Can volumetric magnetic resonance imaging evaluations be helpful in the follow-up of cognitive functions in cognitively normal Parkinson's disease patients?

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Abstract

Background/aim: In this study, besides the evaluation of gray and white matter changes in cognitively normal Parkinson's disease (PD-CN) patients with volumetric magnetic resonance imaging (MRI) parameters, it was tried to show that some neuropsychological tests may be impaired in PD-CN patients.

Materials and methods: Twenty-six PD-CN patients and 26 healthy elderly (HC) participants were included in the current study. Global cognitive status was assessed using the Mini-Mental State Examination (MMSE), and the Montreal Cognitive Assessment Scale (MoCA). Attention and executive functions were evaluated using the Wechsler Memory Scale-Revised (WMS-R) digit span test and Trail Making Test (TMT) Part A and Part B, Stroop test, semantic and phonemic fluency tests, and clock-drawing test. Magnetic resonance imaging (MRI) was acquired according to the Alzheimer's Disease Neuroimaging Initiative (ADNI) protocol.

Results: There were no significant differences among groups regarding age, gender, handedness, and years of education. In the comparison of the PD-CN group and the HC group, there was a statistical decrease in the total animal scores, lexical fluency, TMT part A and TMT part B scores in the PD-CN group. Subcortical gray matter volumes (GMV) were significantly lower in PD-CN patients. The PD-CN group had a significantly reduced total volume of right putamen and left angular gyrus compared to that in the HC group. We observed that putamen and angular gyrus volumes were lower in PD-CN patients. On the other hand, TMT-part B may be a useful pretest in detecting the conversion of mild cognitive impairment in PD.

Conclusion: Significant MRI volumetric measurements and neuropsychological test batteries can be helpful in the clinical follow-up in PD-CN patients.

Key words: Parkinson's disease, volumetric MRI, cognitive function, Wechsler memory scale-revised, trail making test

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease and mainly affects the motor system [1]. Besides motor symptoms, non-motor symptoms such as anosmia, sleep disorders, autonomic findings, pain, depression, anxiety, apathy, and cognitive impairment can occur at any stage of the disease, even before motor symptoms. The causes of cognitive dysfunction in PD are not fully understood, and a rate that is 25% in the early stages of the disease may increase to 80% in the late stages. It has been shown in many studies that there is volume loss in occipital, parietal and frontal cortices and atrophy in the hippocampus in PD with cognitive dysfunction [2-3]. There are few studies showing cortical and subcortical tissue volume loss in cognitively normal PD (PD-CN) patients without a diagnosis of cognitive impairment [4-9]. Testing of multiple cognitive areas in neuropsychological evaluation is quite difficult due to the lack of access to trained neuropsychologists and the variation in the educational and cultural levels of the patients [10]. Previous studies have demonstrated that neuropsychological assessments may be impaired in patients with Parkinson's disease within normal cognitive test scores ranges [11-12].

The aim of this study is to evaluate gray and white matter changes in PD-CN patients with volumetric magnetic resonance imaging (MRI) parameters. In addition, we aimed to show that some neuropsychological tests may be impaired in PD-CN patients.

2. Methods

2.1. Participant selection

Twenty-six PD-CN patients (mean age 65.69 ± 9.20 years; 6 female, and 20 male) and 26 healthy elderly participants (HC) (mean age 66. 38 ± 6.84 years; 8 female, and 18 male) were included in the current study. Patients with PD-CN were recruited from the Movement Disorders Outpatient Clinic in the Department of Neurology at Dokuz Eylül University Hospital. The diagnosis of idiopathic PD was clinically determined based on the UK

Parkinson's Disease Society Brain Bank criteria [13]. The severity of motor symptoms was assessed by The Unified Parkinson's Disease Rating Scale (UPDRS) Part III [14] whereas disease severity was examined using the Hoehn and Yahr scale [15].

The inclusion criteria for patients with PD-CN were: (1) having a clinical diagnosis of idiopathic PD; (2) control of motor symptoms with stable dopaminergic treatment; and (3) Hoehn and Yahr stage III or less. The exclusion criteria for PD-CN group were as follows: (1) a clinical diagnosis of PD-mild cognitive impairment [16] and PD-dementia [17], supported by detailed neuropsychological assessments; (2) a history of psychiatric disorders and/or visual hallucinations with the use of medications affecting cognition (e.g. antidepressants, antipsychotics); (3) patients with a history of drug-induced dopamine dysregulation; (4) the presence and/or a history of vascular lesions, head trauma, seizures, and/or strokes; (5) severe tremors preventing MRI scans and, (6) treatment with deep brain stimulation, jejunal levodopa and/or subcutaneous apomorphine. Accordingly, one patient was excluded due to severe motion artifacts in MRIs.

A further 26 healthy elderly participants were enrolled from various community sources via bulletin board announcements. The exclusion criteria for the healthy elderly group were: (1) a history or presence of any neurological abnormalities and/or cognitive impairment (Mini-Mental State Examination, MMSE, scoring $\leq$ 27), (2) a history of psychiatric disorders, cerebral atrophy, vascular lesions, head trauma, seizures, strokes, alcohol and/or drug abuse misuse. Participants with depressive symptoms (scoring >14 on the Yesavage Geriatric Depression Scale, GDS [18-19]) were also excluded from all groups.

All PD-CN patients were on the following anti-Parkinsonian treatment at the time of assessments: L-dopa monotherapy (n=9), dopamine agonist monotherapy (n=4), MAO-B inhibitor (n=1) or a combined treatment (n=12). Levodopa equivalent daily doses (LEDD) were calculated using a standardized formula for all the dopamine replacement therapies that PD-

CN patients were taking [20]. The neuropsychological and volumetric MRI assessments of the PD-CN patients were performed during their "on" periods.

All subjects in this study were among the participants in the prior study by Hünerli-Gündüz et al. [21]. All participants provided written informed consent prior to voluntary participation in the study, and the study protocol was approved by the Non-Invasive Research Ethics Board of Dokuz Eylul University with the approval number of 2018-10-38 on April 12, 2018.

2.2. Neuropsychological assessment

Neuropsychological performance was evaluated by trained neuropsychologists. Global cognitive status was assessed using the Mini-Mental State Examination (MMSE, [22]) and the Montreal Cognitive Assessment Scale (MoCA, [23]). Attention and executive functions were evaluated using the Wechsler Memory Scale-Revised (WMS-R) digit span test [24] and Trail Making Test (TMT*)* Part A and Part B [25], Stroop test [26], semantic and phonemic fluency tests, and clock-drawing test [27].

2.3. MRI acquisition, preprocessing, and analysis

MRI was acquired according to the Alzheimer's Disease Neuroimaging Initiative (ADNI, www.adni.loni.usc.edu) protocol. For each subject, a high resolution T1-weighted volumetric MRI scan was obtained at the Dokuz Eylül University Neuroradiology Unit, İzmir, Turkey, using the 1.5 Tesla Philips Achieva system, including coronal 3D T1-weighted TFE sequences (TR: 9 ms, TE: 4 ms, FOV: 240 mm, matrix: 256, slice thickness: 1 mm, and NSA: 1). Gray matter volume measurements were performed with the CAT12 Toolbox (Computational Anatomy Toolbox, http://dbm.neuro.uni-jena.de/cat/) in the MATLAB-based (Mathworks, Sherborn, MA, USA) SPM12 software (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/software/spm12).

3D T1-weighted images were first converted from the DICOM format to the NIFTI format. Secondly, the starting points of the images were manually corrected so that the x, y, z coordinates of the anterior commissure corresponded to the 0,0,0 point. This was done to align the MRI images to the Montreal Neurological Institute (MNI) template. Thirdly, the segmentation process was carried out using the parameters recommended in the CAT12 user manual.

As a result of the segmentation process, 3D T1-weighted images were separated into gray matter, white matter, and cerebrospinal fluid. The CAT12 "Estimate Mean Values inside Region of Interest (ROI)" function was applied using the LPBA40 (LONI Probabilistic Brain Atlas, 101) atlas to obtain mean volume values in different ROIs. Average volume values for each ROI were extracted separately.

Gray matter volumes (GMV) were also normalized to eliminate differences due to individuals' head size. The normalization process was performed by multiplying each volume value obtained with the volumetric normalization coefficient automatically calculated by SIENAX (Structural Image Evaluation using Normalization of Atrophy Cross-Sectional, [28]).

2.4. Statistical analysis

SPSS 25.0 (IBM Corporation, Armonk, New York, United States) and Medcalc 14 (Acacialaan 22, B-8400 Ostend, Belgium) programs were used to analyze the variables. The conformity of the data to the normal distribution was evaluated with the Shapiro-Wilk Francia test, while the homogeneity of variance was evaluated with the Levene test. In the comparison of two independent groups according to quantitative variables, the Independent-Samples t-test was used together with the Bootstrap results, while the Mann-Whitney U test was used together with the Monte Carlo results. In the comparison of the categorical variables with each other, the Pearson chi-squared and Fisher’s exact tests were tested with the Monte Carlo Simulation technique. Sensitivity, specificity, positive predictivity and negative predictivity ratios for the

relationship between the classification of the cut-off value were calculated according to the variables and the actual classification. These were analyzed and expressed by ROC (Receiver Operating Curve) analysis. The logistic regression test was used with the Backward method to determine the cause-effect relationship between the categorical dependent group variable and the explanatory variables. While quantitative variables were expressed as mean (standard deviation) and median (Minimum - Maximum) in the tables, categorical variables were shown as n (%). The variables were analyzed at a 95% confidence level, and a p-value of less than 0.05 was considered significant.

3. Results

The demographic, clinical and neuropsychological characteristics of the patients and healthy controls are shown in Tables 1 and 2 (Table 1, 2). There were no significant differences among groups regarding age, gender, handedness, and years of education.

3.1. Neuropsychological tests of PD-CN

In the comparison of the PD-CN group and the HC group, there was a statistically significant decrease in the total animal scores, lexical fluency, TMT part A and TMT part B scores in the PD-CN group (Table 2). The ROC curves for the neuropsychological test scores were demonstrated in Figure 1. Figure 1a represents total animal score, Figure 1b indicates K-A-S score, Figure 1c shows trail making test Part A score, and Figure 1d presents trail making test Part B score are presented in graphics.

3.2. Volumetry

There was a statistically significant decrease in volumes of the right putamen and left angular gyrus of PD-CN patients in comparison to healthy controls. Figure 2 demonstrates the subcortical GMV volume differences between PD patients and healthy controls. A comparison of white matter density changes between PD-CN and HC groups revealed no significant

differences (Table 3, 4, 5). The ROC curves for MRI volumetric analysis correlation graphs were presented in Figure 3; Figure 3a represents left angular gyrus, Figure 3b for left inferior frontal gyrus, Figure 3c for left middle frontal gyrus, Figure 3d for right middle frontal gyrus, Figure 3e for right putamen, and Figure 3f for right superior frontal gyrus.

3.3. Associations between Volumetry and NPT

Regarding the correlations between volumetric analysis and neuropsychological tests in PD-CN, there was a significant effect between the reduction in putamen and angular gyrus volume and the decline in executive function in PD-CN patients (Table 5).

4. Discussion

Cognitive impairments in PD are not limited to a specific cognitive area. Cognitive function deteriorates slowly and heterogeneously in PD, and many different regions can accompany this deterioration. There is no standardized neuropsychological test or a radiological parameter for the early detection of cognitive dysfunction that accompanies PD. This situation becomes more challenging especially in PD-CN. In the current study, the TMT-part B within an extensive neuropsychological test battery differed at group level in the PD-CN. It is noteworthy that commonly used screening tools, such as MMSE [29,30], and MoCA [31] could be unimpaired even at the group level at the stage of normal cognition of PD. Since executive functions are the first to be disrupted in PD, TMT-part B may be impaired. Global cognitive scales such as MMSE and MOCA may not reflect the initial impairment in executive function [32-33]. Therefore, the TMT-part B may be a useful test in detecting cognitive impairment in PD-CN patients.

Volumetric MRI findings of subcortical gray matter in PD-CN patients of the present study indicated a decrease in volumes of the right putamen and left angular gyrus in comparison to healthy controls. This finding implies that regional GMV loss appears in the earliest disease stages, even in cognitively intact patients.

The role of subcortical structures in cognition remains elusive. Several recent studies on healthy participants demonstrated that higher putamen volume has positive effects on attention and executive functions [3, 34-37]. Previous studies frequently reported diffuse

cortical atrophy in limbic, temporal, prefrontal, occipital, and parietal areas in PD patients with cognitive impairment and dementia [2, 7, 38]. However, information in PD-CN patients is scarce and diverse, and several studies indicated normal cortical volume in patients with PD-MCI [39-41], as well as those that report dysfunction in temporal, parietal and occipital cortical involvement patterns [4-9]. It has been shown in the literature that GMV loss becomes more prominent in the temporal, parietal and frontal regions in PD with mild cognitive impairment [1,7,42], and widespread GMV loss occurs when the disease progresses to the dementia phase [36,43-47].

In the present study, we also found that poor performances of PD-CN on TMT-part B test, thus, impairments in executive functions were associated with the reduction in putamen and angular gyrus volume and the decline in executive function in PD-CN patients. In the meta-analysis by He et al. [34], structural and functional changes in the brains of PD's patients occur at different rates and in different brain regions. Furthermore, increasing gray matter loss as the disease progresses leads to functional deterioration. Atrophy was prominent in the midcingulate gyrus and right supramarginal gyrus in PD-MCI, and in the left insula spreading to the bilateral insular area in PD with dementia.

The Pentagon copying test in PD patients without dementia has been shown to be significantly associated with volumetric reductions in cortical regions such as the right complement motor area, left rostral mid-frontal cortex, pars triangularis, and left cuneus. This study demonstrated that subtle changes in multiple cognitive domains in PD without dementia are associated with regional volumes in certain systems that play a role in the development of cognitive impairment [9]. Another study showed that both the MMSE and the Pentagon copying test reflected regional brain degeneration often found in posterior regions, but that the Pentagon copying test was associated with more areas and larger cluster sizes [48]. In a study using TMT B-A scores (the time difference between performance on TMT-A and TMT-B),

significant negative correlations were detected bilaterally in the left precentral/middle frontal cortex, right posterior cingulate area, anterior cingulate and complementary motor area. In addition, more specifically, it was stated that low GM volume values in these regions may be associated with high TMT B-A time scores [49]. Our data support the use of TMT-part B as a tool in patient care to monitor the development of cognitive status in PD-CN patients.

One of the limitations of the current study include a small number of cases and the fact that it was limited to a single tertiary institution. Another point is that identifying patients progressing to PD-MCI, and determining which neuropsychological test scores decline in time may be crucial. This study will enable a more thorough exploration to establish how certain neuropsychological tests associate to cortical and subcortical structural alterations as PD-MCI develops. In this study, the demographic variables and clinical characteristics of PD patients were well matched to eliminate the possible confounding effects of age, gender, education, hand dominance, medication use, and disease onset on our results. We suggest that the subcortical volume reductions detected in volumetric MRI can be used as a tool in the follow-up of cognitive functions in PD-CN patients.

5. Conclusion

As a remarkable result of our study, we observed that putamen and angular gyrus volumes were lower in PD-CN patients at the group level. On the other hand, TMT-part B may be a useful pretest in detecting the conversion of mild cognitive impairment in PD. Therefore, significant MRI volumetric measurements and neuropsychological test batteries can be helpful in the clinical follow-up in PD-CN patients.

Conflict of interest

All authors declare that they have no conflict of interest.

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Informed consent

All participants provided written informed consent prior to voluntary participation in the study, and the study protocol was approved by the Non-Invasive Research Ethics Board of Dokuz Eylul University with the approval number of 2018-10-38 on April 12, 2018.

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TABLES (1-5)

Table 1

The demographic and clinical characteristics of PD patients and healthy controls.

	Total (n=52) Mean±SD	**HC-GMV (n=26) Mean±SD**	**PD-CN GMV (n=26) Mean±SD**	**p**
Age	66.04±8.03	66.38±6.84	65.69±9.20	0.741
MMSE	28.79±1.33	29.12±1.11	28.46±1.48	0.077
	n (%)	**n (%)**	**n (%)**	
Gender				0.755
Female	14 (26.9)	8 (30.8)	6 (23.1)	
Male	38 (73.1)	18 (69.2)	20 (76.9)	
Education (years)	11 (5-17)	11 (5-17)	8 (5-15)	**0.049***
Hand Dominance				0.49
Left	2 (3.8)	2 (7.7)	0 (0.0)	
Right	50 (96.2)	24 (92.3)	26 (100.0)	
PD Medications				
Levodopa	9 (34.6)	-	9 (34.6)	-
Dopamine agonist	4 (15.4)	-	4 (15.4)	-
MAO-B inhibitors	1 (3.8)	-	1 (3.8)	-
Combined	12 (46.2)	-	12 (46.2)	-
	Median (min-max)		**Median (min-max)**	
Hoehn Yahr Score	2 (1-3)	-	2 (1-3)	
UPDRS Motor Score	22.5 (6-36)	-	22.5 (6-36)	
MOCA Score	24.5 (13-30)	-	24.5 (13-30)	
Disease Onset (years)	3 (1-10)	-	3 (1-10)	-
Daily Levodopa Dose	550 (120-1382)	-	550 (120-1382)	-

Abbreviations: HC, healthy elderly participants (control); PD, Parkinson's Disease; GMV, Gray matter volume; SD, Standard Deviation; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; min, minimum; max, maximum; n, number, %, percent; *p<0.05.

Table 2

The neuropsychological test scores of PD patients and healthy controls.

	Total (n=52) Mean±SD	**HC-GMV (n=26) Mean±SD**	**PD-CN GMV (n=26) Mean±SD**	**p**
Volumes				
GM	41.75±2.47	42.24±2.26	41.27±2.61	0.144
WM	36.22±2.27	35.96±2.36	36.49±2.18	0.400
Matter				
Gray	41.75±2.47	42.24±2.26	41.27±2.61	0.144
White	36.22±2.27	35.96±2.36	36.49±2.18	0.400
Neuropsychological Test Scores				
Interference (in seconds)	43.31±13.75	40.81±12.49	45.81±14.72	0.210
Toral Animal	22.33±4.44	23.92±4.65	20.73±3.64	0.013
Total K-A-S	36.06±12.33	40.23±11.87	31.88±11.54	0.014
	Median (min-max)	Median (min-max)	Median (min-max)	
Total GDS	5 (0-11)	3.5 (0-11)	6 (2-11)	0.065
Digit Span Forward	6 (4-8)	5.5 (4-8)	6 (4-8)	0.882
Digit Span Backward	4 (3-7)	4 (3-7)	4 (3-6)	0.420
Total Clock Drawing	10 (6-10)	10 (8-10)	10 (6-10)	0.112
Trail Making Test (measured in the seconds to complete the task				
Part A	60.31±23.71	50.42±14.31	70.19±27.18	0.010*
Part B	138.27±58.58	112.23±31.91	164.31±67.61	0.004*
Part B-A	78.62±39.81	61.85±25.01	95.38±44.97	0.004*

Abbreviations: HC, healthy elderly participants (control); PD, Parkinson's Disease; GMV, Gray matter volume; SD, Standard Deviation; min, minimum; max, maximum; n, number, %, percent; GDS, Geriatric Depression Scale; *p<0.05; **p<0.001

Table 3

The subcortical GMV volumes assessment of the patients and healthy controls

	Total (n=52) Mean±SD	**HC GMV (n=26) Mean±SD**	**PD-CN GMV (n=26) Mean±SD**	**p**
Total Brain	77.98±3.35	78.20±3.03	77.75±3.69	0.635
Bothside Cerebellar Lobe	5.84±0.60	5.81±0.64	5.86±0.57	0.803
Bothside Brainstem	0.13±0.02	0.13±0.02	0.13±0.02	0.939
Superior Frontal Gyrus				
Left	1.91±0.13	1.93±0.10	1.89±0.14	0.286
Right	1.88±0.13	1.89±0.11	1.86±0.15	0.432
Middle Frontal Gyrus				
Left	1.41±0.11	1.43±0.11	1.40±0.10	0.325
Right	1.45±0.12	1.48±0.13	1.42±0.10	**0.046**
Inferior Frontal Gyrus				
Left	0.66±0.06	0.68±0.07	0.65±0.06	**0.036**
Right	0.71±0.06	0.73±0.06	0.70±0.06	0.149
Precentral Gyrus				
Left	0.74±0.08	0.75±0.08	0.73±0.08	0.49
Right	0.72±0.07	0.72±0.07	0.73±0.06	0.79
Middle Orbitofrontal Gyrus				
Left	0.34±0.03	0.35±0.03	0.34±0.04	0.166
Right	0.35±0.03	0.36±0.03	0.35±0.03	0.116
Lateral Orbitofrontal Gyrus				
Left	0.23±0.02	0.23±0.03	0.23±0.02	0.350
Right	0.20±0.02	0.20±0.02	0.20±0.02	0.753
Gyrus Rectus				
Left	0.13±0.01	0.13±0.01	0.13±0.01	0.831
Right	0.13±0.01	0.13±0.01	0.13±0.01	0.623
Postcentral Gyrus				
Left	0.61±0.07	0.61±0.07	0.60±0.06	0.682
Right	0.58±0.06	0.58±0.06	0.58±0.06	0.712
Superior Parietal Gyrus				
Left	0.76±0.07	0.76±0.06	0.76±0.07	0.790
Right	0.75±0.07	0.77±0.07	0.74±0.07	0.216
Supramarginal Gyrus				
Left	0.48±0.04	0.49±0.04	0.48±0.05	0.314
Right	0.48±0.04	0.48±0.04	0.47±0.05	0.478
Angular Gyrus				
Left	0.62±0.06	0.64±0.05	0.60±0.07	**0.022**
Right	0.69±0.07	0.70±0.06	0.68±0.07	0.152
Precuneus				

Left	0.44±0.05	0.45±0.05	0.44±0.04	0.377
Right	0.44±0.05	0.45±0.05	0.44±0.05	0.434
Superior Occipital Gyrus				
Left	0.24±0.03	0.24±0.03	0.24±0.03	0.815
Right	0.26±0.03	0.26±0.03	0.25±0.03	**0.040**

Table 4

The subcortical GMV volumes assessment of the patients and healthy control (continued from Table 3)

	Total (n=52)	**HC-GMV (n=26)**	**PD-CN GMV (n=26)**	**p**
	Mean±SD	**Mean±SD**	**Mean±SD**	
Middle Occipital Gyrus				
Left	0.75±0.08	0.77±0.07	0.72±0.08	**0.031***
Right	0.78±0.07	0.78±0.07	0.77±0.07	0.458
Inferior Occipital Gyrus				
Left	0.41±0.04	0.42±0.04	0.40±0.05	0.074
Right	0.42±0.04	0.42±0.04	0.42±0.04	0.603
Superior Temporal Gyrus				
Left	1.07±0.07	1.09±0.08	1.06±0.07	0.119
Right	1.01±0.09	1.03±0.09	1.00±0.08	0.197
Middle Temporal Gyrus				
Left	0.91±0.08	0.93±0.08	0.89±0.07	0.138
Right	0.96±0.08	0.97±0.10	0.95±0.07	0.336
Inferior Temporal Gyrus				
Left	0.86±0.06	0.87±0.06	0.85±0.05	0.206
Right	0.91±0.08	0.92±0.08	0.89±0.07	0.162
Lingual Gyrus				
Left	0.48±0.05	0.48±0.04	0.47±0.05	0.387
Right	0.49±0.05	0.49±0.04	0.48±0.05	0.176
Fusiform Gyrus				
Left	0.54±0.04	0.55±0.05	0.54±0.04	0.647
Right	0.53±0.04	0.54±0.04	0.53±0.04	0.489
Insula				
Left	0.38±0.04	0.38±0.03	0.37±0.04	0.532
Right	0.36±0.03	0.36±0.03	0.35±0.03	0.581
Cingulate Gyrus				
Left	0.51±0.04	0.52±0.04	0.50±0.04	0.13
Right	0.58±0.05	0.59±0.04	0.58±0.06	0.321
Caudate				
Left	0.16±0.02	0.16±0.02	0.16±0.02	0.651
Right	0.15±0.02	0.15±0.02	0.15±0.02	0.898
Putamen				
Left	0.23±0.03	0.24±0.03	0.22±0.03	0.056
Right	0.23±0.03	0.24±0.03	0.22±0.03	**0.033***

Hippocampus				
Left	0.23±0.02	0.23±0.02	0.23±0.02	0.206
Right	0.24±0.02	0.24±0.02	0.24±0.02	0.252
Cuneus				
Left	0.21±0.03	0.22±0.02	0.21±0.03	0.315
Right, median (min-max)	0.23 (0.16-0.26)	0.23 (0.18-0.25)	0.22 (0.16-0.26)	0.107
Parahippocampal Gyrus				
Left, median (min-max)	0.25 (0.18-0.29)	0.24 (0.21-0.29)	0.25 (0.18-0.28)	0.999
Right	0.25±0.02	0.26±0.02	0.25±0.02	0.317

Table 5

Subcortical GMV and TMT part B assessment

Dependent reference	***Age and Gender Adjusted***				***Age and Gender Not Adjusted***			
Group: (PD-CN-GMV)	**Odds Ratio**	**95% C.I. for Odds Ratio**		**p**	**Odds Ratio**	**95% C.I. for Odds Ratio**		**p**
		Lower	**Upper**			**Lower**	**Upper**	
Trail Making Test Part B (> 154)	94.1	4.7	1882.1	**0.003***	75.6	5.7	997.1	**0.001****
Left Angular Gyrus (≤ 0.61)	12.7	1.5	111.5	**0.022***	9.5	1.5	61.4	**0.018***
Right Putamen (≤ 0.22)	17.2	1.9	152.7	**0.011***	11.0	1.7	69.5	**0.011***
	Cut point	**PD-CN GMV**	**HC GMV**	**All**	**Cut point**	**PD-CN GMV**	**HC GMV**	**All**
Predicted ratio	**0.617**	**76.9**	**92.3**	84.6	**0.617**	**80.8**	**92.3**	86.5

Figure Legends

Figure 1. Total animal score (a), K-A-S (b), trail making test Part A (c) and Part B (d) results are presented in graphics.

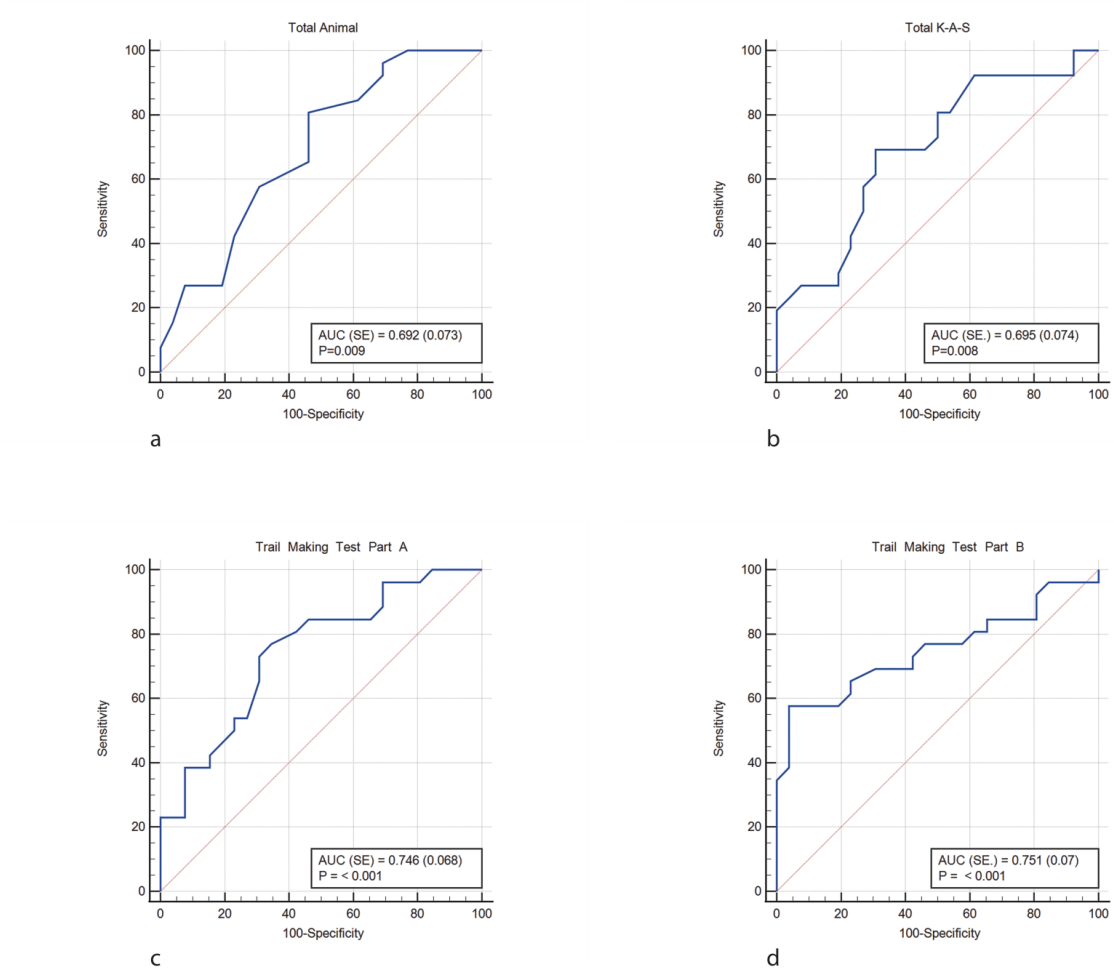


Figure 2. Subcortical GMV volume differences between PD patients and healthy controls are demonstrated in graphics.

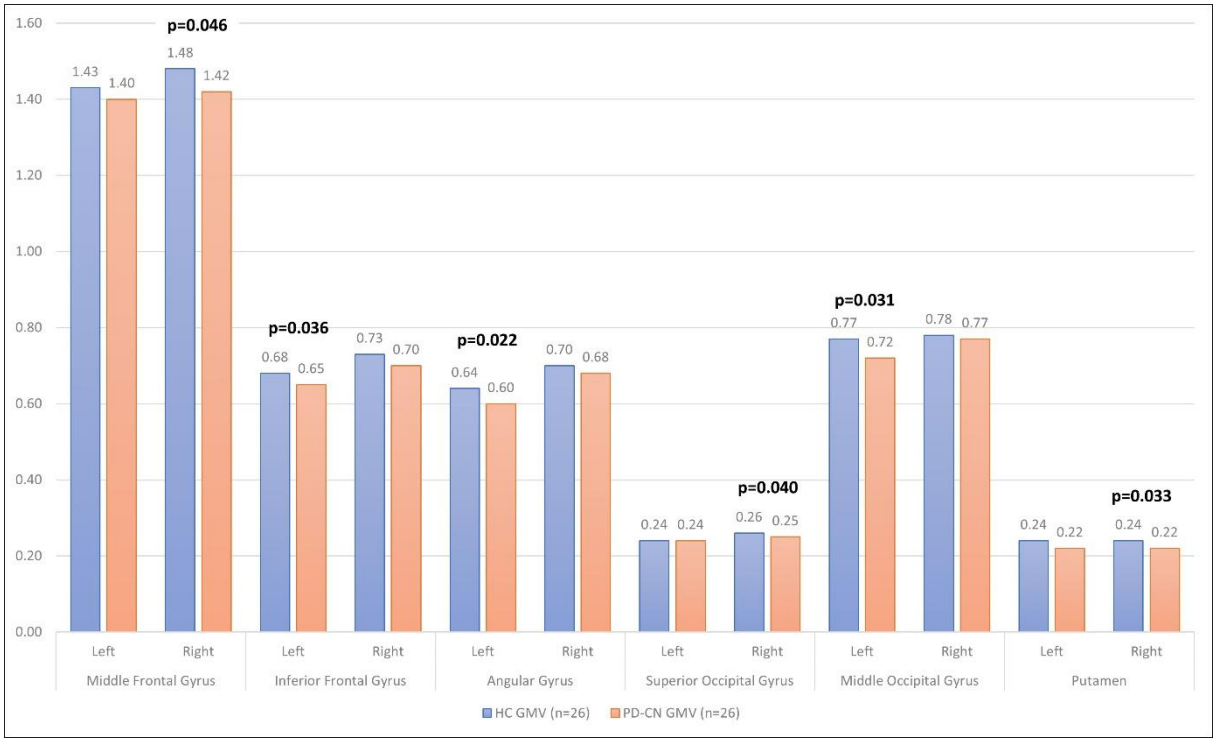
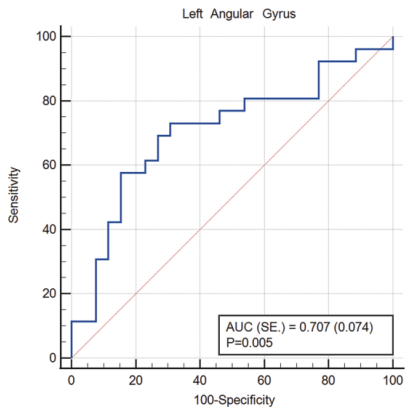


Figure 3. Left angular gyrus (a), left inferior frontal gyrus (b), left middle frontal gyrus (c), right middle frontal gyrus (d), right putamen (e), right superior frontal gyrus (f) MRI volumetric analysis correlation graphs.



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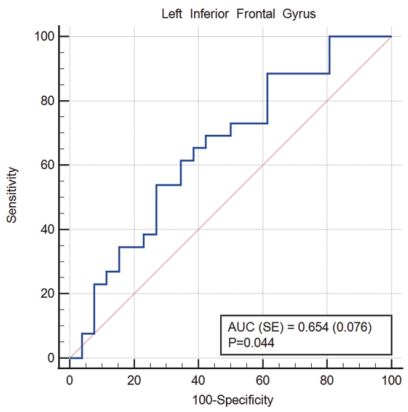

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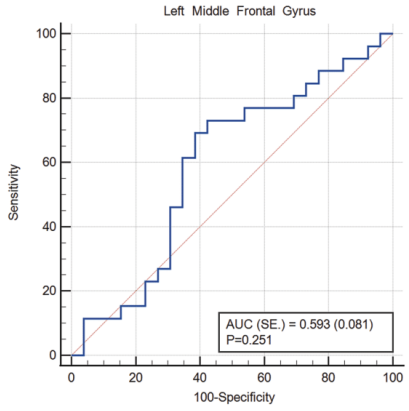

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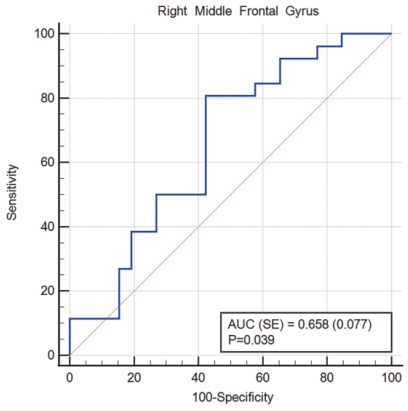

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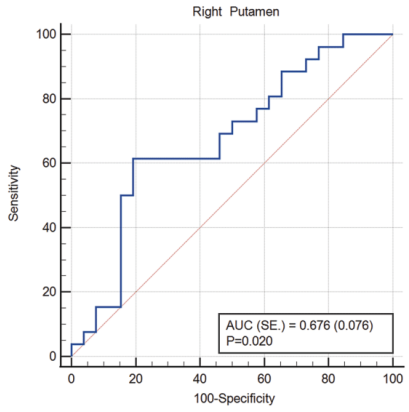

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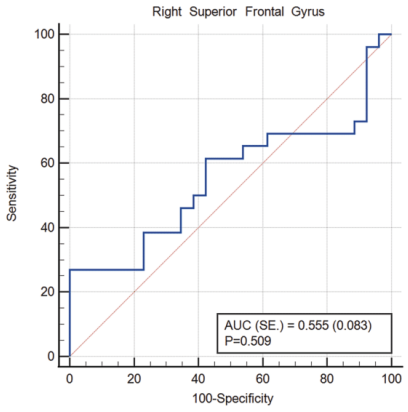

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