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Decreased Ventral Striatal Activity with Impulse Control Disorders in Parkinson's Disease

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Abstract

Purpose—A range of impulse control disorders (ICDs) are reported to occur in Parkinson's disease (PD). However, alterations in brain activity at rest and during risk taking occurring with ICDs in PD are not well understood.

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Methods—We used both arterial spin labeling (ASL) perfusion fMRI to directly quantify resting cerebral blood flow (CBF) and blood oxygenation level dependent (BOLD) fMRI to measure neural responses to risk taking during performance on the Balloon Analogue Risk Task (BART).

Results—18 PD patients, either with a diagnosis of one or more ICDs (N=9) or no lifetime ICD history (N=9), participated. BOLD fMRI data demonstrated that PD patients without an ICD activate the mesocorticolimbic pathway during risk taking. Compared with non-ICD patients, ICD patients demonstrated significantly diminished BOLD activity in the right ventral striatum during risk taking and significantly reduced resting CBF in the right ventral striatum.

Conclusion—ICDs in PD are associated with reduced right ventral striatal activity at rest and diminished striatal activation during risk taking, suggesting that a common neural mechanism may underlie ICDs in individuals with PD and those without PD. Thus, treatments for ICDs in non-PD patients warrant consideration in PD patients with ICDs.

INTRODUCTION

Individuals with Parkinson's disease (PD) may experience impulse control disorders (ICDs), including compulsive gambling, buying, sexual behavior, and eating.¹⁻⁴ As defined in the current Diagnostic and Statistical Manual (DSM-IV-TR),⁵ ICDs constitute a broad range of psychiatric disorders, and an essential feature of ICDs is a failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or to others. ICDs, sometimes called "behavioral addictions",⁶ occur in the context of PD, but also in other disorders (e.g., restless legs syndrome (RLS)⁷ and fibromyalgia) for which dopamine replacement therapies are used.⁸

Human brain imaging and lesions studies have demonstrated an important role for the mesocorticolimbic network in the processing of risk-reward decision-making and impulse control.^{9;10} Recent functional magnetic resonance imaging (fMRI) studies reported diminished ventral striatum and ventromedial prefrontal activation in non-PD pathological gamblers during simulated gambling¹¹, a task involving response inhibition,¹² and following gambling cue exposure.¹³

Although ICDs are observed in PD,^{1;2} functional brain differences in PD patients with and without ICDs in this population remain poorly understood. It is unclear if ICDs in PD, a disease characterized by degeneration of dopaminergic substantia nigra-striatum pathways, demonstrate similar neural deficits in the mesolimbic "reward" system as reported for ICDs in the general population. To investigate ICDs in PD, we used conventional blood oxygenation level dependent (BOLD) fMRI and measured neural responses underlying risk taking in PD patients with and without ICDs during the performance of a modified Balloon Analogue Risk Task (BART).^{14;15} Behavioral studies using the BART support it as an ecologically valid model for the assessment of risk-taking propensity and behavior,^{14;16;17} and a brain imaging study has demonstrated that risk taking during the BART induced robust activation in the mesocorticolimbic "reward" network in healthy controls.¹⁵ In addition, a recent study involving PD patients used the BART to assess risk-taking behavior outside of the scanner and found that dopamine agonists (DAs) significantly strengthened the correlations between risk-taking performance on the BART and regional brain activation in the orbitofrontal cortex during administration of a probabilistic reward task.¹⁸

Since BOLD fMRI measures relative task-induced signal changes and lacks absolute quantification of neural activity, we also used arterial spin labeling (ASL) perfusion fMRI^{19;20} in order to investigate resting neural activity. Using magnetically labeled water in arterial blood as a diffusible tracer, ASL perfusion fMRI provides a non-invasive imaging method of quantifying cerebral blood flow (CBF), a biomarker of regional brain function.²¹

ASL fMRI has been used successfully to characterize resting perfusion changes in neurodegenerative disease disorders, including Alzheimer's disease.²²

Based on previous findings from fMRI studies of pathological gamblers in the general population,^{11;12} we hypothesized that PD patients with ICDs, compared with PD patients without an ICD, would demonstrate diminished neural activity in mesolimbic-prefrontal cortex brain regions, particularly in the ventral striatum. We also hypothesized that ICD patients would demonstrate increased risk-taking behavior, as measured by an increased average adjusted number of inflations per balloon on the BART, compared with non-ICD patients.

SUBJECTS and METHODS

Subjects

Eighteen PD patients (age range 40–75 years, male/female =15/3) participated in the study. Nine patients were diagnosed as having one or more active ICDs at the time of assessment and imaging (**ICD group**), and 9 had no lifetime ICD history (**non-ICD group**). The specific ICDs are presented in Table 1. Based on clinical interview, all ICD patients had no lifetime history of an ICD prior to initiating DA treatment in the context of PD. All subjects in the ICD group and 8 subjects in the non-ICD group were taking a DA at the time of imaging, and 8 of the subjects in each group were taking levodopa. ICD status was ascertained by the Massachusetts Gambling Screen²³ for problem or pathological gambling, the Minnesota Impulsive Disorder Interview²⁴ for compulsive sexual behavior and buying, and DSM-IV-TR research criteria for binge-eating disorder,⁵ and dopamine dysregulation syndrome (DDS) was ruled out in all subjects on the basis of proposed criteria.²⁵ The mean (SD) duration of ICD behaviors was 4.5 (3.2) years.

Mean (SD) values for demographic and clinical variables for the entire sample were: age =55.3 (9.9) years, formal education =16.6 (2.7) years, PD duration =7.4 (5.4) years, Hoehn & Yahr stage²⁶ of PD severity =2.1 (0.3), DA levodopa equivalent daily dosage (LEDD)²⁷ =299 (152) mg, levodopa LEDD =363 (247) mg, 15-item Geriatric Depression Scale (GDS-15)²⁸ score =4.2 (3.4), and Montreal Cognitive Assessment (MoCA)²⁹ score =27.1 (2.1). There were no differences between the ICD group and the non-ICD group on any of these variables (Table 1).

The study was approved by the Institutional Review Board of the University of Pennsylvania, and subjects provided written informed consent prior to study participation. Each participant was compensated \$35 for study participation.

Experimental protocol and procedures

The fMRI BART paradigm has been described elsewhere.¹⁵ In summary, participants completed a modified version of the original BART.¹⁴ Participants pressed a button to sequentially inflate (i.e., “pump”) a virtual balloon presented on a laptop computer screen, which either grows larger or explodes with each inflation. The maximum number of inflations prior to explosion per balloon was 12. Larger balloons were associated with greater risk of explosion, as well as higher virtual monetary reward/loss (i.e., exponential increases). The probability of explosion was set to increase nonlinearly from 0 to 89.6%, and the wager nonlinearly increased from \$0 to \$5.15. Participants were told that they should try to maximize their virtual monetary reward during completion of the task. After electively terminating a trial (“win outcome”) or explosion of a balloon (“loss outcome”), the next balloon presented itself at the smallest balloon size and lowest wager amount.

The timing of inflation during the BART was controlled by a cue, with a jittered time interval of 1.5–2.5 seconds between inflations within a trial, and 2–4 seconds between trials. The number of balloons participants completed during the scan was not pre-determined, but depended on the response speed of subjects.

Imaging data acquisition and analysis

Functional imaging was conducted on a Siemens 3.0T Trio whole-body scanner (Siemens AG, Erlangen, Germany), using a product 8-channel array coil. Before the scan, participants had the opportunity to practice the task to ensure that they could perform it correctly in the scanner.

First, a modified pseudo-continuous ASL perfusion sequence³⁰ was used for the resting state scan. Participants were instructed that there was no specific task and to be in a relaxed awake state during this portion of the scanning process. Interleaved images with and without labeling were acquired using a gradient echo-planar imaging (EPI) sequence. The tagging/control duration was 2s. A delay of 1s was inserted between the end of the labeling pulse and image acquisition to reduce transit artifact. Acquisition parameters consisted of the following: FOV =22cm, matrix =64×64, TR =4s, TE =17ms, flip angle =90°. Sixteen axial slices (6mm thickness with 2mm gap) were acquired from inferior to superior in sequential order. The resting perfusion scanning protocol lasted 4 minutes and consisted of 60 acquisitions. Three patients (1 ICD and 2 non-ICD) did not finish the perfusion scan due to MR technical problems; hence the perfusion data consisted of 15 patients (ICD group =8, non-ICD group =7).

After the perfusion scan, BOLD imaging data were acquired using a standard EPI sequence (TR =3000ms, TE =24ms, flip angle =90°, 50 interleaved axial slices with 3mm thickness, in-plane resolution =3.44mm × 3.44mm) while subjects completed the modified BART. Each participant completed an 8-minute BOLD scan. After the functional scans were completed, high-resolution T1-weighted anatomic images were obtained using 3D MPRAGE (TR =1620ms, TI =950ms, TE =3ms, flip angle =15°, 160 contiguous slices of 1.0mm thickness, in-plane resolution =1mm × 1mm).

Imaging Data Analysis

Functional imaging data processing and analyses were conducted using Statistical Parametric Mapping software (SPM2, Wellcome Department of Cognitive Neurology, UK, implemented in Matlab 6.5, Math Works, Natick, MA), with some additional modifications for perfusion analysis (<http://cfn.upenn.edu/perfusion/software.htm>).

For the perfusion data, images of each subject were realigned to correct head motion, co-registered with the anatomical image, and smoothed in space with a three-dimensional, 10mm FWHM (Full Width at Half Maximum) Gaussian kernel. Perfusion weighted image series were then generated by pair-wise subtraction of the label and control images, followed by conversion to absolute CBF image series based on a single compartment continuous arterial spin labeling (CASL) perfusion model.³¹ For each subject, one mean resting CBF image was generated, normalized to the Montreal Neurological Institute (MNI) template, and then entered into the whole brain voxel-wise analysis using a general linear model (GLM). The GLM analysis used a two-sample t-test to compare the resting CBF in the ICD and non-ICD groups. The threshold was set as uncorrected $P < 0.001$ at voxel, and whole brain corrected $P < 0.05$ for cluster. This threshold identified a cluster in the right ventral striatum, and regional of interest (ROI) analysis were carried out in this cluster by calculating quantitative regional CBF values in this region and comparing the CBF values between the two groups after adjusting for global CBF differences.

For BOLD data, EPI images of each subject were realigned to correct for head motion, corrected for slice acquisition time differences, co-registered with the anatomical image, smoothed in space with a three-dimensional, 10mm FWHM Gaussian kernel, and entered into a voxel-wise analysis using the GLM. A high-pass filter with a cut-off at 128s was used to remove low frequency fluctuations. An event-related design was used and the BOLD time series data were modeled using a standard hemodynamic response function (HRF) with time derivative. The GLM included three regressors representing a balloon inflation, a win outcome, and a loss outcome, respectively. The risk level associated with each balloon (i.e., the probability of explosion, orthogonalized by mean central correction) was entered into the model as a linear parametric modulation of the balloon inflation regressor. For each subject, three contrast images (beta maps) from the risk level, loss outcome, and win outcome regressors were calculated from individual-level GLM analysis, respectively. These beta maps were normalized to the standard MNI template, and then entered into one-sample t-tests for the group-level random-effect analyses. A threshold of whole brain false discovery rate (FDR)³² corrected for $P < 0.05$ and cluster size larger than 30 voxels was used to identify significant activation areas associated with risk (from the parametric regression with risk levels) in the non-ICD group. For other contrasts which showed no activation cluster surviving this corrected threshold, a more liberal threshold of uncorrected $P < 0.001$ was used.

A group-level two sample t-test analysis was also applied to the individual contrast images to compare the risk taking-related activation in the ICD and non-ICD groups. Since our hypothesis focused on the mesolimbic reward system, specifically the ventral striatum, small volume correction (SVC) was applied using bilateral ventral striatum (nucleus accumbens) as the a priori defined region of interest (ROI) from manual structure segmentation (Figure 2c). Bold activation levels (parameter estimates) were also calculated and a two-sample t-test was conducted to examine the difference between the non-ICD and ICD patients in this ROI.

RESULTS

Behavioral performance

The primary outcome measure reported for the BART is the average adjusted number of pumps (for the unexploded balloons only), with a higher score indicating increased risk taking¹⁴. There were no differences between the ICD and non-ICD groups on either of these measures, nor on any of the other exploratory outcome measures (Table 2).

Resting perfusion

Resting perfusion data showed no between-group differences in global CBF (ICD vs. non-ICD groups, 57 vs. 56 ml/100g/min, $P > 0.8$). However, voxel-wise comparisons on regional CBF revealed significantly lower perfusion in the ventral striatum in the ICD group (mainly in the right hemisphere, peak MNI coordinates = [14, 24, 6], uncorrected $P < 0.001$, cluster corrected $P < 0.05$, small volume corrected $P < 0.01$; Figure 1a), and a region-of-interest (ROI) analysis demonstrated a 39% reduction in resting right ventral striatum CBF for the ICD group vs. the non-ICD group (39 vs. 64 ml/100g/min, respectively, $P < 0.001$, Figure 1b).

BOLD fMRI

BOLD data for the BART task demonstrated significant between-group differences in neural activation during risk taking. Using a whole brain-corrected threshold, the non-ICD group demonstrated increased activation that co-varied with risk (i.e., the contrasts of risk regressor) in bilateral visual regions and mesolimbic-frontal regions, including the midbrain, ventral striatum, anterior insula, dorsal lateral prefrontal cortex, and anterior cingulate

cortex/medial frontal cortex (Table 3 and Figure 2a), duplicating activation patterns observed in younger healthy subjects¹⁵.

The ICD group showed no significant activation in any brain region at this level of stringency. Using a more liberal threshold (uncorrected $P < 0.001$), the ICD group demonstrated increased activation that co-varied with risk in visual regions, the anterior cingulate cortex/medial frontal cortex, left striatum, and right prefrontal cortex (Table 3 and Figure 2b), while no activation was found in the right striatum. Direct voxel-wise comparisons showed that the ICD group had reduced activation during risk taking compared with the non-ICD group in the right ventral striatum (peak MNI coordinates = [2, 8, -6], uncorrected $P = 0.001$, small volume corrected $P < 0.05$). Independent ROI analysis confirmed reduced ventral striatal activation for the ICD group compared with the non-ICD group ($P = 0.03$; Figure 2c). The brain regions demonstrating between-group differences in BART task activation overlapped substantially with those showing between-group differences in resting CBF (Figure 2d).

Neither group showed significant regional activations relating to loss or win outcomes, even when employing a more liberal threshold of uncorrected $P < 0.005$.

DISCUSSION

Consistent with our first hypothesis, we found that PD patients with an ICD compared with those without an ICD demonstrated relatively diminished activation in the ventral striatum during risk taking. The between-group difference involved predominantly the right ventral striatum, and this region was also identified as demonstrating between-group differences in resting blood flow as assessed by ASL. In contrast to both the imaging findings and our second hypothesis, no between-group differences were observed in performance on the risk-taking task. Implications are discussed below.

Neural activity during risk taking

In healthy subjects, increasing reward exposure using a gambling task is associated with increased brain activity in mesocorticolimbic regions.^{15;33} In non-PD populations, reduced activation of the mesocorticolimbic “reward” system has been reported in pathological gambling, substance use disorders, and eating disorders.^{6;11–13;34} Thus, our finding of reduced ventral striatum activation during risk taking in PD patients with a range of ICDs suggests that ICDs in PD share a common mechanism with those in the general population. Our finding of differences in the right striatum specifically is similar to that reported in a fMRI study of pathological gamblers in the general population,¹¹ and the ability to detect differences in brain activity in spite of normal task performance was similar to that reported in an fMRI Stroop study of pathological gambling subjects.¹²

Resting cerebral blood flow

The finding of reduced resting CBF in the ventral striatum of the ICD group compared with the non-ICD group, which overlapped with the between-group differences in neural activity in response to risk taking, suggests several possibilities. For example, diminished right ventral striatal function may represent a trait effect of ICDs in PD, and diminished ventral striatal activation might thus be observed across multiple tasks, including ones not directly related to risk taking. However, the specificity of ventral striatal findings to the modeling of the hemodynamic response function to risk-taking and not to win or loss outcomes on the BART does not provide support for this interpretation.

The current ASL findings complement those from a PET study of PD patients with pathological gambling in which diminished ventral striatal dopamine D2/3 receptor binding

potential was observed.³⁵ However, as the current study did not investigate dopaminergic influences, the extent to which the present findings might relate to dopamine function in individuals with PD and ICDs warrants direct investigation.

A recent SPECT study³⁶ in PD patients with pathological gambling showed increased brain perfusion in multiple right hemisphere regions linked with impulse control, including the orbitofrontal cortex, hippocampus, amygdala, insula, and ventral pallidum. Multiple factors, including small sample sizes in both studies, differences in patient populations (e.g., 11 subjects with pathological gambling in the Cilia et al. study versus 4 patients in our study; average ICD duration of 1.7 years in Cilia et al. study versus 4.5 years in our study), resolution of imaging techniques, and analysis methods may have contributed to apparent differences in results from the two studies. Future, larger studies are needed to examine these possibilities.

The ventral striatum and ICD behaviors

Abnormalities in risk-reward processing and decision-making have been reported in PD.^{37–39} Unmedicated PD patients demonstrate an impaired mesolimbic reward prediction response⁴⁰ and diminished functional connectivity of the ventral striatum with other regions of the limbic cortex,^{41;42} suggesting a neural substrate that may predispose to ICD development.

An alternate possibility involves drugs, such as DAs and levodopa, that influence ventral striatal function and have been associated with ICDs in PD. A recent PET neuroimaging study in PD patients with pathological gambling using ¹¹C raclopride, a radioligand that binds to dopamine D2/D3 receptors, demonstrated decreased D2/D3 binding potential at baseline and a relatively greater decrease in binding potential during performance of a gambling task.³⁵ Via action on ventral striatal dopamine function, dopamine replacement therapies in PD patients could potentially alter reward responsivity^{43;44} and abilities to learn from negative decision outcomes.^{45;46} Given the cross-sectional nature of the present study and the study's use of brain imaging techniques that do not measure dopamine function, additional research is needed to examine these and other hypotheses.

The current findings of relatively diminished ventral striatal activation in individuals with ICDs are similar to findings in non-PD populations. Specifically, individuals with pathological gambling have shown relatively diminished ventral striatal activation during simulated gambling and following exposure to gambling cues.^{11;13} As such, the present findings suggest that this pattern may extend to PD samples and be particularly relevant to risk taking. Additionally, as many of the subjects with ICDs in the present study did not have pathological gambling, the findings suggest that diminished ventral striatal function may be relevant to a broader range of ICDs.

Clinical relevance

Although discontinuation of or a reduction in DA treatment may be associated with improvements in or resolution of ICD symptoms,⁴⁷ PD patients are often reluctant to make changes in their pharmacotherapy due to motor or psychological benefits derived from the medications. In addition, reductions or changes in DA dosage may not uniformly lead to resolution of ICD symptoms, so other interventions are needed. If there is an association between ventral striatum activity and ICDs in PD, non-dopaminergic treatments that target this brain region have the potential to improve ICD symptoms without worsening the motor symptoms of PD. For instance, nalmefene and naltrexone, two opioid antagonists, have been shown to be efficacious in the treatment of non-PD pathological gambling^{48;49} and are hypothesized to generate clinical effects through indirect modulation of dopamine function

in the mesolimbic system.⁵⁰ Investigation of the efficacy and tolerability of opioid antagonists in the treatment of ICDs in PD is warranted, as are studies of the biological mechanisms of action.

Study limitations

There are several study limitations. First, with 18 patients for the BOLD study and 15 patients for the ASL perfusion study, the sample sizes may have been too small to detect more subtle between-group differences in other regional neural activity (e.g., the prefrontal cortex) during risk taking, or for activations related to loss and win outcomes. In addition, inclusion and grouping of data for four different ICDs may have contributed to less robust differences between the ICD and non-ICD groups, due to possible differences in the neural substrates for these four ICDs. Second, due to time limitations inherent in the fMRI experimental design, the maximum number of possible balloon inflations in our modified BART task was reduced to 12, and most subjects completed only 20–30 balloon trials during the 8 minutes of BOLD scanning. Thus, the experimental design may have decreased the sensitivity to detect between-group differences in behavioral performance. However, BART performance in PD patients on a DA has previously been shown to correlate with fMRI brain activity in the orbitofrontal cortex despite lack of a direct DA effect on BART behavioral performance,¹⁸ and a recent fMRI study using a probabilistic learning task in PD patients with and without an ICD reported between-group differences in orbitofrontal cortex and dorsolateral putamen activity associated with task prediction error, in spite of no between-group differences in task behavioral performance.⁵¹ The use of a virtual reward may have also decreased our sensitivity to detect between-group differences associated with risk taking. While some neuroimaging studies have identified regional brain activations in “reward system” circuitry when processing virtual non-money rewards,⁵² others have detected greater changes in metabolism when using actual monetary rewards versus non-monetary rewards.⁵³ As the study was cross-sectional in nature, conclusions regarding causality cannot be drawn. Additionally, since the study did not include brain measures evaluating dopamine function, statements relating the findings to dopaminergic function in PD and dopamine replacement therapies must be considered cautiously. Finally, the finding of relatively diminished BOLD activity and CBF in the same region in ICD patients raises the possibility that the BOLD findings may not be specific to risk-taking behaviors.

Conclusions

In summary, ICDs in PD that occur in the context of DA treatment are associated with diminished right ventral striatum activity in resting state as well as in response to risk-taking. Our results provide converging evidence linking alterations in the mesolimbic reward system to a range of behavioral and drug addictions.^{6;13}

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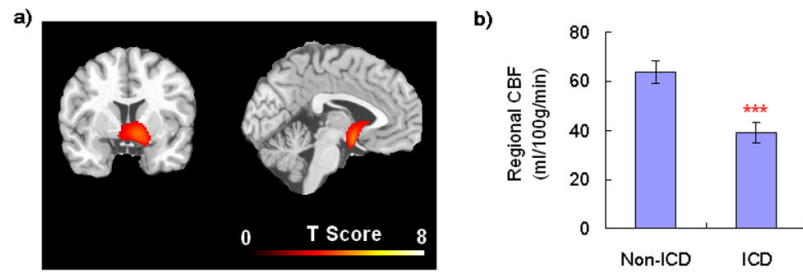


Figure 1.

(a) Resting perfusion imaging data showing significant CBF differences in the ventral striatum between ICD and non-ICD PD patients. Threshold was set as cluster corrected for $P < 0.05$; (b) Quantitative analysis showing regional resting CBF in the right ventral striatum significantly decreased for the ICD group compared with the non-ICD group (error bar represents standard error, *** $P < 0.001$).

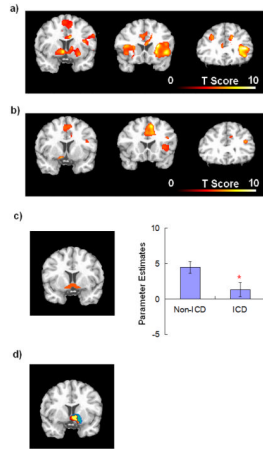


Figure 2.

BOLD imaging data showing (a) increased neural activation for the non-ICD group in bilateral mesolimbic-prefrontal cortex regions during risk taking; (b) increased neural activation for the ICD group in visual regions, the anterior cingulate cortex/medial frontal cortex, left striatum, and right prefrontal cortex, with no activation in the right striatum during risk taking; (c) the ventral striatum region of interest (ROI), a priori defined from manual structure segmentation, and parametric estimates in this ROI showed significantly lower BOLD activation levels for ICD group compared with the non-ICD group (error bar represents standard error; $*P < 0.05$); (d) BOLD activation differences in the right ventral striatum overlapped with resting CBF differences (red=BOLD, blue=CBF, yellow=both).

Table 1

Demographic and clinical characteristics of subjects

Variables ^d	ICD Group (N=9)	Non-ICD Group (N=9)	P value
ICD Type	Eating only (N=2) Gambling only (N=1) Sexual behavior only (N=1) Buying only (N=1) Gambling and sexual behavior (N=1) Buying and eating (N=1) Eating, sexual behavior, and gambling (N=1) All four ICDs (N=1)	-	-
Sex (% male)	77.8	88.9	0.53
Age (years)	56.2 (10.7)	54.4 (9.6)	0.72
Education (years)	17.2 (2.9)	16.0 (2.6)	0.36
PD Duration (years)	7.2 (4.4)	7.6 (6.6)	0.87
Hoehn & Yahr stage	2.1 (0.3)	2.1 (0.2)	>0.99
Dopamine replacement therapy			
- Levodopa LEDD ^b	418 (306)	309 (171)	.36
- DA LEDD	278 (116)	319 (187)	.58
- Total LEDD	696 (399)	628 (313)	.70
GDS-15 score	5.4 (3.2)	2.9 (3.3)	0.12
MoCA score	27.1 (1.8)	27.0 (2.5) ^c	0.78

^aPercentage, mean (SD), or median values^bLEDD = levodopa equivalent daily dosage^cN=8

Table 2

Behavioral performance for the BART

Variables ^a	ICD (N=9)	Non-ICD (N=9)	P value
Average adjusted pumps (unexploded balloons only)	5.6 (1.0)	5.8 (0.9)	0.63
Average adjusted pumps (all balloons)	5.4 (1.1)	5.6 (0.8)	0.77
Balloons completed without explosion	23.4 (5.2)	22.4 (3.7)	0.64
Number of explosions (“loss outcomes”)	5.3 (1.4)	5.1 (1.7)	0.57
Number of completed balloons (“win outcomes”)	17.3 (5.5)	16.9 (4.8)	0.85

^aMean (SD) values

Table 3

Activation during risk taking on the BART

Brain Regions	Peak MNI Coordinates			Z Scores	P Values (corrected)	Cluster size
	X	Y	Z			
Non-ICD group^a						
R. Insula/PFC	40	28	10	5.05	0.014	1893
R. Parietal	36	-32	44	4.58	0.014	983
L. Parietal/Occipital	-14	-80	50	4.27	0.016	110
L. Insula	-26	26	12	4.21	0.016	747
L. Striatum	-8	8	-4	4.13	0.017	
R. Striatum	8	4	4	3.98	0.020	
R. ACC	8	8	28	4.13	0.018	298
R. Occipital	42	-78	22	4.11	0.018	153
R. Midbrain/Thalamus	6	-24	-8	3.94	0.020	91
R. Parietal	22	-58	48	3.74	0.025	234
L. PFC	-30	40	34	3.73	0.025	164
L. ACC	-8	30	14	3.62	0.029	39
R. MFC	10	2	56	3.51	0.034	41
L. ACC	-6	22	32	3.51	0.034	63
R. Parietal	58	-36	22	3.37	0.041	47
ICD group^b						
L. Fusiform/Occipital	-24	-74	-12	5.04	0.055	848
L. Occipital	-34	-82	20	4.81	0.055	466
R. ACC/MFC	8	18	42	4.37	0.055	1274
R. Occipital	32	-84	16	4.35	0.055	456
L. Striatum	-12	8	-12	4.26	0.061	54
R. PFC	26	50	18	3.87	0.065	36
R. PFC	42	12	20	3.42	0.087	35

^aThreshold set as whole brain FDR corrected P<.05 and cluster size larger than 30 voxels.

b Threshold set as the uncorrected $P < .001$ and cluster size larger than 30 voxels