CAN WE PREDICT DEVELOPMENT OF IMPULSIVE-COMPULSIVE BEHAVIOURS IN PARKINSON'S DISEASE?

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LR and CL – Statistical analysis
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ABSTRACT

Objective

To determine clinical and structural imaging predictors of impulsive compulsive behavior (ICB) in de-novo Parkinson's disease (PD).

Methods

From a cohort of 1116 subjects from the Parkinson's Progression Marker Initiative database, we created a sub-cohort of 42 de novo PD without ICB at baseline with available 3T MRI and who developed ICB during follow-up. PD-ICB were matched for age, gender and disease duration to 42 PD patients without ICB over follow-up (PD-no-ICB) and 42 healthy controls (HC). Baseline demographic and clinical predictors of ICB were analyzed. For the longitudinal neuroimaging analysis, we selected 27 PD-ICB patients with available neuroimaging after ICB onset, who were matched with 32 PD-no-ICB and 35 HC. Baseline and longitudinal structural differences were compared using voxel-based morphometry and voxel-based quantification.

Results

People who went on to develop ICB had more severe anxiety, worse autonomic and global cognitive functions and were more likely to have RBD. Logistic regression confirmed that worse autonomic and cognitive functions were predictors of ICB. We could not find any morphological feature on baseline MRI that predicted later onset of ICB. When comparing PD groups at follow-up, a small region of increased atrophy in the anterior limb of the left internal capsule adjacent to the head of the left caudate nucleus was found in PD-ICB, but not surviving correction for multiple comparisons.

Conclusions

Worse autonomic and cognitive functions predict development of ICB at the time of PD diagnosis. Structural imaging fails to identify morphological features associated with the development of ICB.

INTRODUCTION

Impulsive compulsive behaviors (ICB) are disabling neuropsychiatric disturbances occurring in up to 30% of Parkinson's disease (PD) patients. They include impulse control disorders (ICD) such as pathological gambling, hypersexuality, compulsive buying and binge eating, and compulsive behaviors such as punding and compulsive use of dopamine replacement therapy (also known as dopamine dysregulation syndrome)[1]. The pathophysiological basis is unconfirmed, but it is likely that ICB are not simply drug-induced phenomena[2]. Predisposing cognitive profiles have been reported in some cross-sectional studies, but not confirmed by others[3-5]. A novelty seeking personality profile, higher impulsivity[6], impairment in sense of agency[7],more severe depression[8] and anhedonia[9] have been associated with ICB. Genotype may also be a predisposing factor, as PD associated with the Parkin mutation have more severe ICB[10]. Functional[11] and structural cross-sectional neuroimaging studies[12-14] have reported a number of abnormalities in the fronto-striatal circuit and in the limbic areas. Only one previous study has looked for predictors of later development of ICB by analyzing demographic, motor symptom scores and dopamine transporter imaging data from the Parkinson Progressive Markers Initiative (PPMI) cohort of de novo PD patients[15]. However, the potential predictive value of non-motor symptom assessment and structural neuroimaging has not yet been explored.

In the present study, we aimed to evaluate in a de novo PD population from the PPMI cohort: 1) whether there are motor or non-motor features predicting later onset of ICB at the time of PD diagnosis; 2) whether there are any structural MRI abnormalities at baseline or follow-up that can predict later onset of ICB.

METHODS

Subjects

Data were obtained from the PPMI database (http://www.ppmi-info.org/data). The aims and methodology of this database have been previously published[16], and are available through the PPMI website (http://www.ppmi-info.org/study-design). At the time we acquired the data for this work

(downloaded 29th November 2015), 1116 participants had been included in the study.

We searched the database for de novo PD patients not receiving any dopaminergic treatment who screened negative for ICB at baseline visit and converted to positive screening at any study time at follow-up according to the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP)[17]. The PPMI is a large multicenter study, and consequently a mixture of different MRI acquisitions and field strengths have been used in the generation of the imaging dataset. To simplify the analysis and remove a major potential source of non-experimental error, we elected to create a homogenous MRI dataset for this work by selecting only those participants who had undergone 3T MRI scanning and had a T1 MPRAGE acquisition at baseline. Through this process, we identified 42 PD patients converting to ICB (PD-ICB). We matched these patients by age, gender and disease duration with 42 PD patients who did not develop ICB at follow-up (PD-no-ICB) and 42 healthy controls matched by age and gender who had no ICB. These two groups were compared for the baseline clinical and neuroimaging variables at baseline for the cross-sectional analysis.

For the longitudinal analysis, from our group of 42 PD-ICB patients, we included 29 who had the requisite imaging after ICB onset. We acquired the MRI data using the closest time-point following onset of ICB. Two datasets were excluded due to severe movement artifact that prevented pre-processing, leaving 27 subjects in the longitudinal PD-ICB group. For comparison, we also identified the corresponding longitudinal imaging for PD-no-ICB (n=32) and HC (n=35), selecting the time-points to match the ICB group as closely as possible. Figure 1 illustrates the selection process.

Clinical assessment

The presence of ICB was investigated in PD and HC by means of the QUIP[17]. The QUIP is designed as a screening instrument for ICB, based on any single positive response for the four major ICBs (gambling, eating, buying, sexual behaviours), hobbyism, simple motor activities (i.e., punding). A positive response for any of these disorders defined the diagnosis of ICB, as previously described[17].

Demographic (age, gender, level of education) and clinical data were considered in HC and in both groups of PD patients at baseline evaluation, before starting dopaminergic treatment. The following rating scales were assessed at baseline visit in HC and PD: Geriatric depression scale (GDS) and State-trait anxiety inventory (STAI). Autonomic function was rated by the Scales for Outcomes in Parkinson's disease – Autonomic (SCOPA-AUT) and olfaction by the University of Pennsylvania Smell Identification Test (UPSIT). The REM Sleep Behavior Disorder Questionnaire (RBDSQ)[18] was employed to reach the diagnosis of Rapid Eye Movement Sleep Behavior disorder (RBD); the RBDSQ revealed a specificity of 92% when using a cut-off value of 5. Overall cognitive function was evaluated by means of the Montreal cognitive assessment (MoCA) and specific cognitive domains were assessed as it follows: episodic verbal memory by Hopkins verbal learning test – revised; visuo-spatial functions by Benton judgment of line orientation; attention and executive functions by Letter number sequencing, Symbol digit modalities test (SDMT), phonological fluency; language by semantic fluency. In the PD group, disease severity and disability were rated by means of the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)] part III and the Modified Schwab & England Activities of Daily Living. Dopaminergic treatment was expressed in terms of total Levodopa Equivalent Daily Dose (LEDD) and dopamine-agonists (D-Ag) LEDD. We selected the LEDD either at the time of QUIP conversion from negative to positive in PD-ICB, or at the last available follow-up visit for those remaining QUIP-negative (PD-no-ICB).

Pre-Processing - All

The raw DICOMS were downloaded from the PPMI website. These were imported using SPM12 software package (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Each image was manually checked to ensure a common orientation and origin. These varied significantly, and manual realignment in SPM12 was required for some of the datasets to ensure they all were reasonably close to MNI orientation prior to the automated re-alignment pipelines. The original image resolution was between 1mm and 1.1mm isotropic. All available MRI data was then re-aligned to MNI orientation and re-sliced to 1mm isotropic voxel resolution in

subject space using 4th degree b-spline interpolation. All re-orientated T1 weighted images were then segmented into grey, white and CSF tissue classes[19]. These segmentations were used to generate cortical thickness maps using the VBCT toolbox [20] in SPM8 (this toolbox is currently incompatible with SPM12) with a sampling resolution of 0.5mm, CSF smoothness 3mm, CSF thinness 0.65 and number of dilations was set to 1.

Pre-Processing - Baseline

The baseline GM, WM and CSF segmentations were then used to generate a group average template using the diffeomorphic warping "*Shoot*" algorithm in SPM12[21]. The segmentations were then warped using the resulting deformation fields, modulated with the Jacobian determinant data and smoothed with a 6mm full width half maximum (FWHM) Gaussian kernel. The CT maps were also warped using the corresponding deformation fields. The warped CT maps were then used to generate FWHM 6mm smoothed warped weighted images[22]. These warped weighted images avoid the parameter value changes caused by the necessary Gaussian smoothing in standardised space. Total intracranial volume (TIV) was calculated by integrating the Jacobians within the three tissue classes, with the segmentations binarised at a threshold of 0.2.

Pre-Processing - Longitudinal

Using the "*Longitudinal Registration"* toolbox in SPM12[23], the paired longitudinal T1 weighted images were registered together using pairwise longitudinal registration. This produced Jacobian determinant, warp fields and divergence maps for each time-point in addition to the individual average image that is the midpoint between the two time points. The divergence maps quantify the diffeomorphic distance between the subject time-point image from the average image, and represent the rate of expansion or contraction required to warp it to the average image. For the cortical thickness, these were warped to the individual midpoint (using the calculated warp fields from pairwise longitudinal registration), and a voxel-wise linear fit used to calculate the rate of CT change between the two. The midpoint T1 images were then segmented GM, WM and CSF, and used to generate a longitudinal group average space using the diffeomorphic warping "*Shoot*" algorithm. All rate maps (already in individual average space) were then warped to this

longitudinal group average space. To statistically analyze the tissue specific rate maps, a voxel based quantification (VBQ) approach was adopted as previously described[22]. Specifically, the rate maps for GM, WM and CT were treated as parameter maps, and the combined weighting/smoothing procedure used to generate WWA rate-maps using a 6mm full width at half maximum (FWHM) Gaussian kernel.

STATISTICAL ANALYSIS

Two-group comparisons (PD vs HC; PD-ICB vs PD-no-ICB) were computed for all demographic, psychiatric, cognitive, sleep and olfaction data by means of the Mann-Whitney U test. Spearman bivariate correlations analysis was used to investigate possible correlation between clinical variables and psychiatric, cognitive, sleep and olfaction scores in each group and in the PD group as a whole. Binary logistic regression was used to test the association between development of ICB (presence/absence as dependent variable) and the following variables at baseline visit as regressors: age, MOCA, RBD (yes/no), autonomic dysfunction (as per SCOPA-AUT) and anxiety (by STAI).
For the MRI data, all analysis was performed in SPM12. All group analysis was performed in the population group average space. The baseline VBM analysis used the baseline warped modulated GM and WM. The baseline VBQ analysis used the baseline WWA CT maps. The longitudinal rate analysis used the longitudinal WWA GM, WM and CT rate maps. All analysis used an ANOVA in SPM, including age, total intracranial volume and gender as confounding variables. The principal comparisons of interest were PD (ICB and no-ICB) versus HC, and ICB-PD versus no-ICB-PD. In all statistical analyses the regions that survived Family Wise Error (FWE) multiple comparison correction at $p < 0.05$ were considered significant. All significant results are displayed at both $p < 0.001$ uncorrected and FWE corrected $p < 0.05$. The legends are labeled accordingly. All data are given as mean ± standard deviation. All images are displayed using the neurological convention.

RESULTS

Clinical and MRI data at baseline

Tables 1 and 2 show demographical and clinical data comparisons between HC and PD and PD-ICB and PD-no-ICB at the time of baseline evaluation. PD patients differed from HC by severity of anxiety, depression, olfaction impairment and autonomic dysfunction, respectively by STAI, GDS, UPSIT and SCOPA-AUT; moreover, PD were more likely to have RBD and worse phonological fluency (table 1).

When considering the two PD groups, disease duration, motor symptom severity (as per MDS-UPDRS III) and cognitive measures were comparable, except for a lower MOCA score in PD-ICB (table 2). PD patients who later developed ICB were more anxious (p=0.02 for STAI-state, 0.01 for STAI-trait and p=0.009 for STAI total score), had worse autonomic impairment (as per SCOPA-AUT, p=0.004) and were more likely to have RBD (p=0.03) compared to PD patients who remained free of ICB at follow-up. Binary logistic regression analysis showed that only MOCA score and autonomic function as measured by the SCOPA-AUT were significant baseline predictors of later development of ICB (table 3).

At baseline (de novo PD vs HC) we found no differences between HC and PD (FWE $P < 0.05$) and PD-no-ICB and PD-ICB (FWE $P < 0.05$) in any of the analyses (GM and WM VBM, cortical thickness VBQ).

Clinical and MRI data at follow-up

Disease duration was shorter in PD-ICB compared to PD-no-ICB (table 2) at the time of follow-up. Mean latency time between start of dopaminergic treatment and onset of ICB was 14.4±8.8 months; 11 out of 42 PD-ICB patients (26%) were not taking anti-parkinsonian medications at the time of ICB onset. All other PD-ICB patients were treated with levodopa (n=6), dopamine-agonists (n=7), other dopamine replacement therapies (n=6), or a combination of the above treatments (n=12). PD-ICB patients had lower total LEDD driven by a significantly lower dose of Levodopa compared to PD-no-ICB, but the two groups did not differ by D-Ag LEDD at last follow-up.

PD groups were matched by disease duration at the time they received the second MRI scan (PD-ICB=23.60 ± 8.87 months; PD-no-ICB=22.61 ± 4.83 months (p = 0.59). There was a faster rate of grey and white matter atrophy, particularly bilateral hippocampi and striatum, in those with PD compared to HC (FWE P < 0.05).The average annualized rate of atrophy and thresholded t-statistic maps are shown in Figure 2, with FWE *P*<0.05 and uncorrected *P* < 0.001 labeled accordingly. No differences (FWE *P* < 0.05) were observed in atrophy rate of grey matter, white matter and cortical thickness between PD-ICB and PD-no-ICB. Given previous reports of focal atrophy in PD patients with ICB[12 14], we explored the data with a more lenient statistical threshold (uncorrected *P* < 0.001) which revealed a small region of increased atrophy rate in the anterior limb of the left internal capsule adjacent to the head of the left caudate nucleus (Figure 3).

DISCUSSION

Impulsive-compulsive behaviors are a common and disabling feature of Parkinson's disease, whose main risk factor is use of dopaminergic drug, particularly dopamine-agonists[24]. The knowledge of clinical and structural imaging features able to predict their later development in newly diagnosed patients would likely improve clinical management and outcome.

Previous clinical[6 25-27] and neuroimaging studies[11-14] have provided potential insights, but they had a cross-sectional design and were performed in patients with advanced PD. Higher anxiety levels[6 25] and presence of RBD have been associated with an increased risk of developing ICB in PD patients with long disease duration [26 27]. In our study, the strongest predictors of impulsive-compulsive behaviors were worse cognitive and autonomic function, and level of anxiety and presence of RBD did not survive logistic regression analysis.

The role of cognitive dysfunction as a risk factor for impulsive-compulsive behavior is controversial. In our cohort, patients with ICB had lower MOCA scores compared to those without ICB, but the two groups did not differ by any of the specific cognitive domains tested at baseline. A recent longitudinal study analyzing a sample of PD patients with a long disease duration, demonstrated better scores on MMSE, semantic fluency and attentional matrices tasks in patients with ICB compared to PD-no-ICB[28]. However, sub-

group analysis of those who did not have remission of ICB after dopamine-agonist withdrawal showed cognitive scores comparable to PD-no-ICB. In addition, a recent meta-analysis of 34 cross-sectional studies found a significant relationship between ICB and dysfunction in specific cognitive domains [29].

The finding of more severe autonomic dysfunction in those patients who later developed ICB is novel and has not been described in cross-sectional studies. Interestingly, autonomic dysfunction is associated with reduced amygdala grey matter volume[30], an area which has been proposed as part of the anatomical substrate of ICB[24]. However, the lower SCOPA-AUT scores in patients with impulsive-compulsive behaviors might be explained by loss of peripheral sympathetic or parasympathetic nerve terminals[31]. Regardless of the site of autonomic dysfunction, this association might suggest a more severe clinical phenotype of the disease in PD with impulsive-compulsive behavior. Dysautonomia may predict worse disease progression in early PD [32] and lower MOCA score and RBD at the time of PD diagnosis have been found as predictive factors of mild cognitive impairment[33].

In our cohort, 26% of patients developed ICB following their baseline assessment without being exposed to any dopaminergic medication. This is quite a remarkable finding and provides further evidence against the prevailing view that ICB in PD are a pure medication-induced phenomena[8]. Our data instead support the hypothesis that disease-intrinsic factors are involved alongside dopaminergic medication in the pathogenesis of ICB. Indeed, it is important to note that our cohort of patients who developed ICB had comparable dopamine agonist dose, lower levodopa dose and shorter disease duration than the cohort without ICB. Therefore they appear to be prone to develop behavioral disturbances in an earlier phase of the disease and with a lower dose of dopaminergic therapy. A lower dose of dopaminergic treatment has been also associated with more frequent and severe ICB in PD patients carrying the Parkin mutation, with some also developing it before medication use[10].

Following the hypothesis that ICB might be underlined by disease-intrinsic factors in PD, we looked for structural predictors of ICB on brain MRI. Previous cross-sectional studies revealed an increased cortical thickness of

limbic regions[13 14] and thinning of the fronto-striatal regions[12] in PD-ICB. Moreover, brain metabolism and functional imaging studies have shown abnormalities in the fronto-striatal circuit and in the limbic areas such as the orbito-frontal cortex, anterior cingulate cortex, amygdala, nucleus accumbens in patients with advanced PD and ICB[11]. However, these studies had a cross-sectional design and it was unknown if these abnormalities were present at baseline in patients destined to develop ICB. Our study suggests that they are not, as we found no structural difference at baseline or longitudinally between PD-ICB and PD-no-ICB in our analysis. The increased grey and white matter atrophy in PD compared to healthy controls in our longitudinal analysis indicates that the imaging methods we used were sufficiently sensitive to detect changes in this cohort. The lack of any baseline structural predictor of ICB is in keeping with a recent study analyzing DAT binding in new incident ICB patients from the PPMI cohort[15]. DAT binding was unable to predict incident ICB, even when controlling for LEDD which is a main confounder of DAT studies[34]. However, lower DAT binding in the right caudate and right and left putamen at any post-baseline visit was found as a predictor of ICB[15].

On uncorrected analysis of our follow-up MRI scans, there was an increased atrophy rate in the anterior limb of the left internal capsule adjacent to the left caudate nucleus in PD-ICB. The anterior limb of the internal capsule includes fibers connecting the prefrontal and the anterior cingulate cortex[35] and it has been successfully targeted for deep brain stimulation of obsessive-compulsive disorder. Although this finding could link ICB to structural alterations within fronto-limbic connections, it only arose as part of a more lenient statistical analysis and clearly needs to be judged in this light.

It is important to acknowledge some methodological limitations. The presence of ICB was identified only by means of the QUIP, which was designed as a screening instrument with high sensitivity (94%) and lower specificity (72%). Therefore, we cannot exclude false positives or non-clinically relevant ICB[17]. The disease duration in the PD-no-ICB was longer as we selected the last available follow-up in this cohort. Our methodological approach was similar to a previous study on incident ICB from the PPMI cohort[15] and allowed us including a sample of PD-no-ICB with evidence of absent ICB for the longest time possible. Indeed one could argue that this strengthens our assumption

that those patients in the no-ICB group were truly different from those who developed ICB, rather than it simply being an artefact of less opportunity, in terms of disease duration, to develop ICD. We also acknowledge that morphological features predicting ICB could be present in PD at diagnosis, but different image acquisitions or processing methods are needed to detect them. A weakness of the PPMI dataset is the presence of different scanning acquisition methodologies which we sought to overcome by specifying strict criteria for the imaging we did use. However, this had the consequence of reducing the numbers of subjects available for imaging analysis. A strategy for future studies would be to acquire quantitative MRI acquisitions, which can be used to look for changes in tissue properties at a microstructural level and identify structures that cannot be seen using conventional MRI, such as brainstem and thalamic nuclei[36].

Our work suggests that RBD, more severe anxiety and worse autonomic and cognitive function are able to predict future development of ICB in a de novo PD population. Structural imaging of the sort we had available cannot predict risk of development of ICB. Given the major impact of ICB on patients' and caregivers' quality of life, it is critical to identify at-risk individuals to support more tailored prescribing decisions, intensity of follow up and advice to patients and their families.

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TABLE 1: Baseline cognitive, psychiatric and non-motor symptoms in healthy controls (HC) and in Parkinson's disease (PD)

	PD (n=84)	HC (n=42)	p-value
Age	62.4±9.3	61.5±9.0	0.6
Education level	15.4±3.0	15.5±2.9	0.9
Gender (males/females)	58/26	30/12	0.8
MoCA	27.8±2.9	282±1.2	0.8
Symbol Digit Modalities Test	41.7±10.5	49.0±11.3	***0.003***
HVLT-R free recall	24.5±5.5	25.9±4.8	0.1
HVLT-R recognition discrimination	22.3±7.1	24.1±6.3	0.2
Phonemic fluency	13.4±4.4	13.2±4.6	0.4
Benton Judgement of Line Orientation	13.9±1.9	13.6±1.5	0.2
Letter-Number Sequencing	10.4±2.7	11.3±2.6	0.2
Semantic fluency	48.0±11.6	51.1±10.1	0.2
STAI-state	33.7±10.3	27.5±7.4	***0.001***
STAI-trait	33.2±10.0	28.2±6.4	***0.007***
STAI-total	66.9±19.4	55.7±13.3	***0.001***
GDS	2.6±2.6	1.3±2.5	***<0.0001***
UPSIT	21.4±8.9	34±3.6	***<0.0001***
SCOPA_AUT	9.6±6.4	5.4±3.4	***<0.0001***
RBDSQ (Y/N) (%)	34/50 (40.5%)	6/36 (14.3%)	***0.003***

Abbreviations: GDS: Geriatric depression scale; HVLT: Hopkins verbal learning test; MoCA: Montreal cognitive assessment; * RBDSQ = REM Sleep Behavior Disorder Questionnaire (Yes = < 5, No ≥ 5); SCOPA-AUT: Scales for Outcomes in Parkinson's disease – Autonomic; STAI: State-trait anxiety inventory; UPSIT: University of Pennsylvania Smell Identification Test.

TABLE 2: Baseline cognitive, psychiatric and non-motor symptoms in Parkinson's disease (PD) with (PD-ICB) and without (PD-no-ICB) impulsive-compulsive behavior.

	PD-ICB (n=42)	PD-no-ICB (n=42)	p-value
Age (years)	62.6±9.6	62.2±9.1	0.8
Gender (M/F)	30/12	28/14	0.6
UPDRS-III	22.3±9.6	20.6±9.8	0.3
H&Y	1.8±0.5	1.7±0.5	0.3
Schwab & England (%)	94.4±6.1	93.5±6.7	0.5
Disease duration from symptoms onset to baseline (months)	19.9±13.5	21.7±23.9	0.6
Disease duration from symptoms onset to follow-up (months)*	43.8±17.3	61.7±29.5	**0.0001**
LEDD total (mg)*	353.3±281.3	539.0±342.9	**0.01**
LEDD D-ag (mg)*	57.62±96.7	53.6±87.1	0.9
MoCA	27.4±2.1	28.3±1.6	***0.03***
Symbol Digit Modalities Test	41.7±12.0	48.6±11.6	0.9
HVLT-R free recall	24.2±5.7	24.8±5.4	0.6
HVLT-R recognition discrimination	21.5±7.8	23.3±6.2	0.3
Phonemic fluency	12.9±4.6	13.8±4.2	0.3
Benton Judgement of Line Orientation	12.7±2.2	13.4±1.5	0.2
Letter-Number Sequencing	10.3±3.1	10.5±2.2	0.6
Semantic fluency	47.4±11.7	41.6±8.6	0.5
STAI-state	36.2±10.6	31.1±9.5	***0.02***
STAI-trait	35.4±9.6	30.8±10.0	***0.01***
STAI-total	71.5±19.2	61.9±18.4	***0.009***
GDS	2.8±2.24	2.5±3.0	0.2
UPSIT	20.9±9.4	21.9±8.5	0.6
SCOPA_AUT	11.6±7.6	7.4±3.8	***0.004***
RBDSQ (Y/N) (%)	22/20 (52.3%)	12/30 (28.5%)	***0.03***

Abbreviations: GDS: Geriatric depression scale; HVLT: Hopkins verbal learning test; MoCA: Montreal cognitive assessment; RBDSQ = REM Sleep Behavior Disorder Questionnaire (Yes = < 5, No ≥ 5); SCOPA-AUT: Scales for Outcomes in Parkinson's disease – Autonomic; STAI: State-trait anxiety

inventory; UPSIT: University of Pennsylvania Smell Identification Test. H&Y: Hoehn and Yahr stage; D-Ag: dopamine agonists; LEDD: levodopa equivalent daily dose; UPDRS: Unified Parkinson's disease Rating Scale.

*At the time of QUIP conversion from negative to positive in PD-ICB, or at the last available follow-up visit in PD-no-ICB

Table 3: Predictors of ICB development at PD diagnosis by binary logistic regression analysis.

	Beta	Std. Error	p-value	95% C.I.	
				Lower	Upper
Age	.013	.030	0.6	0.9	1.1
MOCA	.310	.149	**0.04***	1.0	1.8
RBD (yes/no)	.408	.544	0.4	0.5	4.4
SCOPA-AUT	-.131	.063	**0.04***	0.7	0.9
STAI total	-.018	.015	0.2	0.9	1.0

Dependent variable: ICB development (yes/no). Predictors: Age; MOCA at baseline; REM Sleep Behavior Disorder (yes/no); SCOPA-AUT (Scales for Outcomes in Parkinson's disease – Autonomic); STAI (State-trait anxiety inventory). * Significant values.

LEGEND TO FIGURES

Figure 1: The flow-chart show how the patients with de novo Parkinson's disease with and without impulsive-compulsive behaviors (PD-ICB, PD-no-ICB) were selected for this study from the PPMI original cohort. HC = healthy controls; QUIP = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease.

Figure 2: Faster rate of grey and white matter atrophy, particularly in the bilateral hippocampi and striatum, in those with PD compared to HC (FWE $P < 0.05$).The average annualized rate of atrophy and thresholded t-statistic maps are shown, with FWE $P<0.05$ and uncorrected $P < 0.001$ labeled accordingly. Bottom row shows regions where the rate of atrophy was higher in PD compared to HC.

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Figure 3: Small region of increased atrophy rate in the anterior limb of the left internal capsule adjacent to the head of the left caudate nucleus in PD-ICB compared to PD-no-ICB at follow-up ($P < 0.001$ uncorrected).

COMPETING INTERESTS

Dr. Ricciardi has received honoraria for speaking from UCB Pharma and Chiesi farmaceutici.

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