RESEARCH ARTICLE

Functional Inhibitory Control Dynamics in Impulse Control Disorders in Parkinson's Disease

Pedro M. Paz-Alonso, PhD,[1*] I. Navalpotro-Gomez, MD,[2,3,4] P. Boddy, MSc,[1] R. Dacosta-Aguayo, PhD,[2,3] M. Delgado-Alvarado, MD, PhD,[2,3,5,6,7] A. Quiroga-Varela, PhD,[2,3,8] H. Jimenez-Urbieta, MSc,[2,3] M. Carreiras, PhD,[1,9] and Maria C. Rodriguez-Oroz, MD, PhD[1,3,8,9,10*]

[1]*BCBL. Basque Center on Cognition, Brain and Language, Donostia-San Sebastián, Spain*
[2]*Neurodegenerative Disorders Area, Biodonostia Health Research Institute, Donostia-San Sebastián, Spain*
[3]*CIBERNED, Network Center for Biomedical Research in Neurodegenerative Diseases, Madrid, Spain*
[4]*Servei de Neurologia, Hospital del Mar, Parc de Salut Mar-IMIM, Barcelona, Spain*
[5]*Neurology Department, Sierrallana Hospital, Torrelavega, Spain*
[6]*IDIVAL, Valdecilla Biomedical Research Institute, Santander, Spain*
[7]*Biomedical Research Networking Center for Mental Health (CIBERSAM), Madrid, Spain*
[8]*Neuroscience Area, Center for Applied Medical Research (CIMA), Universidad de Navarra, Pamplona, Spain*
[9]*Ikerbasque (Basque Foundation for Science), Bilbao, Spain*
[10]*Department of Neurology, Clínica Universidad de Navarra, Universidad de Navarra, Pamplona, Spain*

ABSTRACT: Background: Impulse control disorders related to alterations in the mesocorticolimbic dopamine network occur in Parkinson's disease (PD). Our objective was to investigate the functional neural substrates of reward processing and inhibitory control in these patients.
Methods: Eighteen PD patients with impulse control disorders, 17 without this complication, and 18 healthy controls performed a version of the Iowa Gambling Task during functional magnetic resonance scanning under 3 conditions: positive, negative, and mixed feedback. Whole-brain contrasts, regions of interest, time courses, functional connectivity analyses, and brain-behavior associations were examined.
Results: PD patients with impulse control disorders exhibited hyperactivation in subcortical and cortical regions typically associated with reward processing and inhibitory control compared with their PD and healthy control counterparts. Time-course analyses revealed that only PD patients with impulse control disorders exhibited stronger signal intensity during the initial versus final periods of the negative-feedback condition in bilateral insula, and right ventral striatum. Interestingly, hyperactivation of all the examined right-lateralized frontostriatal areas during negative feedback was positively associated with impulse control disorder severity. Importantly, positive associations between impulse control disorder severity and regional activations in the right insula and right inferior frontal gyrus, but not the right subthalamic nucleus, were mediated by functional connectivity with the right ventral striatum.
Conclusions: During a reward-based task, PD patients with impulse control disorders showed hyperactivation in a right-lateralized network of regions including the subthalamic nucleus that was strongly associated with impulse control disorder severity. In these patients, the right ventral striatum in particular played a critical role in modulating the functional dynamics of right-lateralized inhibitory-control frontal regions when facing penalties.

Key Words: impulse control disorders; inhibitory control; Parkinson's disease; reward processing; ventral striatum

***Correspondence to:** Maria C. Rodriguez-Oroz, Department of Neurology, Clinica Universidad de Navarra, Universidad de Navarra, Av. Pio XII, 36, 31008, Pamplona, Spain; E-mail: mcroroz@unav.es. Pedro M. Paz-Alonso, BCBL, Basque Center on Cognition, Brain and Language, Paseo Mikeletegi, 69, 20009, Donostia-San Sebastián, spain; E-mail: ppazalonso@bcbl.eu.

Pedro M. Paz-Alonso, PhD and I. Navalpotro-Gomez contributed equally to this work as joint first authors.

Received: 29 May 2019; **Revised:** 2 September 2019; **Accepted:** 13 September 2019

Published online 00 Month 2019 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.27885

Impulse control disorders (ICDs), including pathological gambling, binge eating, compulsive shopping, hypersexuality, and other impulsive-compulsive behaviors (ICBs) are reported to occur at least in 13.6% of patients with Parkinson's disease (PD) on dopaminergic medication.[1,2] Importantly, ICDs can result in devastating financial, legal, or psychosocial problems.[3]

Although the neuropathophysiological basis of ICDs in PD patients is not well understood, it has been hypothesized to occur as a result of chronic administration of dopaminergic drugs, which modulate the reward network in PD patients.[4] Confirming the role of dopamine as a reinforcement signal shaping future motivated behaviors, positron emission tomography studies focused on the dopaminergic system have indicated that ICDs in PD are associated with a higher release of dopamine in the ventral striatum (VS) during reward-related tasks.[5,6] However, functional magnetic resonance imaging (fMRI) studies using reward-related tasks in PD patients with ICD (PD-ICD) have shown discrepant results; whereas 2 studies pointed toward diminished activation in the right VS, orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC),[7,8] 3 other studies showed higher activation in the VS, anterior prefrontal cortex (PFC), ACC, and OFC.[9-11] These discrepancies could be because of methodological factors, such as clinical differences in the PD populations studied (eg, PD severity, ICD subtype, with or without treatment), the use of different reward-related tasks (eg, related or unrelated to a specific ICD subtype), MRI imaging protocols, and analytical approaches. Moreover, although few studies have investigated functional connectivity (FC) during incentive-based tasks in PD-ICD patients,[12,13] the limited evidence available indicates mesolimbic pathway alterations and suggests ICDs in PD patients reflect disruptions beyond this pathway.

In addition, studies of PD-ICD patients highlight a critical imbalance between learning from rewards and penalties,[14] suggesting that chronic dopaminergic treatment might cause tonic stimulation of dopamine receptors, desensitizing the dopaminergic reward system by preventing the decreases in dopaminergic transmission that normally occur with penalties.[15] Furthermore, previous evidence has revealed that, in PD patients with or without ICD, dopaminergic drugs decrease or increase activity, respectively, in brain areas implicated in inhibitory control,[16] classically strongly lateralized to the right hemisphere.[17] In this sense, the Iowa Gambling Task (IGT) is a useful experimental paradigm extensively used in clinical research to examine reward-related and inhibitory control processes in a decision-making context, simulating real-life situations that have not been previously used with fMRI to examine the functional dynamics of reward and inhibitory control processes in PD-ICD.

Previous fMRI studies with normal adults using the IGT provide evidence that areas related to reward processing and inhibitory control such as the middle frontal gyrus (MFG), insula, OFC, ventromedial PFC, VS, ACC, and supplementary motor area (SMA) are involved in the execution of this task.[18,19] On the other hand, clinical studies evaluating the performance of the IGT have reported that PD patients may show higher losses[20] or, conversely, intact or even more cautious performance of the task,[21,22] reflecting opposite motivational expressions along a continuous behavioral spectrum involving hypo- and hyperdopaminergic symptoms.[23] Neuroanatomical correlates of studies using the IGT task with PD patients point toward an association with the volumetry of limbic cortical areas[24,25] or with the function of the limbic frontostriatal circuit of the basal ganglia.[26] Interestingly, behavioral studies that have assessed the IGT task in PD-ICD patients have also shown mixed findings,[27,28] further underscoring the need to investigate the neural dynamics of PD-ICD patients during reward-related and inhibitory control processes in a decision-making task such as the IGT.

Our aim is to investigate the neural mechanisms underlying decision making and inhibitory control processes in PD-ICD patients while performing the IGT task using fMRI. Specifically, in this study we sought to examine whether the type of feedback and ICD severity affects regional activation and FC between regions along the mesocorticolimbic circuit in PD-ICD patients. We hypothesized that these patients would exhibit differential functional activation and connectivity patterns involving regions belonging to the mesocorticolimbic circuit, specifically the VS, during their execution of decision making and inhibitory control processes required by the IGT.

Material and Methods

Participants

The final study sample included 53 participants comprising 3 groups: 18 PD-ICD patients, 17 PD patients without ICD symptoms (PD-noICD), and 18 healthy controls (HCs). Participants in each group were matched on age, sex, education, and premorbid intelligence quotient. All PD patients were diagnosed according to the UK Parkinson's Disease Society Brain Bank criteria and recruited from the Movement Disorders Unit of the Hospital Donostia (Spain). Inclusion criteria for the PD-ICD group included at least 1 current ICD that had emerged after PD diagnosis and the initiation of dopamine replacement therapy. Each patient was routinely asked about any abnormal behavior, and both a neurologist and a psychiatrist assessed and confirmed the presence of ICD based on the Diagnostic and Statistical Manual of Mental Disorders research criteria and on

the Questionnaire for Impulsive-Compulsive Disorders in PD.[29] ICD symptom severity was then evaluated via the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS).[30] In addition, we also confirmed that every PD-ICD patient had a QUIP-RS score above the published cutoff for each ICD subtype. Exclusion criteria were dementia[31] or mild cognitive impairment according to the Movement Disorder Society Task Force criteria (level II),[32] dyskinesias, and brain surgery, and those ICD patients who were no longer symptomatic when examined were also excluded. HCs were recruited from the Basque Center on Cognition, Brain and Language (BCBL) pool of participants. This study was approved by the Gipuzkoa Clinical Research Ethics Committee, and written informed consent was obtained from all subjects.

Demographic and Clinical Assessment

All assessments were performed using a comprehensive battery of motor, behavioral, and cognitive tests as described in Table 1 (demographic and clinical characteristics) and in Supplementary Table 1 (neuropsychological test scores). Details of each patient's ICD characteristics are provided in Supplementary Table 2. Decision making was assessed using the computerized version of the classical IGT, in which patients have to choose between 4 decks of cards in an attempt to win as much money as possible, across 5 blocks of task trials.[33] They have to take into account that some decks (advantageous) will tend to reward the player more often that other decks (disadvantageous; see Supplementary Data for a full description of the classical IGT). Afterward, this classical IGT was compared with participants' in-scanner performance on the modified version of the IGT used in the present fMRI study. Details on the statistical analyses conducted on the demographic and clinical data are described in the Supplementary Data. All assessments and MRI scanning of PD patients were done in the morning while they were still under the effect of their first regular dose of dopaminergic medication.

MRI Data Acquisition

Functional and structural images were obtained at the BCBL with a 3T Siemens Magnetom TIM Trio MRI scanner using a 32-channel head coil. See Supplementary Data for further information on MRI data acquisition.

Functional Magnetic Resonance Imaging Paradigm

At the scanner participants performed a modified version of the IGT. Before starting the IGT, participants were instructed that their aim was to gain as much money as possible. However, they were not informed about the IGT contingencies and had to learn them from feedback on their card choices, that is, their monetary gains and losses. The fMRI design conformed to a slow event-related design with gambling-related visual cues alternating with neutral stimuli.

We used a simplified version of the IGT to minimize motor difficulties experienced by PD patients during scanning and to assure that they could understand the IGT contingencies. Instead of the original version (with decks A, B, C, and D), we used a version with only 2 decks (A and B). One of the decks was disadvantageous, providing larger gains but larger losses, resulting in a net loss over time. The other deck was advantageous, providing smaller gains but smaller losses, resulting in a net gain over time. These deck contingencies were kept consistent across conditions (ie, positive, negative, and mixed), regardless of the feedback specifically provided in each of these conditions. The subject chose a card from either of the 2 decks; then a message was displayed on the screen indicating the amount of money the subject had won or lost. The task was divided into 3 conditions always presented in the same sequential order: (1) only positive feedback was presented, so the participants could get familiarized with the decks providing lower and higher gains (positive); (2) negative feedback was presented, so participants could get familiarized with the decks providing higher and lower losses (negative); and, (3) positive and negative rewards were provided, so participants could either win or lose money based on the contingencies learned in sections 1 and 2 (see Supplementary Data for further description of the modified IGT used here). Participants performed this modified version of the IGT across 3 functional runs. Within each of these functional runs, participants performed 2 blocks, each including the 3 sequential sections (6 in total). Blocks presented within the same functional run differed from each other in regard to advantageous and disadvantageous rules applied, and participants were instructed to ignore previous contingencies when moving from one block to the next one. Between blocks participants performed a control task in which they encountered 2 decks (A and B) with different amounts written on each deck, and they just needed to choose the deck with the highest number.

MRI Data Analyses

To examine potential group differences in gray-matter surface, we used participants' T1-weighted images to run Freesurfer's mri_glmfit. This analysis revealed no significant differences for any of the possible group comparisons.

Further details on the MRI data preprocessing and analyses are reported in Supplementary Data. In brief, SPM8 was used to conduct standard preprocessing

TABLE 1. Demographic and clinical characteristics of the sample

	PD-ICD n = 18	PD-noICD n = 17	HC n = 18	*P*	Post hoc (Bonferroni or Mann-Whitney *U*)
Age (years)	62.3 (7.6)	61(8.7)	63 (9.7)	0.809[a]	
Sex, male (%)	16 (88.9%)	15 (88.2%)	15 (83.3%)	0.866[b]	
Education (years)	14.5 (9.8–18.5)	12 (10–17)	15 (9.5–20)	0.570[c]	
Premorbid IQ (WAIS-III Vocabulary)	46 (38.8–51.8)	49 (39–3.5)	50 (44.8–57.3)	0.193[c]	
Disease duration (years)	8 (5.1–10)	7 (4–10)	—	0.960[e]	
UPDRS-III	22.31 (6.6)	25.90 (8.2)	—	0.122[d]	
H&Y stage	2 (1.5–2.5)	2 (1.5–3)	—	0.492[b]	
$LEDD_{DA}$	261.7 (69.5)	211.8 (44.9)	—	0.390[d]	
$LEDD_{TOTAL}$	940.6 (94.9)	841.4 (62.4)	—	0.455[d]	
HADS total	8.1 (7.3)	6.3 (2.8)	5.2 (3.2)	0.092[a]	
HADS–anxiety	4.9 (3.1)	3.5 (2.1)	4.3 (2.8)	0.412[a]	
HADS–depression	3.1 (2.4)	2.2(2.6)	1.9 (1.3)	0.145[a]	
QUIP–RS score	17 (7.5)	0.4 (0.7)	—	**<0.0001**[d]	
TCI-R Novelty-Seeking total	100.5 (14.6)	84.8 (9.8)	84.4 (20.9)	**0.005**[a]	PD-ICD > PD-noICD ($P = 0.016$) PD-ICD > HC ($P = 0.011$)
NS1 exploratory excitability	29.9 (7.2)	26.5 (3.8)	25.3 (5.3)	**0.045**[a]	PD-ICD > HC ($P = 0.049$)
NS2 impulsiveness	25.5 (6.7)	18.9 (3.4)	18.7 (5.5)	**0.002**[a]	PD-ICD > PD-noICD ($P = 0.003$) PD-ICD > HC ($P = 0.003$)
NS3 extravagance	27.1 (4.3)	23.9 (3.5)	24.1 (5)	0.058[a]	
NS4 disorderliness	17.8 (6.1)	14.5 (4)	15.3 (2.8)	0.248[a]	
Barratt impulsiveness total	48.3 (11.7)	30.9 (8.4)	25.4 (8.2)	**<0.001**[a]	PD-ICD > PD-noICD ($P = 0.004$) PD-ICD > HC ($P = 0.003$)
Barratt cognition	15.1 (4.6)	10.3 (3.8)	8.7 (3.3)	**0.004**[a]	PD-ICD > PD-noICD ($P = 0.012$) PD-ICD > HC ($P = 0.004$)
Barratt motor impulsivity	17.6 (6.4)	10.6 (4.5)	8.8 (4.4)	**0.001**[a]	PD-ICD > PD-noICD ($P = 0.013$) PD-ICD > HC ($P = 0.001$)
Barratt nonplanning	16.1 (9)	9.9 (3.2)	8 (4.8)	**0.001**[a]	PD-ICD > PD-noICD ($P = 0.016$)
Starkstein score	6.6 (2.3)	3.5 (2.9)	1.9 (1.2)	**0.013**[a]	PD-ICD > HC ($P = 0.01$)
Iowa Gambling Task outside scanner (CD - AB, %)	39.2 (12.4)	41.3 (23.4)	43.7 (27.7)	0.113[f]	
Modified Iowa Gambling Task in-scanner (no risk - risk, %)	26.8 (18.1)	35.4 (12.5)	38.9 (29.9)	0.548[f]	

Values expressed as mean (SD) for parametric variables, as median and IQ range for nonparametric variables.
[a]One-factor analysis of variance (ANOVA).
[b]Chi-square test.
[c]Kruskall-Wallis test.
[d]Two-sample *t* test.
[e]Mann-Whitney *U* test.
[f]Repeated-measures ANOVA
IQ, intelligence quotient; WAIS-III, Wechsler Adult Intelligence Scale-III; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr scale; $LEDD_{DA}$, levodopa-equivalent daily dose of dopamine agonist was calculated using the formula described by Tomlinson et al (2010); $LEDD_{TOTAL}$, total levodopa-equivalent daily dose was calculated according to the same formula; HADS, Hospital Anxiety and Depression Scale; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale; TCI-R, Revised Temperament and Character Inventory; NS, Novelty-Seeking Subscales.

routines and analyses. Statistical analyses were performed on individual participants' data using the general linear model (GLM). The fMRI time series data were modeled by a series of events convolved with a canonical hemodynamic response function. Four fMRI task experimental conditions were analyzed separately as epochs from the onset of the presentation of the first stimulus within each section (positive feedback, negative feedback, mixed feedback) and the control task. The resulting functions were used as covariates in a GLM, along with the motion parameters for translation and rotation as covariates of noninterest. The model was created to examine the neural changes restricted to the 3 task sections and the control task periods and was used in whole-brain contrast, regions of interest (ROIs), time course, and FC analyses. In addition, brain-behavior associations with ICD severity in PD-ICD patients were examined for ROI and FC analyses. Finally, mediation analyses were conducted to examine whether in PD-ICD patients FC mediates the relation between ICD severity and regional activation (see Supplementary Data for details).

Results

Demographic and Clinical Data

No differences were seen in demographic data, dopaminergic medication, or clinical features with the exception of impulsivity scores, which were significantly higher in PD-ICD patients than in PD-noICD patients and HCs (Table 1 and Supplementary Table 1). There were

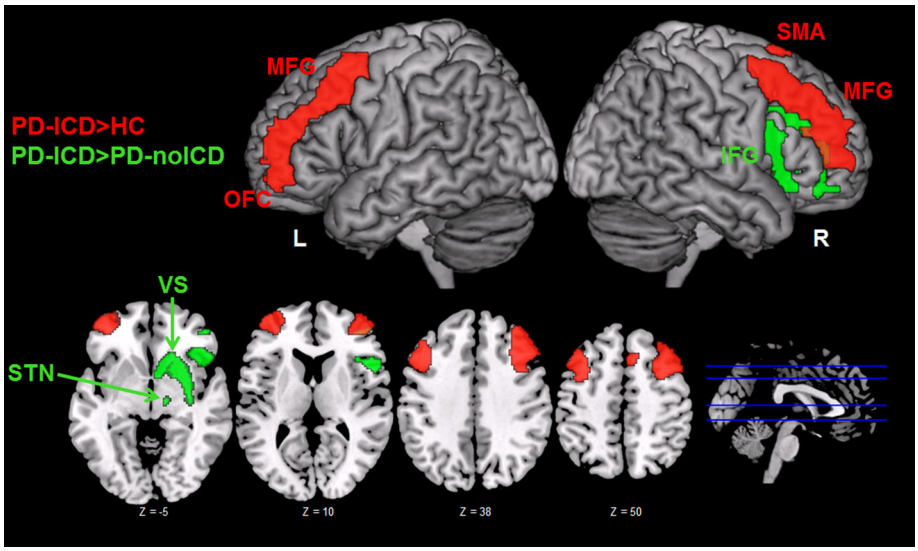

FIG. 1. Brain rendering and axial sections showing ROI analyses that revealed main-group effects in percent signal change. In red are regions with stronger activation for the PD-ICD group compared with the HC group. Regions in green show higher activation for the PD-ICD group compared with the PD-noICD group. MFG, middle frontal gyrus; OFC, orbitofrontal cortex; SMA, supplementary motor area; IFG, inferior frontal gyrus; STN, subthalamic nucleus; VS, ventral striatum. [Color figure can be viewed at wileyonlinelibrary.com]

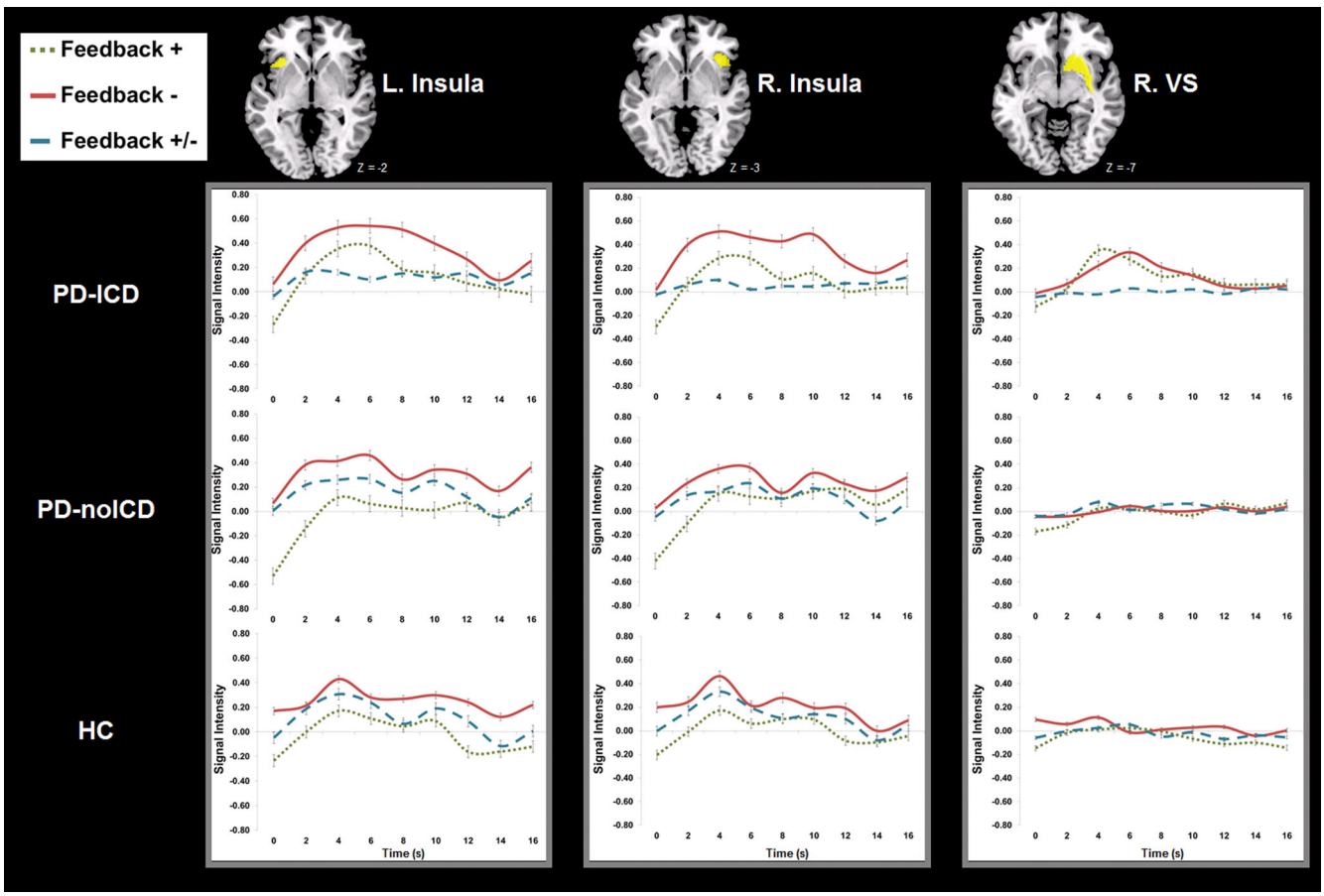

FIG. 2. Time-course analysis of ROIs (in axial sections) showing a group × condition × time interaction: bilateral insula and right VS. All these regions demonstrated larger BOLD signal intensity in the negative-feedback condition for the PD-ICD group during the initial period relative to the PD-noICD and HC groups. This effect was not present in the final period. L, left; R, right; VS, ventral striatum. [Color figure can be viewed at wileyonlinelibrary.com]

6 patients who reported a single "isolated" ICD and 12 patients with "combined" ICD/ICB (Supplementary Table 2).

In- and Out-Scanner IGT Results

The analysis of variance (ANOVA) on the net scores of the classical IGT that participants performed outside the scanner revealed no significant main effects of group ($F_{2,50}$ = 2.28, P = 0.11, η_p^2 = 0.08) and condition ($F_{2,50}$ = 1.61, P = 0.18, η_p^2 = 0.08) or group-by-condition interaction ($F_{2,50}$ = 1.51, P = 0.20, η_p^2 = 0.05). The results on the modified in-scanner IGT task resembled the results obtained with the classical IGT (Supplementary Fig. 1). We also compared classical IGT task results with modified in-scanner IGT task results, revealing no differences between task performances ($F_{2,50}$ = 1.02, P = 0.366, η_p^2 = 0.04).

MRI Results

Whole-brain analysis

To identify brain regions involved in the in-scanner functional IGT task across all participants, we computed a whole-brain contrast for all the activation conditions versus the control condition (all conditions > control). This contrast revealed activation in frontoparietal networks, including bilateral inferior and superior parietal cortices and bilateral inferior, middle, and superior PFC.[18] Also, significant engagement of bilateral insula, OFC, VS, and right STN were shown in this contrast.

ROI analysis

ROI analysis showed stronger regional activation in PD-ICD patients compared with HCs across the 3 conditions of the IGT in the following regions (areas in red in Fig. 1): left MFG ($F_{2,49}$ = 5.84, P = 0.005, η_p^2 = 0.19), left medial OFC ($F_{2,50}$ = 3.81, P = 0.03, η_p^2 = 0.13), right MFG ($F_{2,49}$ = 2.69, P = 0.03, η_p^2 = 0.14), and right SMA ($F_{2,50}$ = 4.43, P = 0.017, η_p^2 = 0.15). Group effects in these regions were not observed for PD-ICD versus PD-noICD.

ROI analysis also showed hyperactivation in PD-ICD patients compared with PD-noICD patients across the 3 conditions of the IGT in the following regions (areas in green in Fig. 1): right STN ($F_{2,49}$ = 3.36, P = 0.04, η_p^2 = 0.12), right IFG ($F_{2,50}$ = 3.38, P = 0.04, η_p^2 = 0.12), and right VS ($F_{2,50}$ = 3.58, P = 0.03, η_p^2 = 0.13). Moreover, PD-noICD patients showed hypoactivation compared with HCs only in the bilateral dorsal striatum ($Fs_{2,50}$ = 3.19, $Ps \leq 0.04$, $\eta_p^2 \geq 0.12$).

Time-course analysis

The ANOVA conducted on the BOLD signal intensity extracted from time-course analyses in each ROI

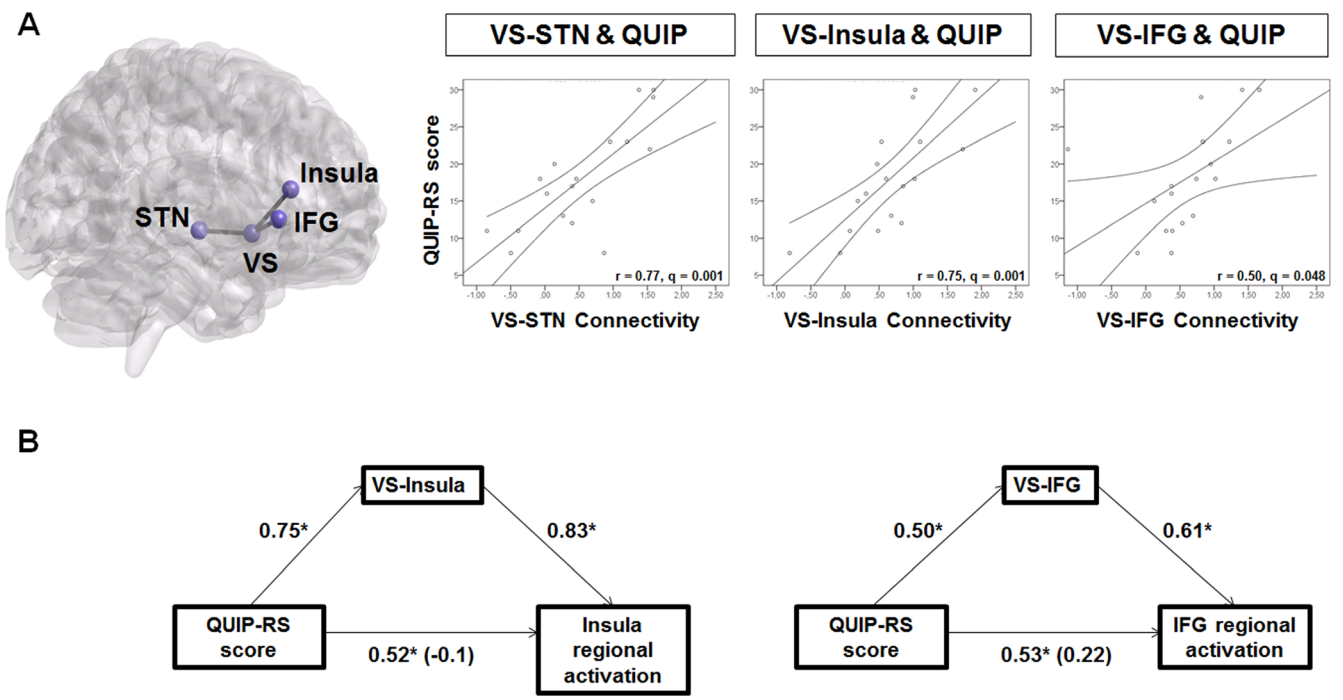

FIG. 3. (A) Right brain rendering including pairs of nodes (VS-STN, VS-IFG, VS-insula) that show significant positive associations between the functional connectivity among them during the negative-feedback condition and ICD severity (QUIP-RS). (B) Mediation analyses revealing that positive associations between ICD severity and regional activation of right insula and right IFG during negative feedback were mediated by the functional connectivity of these respective regions with the right VS. STN, subthalamic nucleus; VS, ventral striatum; IFG, inferior frontal gyrus. [Color figure can be viewed at wileyonlinelibrary.com]

revealed a group × condition × time interaction in the left insula ($F_{2,50}$ = 1.7, P = 0.01, η_p^2 = 0.264), right insula ($F_{2,50}$ = 1.72, P = 0.01, η_p^2 = 0.25), and right VS ($F_{2,50}$ = 1.48, P = 0.04, η_p^2 = 0.16). Post hoc analyses in all 3 regions revealed that only PD-ICD patients exhibited significantly higher signal intensity during the negative-feedback condition in the initial bin of the period (0–8 seconds) compared with the second bin of the period (8–16 seconds) in the left insula ($F_{2,18}$ = 6.7, P = 0.003, η_p^2 = 0.45), right insula ($F_{2,18}$ = 7.2, P = 0.002, η_p^2 = 0.30), and right VS ($F_{2,18}$ = 5.3, P = 0.01, η_p^2 = 0.24); see Figure 2. These effects were not observed in PD-noICD patients or in HCs (Ps ≥ 0.09).

QUIP correlates, functional connectivity, and mediation analysis

In PD-ICD patients, positive associations were found between regional activation during negative feedback and QUIP-RS scores for some of the right-lateralized ROIs: STN (r_{16} = 0.75, q = 0.001), MFG (r_{16} = 0.50, q = 0.02), IFG (r_{16} = 0.53, q = 0.02), SMA (r_{16} = 0.50, q = 0.02), insula (r_{16} = 0.52, q = 0.02), and VS (r_{16} = 0.62, q = 0.01).

To examine if the association between regional activation during the negative-feedback condition and ICD severity was mediated by specific patterns of FC among these areas, we first examined whether pairwise FC among the above-mentioned 6 right-lateralized ROIs was associated with ICD severity (Fig. 3A). FC during the negative-feedback condition among 4 of these 6 areas (ie, STN, VS, IFG, and insula) was associated with ICD severity: VS-STN (r_{16} = 0.77, q = 0.001), VS-insula (r_{16} = 0.75, q = 0.001), and VS-IFG (r_{16} = 0.50, q = 0.048).

Mediation analyses (Fig. 3B) revealed that (1) the FC strength between VS-insula mediated the association between ICD severity and right insula regional activation ($F_{2,17}$ = 10.28, P = 0.002), and (2) connectivity between VS-IFG mediated the association between ICD severity and right IFG regional activation ($F_{2,17}$ = 9.52, P = 0.002).

Discussion

Based on previous evidence, we postulated that PD-ICD patients would exhibit differential neural dynamics involving the mesocorticolimbic dopaminergic circuit during the execution of a reward-related task. This was in fact the case, and even when behavioral performance was equivalent, PD-ICD patients exhibited differential patterns of activation and FC compared with PD-noICD patients and HCs. Compared with PD-noICD patients, PD-ICD patients showed hyperactivation that was restricted to the right-hemisphere cortical and subcortical regions associated with reward processing and inhibitory control. In fact, the higher was the severity of ICD, the higher was the regional activation of these areas, especially when patients were faced with penalties. Moreover, PD-ICD patients exhibited higher peaks in signal intensity during early processing of negative rewards in conflict detection areas, such as the insula; and reward-processing regions, such as the right VS. A compelling finding was that functional coupling with right VS mediated the relation between ICD severity and the engagement of right-lateralized inhibitory control regions (insula, IFG) during negative rewards in PD-ICD patients. These observations demonstrated that inhibitory control regions in PD-ICD patients are modulated by the right VS, which appears to orchestrate reward-processing dynamics when patients face penalties requiring inhibitory control. A novel finding of this study was the involvement of the right STN in this process. However, unlike the insula and IFG, STN activity was not mediated by functional coupling with VS. Importantly, although previous works investigated motor inhibition in PD patients with and without ICD, this was the first study to investigate the neural correlates of reward and inhibitory control processes during a decision-making IGT in PD-ICD patients and the first to show the involvement of the STN in cognitive inhibitory control.

ICD in PD is a multidimensional concept engaging alterations in certain cognitive functions, such as reward processing, learning from reward and loss, inhibitory control, risk taking, and conflict processing.[4] In this regard, the IGT assesses patterns of decision making under risk,[34] which requires the integration of processes conducted by different neural systems related to inhibitory control, memory, and the limbic system.[18] Accordingly, it has been previously reported that a disruption of ventral frontostriatal circuits in PD-ICD patients might result in reduced ability to resist an immediate reward, despite long-term consequences, termed "myopia for the future."[35] Clinical studies examining IGT performance in PD patients with or without ICD have reported impaired decision making,[20,24,27] absence of differences,[28,36] or even a conservative attitude in PD patients compared with HCs.[37] Because of the aforementioned discrepancies, here we used an in-scanner-modified IGT task and out-scanner classical IGT task, with both tasks showing lack of behavioral differences among the groups here examined in line with previous evidence.[28,36,38] Of interest, despite this equivalence in behavioral performance, important differences in functional regional activation were observed between groups and in terms of FC in the PD-ICD group.

PD-ICD patients exhibited hyperactivation of bilateral MFG, left OFC, and right SMA when compared with HCs. These results complement previous fMRI

studies in PD-ICD patients, which have underscored the critical role of the mesocorticolimbic cortical system, encompassing the insular cortex, PFC, and OFC.[7,10] In addition, lateral PFC, MFG, and SMA are part of the same frontostriatal pathway that exhibits an activation pattern associated with interference inhibition, inhibitory control, and action cancellation.[39,40] In this sense, ICD in PD patients is a multifaceted construct, including choice impulsivity and impairments in goal-directed behavior,[41] which have been shown to rely on different neural networks.[42,43] Compared with PD-noICD patients, PD-ICD patients showed stronger activation in right hemisphere subcortical areas (STN and VS) and in a cortical region strongly associated with inhibitory control: the IFG.[44] The involvement of the STN in impulsive behavior in PD has been widely investigated. Oscillatory activity recorded in the STN of PD patients treated with deep brain stimulation is modified during the execution of motor inhibition tasks[45-47] and during inhibition of inappropriate or habitual prepotent responses.[48,49] fMRI studies have also revealed that during motor inhibition tasks there is hyperactivation of the right STN in control subjects, which is functionally connected to the right IFG and right pre-SMA through the hyperdirect pathway.[50] The IFG and STN are considered key nodes in the motor inhibition network; their activity is interrelated and also correlates with the extent of inhibition exercised.[51] Moreover, PD-ICD patients exhibit higher power in low-frequency oscillations that is coherent with the oscillatory activity recorded in the prefrontal cortex.[52] On the other hand, the VS plays a central role in the mesocorticolimbic incentive network, enabling the behavior-reinforcing effects of rewarding activities. Indeed, it has been extensively found that the VS, mostly in the right hemisphere, is implicated in the physiopathology of ICD in PD patients, and in keeping with these results, increased activation in the right VS could be related to increased dopamine release consistent with previous neuroimaging data.[5] Finally, the right IFG has been classically involved in inhibitory control along with the lateral PFC and SMA.[44] The stronger engagement of all these regions in PD-ICD patients could be determined by the dopaminergic overstimulation of the mesolimbic areas that occurs in these patients, leading them toward aberrant reward evaluation. Our results also open the door for further research and therapeutic interventions, especially in the right STN and right VS, both areas in which activation can be modulated by deep brain stimulation.

Time-course analysis pointed toward higher early BOLD signal intensity during the processing of negative rewards in PD-ICD patients in the bilateral insula and right VS. It is known that dopaminergic medications can influence cognitive processes in PD patients, and supporting evidence points toward impaired learning from negative feedback that in PD-ICD patients has been characterized by a VS critic model.[4,53,54] In the present study, PD-ICD group differences in processing negative rewards occurred at the neural level without showing a differential group effect on behavioral performance. By contrast, PD patients without this complication have been characterized by a dorsal actor model with higher learning rates from positive feedback.[54] Murine models have also endorsed this theory, as nucleus accumbens D2 stimulation with dopamine agonists reduced the ability to learn from negative feedback.[15] Our results showing earlier peaks when facing penalties in regions involved in conflict monitoring, such as the right insula,[55] and in reward processing, such as the right VS,[12] might underlie a differential processing of negative rewards in PD-ICD patients during initial prediction errors and evaluation of rewards that precedes the normal posterior course of activation. So, this initial activation peak may be necessary to adjust PD-ICD neural responses to process subsequent penalties in a reward-processing context. Future neuroimaging studies using tasks requiring more transient functional processing of negative rewards in PD-ICD patients may lead to the identification of concomitant group differences at the neural and behavioral levels.

Regarding FC, we observed that right VS functional coupling mediated the relation between ICD severity and the engagement of regions involved in conflict evaluation processes (insula) and inhibitory control (IFG) during negative rewards in PD-ICD patients.[56] Thus, in this context the right VS appears to be a critical hub. Previous evidence has revealed altered striatocortical connectivity in PD-ICD patients, showing controversial results such as, on the one hand, reduced connectivity between dorsal striatum and temporal and cingulate cortices[57] and, on the other hand, stronger connectivity between the right VS and frontotemporal cortical areas.[12] Our results suggest that the coupling of the right VS with these 2 regions may serve as a bridge for communication between the reward system and cognitive control areas, resulting in higher activation of those inhibitory control regions.

It is remarkable that although the connectivity between the STN and VS was positively correlated with ICD severity, the VS did not mediate the association between STN recruitment and ICD severity. Although it is hard to make further sense of a null effect, the STN seems to be specifically engaged in late-response inhibitory processes, as reflected by studies showing a correlation between STN activation and longer stop signal delays.[58] As our time-course analysis revealed that only PD-ICD patients showed different signal intensities in the initial periods after being presented with negative feedback, it could be that STN and IFG involvement would be greater in later phases. In fact, the STN-IFG pathway is more activated in the global inhibition[59]

and late inhibition phases, as has been observed after right STN lesions in PD patients.[60] Future neuroimaging research including both response and cognitive inhibitory tasks with PD-ICD patients could further disentangle these possibilities.

These findings should be considered in the context of several limitations. First, all patients in this study were on their regular medication; this was intentional, as ICD is a complication to which dopaminergic medication is the main contributor. However, we ensured that both groups of patients were receiving similar daily doses of antiparkinsonian medication to avoid any pharmacological confound. Second, as our sample was heterogeneous because of mixed ICD types, we decided to choose a global reward (an economic reward) and interpreted the results on this basis. Also for this reason, we tried not to choose PD-ICD patients with problems in only one ICD modality to avoid introducing a bias and because based on previous evidence it is reasonable to assume that the neural substrates in PD-ICD patients are similar for all modalities.

The theoretical and neurological framework presented here suggests that PD-ICD patients have enhanced activation in regions involved in the encoding of rewards and inhibitory control during disadvantageous outcomes, compared with PD-noICD patients and healthy controls. PD-ICD patients show hyperactivation during stimuli evaluation, conflict detection, and monitoring areas during the early processing of negative rewards. In addition, in these patients, right VS appears to be a critical region that orchestrates hyperactivation in right-lateralized inhibitory-control frontal regions when facing penalties. Interestingly, the right STN is also a relevant area for cognitive inhibitory control, although its activation is not modulated by the right VS. Importantly, although we found no group differences in behavioral performance, the neural dynamics in PD-ICD patients were different than those in PD-noICD patients and HCs, providing new insights into the investigation of neural functional alterations in these patients.

References

1. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol 2010;67:589–595.
2. Weintraub D, Claassen DO. Impulse Control and Related Disorders in Parkinson's Disease. Int Rev Neurobiol 2017;133:679–717.
3. Phu AL, Xu Z, Brakoulias V, et al. Effect of impulse control disorders on disability and quality of life in Parkinson's disease patients. J Clin Neurosci 2014;21:63–66.
4. Voon V, Napier TC, Frank MJ, et al. Impulse control disorders and levodopa-induced dyskinesias in Parkinson's disease: an update. Lancet Neurol 2017;16:238–250.
5. O'Sullivan SS, Wu K, Politis M, et al. Cue-induced striatal dopamine release in Parkinson's disease-associated impulsive-compulsive behaviours. Brain 2011;134:969–978.
6. Steeves TDL, Miyasaki J, Zurowski M, et al. Increased striatal dopamine release in Parkinsonian patients with pathological gambling: a [11C] raclopride PET study. Brain 2009;132:1376–1385.
7. Voon V, Gao J, Brezing C, et al. Dopamine agonists and risk: impulse control disorders in Parkinson's; disease. Brain 2011;134:1438–1446.
8. Rao H, Mamikonyan E, Detre JA, et al. Decreased ventral striatal activity with impulse control disorders in Parkinson's disease. Mov Disord 2010;25:1660–1669.
9. Frosini D, Pesaresi I, Cosottini M, et al. Parkinson's disease and pathological gambling: results from a functional MRI study. Mov Disord 2010;25:2449–2453.
10. Politis M, Loane C, Wu K, et al. Neural response to visual sexual cues in dopamine treatment-linked hypersexuality in Parkinson's disease. Brain 2013;136:400–411.
11. Girard R, Obeso I, Thobois S, et al. Wait and you shall see: sexual delay discounting in hypersexual Parkinson's disease. Brain J Neurol 2019;142:146–162.
12. Petersen K, Van Wouwe N, Stark A, et al. Ventral striatal network connectivity reflects reward learning and behavior in patients with Parkinson's disease. Hum Brain Mapp. 2018;39(1):509–521.
13. Filip P, Linhartová P, Hlavatá P, et al. Disruption of Multiple Distinctive Neural Networks Associated With Impulse Control Disorder in Parkinson's Disease. Front Hum Neurosci 2018;12:462.
14. Cilia R. How neurodegeneration, dopamine and maladaptive behavioral learning interact to produce impulse control disorders in Parkinson's disease. Basal Ganglia 2012;2:195–199.
15. Goto Y, Grace AA. Dopaminergic modulation of limbic and cortical drive of nucleus accumbens in goal-directed behavior. Nat Neurosci 2005;8:805–812.
16. Jahanshahi M, Obeso I, Rothwell JC, Obeso JA. A fronto–striato–subthalamic–pallidal network for goal-directed and habitual inhibition. Nat Rev Neurosci 2015;16:719–732.
17. Garavan H, Ross TJ, Stein EA. Right hemispheric dominance of inhibitory control: an event-related functional MRI study. Proc Natl Acad Sci U S A 1999;96:8301–8306.
18. Li X, Lu Z-L, D'Argembeau A, Ng M, Bechara A. The Iowa Gambling Task in fMRI images. Hum Brain Mapp. 2010;31(3):410–423.
19. Eckert MA, Menon V, Walczak A, et al. At the heart of the ventral attention system: the right anterior insula. Hum Brain Mapp 2009;30:2530–2541.
20. Pagonabarraga J, García-Sánchez C, Llebaria G, Pascual-Sedano B, Gironell A, Kulisevsky J. Controlled study of decision-making and cognitive impairment in Parkinson's disease. Mov Disord 2007;22:1430–1435.
21. Poletti M, Cavedini P, Bonuccelli U. Iowa gambling task in Parkinson's disease. J Clin Exp Neuropsychol 2011;33:395–409.
22. Poewe W, Karamat E, Kemmler GW, Gerstenbrand F. The premorbid personality of patients with Parkinson's disease: a comparative study with healthy controls and patients with essential tremor. Adv Neurol 1990;53:339–342.
23. Sierra M, Carnicella S, Strafella AP, et al. Apathy and Impulse Control Disorders: Yin & Yang of Dopamine Dependent Behaviors. Korczyn AD, Reichmann H, Chaudhuri KR, editors. J Park Dis 2015;5:625–636.
24. Ibarretxe-Bilbao N, Junque C, Tolosa E, et al. Neuroanatomical correlates of impaired decision-making and facial emotion recognition in early Parkinson's disease. Eur J Neurosci 2009;30:1162–1171.
25. Kobayakawa M, Tsuruya N, Kawamura M. Decision-making performance in Parkinson's disease correlates with lateral orbitofrontal volume. J Neurol Sci 2017;372:232–238.
26. Gescheidt T, Czekóová K, Urbánek T, et al. Iowa Gambling Task in patients with early-onset Parkinson's disease: strategy analysis. Neurol Sci 2012;33:1329–1335.
27. Rossi M, Gerschcovich ER, De Achaval D, et al. Decision-making in Parkinson's disease patients with and without pathological gambling: Decision-making in PD with pathological gambling. Eur J Neurol 2010;17:97–102.

28. Biars JW, Johnson NL, Nespeca M, Busch RM, Kubu CS, Floden DP. Iowa Gambling Task Performance in Parkinson Disease Patients with Impulse Control Disorders. Arch Clin Neuropsychol 2019;34(3):310–318.
29. Weintraub D, Hoops S, Shea JA, et al. Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease. Mov Disord 2009;24:1461–1467.
30. 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.
31. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007;22: 1689–1707; quiz 1837.
32. Litvan I, Goldman JG, Tröster 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.
33. Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 1994;50:7–15.
34. Fellows LK, Farah MJ. Different underlying impairments in decision-making following ventromedial and dorsolateral frontal lobe damage in humans. Cereb Cortex 2005;15:58–63.
35. Castrioto A, Funkiewiez A, Debû B, et al. Iowa gambling task impairment in Parkinson's disease can be normalised by reduction of dopaminergic medication after subthalamic stimulation. J Neurol Neurosurg Psychiatry 2015;86:186–190.
36. Pineau F, Roze E, Lacomblez L, et al. Executive functioning and risk-taking behavior in Parkinson's disease patients with impulse control disorders. J Neural Transm (Vienna) 2016;123:573–581.
37. Czernecki V, Pillon B, Houeto JL, Pochon JB, Levy R, Dubois B. Motivation, reward, and Parkinson's disease: influence of dopatherapy. Neuropsychologia 2002;40:2257–2267.
38. Santangelo G, Raimo S, Barone P. The relationship between Impulse Control Disorders and cognitive dysfunctions in Parkinson's Disease: A meta-analysis. Neurosci Biobehav Rev 2017;77:129–147.
39. Sebastian A, Pohl MF, Klöppel S, et al. Disentangling common and specific neural subprocesses of response inhibition. Neuroimage 2013;64:601–615.
40. Jahfari S, Waldorp L, van den Wildenberg WPM, 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 Off J Soc Neurosci 2011;31:6891–6899.
41. Jahanshahi M, Obeso I, Baunez C, Alegre M, Krack P. Parkinson's Disease, the Subthalamic Nucleus, Inhibition, and Impulsivity: PD, The STN, Inhibition, and Impulsivity. Mov Disord 2015;30:128–140.
42. Antonelli F, Ko JH, Miyasaki J, et al. Dopamine-agonists and impulsivity in Parkinson's disease: Impulsive choices vs. impulsive actions: Dopamine-Agonists and Impulsivity in PD. Hum Brain Mapp 2014; 35:2499–2506.
43. Verger A, Klesse E, Chawki MB, et al. Brain PET substrate of impulse control disorders in Parkinson's disease: A metabolic connectivity study. Hum Brain Mapp 2018;39(8):3178–3186.
44. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. Trends Cogn Sci 2004;8:170–177.
45. Ray NJ, Brittain J-S, Holland P, et al. The role of the subthalamic nucleus in response inhibition: Evidence from local field potential recordings in the human subthalamic nucleus. Neuroimage 2012;60:271–278.
46. Alegre M, Lopez-Azcarate J, Obeso I, et al. The subthalamic nucleus is involved in successful inhibition in the stop-signal task: A local field potential study in Parkinson's disease. Exp Neurol 2013; 239:1–12.
47. Benis D, David O, Lachaux J-P, et al. Subthalamic nucleus activity dissociates proactive and reactive inhibition in patients with Parkinson's disease. Neuroimage 2014;91:273–281.
48. Anzak A, Gaynor L, Beigi M, et al. Subthalamic nucleus gamma oscillations mediate a switch from automatic to controlled processing: a study of random number generation in Parkinson's disease. Neuroimage 2013;64:284–289.
49. Anzak A, Gaynor L, Beigi M, et al. A gamma band specific role of the subthalamic nucleus in switching during verbal fluency tasks in Parkinson's disease. Exp Neurol 2011;232:136–142.
50. Aron AR. Cortical and Subcortical Contributions to Stop Signal Response Inhibition: Role of the Subthalamic Nucleus. J Neurosci 2006;26:2424–2433.
51. Aron AR, Behrens TE, Smith S, Frank MJ, Poldrack RA. Triangulating a Cognitive Control Network Using Diffusion-Weighted Magnetic Resonance Imaging (MRI) and Functional MRI. J Neurosci 2007;27:3743–3752.
52. Rodriguez-Oroz MC, López-Azcárate J, Garcia-Garcia D, et al. Involvement of the subthalamic nucleus in impulse control disorders associated with Parkinson's disease. Brain 2011;134:36–49.
53. Voon V, Pessiglione M, Brezing C, et al. Mechanisms underlying dopamine-mediated reward bias in compulsive behaviors. Neuron 2010;65:135–142.
54. Piray P, Zeighami Y, Bahrami F, Eissa AM, Hewedi DH, Moustafa AA. Impulse Control Disorders in Parkinson's Disease Are Associated with Dysfunction in Stimulus Valuation But Not Action Valuation. J Neurosci 2014;34:7814–7824.
55. Naqvi NH, Gaznick N, Tranel D, Bechara A. The insula: a critical neural substrate for craving and drug seeking under conflict and risk. Ann N Y Acad Sci 2014;1316:53–70.
56. Xue G, Lu Z, Levin IP, Bechara A. The impact of prior risk experiences on subsequent risky decision-making: the role of the insula. Neuroimage 2010;50:709–716.
57. Carriere N, Lopes R, Defebvre L, Delmaire C, Dujardin K. Impaired corticostriatal connectivity in impulse control disorders in Parkinson disease. Neurology 2015;84:2116–2123.
58. Aron AR, Fletcher PC, Bullmore ET, Sahakian BJ, Robbins TW. Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. Nat Neurosci 2003;6:115–116.
59. Sano H, Chiken S, Hikida T, Kobayashi K, Nambu A. Signals through the striatopallidal indirect pathway stop movements by phasic excitation in the substantia nigra. J Neurosci Off J Soc Neurosci 2013;33:7583–7594.
60. Obeso I, Wilkinson L, Casabona E, et al. The subthalamic nucleus and inhibitory control: impact of subthalamotomy in Parkinson's disease. Brain 2014;137:1470–1480.

Supporting Data

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