Original Article

Abnormal Subcortical Volumes and Cortical Thickness in Parkinson's Disease with Impulse Control Disorders

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Abstract

Background: The occurrence of impulse control disorders (ICDs) in Parkinson's disease (PD) is frequently attributed to dopamine replacement therapy. However, not all patients who receive medication develop ICDs. Recent imaging studies have suggested specific neuroanatomical abnormalities in patients with PD and ICD. **Objectives:** This study aims to identify changes in volumes of subcortical structures and cortical thickness specific to patients with PD and ICDs. **Methodology:** A total of 11 patients with PD and ICD ($PD_{ICD(+)}$), 15 patients with PD without ICD ($PD_{ICD(-)}$), and 15 healthy controls were analyzed in this study. ICDs were diagnosed and quantified using the Questionnaire for Impulsive-Compulsive Disorders in PD-Rating Scale (QUIP-RS). Structural imaging was performed on a 3T scanner; volumes of subcortical structures and cortical thickness were obtained using first in FSL and FreeSurfer. **Results:** Significant volume loss of the nucleus accumbens was observed in the $PD_{ICD(+)}$ group. Several areas of significant cortical thinning were observed in the $PD_{ICD(+)}$ group in comparison $PD_{ICD(-)}$ group. Thinning of the left middle temporal gyrus, transverse temporal gyrus, and bilateral temporal poles was observed in the $PD_{ICD(+)}$ group. No correlations were observed between QUIP-RS scores and areas of cortical thinning. **Conclusions:** The $PD_{ICD(+)}$ group has specific neuroanatomical variations in the nucleus accumbens and temporal lobes, which may contribute to the development of ICD and perhaps predispose a patient to ICDs on exposure to dopamine replacement therapy.

Keywords: Cortical thickness, impulse control disorder, Parkinson's disease, subcortical volumetry

Introduction

Impulse control disorders (ICDs) are a group of complex behavioral conditions defined as "a failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or to others."[1] The frequency of ICDs in patients with Parkinson's disease (PD) ranges from 6.1% to 31.2%.[2] The ICDs commonly observed in PD include pathological gambling, hypersexuality, compulsive buying, compulsive eating, and other repetitive and compulsive behaviors such as punding and dopamine dysregulation syndrome (DDS).[3] Patients may often present with more than one of the above-mentioned ICDs.[4]

The development of ICDs is often attributed to the use of dopamine agonists (DAs)[5,6] and symptoms are known to resolve postcessation of the drug. However, not all patients who receive DAs develop ICDs. This conundrum doubts the premise of DAs being wholly responsible for the production of ICDs in PD. The exact neural mechanisms underlying the development of ICDs in PD are relatively obscure. Studies investigating ICDs and genetic polymorphisms have identified genes involved in the dopamine metabolism pathway, dopamine receptors, serotonin receptors and its transporter, and glutamate receptors.[7] Functional magnetic resonance imaging and positron emission tomography studies in patients of PD with ICDs have reported limbic network and mesocortical dysfunction during risk-reward processing, decision-making, motivation, and inhibitory control.[8-10] Volume loss of the nucleus accumbens, caudate, hippocampus, and amygdala has been reported in patients with PD and ICDs.[11] Results of studies exploring cortical thickness in these patients are inconsistent and vary from reports of increased cortical thickness in mesolimbic regions[11,12] to reports of no alterations in cortical thickness.[13,14] A reduction in cortical thickness, especially in the frontostriatal regions has been reported to be specific to patients with PD and ICDs.[15-17]

This study aims to identify the changes in volumes of subcortical structures and cortical thickness specific to patients with PD and ICDs.

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Methodology

Subject recruitment and clinical evaluation

This study was conducted at the Department of Neurology at the National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, India. Patients were recruited from the general neurology outpatient clinic and movement disorder services at NIMHANS. The diagnosis of PD was based on the United Kingdom PD Society Brain Bank criteria[18] and confirmed by a movement disorder specialist (PKP). The Questionnaire for Impulsive-Compulsive Disorders in PD-Rating Scale (QUIP-RS) was administered to all patients in order to identify patients with ICD and quantify the severity of ICDs. Based on the QUIP-RS, the types of ICDs considered were pathological gambling, compulsive buying, compulsive eating, hypersexuality, compulsive hobby participation, punding, and DDS. Fifteen patients with PD and ICDs ($PD_{ICD(+)}$) and fifteen patients with PD without ICDs ($PD_{ICD(-)}$) matched for age and duration of illness were included in the study. Fifteen healthy participants matched for age with no history of neurological or psychiatric disorders served as the control group.

Demographic and clinical details such as gender, age, age at onset (AAO) of motor symptoms and disease duration, and the severity of motor symptoms (Unified PD Rating Scale [UPDRS] Part-III and Hoehn and Yahr [H and Y] scale) were documented. Dopamine replacement therapy was calculated as total daily levodopa equivalents (LEEDs) for each patient. The LEED included the LEEDs of levodopa, DAs, monoamine oxidase type B inhibitors, catechol-O-methyl transferase inhibitors, and N-methyl-D-aspartate receptor blockers.[19] In addition, LEDs for levodopa ($LED_{levodopa}$) and DAs (LED_{DA}) were also individually recorded. All underwent magnetic resonance imaging (MRI) as part of the routine diagnostic evaluation of PD.

Image acquisition

All participants were scanned on a 3-T Philips Achieva MRI scanner with an 8-channel head coil. T1-weighted-three-dimensional (3D) turbo field echo sequences were obtained (TR = 3.8 ms, TE = 8.2 ms, field of view = 240 mm × 240 mm × 160 mm, voxel size = 1 mm × 1 mm × 1 mm, slice thickness = 1 mm). All images were screened for gross cortical structural abnormalities by an experienced neuroradiologist (author-JS). Images of four patients from the $PD_{ICD(+)}$ subgroup were found to be suboptimal owing to movement artifacts, hence were excluded from the study. Owing to this, a total of 11 patients from the $PD_{ICD(+)}$ considered for further analysis.

Image processing: volumes of subcortical structures

Oxford Centre for Functional MRI of the Brain's (FMRIB) Integrated Registration and Segmentation Tool (FIRST) in FMRIB software library (FSL) version 5.0 (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) was applied to the 3D T1-weighted images and used to segment grey matter (GM) regions of interest in order to acquire volumes of subcortical structures. Volumes of the following structures were acquired: thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and nucleus accumbens.

Image processing: cortical thickness

Estimation of cortical thickness was performed for patients in $PD_{ICD(+)}$ and $PD_{ICD(-)}$ subgroups using the FreeSurfer image analysis suite version 5.3 (http://surfer.nmr.mgh.harvard.edu).[20] In brief, the images were first registered to Montreal Neurological Institute space and intensity normalization was performed. Post this using watershed algorithms and deformable surface models, automatic skull stripping was performed in order to remove extracerebral structures, cerebellum, and brain stem. Images were reviewed for skull stripping errors and segmented into GM, white matter (WM), and cerebrospinal fluid (CSF), following which the cerebral hemispheres were separated. The WM and pial surfaces were obtained by tessellating the WM/GM boundary and deforming the surface by following intensity gradients in order to optimally place WM/GM and GM/CSF boundaries.[21] Surface inflation and registration to a spherical atlas were performed and based on the gyral and sulcal structures described by Desikan *et al*.[22] The cerebral cortex was parcellated into 34 regions per hemisphere. Finally, the cortical thickness was estimated as the average shortest distance between the pial surface and WM boundary.

Statistical analysis

Participants were divided into two groups: (a) patients with PD and (b) healthy controls (HCs). The first group was subdivided into (a) $PD_{ICD(+)}$ and (b) $PD_{ICD(-)}$. The Kolmogorov–Smirnov test was used as a test for normality. Parametric variables were analyzed using the *t*-test and nonparametric variables were analyzed using the Mann–Whitney U-test. The Chi-square test was used for categorical variables. Analysis of variance followed by *post hoc* Bonferroni correction was performed where applicable.

Although cortical thickness was acquired for all three groups, a comparison was performed between the $PD_{ICD(+)}$ and $PD_{ICD(-)}$ groups to ascertain variations which may be specific to the $PD_{ICD(+)}$ group. Cortical thickness of the $PD_{ICD(+)}$ and $PD_{ICD(-)}$ groups were compared with the multivariate analysis of variance using age of the patient and disease duration as covariates. Correlations between QUIP-RS scores and results of cortical thickness were evaluated by performing Spearman's correlation. Statistical significance was set at $P < 0.05$.

Results

Demographic and clinical data

Eleven patients with $PD_{ICD(+)}$, 15 patients with $PD_{ICD(-)}$, and 15 HC were included in the study. Men outnumbered women in all the three groups, and there were no significant statistical

differences in the mean age of the participants in these 3 groups. The AAO of motor symptoms and duration of illness were similar in the $PD_{ICD(+)}$ and $PD_{ICD(-)}$ subgroups. Both subgroups had similar UPDRS-III OFF scores and H and Y stages. The LEED and $LED_{levodopa}$ were not significantly different between the subgroups. However, the $PD_{ICD(+)}$ group had a significantly higher LED of DA compared to the $PD_{ICD(-)}$ group. Although statistically insignificant, a higher percentage of the $PD_{ICD(+)}$ group were on DAs in comparison to the $PD_{ICD(-)}$ group [Table 1].

Among the 11 patients with ICDs, 6 had a single ICD while the rest had multiple ICDs. Punding was reported by four patients, followed by hypersexuality, compulsive hobby participation, and DDS reported by three patients per symptom [Table 2].

Volumes of subcortical structures

In comparison to HC, the $PD_{ICD(+)}$ subgroup had significant atrophy of bilateral nucleus accumbens [Figure 1 and Table 3]. The right hippocampus and left caudate nucleus volumes showed a trend toward significance. Comparison of the volumes of subcortical structures between the $PD_{ICD(+)}$ and $PD_{ICD(-)}$ subgroups revealed significant volume loss of the left nucleus accumbens in the $PD_{ICD(+)}$ subgroup [Figure 1 and Table 3]. There were no statistically significant differences between the $PD_{ICD(-)}$ subgroup and HC [Figure 1 and Table 3].

Cortical thickness

Cortical thickness was compared between $PD_{ICD(+)}$ and $PD_{ICD(-)}$ subgroups. The significant results are summarized in Figure 1 and Table 4.

Significant thinning of bilateral temporal poles was observed in the $PD_{ICD(+)}$ subgroup. The left middle temporal gyrus and transverse temporal gyrus showed a trend toward significance. There were no areas of cortical thickening. No significant

Table 1: Demographic and clinical features of patients and controls

	$PD_{ICD(+)}$ (n=11)	$PD_{ICD(-)}$ (n=15)	HC (n=15)
Gender (men:women)	8:3	12:3	11:4
Age (years)	57.18±7.90	54.20±7.60	53.06±6.71
Age at onset (years)	49.54±6.84	50.06±8.90	-
Duration of illness (years)	7.63±2.49	6.45±2.3	-
UPDRS-III (OFF score)	37.54±10.43	30.9±8.17	-
H and Y stage	2.09±0.41	1.90±0.50	-
Daily LED_{total} (mg)	735.59±247.12	610.60±220.75	-
Daily $LED_{levodopa}$ (mg)	502.75±120.95	541.15±191.49	-
Daily LED_{DA} (mg)*	253.88±124.18	109.50±65.89	-
Patients treated with DA (%)	9/11 (81.81)	10/15 (66.66)	-

*P<0.01. DA=Dopamine agonist, LED=Levodopa equivalent dose, HC=Healthy control, H and Y=Hoehn and Yahr, $PD_{ICD(+)}$=Parkinson's disease with ICD, $PD_{ICD(-)}$=Parkinson's disease without ICD, UPDRS=Unified Parkinson's Disease Rating Scale, ICD=Impulse control disorder, OFF= Not an acronym

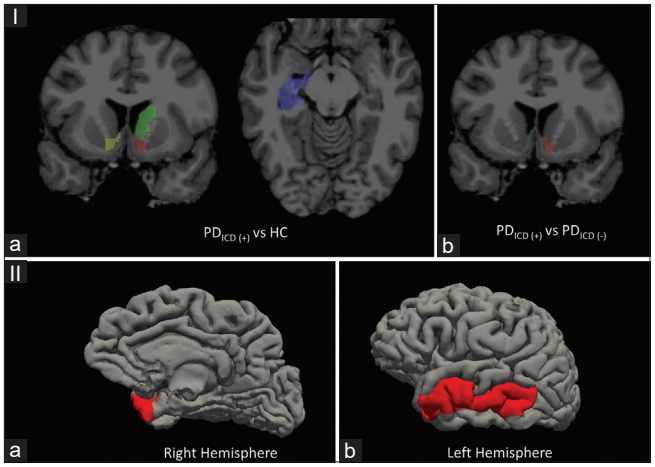

Figure 1: (I) Subcortical nuclei with significant volume loss. (a) $PD_{ICD(+)}$ versus HC: Nucleus accumbens and hippocampus. (b) $PD_{ICD(+)}$ versus $PD_{ICD(-)}$: Nucleus accumbens and (II) Regions with cortical thinning observed between $PD_{ICD(+)}$ and $PD_{ICD(-)}$. (a) Right hemisphere: Temporal pole. (b) Left hemisphere: Middle temporal gyrus, transverse temporal gyrus, and temporal pole. HC: Healthy controls, $PD_{ICD(+)}$: Patients with Parkinson's disease and impulse control disorders, $PD_{ICD(-)}$: Patients of Parkinson's disease without impulse control disorders

Table 2: Patients with Parkinson's disease and impulse control disorders

Subject	Gender	Age	Type of ICD	QUIP-RS score	TLED (mg)	LED (mg)	LED_{DA} (mg)
1	Male	61	P	17	700	400	300
2	Male	48	CHP	13	875	400	375
3	Male	52	DDS	16	475	475	0
4	Male	57	CB, HS	32	750	500	250
5	Male	67	DDS	12	976.5	712.5	0
6	Male	57	HS	25	280	0	180
7	Female	70	CB, CE, DDS, HS, P	52	690	590	100
8	Male	53	P	10	850	350	300
9	Male	66	CE, CHP	23	1250	700	450
10	Female	43	CHP, PG	26	700	400	300
11	Female	55	P	14	545	500	30

CB=Compulsive buying, CE=Compulsive eating, CHP=Compulsive hobby participation, DA=Dopamine agonist, DDS=Dopamine dysregulation syndrome, HS=Hypersexuality, ICD=Impulse control disorder, LED=Levodopa equivalent dose for levodopa, P=Punding, PG=Pathological gambling, TLED=Total levodopa equivalent dose, QUIP-RS=Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale

Table 3: Subcortical volumes (mm^3) in patients and controls

	$PD_{ICD\ (+)}$	$PD_{ICD\ (-)}$	HC
Right hemisphere			
Thalamus	6650.24±892.75	6485.80±649.03	6957.84±260.63
Caudate**	3165.17±578.59	3417.48±381.04	3480.94±446.55
Putamen	4452.22±700.85	4488.22±416.80	4839.79±326.52
Pallidum	1638.47±314.41	1800.58±442.00	1760.15±217.35
Hippocampus**	3688.70±408.41	3872.99±324.78	4011.39±398.01
Amygdala	1180.094±371.53	1079.00±273.52	1088.08±267.66
Nucleus accumbens*	320.60±116.44	376.17±81.86	417.12±93.32
Left hemisphere			
Thalamus	6891.41±761.02	6730.72±658.00	7159.81±422.44
Caudate**	3010.08±381.67	3308.50±428.77	3342.83±438.97
Putamen	4449.42±621.80	4367.992±417.80	4791.09±426.09
Pallidum	1734.58±376.54	1764.84±448.79	1830.00±209.03
Hippocampus	3635.48±446.27	3700.377±419.20	3913.36±318.48
Amygdala	1120.44±252.81	1025.50±269.37	1209.84±151.46
Nucleus accumbens*,#	394.07±114.82	523.24±68.64	553.24±89.76
Brainstem	21,445.36±1694.43	20,984.32±2115.715	21,522.92±1718.33

*$PD_{ICD\ (+)}$ versus HC: $P<0.05$; **$PD_{ICD\ (+)}$ versus HC: $P=0.05$; #$PD_{ICD\ (+)}$ versus $PD_{ICD\ (-)}$: $P<0.01$. HC=Healthy controls, $PD_{ICD\ (+)}$=Patients of Parkinson's disease with ICD, $PD_{ICD\ (-)}$=Patients of Parkinson's disease without ICD, ICD=Impulse control disorder

correlations were observed between the QUIP-RS scores and results of cortical thickness.

Discussion

ICDs in patients with PD are distressing symptoms attributed to dopamine replacement therapy.[6] However, not all patients who receive dopamine replacement therapy develop ICDs. This suggests the possibility of underlying neuroanatomical alterations which may predispose the patient to develop ICDs.[4,5,9] Involvement of prefrontal and motor cortices, pedunculopontine pathways, and limbic WM tracts have been observed in patients with PD and ICD.[8,10,11] These regions are part of the direct and indirect basal ganglia loops which are part of the reward network. This network is comprised of the corticoventral basal ganglia circuit which includes the orbitofrontal cortex, anterior cingulate cortex, and ventral striatum.[23] The latter comprises of nucleus accumbens, amygdala, hippocampus, and midbrain dopamine neurons.[24] Abnormalities of these structures in patients with $PD_{ICD(+)}$ may lead to disinhibition of dysfunctional behavior despite the possibility of a negative outcome.

In our study, the $PD_{ICD(+)}$ subgroup had significant volume loss of subcortical structures, specifically the hippocampus, nucleus accumbens, and caudate. These structures have been implicated in the pathophysiology of ICDs.[25-27] The novelty-loop theory suggests the involvement of the hippocampus, amygdala, and ventral striatal pathways in novelty-seeking behavior.[25] The hippocampus serves to detect the presence of a sensory prediction error, that is, when a sensory input differs from the memory-driven expectation,[28] and the amygdala is involved in modulation of striatal and hippocampal activity during emotional memory encoding or in novel environments.[29] Volumetric reduction in the nucleus accumbens and amygdala has also been reported in individuals with high levels of trait impulsivity[26] and an increased genetic risk for addiction.[27]

Results from our study pertaining to cortical thickness revealed thinning in the mesocortical and limbic reward-related areas which are similar to reports from other studies.[15,16] We did not observe any areas with cortical thickening. Although results of cortical thinning or thickening are variable,[11,12,14,16] the areas implicated are consistent. Biundo *et al*.[16] reported thinning of similar cortical areas and a direct correlation between ICD severity measured by the QUIP-RS and the cortical thickness. This implies a key role of these anatomical changes in the genesis of ICDs. Patients with PD and pathological gambling were found to have atrophy of the orbitofrontal cortex in comparison to patients of PD without pathological gambling.[15] Left precentral and superior frontal cortical thinning along with impaired functional connectivity and the frontal, mesolimbic, and motor circuits have been reported in $PD_{ICD(+)}$.[17] These findings of cortical thinning and impaired connectivity suggest that ICD in PD could be attributable to a disconnection between associative, sensorimotor, and cognitive networks.

Pellicano *et al*.[11] reported increased cortical thickness in the rostral anterior cingulate and frontal polar cortex in patients with $PD_{ICD(+)}$. These areas are involved in mediating the reward experience and are important in action selection, conflict and error monitoring, and value-based decision-making. The authors suggested that the findings of increased thickness may be secondary to adaptations occurring due to the nonphysiological dopaminergic stimulation and may occur only in participants with an increased susceptibility to neural sensitization. In addition, the thickness could be a preexisting trait which makes subjects more susceptible to developing ICDs.

Table 4: Mean cortical thickness in patients with PD

	Right hemisphere		Left hemisphere	
	$PD_{ICD\ (+)}$	$PD_{ICD\ (-)}$	$PD_{ICD\ (+)}$	$PD_{ICD\ (-)}$
Mean cortical thickness (mm)	2.29±0.07	2.34±0.09	2.29±0.08	2.35±0.10
Frontal				
Rostral anterior cingulate	2.70±0.17	2.80±0.24	2.75±0.29	2.76±0.19
Pars opercularis	2.37±0.10	2.41±0.14	2.38±0.13	2.46±0.17
Pars triangularis	2.20±0.07	2.29±0.15	2.21±0.13	2.30±0.13
Parietal				
Inferior parietal	2.24±0.10	2.27±0.11	2.24±0.15	2.26±0.14
Postcentral	1.83±0.10	1.86±0.09	1.82±0.10	1.89±0.10
Supramarginal	2.31±0.11	2.36±0.12	2.29±0.12	2.35±0.12
Temporal				
Banks STS	2.39±0.18	2.50±0.16	2.23±0.19	2.41±0.15
Fusiform	2.54±0.15	2.57±0.13	2.51±0.14	2.60±0.13
Inferior temporal	2.65±0.18	2.64±0.13	2.59±0.17	2.62±0.14
Middle temporal**	2.73±0.12	2.77±0.15	2.61±0.13	2.74±0.13
Parahippocampal	2.46±0.26	2.78±0.34	2.52±0.31	2.80±0.29
Superior temporal	2.57±0.21	2.65±0.15	2.51±0.13	2.62±0.14
Temporal pole*,#	3.54±0.24	3.79±0.19	3.59±0.24	3.82±0.26
Transverse temporal#	2.06±0.22	2.20±0.21	1.98±0.21	2.13±0.23
Occipital				
Lateral occipital	1.98±0.08	2.04±0.13	1.95±0.12	2.00±0.15

*Right hemisphere $P<0.05$; **Left hemisphere $P<0.05$; #Left hemisphere $P=0.05$. $PD_{ICD\ (+)}$=Patients of Parkinson's disease with ICD, $PD_{ICD(-)}$=Patients of Parkinson's disease without ICD, STS=Superior temporal sulcus, ICD=Impulse control disorder

In our cohort, the $PD_{ICD(+)}$ group had a significantly higher LED of DA compared to the $PD_{ICD(-)}$ group. However, there were a few patients who developed ICD despite not receiving DAs. Although the exact role of dopamine replacement therapy in the genesis of ICD is controversial, there are several robust theories which strongly suggest their role. Berridge[30] proposed the incentive sensitization theory which states that chronic dopaminergic overstimulation elevates the mesolimbic dopamine reactivity and produces a craving for rewarding stimuli. Cools *et al*.[31] suggested the possibility of an imbalance between the depleted dorsal striatum and intact ventral striatum in the early stages of PD. As a result, dopaminergic treatment may recover functionality of the dorsal striatum and resolve sensory-motor symptoms while "overdosing" the ventral striatum, hence producing ICDs. The possible role of the ventral frontostriatal loops was supported by reports of abnormalities in tests associated with frontal lobe functions and on the Iowa gambling test in patients with PD and ICD.[32]

Although withdrawal of DAs is known to resolve ICDs, this observation may not occur in all patients.[6] This validates the possibility of anatomical changes in patients of PD with ICD. It is unclear whether the anatomical changes observed predate the onset of ICD or are secondary to medication and the ongoing disease process. Dopamine plays a significant role in the development of neuronal cytoarchitecture, especially in the frontal cortex and striatum by modulating neuron arborization, synaptogenesis, and neurogenesis.[33] Long-term dopamine therapy has been reported to produce cytotoxic effects in the cortex. Hence, prolonged dopamine replacement therapy may induce changes in cortical thickness.[34] Several studies have suggested that cortical thickness may express the cytoarchitectural and microstructural remodeling produced by neuropathological and macrostructural processes.[12]

It is evident that no single causative factor can be implicated in the pathogenesis of ICDs in PD. There is a complex interplay between medications and anatomical alterations and perhaps both play crucial roles. Future studies are warranted to explore the neuroanatomical alterations in drug naïve patients with PD who develop ICDs.

There are several limitations of this study. The sample size was small due to which we were unable to provide significant inputs regarding the gender-based predilection to develop ICD. Due to the heterogeneity of ICDs in this cohort, we were unable to specifically describe anatomical changes associated with a single type of ICD. Evaluation of neuroanatomical changes in cohorts with a single type of ICD is essential to localize specific abnormalities. The lack of correlations between the QUIP-RS scores and cortical thickness may be attributable to the small sample size and heterogeneity of the ICD cohort. We were unable to elicit the exact duration of ICDs from the patients or their caregivers owing to which the relationship between the structural changes and duration of ICD could not be assessed. We could not assess the association between preexisting personality traits and a predilection to ICD as we did not perform neuropsychiatric assessments for our patients. In addition, since we did not perform a detailed cognitive assessment for patients, we were unable to exclude

the possibility of ICDs being neuroanatomical dysfunctions related to cognitive decline.

Conclusions

The $PD_{ICD(+)}$ group has specific neuroanatomical variations in the mesocortical and limbic reward-related areas, which may contribute to the development of ICDs and perhaps predispose a patient to ICDs on exposure to dopamine replacement therapy. ICDs in PD cannot be attributed to dopamine replacement therapy alone; both drugs and the disease process play a significant, if not, an equal role.

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Conflicts of interest

There are no conflicts of interest.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). Arlington, VA: American Psychiatric Publishing; 2013.
2. Callesen MB, Scheel-Krüger J, Kringelbach ML, Møller A. A systematic review of impulse control disorders in Parkinson's disease. J Parkinsons Dis 2013;3:105-38.
3. Weintraub D, David AS, Evans AH, Grant JE, Stacy M. Clinical spectrum of impulse control disorders in Parkinson's disease. Mov Disord 2015;30:121-7.
4. Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V, *et al.* Impulse control disorders in Parkinson disease: A cross-sectional study of 3090 patients. Arch Neurol 2010;67:589-95.
5. Santangelo G, Barone P, Trojano L, Vitale C. Pathological gambling in parkinson's disease. A comprehensive review. Parkinsonism Relat Disord 2013;19:645-53.
6. Grall-Bronnec M, Victorri-Vigneau C, Donnio Y, Leboucher J, Rousselet M, Thiabaud E, *et al.* Dopamine agonists and impulse control disorders: A Complex association. Drug Saf 2018;41:19-75.
7. Cormier F, Muellner J, Corvol JC. Genetics of impulse control disorders in Parkinson's disease. J Neural Transm (Vienna) 2013;120:665-71.
8. O'Sullivan SS, Wu K, Politis M, Lawrence AD, Evans AH, Bose SK, *et al.* Cue-induced striatal dopamine release in Parkinson's disease-associated impulsive-compulsive behaviours. Brain 2011;134:969-78.
9. van Eimeren T, Pellecchia G, Cilia R, Ballanger B, Steeves TD, Houle S, *et al.* Drug-induced deactivation of inhibitory networks predicts pathological gambling in PD. Neurology 2010;75:1711-6.
10. Voon V, Pessiglione M, Brezing C, Gallea C, Fernandez HH, Dolan RJ, *et al.* Mechanisms underlying dopamine-mediated reward bias in compulsive behaviors. Neuron 2010;65:135-42.
11. Pellicano C, Niccolini F, Wu K, O'Sullivan SS, Lawrence AD, Lees AJ, *et al.* Morphometric changes in the reward system of Parkinson's disease patients with impulse control disorders. J Neurol 2015;262:2653-61.
12. Tessitore A, Santangelo G, De Micco R, Vitale C, Giordano A, Raimo S, *et al.* Cortical thickness changes in patients with Parkinson's disease and impulse control disorders. Parkinsonism Relat Disord 2016;24:119-25.
13. Biundo R, Formento-Dojot P, Facchini S, Vallelunga A, Ghezzo L, Foscolo L, *et al.* Brain volume changes in Parkinson's disease and their relationship with cognitive and behavioural abnormalities. J Neurol Sci 2011;310:64-9.
14. Carriere N, Lopes R, Defebvre L, Delmaire C, Dujardin K. Impaired corticostriatal connectivity in impulse control disorders in Parkinson disease. Neurology 2015;84:2116-23.
15. Cerasa A, Salsone M, Nigro S, Chiriaco C, Donzuso G, Bosco D, *et al.* Cortical volume and folding abnormalities in Parkinson's disease patients with pathological gambling. Parkinsonism Relat Disord 2014;20:1209-14.
16. Biundo R, Weis L, Facchini S, Formento-Dojot P, Vallelunga A, Pilleri M, *et al.* Patterns of cortical thickness associated with impulse control disorders in Parkinson's disease. Mov Disord 2015;30:688-95.
17. Imperiale F, Agosta F, Canu E, Markovic V, Inuggi A, Jecmenica-Lukic M, *et al.* Brain structural and functional signatures of impulsive-compulsive behaviours in Parkinson's disease. Mol Psychiatry 2018;23:459-66.
18. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181-4.
19. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE, *et al.* Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010;25:2649-53.
20. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A 2000;97:11050-5.
21. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 1999;9:179-94.
22. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, *et al.* An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 2006;31:968-80.
23. Arias-Carrión O, Stamelou M, Murillo-Rodríguez E, Menéndez-González M, Pöppel E. Dopaminergic reward system: A short integrative review. Int Arch Med 2010;3:24.
24. Robinson TE, Berridge KC. Addiction. Annu Rev Psychol 2003;54:25-53.
25. Cohen MX, Schoene-Bake JC, Elger CE, Weber B. Connectivity-based segregation of the human striatum predicts personality characteristics. Nat Neurosci 2009;12:32-4.
26. Muhlert N, Lawrence AD. Brain structure correlates of emotion-based rash impulsivity. Neuroimage 2015;115:138-46.
27. Hill SY, De Bellis MD, Keshavan MS, Lowers L, Shen S, Hall J, *et al.* Right amygdala volume in adolescent and young adult offspring from families at high risk for developing alcoholism. Biol Psychiatry 2001;49:894-905.
28. Lisman JE, Grace AA. The hippocampal-VTA loop: Controlling the entry of information into long-term memory. Neuron 2005;46:703-13.
29. Sheth A, Berretta S, Lange N, Eichenbaum H. The amygdala modulates neuronal activation in the hippocampus in response to spatial novelty. Hippocampus 2008;18:169-81.
30. Berridge KC. The debate over dopamine's role in reward: The case for incentive salience. Psychopharmacology (Berl) 2007;191:391-431.
31. Cools R, Barker RA, Sahakian BJ, Robbins TW. Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. Cereb Cortex 2001;11:1136-43.
32. Bentivoglio AR, Baldonero E, Ricciardi L, De Nigris F, Daniele A. Neuropsychological features of patients with Parkinson's disease and impulse control disorders. Neurol Sci 2013;34:1207-13.
33. Money KM, Stanwood GD. Developmental origins of brain disorders: Roles for dopamine. Front Cell Neurosci 2013;7:260.
34. Tamnes CK, Ostby Y, Fjell AM, Westlye LT, Due-Tønnessen P, Walhovd KB, *et al.* Brain maturation in adolescence and young adulthood: Regional age-related changes in cortical thickness and white matter volume and microstructure. Cereb Cortex 2010;20:534-48.