	NS	NS

Values are presented as mean ± standard deviation unless indicated otherwise.
HC: Healthy controls, PD-CN: Cognitively normal Parkinson's disease, PD-MCI: Mild cognitive impairment in Parkinson's disease, NS: Not significant, LED: Levodopa equivalent dose, M: Male, F: Female, R: Right, L: Left, UPDRS: Unified Parkinson's Disease Rating Scale. [a]Analysis of covariance test, [b]Chi-square test, [c]Independent-samples t-test. MMSE: Mini-Mental State Examination, MoCA: Montreal Cognitive Assessment. Results of the ANOVA model (p-values) and pairwise comparisons with Bonferroni correction (p-values) are reported. Values, where the model is significant, are highlighted in bold.

administrated to all participants and performance 1.5 SD below the local norm was considered as abnormal. Global cognitive status was assessed using Mini-Mental State Examination, *MMSE* (Folstein et al., 1975) and the Montreal Cognitive Assessment, *MoCA* (Nasreddine et al., 2005) with a cut-off score of 21 in the detection of cognitive impairment in PD for the Turkish population (Özdilek and Kenangil, 2014). Verbal memory was assessed using Oktem Verbal Memory Processes Test, *OVMPT*, (Öktem, 1992); visual memory using Wechsler Memory Scale–Revised, *WMS-R*, visual reproduction subtest (Wechsler, 1987); attention using WMS-R digit span test (Wechsler, 1987) and Trail Making Test, *TMT* part A; executive functions using Stroop Test Çapa version (Emek-Savaş et al., 2019), phonemic fluency test (F-A-S), Wisconsin Card Sorting Test, *WCST* (Heaton et al., 1993), TMT part B (Reitan & Wolfson, 1985); language using 15 item Boston Naming Test, *BNT* (Kaplan et al., 2001) and semantic fluency test; and visuospatial skills using Benton Line Judgment Orientation Test, *BLOT* and simple copying tests (Benton et al., 1978). For PD-MCI diagnosis, impaired performance in at least two neuropsychological tests was required (i.e., either two tests assessing one cognitive domain or at least two tests assessing different cognitive domains) (Litvan et al., 2012).

Composite scores were generated for each cognitive domain by calculating the average z-scores of tests pertaining to the same domain. PD-MCI patients demonstrated significantly poorer performance in the domains of memory (for all, $p < 0.001$), attention (for all, $p < 0.001$), and executive functions (for all, $p = 0.007$) compared with both PD-CN patients and healthy controls. Moreover, as expected, PD-MCI patients had significantly lower scores on MoCA than PD-CN patients, and on MMSE than both PD-CN patients and healthy controls. The composite scores for five cognitive domains along with demographic and clinical data of study groups are presented in Table 1.

2.3. Electrophysiological recording, paradigm and analysis

EEG recordings were performed in an electrically shielded and sound-attenuated room using 30 Ag-AgCI electrodes placed on an elastic cap (EasyCap; Brain Products GmbH; Gliching, Germany) in the international 10/20 montage system. Additionally, two linked earlobe electrodes (A1 + A2) were used as references. The electrooculogram (EOG) was recorded from the medial upper and lateral orbital rim of the right eye. Impedances were maintained below 10 kOhm for all electrodes. EEGs were digitized at a sampling rate of 500 Hz, using a BrainAmp 32-channel DC amplifier (Brain Products GmbH; Gilching, Germany) with band-pass limits of 0.03–70 Hz.

A classical visual oddball paradigm was used to elicit ERPs. The probability of the target stimuli was 40/120 and that of the standard stimuli was 80/120. The luminance of standard stimuli was 10 cd/cm^2 and target stimuli was 40 cd/cm^2. The visual stimuli were displayed on a 22-inch flat monitor screen at full size, with a refresh rate of 75 Hz. The stimuli had a duration of 1000 ms with a 10 ms r/f time. The inter-stimulus interval varied between 3 and 7 seconds. All participants were asked to mentally count the target stimuli and maximum 10% error rate was allowed. All participants counted target stimuli sufficiently without any significant difference among groups ($p = 0.295$).

Offline data analysis was performed with Brain Vision Analyzer 2.1 (Brain Products GmbH; Gilching, Germany). Raw EEG data were filtered between 0.5–30 Hz at 12 dB per octave and segmented into 1000 ms epochs, time-locked to the stimulus onset (800 ms post-stimulus with a 200 ms pre-stimulus baseline). Epochs containing artifacts (e.g., eye-movements, muscle activity) were rejected offline by visual inspection. EEG data with at least 25 artifact-free epochs were averaged to obtain ERPs. Two PD-CN patients, one PD-MCI patient and two healthy controls were excluded at the beginning of the study due to insufficient number of epochs. The remaining 23 healthy controls, 23 PD-CN and 21 PD-MCI patients were included in further analysis. The number of artifact-free epochs did not differ among groups ($p = 0.081$). Mean P300 amplitudes and peak latency values for target stimuli were automatically measured from F_z, C_z, and P_z electrode sites in the 280–550 ms time window. Grand average ERP waveforms were computed for all groups.

2.4. MRI acquisition, preprocessing and analysis

Volumetric MRI scans were obtained according to the Alzheimer's Disease Neuroimaging Initiative (ADNI, www.adni.loni.usc.edu) protocol using a 1.5 Tesla Philips Achieva scanner (Philips Medical Systems, Best, The Netherlands) at Dokuz Eylul University Neuroradiology Unit, Izmir, Turkey. For each participant, a high resolution MRI scan was acquired with techniques including axial T2 weighted dual-echo (TR: 3000 ms, TE: 96/12 ms, FOV: 240 mm, matrix: 256, slice thickness: 3 mm, NSA: 1) and 3D T1 weighted TFE sequence (TR: 9 ms, TE: 4 ms, FOV: 240 mm, matrix: 256, slice thickness: 1 mm, NSA: 1).

The FMRIB Software Library (FSL; version 5.0; www.fmrib.ox.ac.uk/fsl) software package was used for volumetric analysis. Automatic segmentation of the subcortical GM structures (thalamus, caudate nucleus, putamen, globus pallidus, amygdala, hippocampus and nucleus accumbens) was performed on 3D T1 weighted scans by using FIRST (FMRIBs integrated registration and segmentation tool) (Patenaude et al., 2011) module from FSL. FIRST registers 3D T1 images to the MNI template and searches the most-probable shape. Next, the algorithm transfers the images back to native space, and then applies boundary correction before the final volume estimation. All structural volumes obtained from FIRST were normalized for head size by multiplying by volumetric scaling factor, automatically calculated using SIENAX (Structural Image Evaluation using Normalization of Atrophy Cross-Sectional) (Smith et al., 2002).

2.5. Statistical analysis

The SPSS version 22.0 for Windows (IBM; Armonk, NY, USA) was used for statistical analysis. Demographic and neuropsychological data of groups were compared with one-way ANOVA. Clinical characteristics such as Hoehn&Yahr score, UPDRS motor score, disease onset, and LED of the PD groups were analyzed using independent samples t-test.

Mean P300 amplitude and peak latency values for target stimuli were analyzed using repeated measures ANOVA. The repeated measures ANOVA included GROUP (3 levels: PD-CN, PD-MCI, healthy controls) as a between-subject factor and anterior-posterior electrode location [AP (3 levels: frontal, central, parietal)] as a within-subject factor. Greenhouse-Geisser corrected p-values were reported. Bonferroni correction was employed for post-hoc analyses. Receiver operating characteristic (ROC) curves with area under the curve (AUC) (95% CI) were computed in order to assess the cut-off value of P300 for distinguishing PD-MCI from PD-CN. The ROC analysis was performed only for P300 measures distinguishing PD-MCI from PD-CN.

One-way ANOVA was used to compare the subcortical GMV among groups and pairwise comparisons with Bonferroni correction were reported. The cross-correlations of P300 measures, composite z-scores for cognitive domains and subcortical GMV were explored using Pearson correlation analysis. Level of significance was corrected for multiple comparisons with Bonferroni correction. Correlations were computed on the whole sample as well as

within each group. $p < 0.05$ was considered as statistically significant in all analyses.

3. Results

3.1. Mean P300 amplitude values

There was a main GROUP effect on mean P300 amplitude values [$F_{(2,64)} = 15.336$; $p < 0.001$]. PD-CN patients showed reduced P300 amplitudes compared to healthy controls ($p = 0.044$). PD-MCI patients had lower P300 amplitudes than both PD-CN patients ($p = 0.009$) and healthy controls ($p < 0.001$). Mean P300 amplitudes across all groups are presented in Table 2.

Moreover, an interaction effect for AP × GROUP was detected [$F_{(4,3006)} = 4.143$; $p = 0.008$]. PD-CN patients had significantly lower P300 amplitudes at F_z electrode location compared with healthy controls ($p = 0.001$). PD-MCI patients showed lower P300 amplitudes than PD-CN patients at C_z ($p = 0.006$), and P_z ($p = 0.003$) and decreased amplitudes than healthy controls at F_z ($p < 0.001$), C_z ($p < 0.001$), and P_z ($p < 0.001$). A main effect of AP was also found [$F_{(2,1.503)} = 4.265$; $p = 0.026$], indicating P300 amplitudes were higher in central than frontal location ($p = 0.004$). The grand averages of P300 waveforms at F_z, C_z, P_z electrode locations and topographical maps of P300 for all groups between 300–550 milliseconds are shown in Figs. 1 and 2, respectively.

The ROC curve analyses for distinguishing PD-MCI from PD-CN demonstrated that the area under the curve of C_z electrode location was 0.758 [95% confidence interval (CI): 0.605–0.874]; whereas, the cut-off value to identify PD-MCI was 2.23 μv (sensitivity = 80.9%, specificity = 56.5%). For P_z electrode location, the area under the curve was 0.783 [95% CI: 0.633–0.893] and the optimal cut-off value was 1.66 μv (sensitivity = 80.9%, specificity = 69.6%).

3.2. Peak P300 latency values

There were no main GROUP effect on peak P300 latency values among groups [$F_{(2,64)} = 0.825$; $p = 0.443$]. No main effect of AP [$F_{(2,1.749)} = 1.750$; $p = 0.182$] or no interaction effect for AP × GROUP were detected [$F_{(4,3.498)} = 1.278$; $p = 0.285$]. The mean peak latency value was 393.71 ms (SE 6.83) in healthy controls, 376.14 ms (SE 8.85) in PD-CN patients, and 401.63 ms (SE 10.73) in PD-MCI patients.

3.3. Comparisons of subcortical GMV

One PD-MCI, two PD-CN patients and one healthy control did not participate in the MRI phase of the study. Thus, 22 healthy controls, 21 PD-CN, and 20 PD-MCI patients were included in the volumetric MRI analysis. No significant differences among groups regarding age ($p = 0.351$), gender ($p = 0.809$), education ($p = 0.127$) and hand dominance ($p = 0.807$) were present. The PD groups did not differ in terms of disease duration ($p = 0.261$), UPDRS motor score ($p = 0.386$), or Hoehn & Yahr stage ($p = 0.527$).

ANOVA results indicated that there was a statistically significant difference in putamen volume among groups ($p = 0.001$). Pairwise comparisons with Bonferroni correction demonstrated that the PD-MCI group had a significantly lower total volume of putamen compared to healthy controls ($p = 0.001$). There were no other significant subcortical GMV differences between PD-CN patients and healthy controls, or between PD-CN and PD-MCI patients. Comparisons of subcortical GMV among groups are presented in Table 3.

3.4. Correlations among P300, cognitive measures and subcortical GMV

Correlations were analyzed on the whole sample, as well as within each group. Only statistically significant correlations after Bonferroni correction were reported.

Whole sample. Moderate correlations were observed between P300 amplitudes and memory [for F_z ($r = 0.334$, $p = 0.006$); C_z ($r = 0.432$, $p < 0.001$); and P_z ($r = 0.470$, $p < 0.001$) electrode sites], and executive functions [for P_z ($r = 0.387$, $p = 0.001$)]. A negative moderate correlation was detected between globus pallidus volume and P300 latency [F_z ($r = -0.429$, $p < 0.001$)]. Moreover, putamen volumes were associated with attention ($r = 0.414$, $p = 0.001$) and executive functions ($r = 0.546$, $p < 0.001$).

Separate groups. No significant correlations were observed in PD-CN or healthy control groups. In the PD-MCI group, a negative strong correlation between globus pallidus volume and P300 latency [C_z ($r = -0.639$, $p = 0.002$)] was found.

All PD patients. Moderate correlations were found for P300 amplitudes with memory [P_z ($r = 0.466$, $p = 0.001$)] and executive functions [P_z ($r = 0.450$, $p = 0.002$)], and between P300 latency and attention [F_z ($r = -0.431$, $p = 0.005$)]. A negative strong correlation was detected between globus pallidus volume and P300 latency [F_z ($r = -0.520$, $p < 0.001$), C_z ($r = -0.517$, $p = 0.001$)]. Moreover, putamen volume was associated with executive functions ($r = 0.492$, $p = 0.001$). Correlation plots for PD patients are presented in Fig. 3.

4. Discussion

To the best of our knowledge, this is the first study investigating changes in ERP P300 and subcortical GMV of PD-CN and PD-MCI patients in comparison to healthy controls, using the current diagnostic criteria for PD-MCI (Litvan et al., 2012). The present study has revealed significant differences in P300 amplitudes among groups, and reduced putamen volumes in PD-MCI patients compared with healthy controls. We previously demonstrated reduced P300 amplitudes in PD-CN patients (Özmüş et al., 2017). The present study provides further support for P300 measures as an indicator of altered brain functions in PD-CN patients, where no structural or clinical evidence is present. In PD-MCI stage, a more diffused reduction in P300 amplitude was also accompanied by putaminal atrophy.

Cognitive ERPs have demonstrated a significant promise as an electrophysiological measure of cognitive functions in several psychiatric and neurological disorders in, which were linked to changes in levels of various neurotransmitters (Polich and

Table 2
Mean P300 amplitude values (in microvolts) to target stimuli of healthy controls, PD-CN and PD-MCI patients.

Electrode Locations	HC (n = 23)	PD-CN (n = 23)	PD-MCI (n = 21)	*p*	PD-CN vs HC	PD-MCI vs HC	PD-CN vs PD-MCI
F_z	3.27 ± 1.57	1.59 ± 1.05	0.83 ± 1.60	**<0.001**	**0.001**	**<0.001**	0.244
C_z	3.37 ± 1.73	2.50 ± 1.25	0.89 ± 1.93	**<0.001**	0.242	**<0.001**	**0.006**
P_z	3.11 ± 1.74	2.39 ± 1.36	0.67 ± 1.80	**<0.001**	0.431	**<0.001**	**0.003**

Values are presented as mean ± standard deviation unless indicated otherwise. HC: Healthy controls, PD-CN: Cognitively normal Parkinson's disease, PD-MCI: Mild cognitive impairment in Parkinson's disease. Results of the ANOVA model and pairwise comparisons with Bonferroni correction are reported. Values where the model is significant ($p < 0.05$) are highlighted in bold.

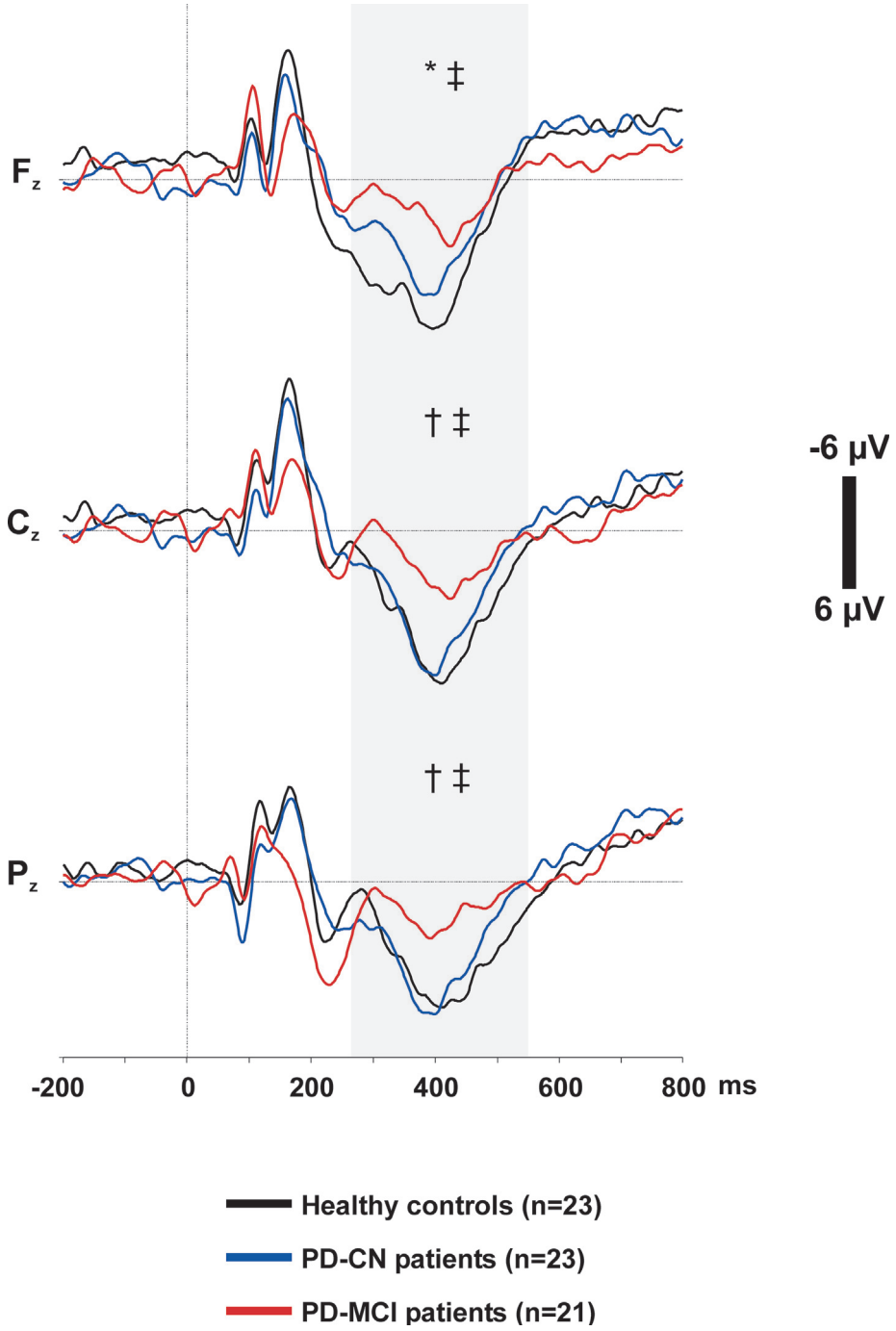

Fig. 1. The grand average ERP waveforms of study groups, time-locked to the target stimulus onset at F_z, C_z and P_z electrodes. The "*" indicates statistical significance between PD-CN and healthy controls, "†" between PD-MCI and PD-CN, and "‡" between PD-MCI and healthy controls.

Herbst, 2000). P300 is a sensitive measure of the allocation of attention toward a task-relevant event, working memory updating and decision making processes (Donchin and Coles, 1988; Polich, 2007). P300 alterations were found not specifically to cognitive impairments in PD, but can be observed in normal aging, and patients with Alzheimer's dementia, mild cognitive impairment or traumatic brain injury (Duncan et al., 2009). Considering its sensitivity in assessing impaired attention, it has been proposed as an indicator of neural events related to cognitive functions in also patients with PD (Seer et al., 2016).

The P300 arises from averaging the underlying oscillations. Previous studies of our group demonstrated decreased delta oscillatory responses among PD groups with various cognitive status (Emek-Savaş et al., 2017; Güntekin et al. 2018). These alterations in PD could be related to the progressive deterioration of the nigrostriatal dopaminergic system that lead to a disruption in circuits formed by cortico-basal ganglia-thalamo-cortical connections (Rodriguez-Oroz et al., 2009). Since non-dopaminergic neurotransmitter systems are associated to corticopetal projections and regulate synaptic features at cortical levels, they might take a role in alterations of post-synaptic pyramidal cells membrane potentials (see the recent review by Bočková and Rektor, 2018).

In the current study, consistent with our a priori hypotheses, PD-CN patients showed decreased P300 amplitudes over frontal

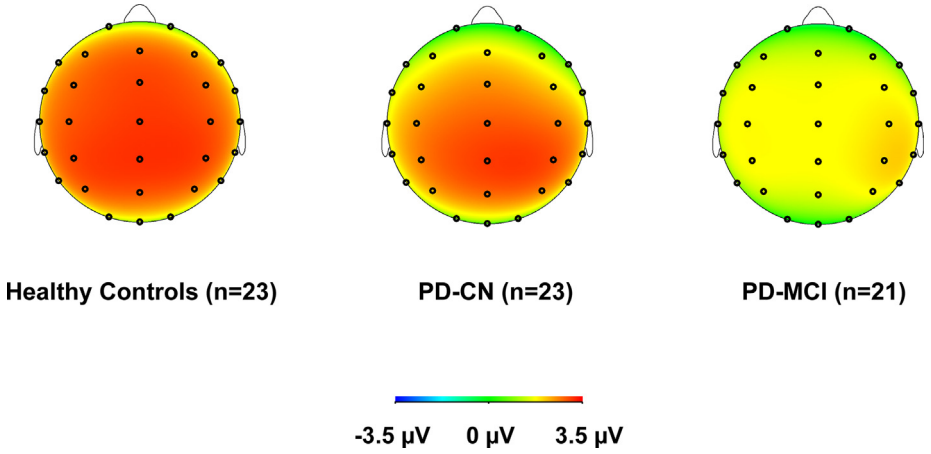

Fig. 2. Topographical map of P300 mean amplitude for all groups in time window of 300–550 milliseconds.

Table 3
Subcortical GMV among healthy controls, PD-CN and PD-MCI patients.

Subcortical GM Structures[a]	HC (n = 22)	PD-CN (n = 21)	PD-MCI (n = 20)	*p*
Thalamus	17.98 ± 1.48	18.43 ± 1.66	17.40 ± 1.83	0.147
Caudate	8.64 ± 0.82	8.62 ± 0.92	8.40 ± 0.83	0.604
Putamen	12.72 ± 1.45	11.99 ± 0.99	11.25 ± 1.22	**0.001**[‡]
Globus Pallidus	4.70 ± 0.61	4.79 ± 0.71	4.43 ± 0.74	0.224
Hippocampus	10.03 ± 1.17	9.50 ± 1.73	9.14 ± 1.48	0.152
Amygdala	3.23 ± 0.54	3.19 ± 0.52	3.12 ± 0.76	0.844
Nucleus Accumbens	1.27 ± 0.29	1.22 ± 0.33	1.10 ± 0.35	0.247

[a] Total volumes (mean ± standard deviation) are reported in cm^3. GMV: Gray matter volumes, HC: Healthy controls, PD-CN: Cognitively normal Parkinson's disease, PD-MCI: Mild cognitive impairment in Parkinson's disease. Results of the ANOVA model and pairwise comparisons with Bonferroni correction are reported.
[‡] Indicates statistical significance ($p < 0.05$) between PD-MCI and healthy controls.

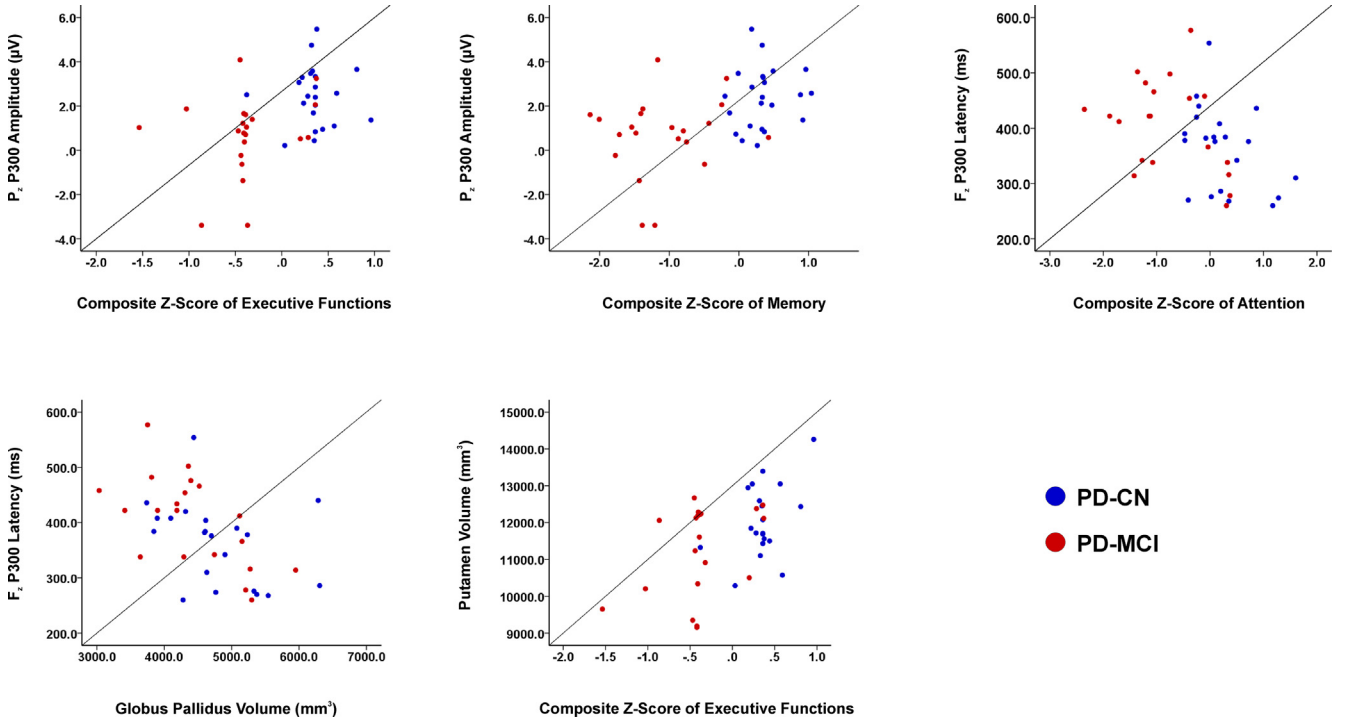

Fig. 3. Scatter-plots showing the significant associations between P300, Movement Disorders Society (MDS) cognitive domains and subcortical gray matter volumes (GMV) in the PD sample.

region, and a prominent reduction was observed over frontal-central-parietal regions in PD-MCI patients. Moreover, higher P300 amplitudes were associated with better performance in executive functioning and memory tests. There have been some discrepancies in previous literature regarding P300 amplitude. Many studies demonstrated reduced P300 amplitudes in non-demented

PD patients compared to healthy controls (Antal et al., 1996; Philipova et al., 1997; Jiang et al., 2000; Tsuchiya et al. 2000; Li et al., 2005), while others reported no difference (Toda et al., 1993; Karayanidis et al., 1995; Sagliocco et al., 1997; Wang et al., 1999; Katsarou et al., 2004). It is reasonable to assume that the previous study samples of non-demented PD included both PD-CN and PD-MCI patients. To the best of our knowledge, there is a single study in the literature comparing PD-CN and PD-MCI patients using an auditory oddball task, which reported lower frontal P300 amplitude and delayed latency in PD-MCI patients only (Yılmaz et al., 2017). More prominent findings in the current study can be explained by modality-specific impairment in PD. As previously shown in several studies, visual impairment is more prevalent than that of the auditory system in PD and causes dysfunction at both sensory and cognitive levels (Arrigo et al., 2017).

A recent review concluded that delayed P300 latency was associated with dementia in PD rather than PD itself (Seer et al., 2016). The current study provides further support as no significant difference in P300 latency was detected among groups. However, globus pallidus volume was found to be associated with P300 latencies in the whole sample as well as in PD patients, indicating the more P300 latencies were delayed, the lower are globus pallidus volumes. Moreover, lower scores in attention/working memory tests were related to delayed P300 latency in PD patients, supporting the role of globus pallidus in attentional networks (Bočková et al., 2011). The correlation with subcortical nuclei volumetry and P300 is novel. However, the literature data are rather scarce so far (Bočková et al., 2011; Beck et al., 2018) and the low sample size of the cohorts in the present study cannot provide a robust answer.

Subcortical GMV analyses elucidated another important finding of the current study as reduced putamen volume in PD-MCI compared with healthy controls. In line with our results, previous studies reported loss of dopaminergic innervation and/or metabolism (Kish et al., 1988; Nandhagopal et al., 2009) and decreased dendritic spine density (Zaja-Milatovic et al., 2005) in the putamen in PD patients. Several studies including non-demented PD samples found reduced putamen volumes compared to controls (Geng et al., 2006; Tinaz et al., 2011; Bilgiç et al., 2012; Melzer et al., 2012; Lee et al., 2014), while some others did not (Ghaemi et al., 2002; Peran et al., 2010; Messina et al., 2011). These discrepancies may be attributed to including a non-demented PD sample without differentiating PD-CN and PD-MCI patients. Differences in MRI parameters (e.g., magnet strength, voxel size), sample sizes, statistical methods, and disease severity may also explain the inconsistencies in the literature. A recent study by Gao et al. (2017) reported reduced putaminal volumes in PD-MCI patients compared to healthy controls, consistent with our study.

Previous studies reported reduced volumes of thalamus and nucleus accumbens in PD-MCI patients compared with both PD-CN patients (Mak et al., 2014; Foo et al. 2017) and healthy controls (Mak et al., 2015). Although controlling for clinical features between PD groups, studies by Mak et al. (2014) and Foo et al. (2017) did not include a healthy control group. In the present study, demographical variables, as well as clinical features of PD patients were well-matched in order to eliminate the possible confounding effects of age, gender, education and disease severity on our results. In line with previous studies (Melzer et al., 2012; Menke et al., 2014; Koshimori et al., 2015), we did not find any volumetric differences in caudate, hippocampus, amygdala, nucleus accumbens, thalamus and globus pallidus volumes among groups.

Very little is known about the role of putamen in cognition, despite the traditional role in motor symptoms of the disease. In the present study, putamen volume demonstrated the most robust associations with the measures of attention and executive functions. Higher volumes of putamen were related to better performances in tests assessing psychomotor speed, interference control, inhibition, mental flexibility, and verbal fluency, supporting the involvement of putamen in cognitive functions. Consistent with our findings, associations between structural and functional putaminal measures with executive functions and verbal fluency were reported in non-demented PD patients (van Beilen and Leenders, 2006; Mak et al., 2014). In a case study of Sefcsik et al. (2009), a left putaminal lesion was related to specific deficits in executive functions, suggesting circuits between putamen and frontal areas play a role in higher cognitive processing. In a recent study investigating subregional pattern of striatal dopamine depletion, it was detected that dopamine transporter availability in the anterior putamen was associated with attention/working memory, executive functions and visuospatial functions in drug naïve PD patients (Chung et al., 2018). Cortico-striatal circuity had greater complexity than the suggested traditional closed-loop models, which may not be segregated as once thought, highlighting the convergence of fields from different functional cortical regions (Haber, 2016).

Taken together, neuropsychological tests and subcortical GMV did not differ between PD-CN and healthy controls. Reduced P300 amplitudes in PD-CN patients were found whilst the neuropsychological test scores and volumetric measurements were within normal values. At the PD-MCI stage, a reduction in putaminal volume and P300 measures were observed in comparison to healthy controls. At this point, it can be only speculated that the reduced P300 amplitudes in PD-CN imply cognitive alterations before neuropsychological manifestations appear. Further longitudinal studies should be done to investigate this speculation.

The strengths of the current study include using cognitive electrophysiology and volumetric MRI measures together to assess functional and structural differences between PD-CN and PD-MCI patients in relation to healthy controls, while controlling for possible confounding factors such as demographic and clinical variables between PD groups. The possible limitations of this study are its relatively small sample size and not including PDD patients for comparison. This constraint impeded us to explore further associations between P300, subcortical GMV and cognitive impairment over a wider range of cognitive stages in PD.

5. Conclusions

By virtue of the growing recognition of PD-MCI as an important risk factor for progression to PDD, our findings provide support that cognitive changes in PD-CN patients not detected by either neuropsychological tests or subcortical GMV were revealed with P300 amplitudes. Neural changes were reflected as reduced P300 amplitudes over the frontal regions at PD-CN patients, which further spread to centro-parietal areas along with cognitive decline at the stage of PD-MCI. Moreover, putamen volume which was the sole structure having associations with cognitive functions was found to be reduced in PD-MCI in comparison to healthy controls. We, therefore, suggest that P300 amplitude may be a useful marker for the detection of preclinical changes before the appearance of cognitive and structural deterioration in PD.

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Compliance with Ethical Standards

Written informed consent was obtained from all patients/caregivers and healthy controls who participated in the study. Ethics

committee approval for this study was received from Non-Invasive Research Ethics Board of Dokuz Eylül University.

Declaration of Competing Interest

The authors have no actual or potential conflicts of interest.

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