RESEARCH ARTICLE

Patterns of Cortical Thickness Associated With Impulse Control Disorders in Parkinson's Disease

Roberta Biundo, PhD,[1]* Luca Weis, PhD,[1] Silvia Facchini, BS,[1] Patrizia Formento-Dojot, BS,[1] Annamaria Vallelunga, BS,[1] Manuela Pilleri, MD,[1] Daniel Weintraub, MD, PhD,[2,3,4,5] and Angelo Antonini, MD, PhD[1]

[1]*"Fondazione Ospedale San Camillo"—I.R.C.C.S., Parkinson and Movement Disorders Unit, Venice, Italy*
[2]*Department of Psychiatry, University of Pennsylvania, Philadelphia, USA*
[3]*Department of Neurology, University of Pennsylvania, Philadelphia, USA*
[4]*Parkinson's Disease Research, Education and Clinical Center (PADRECC), Philadelphia Veterans Affairs Medical Center, Philadelphia, USA*
[5]*Mental Illness Research, Education and Clinical Center (MIRECC), Philadelphia Veterans Affairs Medical Center, Philadelphia, USA*

ABSTRACT: Previous functional neuroimaging studies in Parkinson's disease (PD) patients with impulse control disorders (ICDs) demonstrated dysfunction of the reward network, although the extent of anatomical changes is unclear. The aim of this study was to measure brain cortical thickness and subcortical volumes, and to assess their relationship with presence and severity of symptoms, in PD patients with and without ICDs. We studied 110 PD patients (N = 58 with ICDs) and 33 healthy controls (all negative for ICDs) who underwent an extensive neurological, neuropsychological, and behavioral assessment as well as structural 1.5 Tesla magnetic resonance imaging (MRI). Between-group differences in brain cortical thickness and subcortical volumes, assessed with the FreeSurfer 5.1 tool, were analyzed. In patients with ICDs, we found significant cortical thinning in fronto-striatal circuitry, specifically in the right superior orbitofrontal, left rostral middle frontal, bilateral caudal middle frontal region, and corpus callosum, as well as volume reduction in the right accumbens and increase in the left amygdala. Finally, we observed a positive association relationship between severity of impulsive symptoms and left rostral middle frontal, inferior parietal, and supramarginal areas. These results support the involvement of both reward and response inhibition networks in PD patients with ICDs. Moreover, their severity is associated with alterations in brain regions linked with reward and top-down control networks. Increased understanding of the mechanisms underlying impulsive and compulsive behaviors might help improve therapeutic strategies for these important disorders.

Key Words: Parkinson's disease; impulse control disorders; fronto-striatal-limbic networks; QUIP-RS; cortical thickness

Behavioral disorders are common in Parkinson's disease (PD) and represent a significant challenge in clinical management. In this context, increased impulsivity, a complex dimension with separate motor and cognitive components, triggered by chronic exposure to dopaminergic agents, particularly dopamine agonists, plays an important role.[1] Impulse control disorders (ICDs) in PD include pathological gambling, hypersexuality, compulsive eating, compulsive buying,[2] and hoarding.[3] Behaviorally, ICDs involve repetitive or compulsive engagement in specific activities with inability to learn from negative outcomes and control impulses, and increased state of tension before the initiation of the maladaptive behavior.

In addition to the associative-prefrontal cortical loop, the ventromedial prefrontal cortex (vmPFC), anterior cingulate cortex, and amygdala are associated with abnormal emotions, decision-making, and impulse control.[4,5] Specifically, in PD with ICDs

*Correspondence to: Dr. Roberta Biundo, "Fondazione Ospedale San Camillo"—I.R.C.C.S., Parkinson and Movement Disorders Unit, Via Alberoni 70, 30126 Venice Lido, Italy.
E-mail: roberta.biundo@ospedalesancamillo.net

Funding agencies: This study was supported by Italian Research Grant N RF-2009-1530177.

Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Received: 28 July 2014; **Revised:** 16 December 2014; **Accepted:** 17 December 2014

Published online 00 Month 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.26154

decreased connectivity has been seen between the anterior cingulate cortex, vmPFC, and the striatum.[6] In a previous study using voxel-based morphometry, we showed only marginal contribution of prefrontal regions in PD-ICD, likely attributable to VBM technical limitations and small sample size.[7]

We now applied a new analytic magnetic resonance imaging (MRI) technique and compared cerebral cortical thickness and subcortical volume in a new, larger PD cohort screened for the presence and severity of ICD symptoms. Our hypothesis was that fronto-striatal-limbic alterations would be associated with the presence and severity of ICDs.

Methods

Participants

From January 2011 to March 2013, we examined a total of 790 PD patients diagnosed based on UK Brain Bank criteria[8] at the Parkinson Disease Unit of "San Camillo" Hospital in Venice and at the 1st Neurology Clinic of the University of Padua. From the whole sample who underwent an extensive neurological and clinical assessment, 430 outpatients performed only a global cognitive and behavioral examination, leaving the sample with 360 patients who underwent an extensive neuropsychological battery to allow a formal cognitive and behavioral diagnosis. Demographic data (age, sex, and education level) and neurological details (Hohen &Yahr,[9] age at disease onset, and disease duration) were also collected. The severity of parkinsonism was rated using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III).[9] We did not include individuals with evidence of cortical or subcortical vascular lesions on MRI scan (as seen on T2-weighted axial and T2-weighted fluid attenuated inversion recovery (FLAIR)). Additionally, we excluded patients with atypical parkinsonism (eg, multiple system atrophy and progressive supranuclear palsy) and those with a history of neurosurgical procedures (including deep brain stimulation). For comparative purposes, we also included 38 unrelated healthy controls (HCs) who underwent the same neuropsychological and MRI protocol as the PD patients.

The study was approved by the ethic committee of the S. Camillo Hospital. A written informed consent was obtained from each individual according to the Declaration of Helsinki.

Neuropsychological and Behavioral Assessment

Parkinson's disease patients underwent a comprehensive behavioral and neuropsychological assessment by trained neuropsychologists (R.B., S.F., P.F.D.) in the morning and in the "on" medication state.

The PD patients, their caregivers, and HCs were interviewed about presence of ICDs during routine clinical assessment, and if behavioral problems were suspected, they underwent additional interview by a trained behavioral neuropsychologist (R.B.) to formally diagnose an ICD. In case of discrepant information, we deferred to the caregiver's report. Specifically, PD patients were recruited during regularly scheduled clinic visits; frequent breaks were introduced to avoid fatigue. We then administered the Minnesota Impulsive Disorder Interview, which investigates the presence of selected ICDs (eg, pathological gambling, compulsive buying, and compulsive sexual behavior). It evaluates these disturbances beginning with a general question, which, if answered affirmatively, allows the interviewer to ask a series of questions following the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria.[10] In addition, patients were asked about the presence of ICDs that were not included in the Minnesota Impulsive Disorder Interview but were already well known to occur in the PD population, namely binge eating, punding, and excessive medication use. All patients diagnosed with an ICD answered affirmatively one gateway question plus an affirmative answer to one or more of the remaining questions.

In addition, to further confirm the ICD diagnosis and evaluate symptom severity, starting from January 2012 we also applied the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS)[11] (58 PD of 110, 36 PD with current impulse controls disorders [PD-ICD+], and 22 PD without impulse controls disorders [PD-ICD-]). The advantage of this scale is that it also includes scoring for ICDs not listed in the Minnesota Impulsive Disorder Interview, providing a severity score for each ICD or related behavior. It had been validated in English[11] and recently in the German population,[12] with good validity and reliability overall, making it an appropriate instrument for both clinical and research purposes.

Based on the Minnesota Impulsive Disorder Interview together with the clinical interview, assessing abnormal behaviors and all types of ICDs (including those not listed in Minnesota Impulsive Disorder Interview), we identified two PD cohorts: 139 PD-ICD+ and 221 PD-ICD-. From this sample 75 PD-ICD+ and 67 PD-ICD- consented to have an MRI. We also performed an extensive cognitive assessment (PD subgroups and HCs), using a previously published neuropsychological battery[13] and applied established diagnostic criteria for PD mild cognitive impairment (PD-MCI) and dementia (PDD).[14,15] According to this classification, 25 subjects with no cognitive deficits (PD-CNT) and 27 PD-MCI were in the PD-ICD- cohort, and 27 PD-CNT and 31 PD-MCI were in the PD-ICD+ cohort. We excluded patients with PDD because these patients commonly present significant structural brain alterations. Therefore, our final PD sample included 58 PD-ICD+ and 52 PD-ICD-. In

particular, 15 ICD- and 17 ICD+ were on pramipexole (total of 32), 18 in each cohort on ropinirole (total of 36), and 1 in each group on rotigotine (total of 2).

For comparison, we also included 33 HCs who were negative for ICDs and dementia.[16] (Figure 1 summarizes the inclusion criteria applied).

Of the 58 PD-ICD+ patients, 18 PD patients had a single ICD (6 with hypersexuality, 7 with compulsive shopping behavior, 2 with pathological gambling, 2 with hoarding disorder, 1 with impulsive aggression), and 40 PD patients had multiple ICDs (5 with pathological gambling and hypersexuality, 7 with binge-eating and compulsive shopping, 8 with hypersexuality and collecting disorders, 12 with hypersexuality and compulsive shopping, and 8 with compulsive shopping and collecting disorders).

Image Acquisition

All subjects were scanned on a 1.5T Achieva Philips scanner (Philips Medical Systems, Best, The Netherlands) with an 8-channel head coil. Participants' heads were immobilized accurately with head cushions. A whole-head three-dimensional sagittal T1-weighted-3D TFE (TR = 8.3 ms, TE = 4.1 ms, FA = 8°, matrix size = 288 × 288, slice thickness = 0.87 mm isotropic voxel) was acquired for each participant. Only MRI scans without cerebral small vessel disease (appearing in T1 as a signal dropout), periventricular white matter hypointensities in T1, or space-occupying lesions, and without head motion artifact assessed by visual inspection, were included.

Cortical Thickness Acquisition and Analysis

We used the software package FreeSurfer (version 5.1),[17,18] which is freely available on-line at http://surfer.nmr.mgh.harvard.edu/ and has a specialized tool for automated parcellation of the neocortical gray matter and subcortical volumes. The technical details of these procedures are described in prior publications.[17,19] The hallmarks of the process are the computation of the curvature of the gray and white matter interface to characterize the sulci and gyri, and inflation of the whole brain into a sphere for the purpose of registering subjects to the Talairach standard atlas. Mapping between subjects and the atlas was performed using a nonrigid registration on the inflated surface. The end result is the parcellation of the human cortex into 34 cortical regions of interest in each hemisphere and into 19 subcortical white matter, and deep gray matter volumetric structures (such as hippocampus, amygdala, caudate, putamen, and ventricles).[19]

Vertex-wise general linear model (GLM) (between-group comparisons) comparing cerebral cortical thickness of the PD subgroups and HCs were run using the Freesurfer qdec tool after surface-based smoothing of

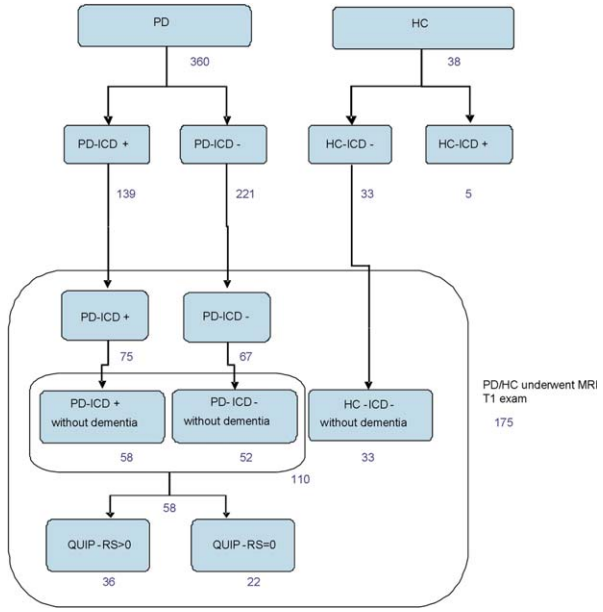

FIG. 1. Flow diagram: inclusion criteria for selecting participants. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

15 mm full width at half maximum (FWHM). Age and Mini-Mental State Examination (MMSE)[20] score were used as covariates in the models. Disease duration and levodopa equivalent daily dose (LEDD)[21] were also included as covariates in the PD-ICD+ versus PD-ICD- comparison. For all comparisons, a cluster-wise False Discovery Rate correction for multiple comparisons across space was applied. A corrected P value less than 0.05 was then used for plot purpose. Differences in subcortical volume provided by the Freesurfer segmentation and parcellation were assessed using similar analysis to the cortical areas, adding the intracranial volume parameter calculated as estimated total intracranial volume as a covariate. A p value of <0.05 Sidak corrected was applied.

To obtain a representative model of areas involved in PD-ICDs, we ran a multivariate analysis using a stepwise backward binary logistic regression. As model factors we used all cortical and subcortical areas showing statistical significance ($p < 0.05$ corrected) in PD-ICD+ vs. PD-ICD- comparison covarying for LEDD age, disease duration, and MMSE score. Finally, to evaluate areas sensitive to ICD symptoms severity, we ran a correlation analysis between QUIP-RS >0 scores and cortical and subcortical areas. LEDD and MMSE score were included as covariates. MonteCarlo and Sidak corrections for multiple comparisons at $p < 0.05$ were applied.

Statistical Analysis

Chi-squared test was used to assess differences in the distribution of categorical variables among PD subgroups. Independent t test and analysis of variance

TABLE 1. Demographics of PD subgroups and healthy controls

	PD-ICD- (n = 52)	PD-ICD+ (n = 58)	HCs ICD- (n = 33)	*P* Value
Sex (M/F)[a]	32/20	38/20	13/20	
Age (yrs)	63.1 (10.2)[b]	60.3 (9.3)	55.3 (9.0)	**0.01**
Education (yrs)	11.3 (4.7)	10.9 (4.3)	11.6 (4.1)	0.15
BDI-II	8.8 (7.5)	11.07 (10.6)	9 (12.5)	0.22
PD-CNT/PD-MCI[a]	25/27	27/31		
MMSE	27 (2.2)	26.4 (2.6)[c]	28.2 (2.0)	**0.001**
Disease duration (yrs)	8.0 (5.7)	9.0 (5.5)		**0.034**
Age of onset	54.7 (11.6)	50.1 (12.1)		**0.04**
H&Y stage	2.3 (0.7)	2.4 (0.7)		0.45
UPDRS-III	28.5 (12.3)	26.7 (16.5)		0.52
LEDD	722.6 (498.5)	923.1 (474.1)		**0.033**
DAED	148.9 (105.0)	163.7 (111.3)		0.47

Note: Comparison between PD subgroups and HC-ICD-;
[a]χ^2 test comparison between PD-ICD subgroups or HC-ICD-.
[b]Post-hoc ANOVA between PD-ICD- vs HCs-ICD- ($P < 0.05$ Bonferroni corrected).
[c]Post-hoc ANOVA between PD-ICD+ vs HCs-ICD- ($P < 0.05$ Bonferroni corrected).
PD, Parkinson's disease; HCs, healthy controls; PD-ICD, Parkinson's disease patients with impulse control disorders; HCs-ICD-, healthy controls without impulse control disorders; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorder in Parkinson's Disease-Rating Scale; BDI-II, Back Depression Inventory scale; H&Y, Hohen and Yahr Scale; UPDRS-III, United Parkinson's disease rating scale, part III; LEDD, levodopa equivalent dose; DAED, dopamine equivalent dose; PD-CNT, Parkinson's disease patient without cognitive impairment; PD-MCI, Parkinson's disease patient with mild cognitive impairment; MMSE, Mini-Mental State Examination.

with post-hoc Bonferroni correction was used to assess continuous clinical and demographic variables. The statistical analysis was carried out using SPSS 20.0 (http://www-01.ibm.com/software/analytics/spss/products/statistics/).

Results

Participant Characteristics

Analysis of variance and chi squared analysis showed that there were no differences in education, sex, MCI frequency, and beck depression inventory-II (BDI-II) scores among the three groups (HCs, PD-ICD+, and PD-ICD-). Bonferroni post-hoc test showed that MMSE scores were significantly higher in HCs compared with PD-ICD+ and PD-ICD- ($p < 0.001$ and $p = 0.048$). Moreover, PD-ICD- patients were older compared with HCs ($p < 0.007$).

The PD-ICD+ versus PD-ICD- *t* test comparison showed no significant differences in disease severity, UPDRS-III score, and dopamine agonist treatment.

Moreover, PD-ICD+ patients had earlier age of onset ($p < 0.05$), longer disease duration ($p < 0.05$), and higher LEDD ($p < 0.05$) compared with PD-ICD- patients. For this reason age, disease duration, and LEDD were included as covariates in the cortical thickness GLM analysis in addition to MMSE score. Table 1 summarizes clinical characteristics of HCs and PD subgroups.

Cortical Thickness Analysis

General linear model analysis showed thickness and volume differences between PD-ICD subgroups and HCs in several areas.

PD-ICD- vs. HCs

A trend for cortical thinning in left middle temporal, left posterior cingulated area, right supramarginal, and right inferior parietal regions in PD-ICD- was seen compared with HCs ($p < 0.005$ clusterwise uncorrected).

PD-ICD+ vs. HCs

Areas of significant cortical thinning were found in PD-ICD+ bilaterally in the superior and caudal middle frontal regions, in the supramarginal, in the superior and inferior parietal, in the precuneus, and in the lateral occipital areas compared with HCs. In the right hemisphere, thinning was found in the rostral middle, lateral, and medial orbital frontal areas, pars triangularis, superior temporal, and fusiform areas. In the left hemisphere, the PD-ICD+ group showed cortical thinning in the precentral areas, posterior cingulate, transverse middle and inferior temporal areas, insula, and lingual gyrus.

PD-ICD+ vs. PD-ICD-

The PD-ICD+ presented significant cortical thinning in the left precentral and postcentral area, superior frontal and rostral middle frontal area, in the pars orbitalis, in the pars opercularis, in the superior and inferior parietal areas, in the lingual and parahippocampal gyrus, and bilaterally in the caudal middle frontal and supramarginal areas. Supplemental Data e-Table 1 and Figure 2A summarize details of PD subgroups and HCs comparisons.

Analysis of Subcortical Regions

Compared with HCs, we found right hippocampal atrophy in PD-ICD-, and volume reduction in the left putamen and in the middle posterior corpus callosum in PD-ICD+. The PD-ICD subgroups comparison showed volume reduction in the right accumbens and in the central and middle anterior corpus callosum, as well as increased volume in the left amygdala in the PD-ICD+ compared with the PD-ICD- subgroup (see Supplemental Data e-Table 2 and Figure 2B).

Using logistic regression models, atrophy in the left rostral middle frontal areas, right superior frontal areas, caudal middle frontal areas bilaterally, right accumbens, corpus callosum, and increased volume in the left amygdala were present in the PD-ICD+ subgroup (Table 2).

Correlation with ICD Symptoms Severity

In the subset of PD-ICD+ patients with a QUIP-RS score (n = 36), correlation analysis showed a positive

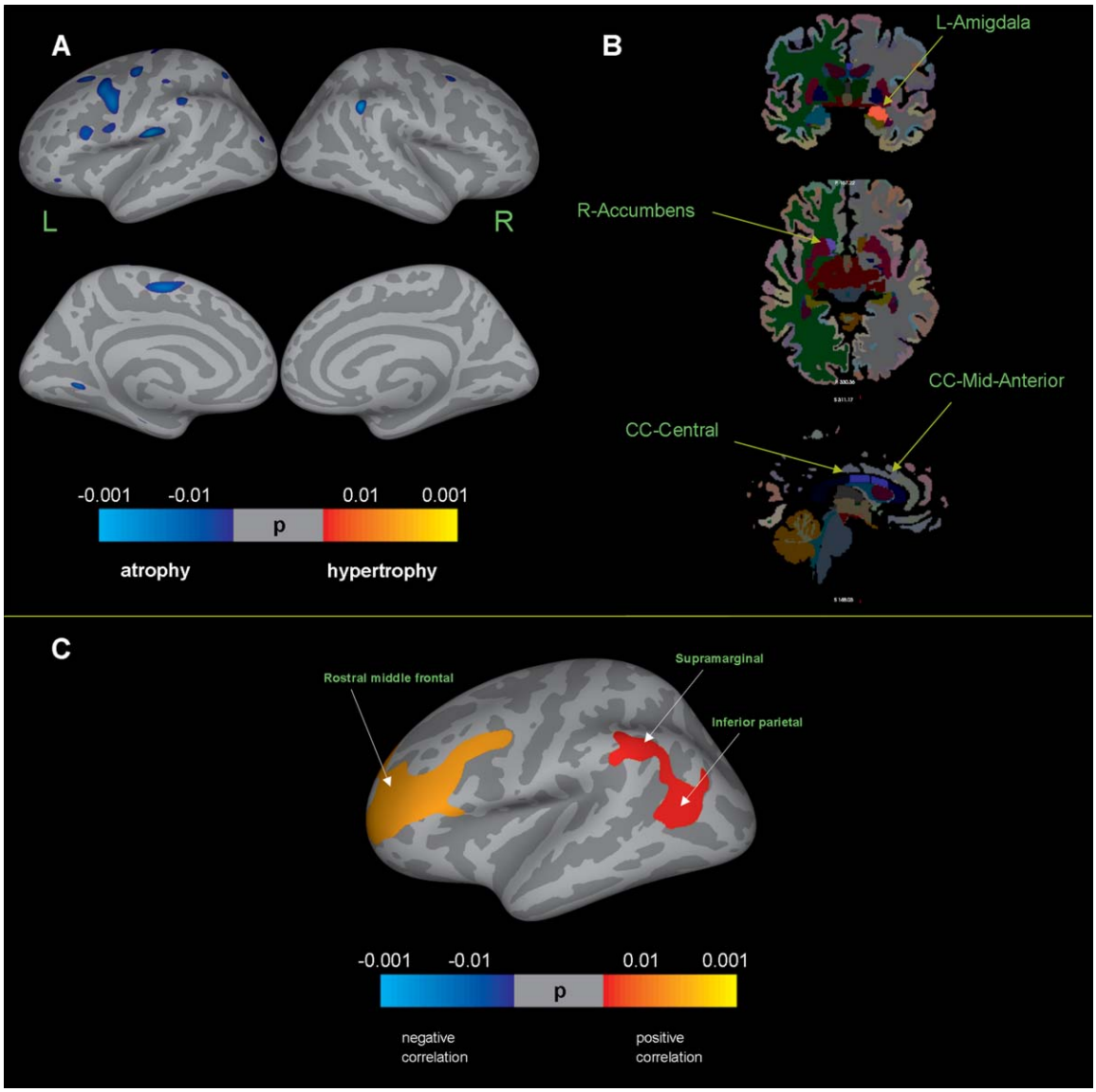

FIG. 2. Pattern of cortical thickness and subcortical volume between PD-ICD subgroups. (**A**) Cortical atrophy in ICD+ vs. ICD- patients. (**B**) ICD+ significant subcortical areas alteration obtained using a superimposed mask. GLM analysis, covarying for age, disease duration, LEDD, MMSE. (**C**) Correlation analysis between QUIP-RS > 0 scores and cortical and subcortical areas. LEDD and MMSE score were included as covariates. Monte Carlo and Sidak corrections for multiple comparisons at $p < 0.05$ were applied. Areas survival the threshold of $p < 0.05$ FDR corrected. Blue, atrophy. Red, hypertrophy. PD-ICD, Parkinson's disease patients with impulse control disorders; LEDD, levodopa equivalent dose; MMSE, Mini-Mental State Examination; CC_Central, central part of the corpus callosum; CC_Mid_Anterior, middle anterior part of the corpus callosum**.** [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 2. Cortical and subcortical area that best describe ICD+ model in PD

				95% CI for EXP(B)		
	B Coefficent	Wald	Odds Ratio	Lower	Upper	*P* Value
L amygdala	0.005	10.643	1.005	1.002	1.008	0.001
L caudal middle frontal	−4.902	3.382	0.007	0.000	1.381	0.066
L rostral middle frontal	4.488	3.312	88.976	0.708	11180.210	0.069
R caudal middle frontal	−4.765	3.501	0.009	0.000	1.254	0.061
R accumbens	−0.005	2.806	0.995	0.989	1.001	0.094
R superior orbito frontal	5.473	3.572	238.270	0.816	69549.466	0.059
CCcentral	−0.010	8.233	0.990	0.983	0.997	0.004

Backward logistic regression. Enter variable if $p < 0.05$. Remove variable if $p > 0.1$. Overall Model Fit: significance level $p < 0.0001$. CCcentral, central part of the corpus callosum; CI, confidence interval.

linear relationship between QUIP-RS scores and left rostral middle frontal areas, left inferior parietal, and left supramarginal areas. No significant subcortical volume correlation was found after correction (Fig. 2C and Supplemental Data e-Table 3).

Discussion

In this study, we found significant cortical deficits in PD-ICD+ patients in fronto-striatal-limbic circuitry in line with our initial hypothesis. Moreover, regression analyses underlined an association of meso-cortical-limbic circuits with ICDs. Specifically, atrophy in bilateral caudal middle frontal areas, left rostral middle frontal areas, right superior frontal areas, right accumbens, and corpus callosum and relative volume increase of left amygdala were associated with ICDs. These findings should be interpreted in the context of general cortical atrophy in PD versus HCs.

Cortical limbic networks are involved in the cognitive component of impulsivity, and preserved prefrontal cortex control is required for decision making under risk.[22] Evidence shows increased impulsive decision-making in PD patients with compulsive eating and pathological gambling indicating inability to delay reward despite intact reward learning.[2,23]

We found thinning of the prefrontal cortex, along with relative volume increases in the amygdala, both working in association with the vmPFC/orbitofrontal cortex in decision making. In particular, the amygdala plays a central role in associating sensory cues with their motivational and emotional significance.[24,25] Our results support models of amygdala–frontal interaction in which motivational significance, coded by the amygdala, projects to the orbital-prefrontal cortex for action control,[26] as well as for a role of prefrontal cortex in rejecting behavior-guiding rules when they become maladaptive.[27] These findings could suggest that PD-ICD+ may have preserved stimuli–reward association abilities despite their altered reversal learning ability.

Amygdala volume was greater in PD with ICDs than without ICDs, but similar to HC subjects. This is an intriguing finding, suggesting that PD with relatively preserved amygdala may be more prone to develop ICD than those presenting reduced amygdala volume. Behavioral studies have shown that PD with ICDs may present high novelty seeking (NS) scores in the same range as HCs.[28,29]

Novelty seeking is characterized by impulsivity, exploratory drive, and excitability, and possibly is driven by individual differences in dopamine system sensitivity.[30] Cohen[31] postulated the novelty-loop theory where hippocampus and amygdala-ventral striatal pathways are related to stable individual differences in NS personality. In particular, the network associated with the NS trait involves the hippocampus, which signals the presence of a sensory prediction error (when sensory input differ from memory-driven expectation),[32] and the amygdala, which modulates hippocampal and striatal activity in novel environments or during emotional memory encoding.[33,34] In this context, the NS trait could be affected in PD because of the involvement in the limbic areas. Future studies supported by multiple neuroimaging techniques are needed to explore this hypothesis.

We also found thinning of the rostral portion of the corpus callosum in PD-ICD+. Previous neuroimaging data showed fractional anisotropy reduction in the rostrum of the corpus callosum of psychiatric patients with compulsive behaviors[35,36] and reduced functionality of the network connecting medial frontal areas with paralimbic regions in cocaine users.[37] These findings support the notion of a psychological alteration in impulsivity, leading to an overestimation of the motivational relevance of stimuli-related reinforcement and of the reflective system that activates inhibitory processes.[38] As previously mentioned fronto-striatal disconnection was already reported in PD with ICD+[6]. Thinning of the corpus callosum might therefore express such disconnection and unbalance between the impulsivity and the inhibitory system.

We also observed that rostral middle frontal, supramarginal, and inferior parietal areas in the left hemisphere positively correlated with QUIP-RS scores, suggesting that ICD severity explains some of the variance associated with thickness changes in regions that play a key role in their occurrence. Frontal and parietal areas together with motor areas share the same neuronal inhibitory-attentional network with a specific activation pattern associated with network subcomponents such as interference inhibition, action withholding, and action cancellation.[39-41] In particular, inhibiting an already initiated reaction might rely more strongly on the frontal-striatal pathway.[39,42] Anterior parietal regions, in particular the left supramarginal gyrus, are associated instead with motor attention and particularly with disengaging and redirecting such attentional processes.[43] Evidence shows that the "top-down network" controlling attention, working memory, and executive function is involved in ICDs. Functional imaging studies in PD patients with pathological gambling[44] showed altered areas (fronto-subcortical regions) in the "top-down control network" of behaviors causing negative consequences. In non-PD problem gamblers, a fronto-parietal activation pattern was seen during high-risk compared with low-risk trials in problem gamblers, reflecting a probable cue-induced addiction memory network that in turn activates gambling behavior.[45] Thus, in patients with ICDs, interference inhibition problems may relate mostly to fronto-parietal alterations, whereas deficits in action cancellation depends more on fronto-striatal

dysfunction. Prospective studies will be required to define regional cortical thickness before treatment initiation and assess how this is modulated individually by development of ICD severity and duration.

Limitations of the study include the relatively young HCs group, although we corrected for age in all analyses. We also administered the Italian back-translated English version of QUIP-RS (Italian validation currently in progress), and our findings in an Italian population could be partially biased. However, recent validation of this scale in another European languages showed a high concordance.[13] Moreover, the high confidence interval (CI) values in the orbitofrontal area and the rostral middle frontal areas observed as outcome of regression analysis could be related to the involvement of these regions only in specific ICD subtypes. Nonetheless, we did not perform a separate analysis because of the small number of subjects presenting single ICD-subtypes in our sample.

We acknowledge that, given the characteristics of our hospital (movement disorder specialized unit), the prevalence of ICDs may not reflect that of the whole PD population. Finally we did not analyze our MRI data based on presence of individual ICDs because most patients showed multiple ICDs.

In conclusion, our results suggest that mesolimbic and cortical-cortical pathways are involved in ICD behaviors in PD, and that their severity is associated with gray matter alterations in regions linked to the reward and control networks.

References

1. Bechara A. Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. Brain 2000; 123:2189-2202.
2. Voon V, Gao J, Brezing C, et al. Dopamine agonists and risk: impulse control disorders in Parkinson's disease. Brain 2011;134: 1438-1446.
3. O'Sullivan SS, Djamshidian A, Evans AH, Loane CM, Lees AJ, Lawrence AD. Excessive hoarding in Parkinson's disease. Mov Disord 2010;25:1026-1033.
4. Bechara A, Van Der Linden M. Decision-making and impulse control after frontal lobe injuries. Curr Opin Neurol 2005;18:734-739.
5. Anderson SW, Barrash J, Bechara A, Tranel D. Impairments of emotion and real-world complex behavior following childhood- or adult-onset damage to ventromedial prefrontal cortex. J Int Neuropsychol Soc 2006;12:224-235.
6. Cilia R, Siri C, Marotta G, et al. Functional abnormalities underlying pathological gambling in Parkinson disease. Arch Neurol 2008; 65:1604-1611.
7. Biundo R, Formento-Dojot P, Facchini S, et al. Brain volume changes in Parkinson's disease and their relationship with cognitive and behavioural abnormalities. J Neurol Sci 2011;310:64-69.
8. 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;55:181-184.
9. Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease. The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations. Mov Disord 2003;18:738-750.
10. Weintraub D, Nirenberg MJ. Impulse control and related disorders in Parkinson's disease. Neurodegener Dis 2013;11:63-71.
11. Weintraub D, Mamikonyan E, Papay K, Shea Ja, Xie SX, Siderowf A. Questionnaire for impulsive-compulsive disorders in Parkinson's disease-rating scale. Mov Disord 2012;27:242-247.
12. Probst CC, Winter LM, Moller B, et al. Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease (QUIP) and the QUIP-rating scale in a German speaking sample. J Neurol 2014;261:936-942.
13. Biundo R, Weis L, Pilleri M, Facchini S, Formento-Dojot P, Vallelunga A, Antonini A. Diagnostic and screening power of neuropsychological testing in detecting mild cognitive impairment in Parkinson's disease. J Neural Transm 2013;120:627-633.
14. Litvan I, Goldman JG, Troster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord 2012;27:349-356.
15. Dubois B, Burn D, Goetz C et al. Diagnostic procedures for Parkinson's disease dementia: recommendations from the Movement Disorder Society Task Force. Mov Disord 2007;22:2314-2324.
16. Prince M, Jackson J. *World Alzheimer's Report 2009*. Alzheimer's Disease International, 2009.
17. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 1999;9:179-194.
18. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage 1999;9:195-207.
19. Desikan RS, Segonne F, Fischl B et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 2006;31:968-980.
20. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.
21. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010;25:2649-2653.
22. Euteneuer F, Schaefer F, Stuermer R, et al. Dissociation of decision-making under ambiguity and decision-making under risk in patients with Parkinson's disease: a neuropsychological and psychophysiological study. Neuropsychologia 2009;47:2882-2890.
23. Voon V, Dalley JW. Parkinson disease: impulsive choice—Parkinson disease and dopaminergic therapy. Nat Rev Neurol 2011;7: 541-542.
24. Everitt BJ, Cardinal RN, Parkinson JA, Robbins TW. Appetitive behavior: impact of amygdala-dependent mechanisms of emotional learning. Ann N Y Acad Sci 2003;985:233-250.
25. Kalivas PW, Volkow N, Seamans J. Unmanageable motivation in addiction: a pathology in prefrontal-accumbens glutamate transmission. Neuron 2005;45:647-650.
26. Gallagher M, Schoenbaum G. Functions of the amygdala and related forebrain areas in attention and cognition. Ann N Y Acad Sci 1999;877:397-411.
27. Wise SP, Murray EA, Gerfen CR. The frontal cortex-basal ganglia system in primates. Crit Rev Neurobiol 1996;10:317-356.
28. Djamshidian A, O'Sullivan SS, Wittmann BC, Lees AJ, Averbeck BB. Novelty seeking behaviour in Parkinson's disease. Neuropsychologia 2011;49:2483-2488.
29. Voon V, Thomsen T, Miyasaki JM, et al. Factors associated with dopaminergic drug-related pathological gambling in Parkinson disease. Arch Neurol 2007;64:212-216.
30. Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. Arch Gen Psychiatry 1993; 50:975-990.
31. Cohen MX, Schoene-Bake JC, Elger CE, Weber B. Connectivity-based segregation of the human striatum predicts personality characteristics. Nat Neurosci 2009;12:32-34.
32. Lisman JE, Grace AA. The hippocampal-VTA loop: controlling the entry of information into long-term memory. Neuron 2005;46: 703-713.

33. Sheth A, Berretta S, Lange N, Eichenbaum H. The amygdala modulates neuronal activation in the hippocampus in response to spatial novelty. Hippocampus 2008;18:169-181.

34. Rolls ET. Neurophysiology and cognitive functions of the striatum. Rev Neurol (Paris) 1994;150:648-660.

35. Garibotto V, Scifo P, Gorini A, Alonso CR, Brambati S, Bellodi L, Perani D. Disorganization of anatomical connectivity in obsessive compulsive disorder: a multi-parameter diffusion tensor imaging study in a subpopulation of patients. Neurobiol Dis 2010;37:468-476.

36. Saito Y, Nobuhara K, Okugawa G, et al. Corpus callosum in patients with obsessive-compulsive disorder: diffusion-tensor imaging study. Radiology 2008;246:536-542.

37. Gu H, Salmeron BJ, Ross TJ, Geng X, Zhan W, Stein EA, Yang Y. Mesocorticolimbic circuits are impaired in chronic cocaine users as demonstrated by resting-state functional connectivity. Neuroimage 2010;53:593-601.

38. Verdejo-Garcia A, Bechara A. A somatic marker theory of addiction. Neuropharmacology 2009;56(Suppl 1):48-62.

39. Sebastian A, Pohl MF, Klöppel S, et al. Disentangling common and specific neural subprocesses of response inhibition. Neuroimage 2013;64.

40. Levy BJ, Wagner AD. Cognitive control and right ventrolateral prefrontal cortex: reflexive reorienting, motor inhibition, and action updating. Ann N Y Acad Sci 2011;1224:40-62.

41. Pratt N, Willoughby A, Swick D. Effects of working memory load on visual selective attention: behavioral and electrophysiological evidence. Front Hum Neurosci 2011;5:57.

42. Jahfari S, Waldorp L, van den Wildenberg WP, Scholte HS, Ridderinkhof KR, Forstmann BU. Effective connectivity reveals important roles for both the hyperdirect (fronto-subthalamic) and the indirect (fronto-striatal-pallidal) fronto-basal ganglia pathways during response inhibition. J Neurosci 2011;31:6891-6899.

43. Schiff S, Bardi L, Basso D, Mapelli D. Timing spatial conflict within the parietal cortex: a TMS study. J Cogn Neurosci 2011; 23:3998-4007.

44. Antonelli F, Ko J, Miyasaki J, et al. Dopamine-agonists and impulsivity in Parkinson's disease: impulsive choise vs. impulsive actions. Hum Brain Mapp 2014;35:2499-2506.

45. Miedl SF, Fehr T, Meyer G, Herrmann M. Neurobiological correlates of problem gambling in a quasi-realistic blackjack scenario as revealed by fMRI. Psychiatry Res 2010;181:165-173.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.