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The Comparison of Functional Connectivity in Parkinson's Disease Patients with and without Parkin Gene Mutations

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ABSTRACT

Aim: Mapping the functional connectivity of brain regions became appealing in recent research in neurology. Accordingly, a growing body of evidence shows resting-state functional connectivity (rsFC) changes in neurodegenerative disorders including Parkinson's Disease (PD). As characterised by extensive and progressive dopaminergic loss in the substantia nigra, PD emerges with serious motor and non-motor dysfunctions. In the literature, the minority of PD cases have been associated with certain genetic mutations. The aim of this study was to investigate the rsFC in a group of PD patients having Parkin gene mutation.

Method: Twelve PD patients with Parkin mutation (PP-PD), 12 PD patients without Parkin mutation (PN-PD) and 12 healthy controls (HC) were included in the study. All participants underwent a resting-state functional magnetic resonance imaging as well as a neuropsychological assessment and clinical examination.

Results: Results indicated that PP-PD had longer disease duration, a higher rate of dyskinesia and lower scores on complex visual perception tests. The resting state networks showed that all PD (consisting of PP-PD and PN-PD) and PP-PD groups had increased functional connectivity in the frontoparietal network as compared to the HC. In addition, the PP-PD group displayed decreased functional connectivity in the dorsal attention network compared to the PN-PD.

Conclusion: In conclusion, our data suggests that PD with Parkin gene mutation might be emerging with distinct resting state functional connectivity changes in the brain.

Keywords: functional connectivity, functional magnetic resonance imaging, independent component analysis, Parkin, Parkinson's Disease

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INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder characterised by motor symptoms such as bradykinesia, rigidity, tremor, and postural instability; commonly accompanied by several non-motor symptoms such as pain, autonomic disturbances, sleep disturbances, and cognitive dysfunction (1). Affecting more than 10 million patients worldwide, it is listed as the most prevalent neurodegenerative disorder following Alzheimer's disease. The progressive death of dopaminergic neurones in substantia nigra pars compacta is accepted to be the core neuropathology of PD.

In the last decades, functional magnetic resonance imaging (fMRI) has allowed researchers to explore disease-specific functional network alterations in brain disorders, including PD. The majority of these studies

Highlights

- **Parkin gene mutation may alter resting state functional connectivity (rs-FC) in PD.**
- **Parkin gene mutation is related with longer disease duration and more dyskinesia.**
- **Parkin gene mutation may alter rs-FC of frontoparietal and dorsal attention networks.**
- **rs-FC of dorsal attention network may be linked to visuospatial functions in PD.**

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focus on patterns of functional connectivity changes during resting state. Accordingly, resting state fMRI studies conducted with PD patients have consistently reported disrupted connectivity in widely distributed cortical and subcortical networks that have been associated with motor and non-motor symptoms of the disease (2,3). In addition to bridging a gap between neural network patterns and clinical progression; resting-state functional connectivity might be a potential biomarker for different types of PD.

While most cases of PD are reported as sporadic, young-onset PD is mostly associated with various genetic mutations. Amongst them, Parkin gene (PARK2) mutations are considered to be the most frequent form of autosomal recessive PD (4). Although different mutation frequencies have been reported across studies, Parkin gene mutations account for approximately % 15 of early-onset PD cases (5,6). It is also the most frequently reported mutation amongst early-onset PD cases in Turkey (7).

Bilgiç et al. (8) reported that PD patients with Parkin gene mutations had decreased volume in bilateral caudate nuclei compared to idiopathic early-onset PD. However, there is a lack of literature regarding neural connectivity changes in PD with Parkin mutations. The present study aims to assess resting state functional connectivity changes of PD patients having Parkin gene mutations and to show whether there is an association between the connectivity changes and cognitive performance.

METHOD

Participants

Patients having PD were recruited from Istanbul University Istanbul Faculty of Medicine Department of Neurology Behavior and Movement Disorders Polyclinic. The diagnosis was made by professors of neurology, based on the UK Parkinson Society Brain Bank criteria. Patients with the diagnosis of dementia, current major depression or psychosis, or any neurodegenerative disorder except PD were not included in the study. History of PD surgery was also set as exclusion criteria. Minimum primary school graduation was also required. Twelve PD patients with homozygous Parkin mutation (PP-PD) (4 women, 8 men; mean age 45.67 ± 5.33 years) and 12 PD patients (PN-PD) without Parkin mutation (3 women, 9 men; mean age 49.08 ± 5.63 years) were selected for the study. Twelve neurologically healthy individuals (4 women, 8 men; mean age 49.58 ± 7.16 years) were included as the healthy control group (HC). No significant group differences were present regarding age and gender. The mean education years were 7.00 ± 2.92 for the PP-PD group, 9.42 ± 2.96 for the PN-PD group, and 9.58 ± 3.11 for the HC group ($p > 0.05$). A venous whole blood sample was collected from all PD patients to screen for Parkin gene mutation. Accordingly, pedigrees are drawn, and peripheral blood samples are collected following the signed informed consent. Gross mutations by MLPA (Multiplex Ligation-dependent Probe Amplification) and small ones by Parkinson-gene-panel on Ion Torrent platform (next generation sequencing) are searched (SNCA, PRKN, UCHL1, PINK1, DJ1, LRRK2, ATP13A2, TH, MAPT, CP, C10orf72, GAK, ATP1A3, GBA, DCTN1, PRKRA, SLC6A3, EIF4G1, GCH1, EEF1D, NPC1, SMPD1, DNAJC13, GRN, TREM2, POLG). Parkin mutation-negative cases are also searched through panel gene tests and found normal autosomal dominant and recessive mutations.

Motor symptoms of all PD patients were evaluated by the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), during their on-state. Cognitive functions were evaluated through a neuropsychological battery including ACE-R, Wisconsin Card Sorting Test, Judgement of Line Orientation Test, Stroop Test, and Symbol Digit Modalities Test. All participants signed an informed consent prior to the data collection, and the study was approved by the ethics committee of Istanbul University (2016/349).

MRI data acquisition

The structural and functional MR imaging was performed using a 3T clinical MRI scanner (Philips Achieva, Best, the Netherlands). The high-resolution anatomical T1-weighted images were acquired based on the following scanning parameters: repetition time (TR) = 8.3 ms, echo time (TE) = 3.8 ms, inversion time = 1000 ms, flip angle = 8°, field of view (FOV)= 240×240 mm, number of slices = 180, voxel size = 1 mm^3 and total scan duration= 5:55 min. Scanning parameters for the functional imaging data were as follows: TR = 2000 ms, TE = 30 ms, FOV = 224×240 mm, number of slices = 36, voxel size = 2×2×4mm^3, total scan duration = 7:30 min.

Data analysis

Functional MRI data analysis

Data processing for functional magnetic resonance imaging (fMRI) was done with FSL's FEAT (FMRI Expert Analysis Tool, www.fmrib.ox.ac.uk/fsl) version 6.00. Pre-processing included the following steps: motion correction (9); non-brain removal (10); spatial smoothing (5 mm); multiplicative mean intensity normalisation of the volume at each timepoint; and high-pass temporal filtering. FLIRT was used to perform registration to high-resolution structural and standard space (9-11).

Utilising MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components) version 3.15, as a tool of FSL, probabilistic independent component analysis was used to do a dual regression analysis. The present study used the MELODIC methods similar to those in prior publications (12-15). Using principal component analysis, pre-processed data were projected onto a 40-dimensional subspace. Afterwards, we investigated for group differences via FSL randomize with

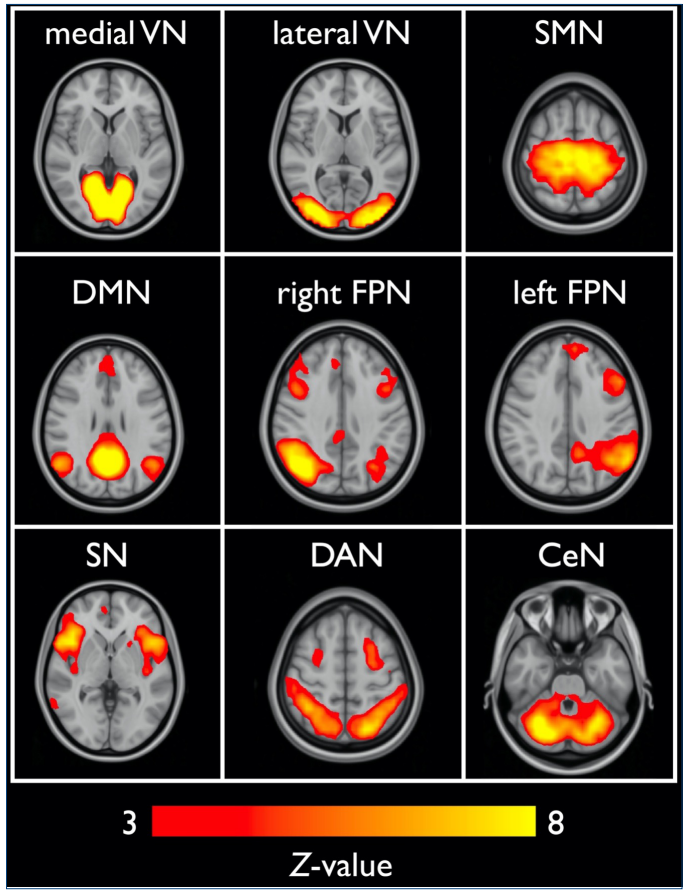

Figure 1. Identified ICs as output of the Group Independent Component Analysis
CeN: Cerebellar network, DAN: Dorsal attention network, DMN: Default mode network, FPN: Frontoparietal network, SMN: Somatomotor network, SN: Salience network, VN: Visual network. All images follow radiological convention (left is on the right).

5000 permutations. Using FSL's implementation of the Harvard-Oxford cortical and subcortical atlas, significant areas were found. Finally, using the fslstats command, the mean connectivity values of the areas that significantly altered across groups were obtained, and these values were analysed in correlation analyses with neuropsychological data from the patient groups.

Statistical data analysis

All data were statistically analysed with the SPSS program (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Post-hoc pair-wise comparisons were corrected by Bonferroni correction. Clinical symptoms were compared between groups with independent sample t-tests and one-way ANOVA. The gender distribution amongst the groups as well as the UPDRS and Hoehn & Yahr score of the PD groups were analysed with the chi-square test. Statistical maps found with group ICA were thresholded using Threshold-Free Cluster Enhancement (TFCE). Multiple comparisons were adjusted by family-wise error (FWE). Since 9 RSNs were identified that were compared between the three groups, the significance threshold was set at $p < 0.0018$ (0.05 / 3x9).

RESULTS

Clinical findings

As a result of mutation analyses, the following Parkin gene (PARK2) mutations were identified in 12 Parkin-positive patients; 7 homozygous gross deletions, 4 homozygous substitutions, and 1 case which one allele has gross deletion and the other has homozygous substitution.

According to the comparison analyses of clinical characteristics, it was revealed that PP-PD group (12.41 ± 6.22 yrs.) had significantly longer disease duration as compared to the PN-PD group (7.14 ± 4.68 yrs.) ($p < 0.05$). While no significant difference was detected for the mean UPDRS scores (UPDRS total, UPDRS part 1, UPDRS part 2, and UPDRS part 3) between the PD groups ($p > 0.05$ for all); based on UPDRS 4. Part scores, the PP-PD group was found to have more dyskinesia than the PN-PD group ($p < 0.05$). Finally, a chi-square analysis showed that the H&Y stage of the PN-PD group (2.33 ± 0.65) was significantly higher than that of the PP-PD group (1.83 ± 0.38), ($p< 0.05$).

All the groups' mean scores for neuropsychological tests were statistically compared using one-way ANOVA, and the results showed that groups significantly differed in their total ACE-R, JLOT, and SDMT performances ($p < 0.05$ for all). No significant difference was found between the groups in terms of WCST and Stroop test scores. Bonferroni post hoc analysis revealed that the PP-PD group's total ACER score, JLOT score and SDMT score were significantly lower than the HC group. In addition, the total JLOT scores of the PP-PD group were also significantly lower than the PN-PD group. On the other hand, the PN-PD group did not show any significant difference from the HC group in any neuropsychological test scores ($p > 0.05$). Group means are shown in Table 1.

Functional connectivity findings

As a result of dual regression, it was determined that there were changes in functional connectivity between the groups (Figure 2). It was found that there was increased connectivity in the angular gyrus region of the left FPN in the all-PD group, which consisted of merging the PP-PD and PN-PD groups, compared to the healthy controls (p= 0,0013). In addition, there was increased functional connectivity in the angular gyrus region of the left FPN compared to HC in the PP-PD group (p= 0.0004). In the analysis comparing the two patient groups, a decreased connectivity was found in the superior parietal lobule region of the right DAN in the PP-PD group compared to the PN-PD group (p= 0.00123).

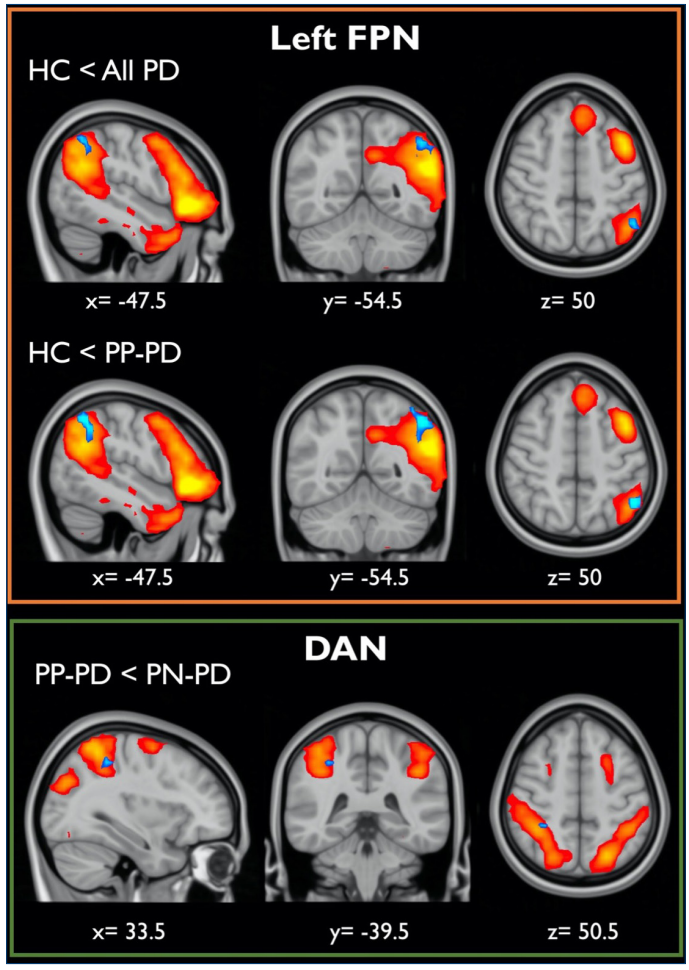

Figure 2. Data-driven analysis intergroup connectivity comparisons. The clusters of significant ($P < 0.0018$, FWE-corrected) connectivity group differences for all PD patients versus healthy controls (HC)(top) or PD patients with Parkin mutation (PP-PD) versus HC (middle) or PD patients without Parkin mutation (PN-PD) versus PP-PD (bottom) for the left frontoparietal network (FPN) and dorsal attention network (DAN). MNI X, Y and Z coordinates of the slices shown are indicated. The images are displayed in radiological convention meaning the right is on the viewer's left.

Table 1. Neuropsychological evaluations of the groups

Tests	PP-PD (n = 12) Mean ± SD	PN-PD (n = 12) Mean ± SD	HC (n = 12) Mean ± SD	Statistics	p	Post-hoc
ACE-R total score	84.41 ± 5.35	88.75 ± 5.87	92.00 ± 3.94	$F(2)$= 6.278	0.005	PP-PD < HC
Stroop interference time	63.83 ± 16.28	50.50 ±13.99	48.00 ±18.85	$F(2)$= 3.155	0.056	-
JLOT score	21.33 ± 3.77	25.00 ± 3.07	26.18 ± 2.52	$F(2)$= 7.363	0.002	PP-PD < PN-PD PP-PD < HC
WCST, perseverative error %	13.14 ± 3.14	17.92 ± 8.39	16.60 ± 8.53	$F(2)$= 1.349	0.275	-
SDMT total score	24.58 ± 7.45	33.16 ± 7.14	42.90 ± 14.67	$F(2)$= 9.269	0.001	PP-PD < HC

ACE-R: Addenbrooke Cognitive Examination-Revised, JLOT: Judgement Line Orientation Test, SDMT: Symbol Digit Modalities Test, WCST: Wisconsin Card Sorting Test.

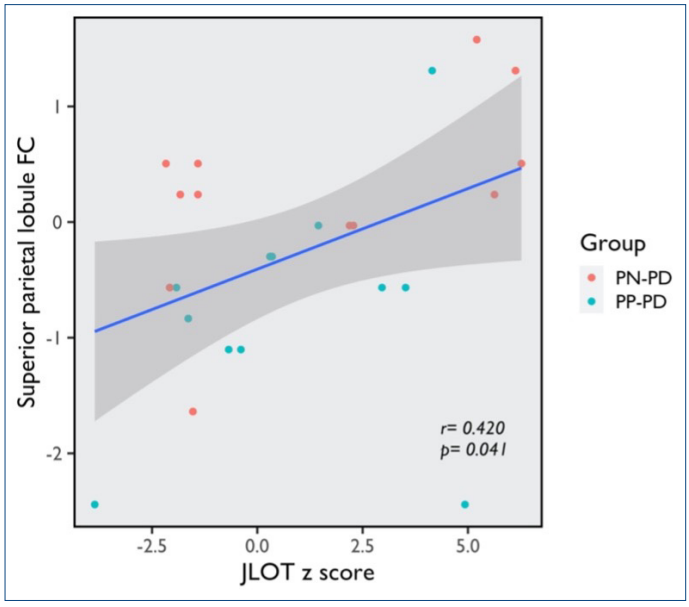

Figure 3. The scatter plot demonstrates that the mean connectivity estimates from the superior parietal lobule (y axis) are plotted against JLOT total score (x axis). The blue line represents the slope of the association. The grey bands represent the 95% CI of the slope.

Then, the correlations between the functional connectivity values of the three clusters that differed significantly between the groups and neuropsychological test scores were examined in the patient's groups. Correlation analyses indicated a positive correlation (r= 0.420, p= 0,041) between the functional connectivity of the DAN region containing the superior parietal lobule, which differed between the PN-PD and PP-PD groups and the JLOT score (A quantitative visualization of this effect is presented in Figure 3). No significant correlation was found between other neuropsychological test scores and functional connectivity.

DISCUSSION

Parkin gene is one of the largest human genes mapped to chromosome 6q25.2-q27 (16). Since its first identification in 1998, various mutations in the Parkin gene have been shown as the primary cause of autosomal recessive PD (17,18). The pathological findings of patients with Parkin gene mutations generally show no Lewy-body formation, regarded as the histological hallmark of sporadic PD (19). The clinical features of Parkin gene mutations are also slightly different from sporadic PD cases. Accordingly, slow disease progression, presence of hyperreflexia and sleep benefit can be listed as the most prominent differences. Based on these pathological and clinical differences, the present study mainly aimed to examine the resting state functional connectivity changes in PD patients with Parkin gene mutation.

Our results revealed longer disease duration and more dyskinesia in PD with Parkin gene mutation. Considering the earlier onset of PD in the PP-PD group, it could be argued that increased dyskinesia might stem from outlasting levodopa treatment compared to the PP-PN group. Despite the literature showing preserved cognition in PD patients with Parkin mutation (20), we showed impaired performance of the PP-PD group, especially in tests measuring visuospatial abilities and attention. A similar finding was reported by Uslu et al. (21), who reported impaired complex visuospatial abilities in PD patients with Parkin mutation.

As the main findings of our study, we reported alterations in functional connectivity of two cognitive networks in PP-PD group as compared to other groups. While the literature has conflicting findings regarding the cognitive networks in PD (22); our data support the existence of functionally disorganised networks in PD and provide the first exploratory data about the resting state brain networks of PD patients with Parkin gene mutation.

Our study's first major connectivity finding was the increased functional connectivity in the FPN in the PP-PD and all-PD groups compared with the HC group. In the literature, the FPN is known as a central control network, flexible in interaction with nodes of other networks on cognitive demand (23). As a large-scale network considered the source of attentional control, the FPN primarily comprises the lateral dorsolateral prefrontal cortex and posterior parietal cortex. Many studies confirm the functional connectivity alterations of FPN in PD (24-26). Similar to our findings, Matt et al. (25) reported hyperactivation in the left frontoparietal network in early PD patients. According to our results, the left FPN notably showed increased functional connectivity in the angular gyrus, considered one of the major connecting hubs activated during several cognitive tasks (27). Previously, researchers also reported increased cerebral regional homogeneity in the left angular gyrus in PD (28).

Another important finding of this study was disrupted functional connectivity of the right DAN in PP-PD patients. Namely, a decreased functional connectivity in the right dorsal attention network was present in the PP-PD group compared to the PN-PD group. The dorsal attention network is known as one of the two main attentional networks in the brain, mainly mediating top-down driven voluntary visuospatial attentional processes (29). It includes bilateral intraparietal sulci (IPS) and frontal eye fields (FEF). In literature, the DAN is generally associated with working memory and visuospatial orienting skills (30). In line with the literature, we reported a positive correlation between the right DAN functional connectivity level and JLOT total score. Given that JLOT is a widely used neuropsychological test to assess complex visuospatial perceptual processes, our results seem to confirm evidence for DAN's role in visuospatial functions. Additionally, since the JLOT is accepted to be highly sensitive to the right hemisphere abnormalities, this finding further highlights the role of right hemisphere structures on visuospatial functions. Lastly, the newly emerging literature indicates disrupted attentional control networks in PD that are particularly associated with dopaminergic drug-related hallucinations, visual misperceptions and freeze of gait symptoms (31-33).

One of the limitations of this study was the effect of medical treatment. Due to tapering the therapy was unethical, we could not eliminate the dopaminergic treatment effect. However, since participants in both PD groups were involved in the study during their ON state, it would not be wrong to think that PD group comparisons were not confounded by medical treatment. Also, it is worth mentioning that the L-dopa equivalent daily dose of the PD patients in both groups was at the same level. Finally, the small sample size of our study was also another limitation.

To our knowledge, this was the first study that investigated functional connectivity changes in PD patients with and without Parkin gene mutations. Our findings particularly suggest that functional connectivity changes in the frontoparietal and dorsal attention networks can differ in PD patients with Parkin gene mutations. Supported by the clinical data, altered functional connectivity in the dorsal attention network can be associated with cognitive deficits, particularly with the visuospatial processes. It would be worthwhile for future studies to focus on the specific networks in Parkin gene mutations and relate the connectivity findings to the clinical observations.

Ethics Committee Approval: The study was approved by the Istanbul University ethics committee (2016/349).

Hasta Onamı: All participants signed informed consent before data collection.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept-- MÇ, HAH; Design- TD ; Supervision- HAH, TD; Resource- TD, HAH; Data Collection and/or Processing- MÇ, AK, EE, FT, BS, ZT; Analysis and/or Interpretation- UA, MÇ; Literature Search MÇ, UA, HAH; Writing- MÇ, UA; Critical Reviews- BB, ME, ZOU.

Conflict of Interest: The authors declared that there is no conflict of interest.

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