Functional Abnormalities Underlying Pathological Gambling in Parkinson Disease

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Background: Pathological gambling (PG) may develop in patients with Parkinson disease (PD) during dopamine replacement therapy, but the underlying neural correlates are still unclear.

Objective: To investigate resting state brain perfusion in PD patients with active PG compared with matched PD controls and healthy controls.

Design: Case-control study.

Setting: Outpatient tertiary clinic.

Participants: Eleven right-handed PD patients with active PG according to Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision) criteria, 40 matched PD controls, and 29 age-matched healthy controls.

Intervention: All the participants underwent resting state brain perfusion single-photon emission computed tomography using technetium TC 99m ethylcysteinate dimer bicisate. All PD subjects were taking dopaminergic medication.

Main Outcome Measure: Statistical Parametric Mapping was used for data analysis (P < .005, false discovery rate corrected).

Results: PD patients with PG showed resting state overactivity in a right hemisphere network that included the orbitofrontal cortex, the hippocampus, the amygdala, the insula, and the ventral pallidum. No areas of perfusion reduction were detected.

Conclusions: We found that PD patients with PG have abnormal resting state dysfunction of the mesocorticolimbic network possibly associated with a drug-induced overstimulation of relatively preserved reward-related neuronal systems. These findings support the concept that PG is a "behavioral" addictive disorder.

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Background: Pathological gambling (PG) is defined by failure to resist the urge to gamble, with persistent and recurrent maladaptive gambling behavior despite disruptive consequences on familial, occupational, and social functions. It is classified as an impulse control disorder (ICD) in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision) and is reported in patients with Parkinson disease (PD) in association with dopamine replacement therapy (DRT).

Imaging studies in PG have demonstrated abnormal functioning in the prefrontal and limbic brain areas during gambling-related activation tasks. ICDs (including PG) in PD are associated with specific traits, such as high impulsivity and novelty seeking. Several studies on impulsivity and addiction have underlined the critical role of brain pathways in the development of compulsive reward-seeking behaviors, whereas the role of dopamine neuron loss and medications in the occurrence of ICDs in PD is debated. Indeed, whereas untreated PD patients display an abnormal response to monetary reward secondary to reduced dopamine availability in the mesocorticolimbic pathways, DRT may increase impulsivity and sensitivity to reward.

In the present study, we used perfusion single-photon emission computed tomography (SPECT) to determine whether PD patients with PG exhibit differential brain activity compared with matched PD controls and healthy controls.

METHODS

PATIENTS

We included outpatients with PD who attended the Parkinson Institute, Istituti Clinici di Perfezionamento, Milan (Drs Cilia, Siri, Isaias, Canesi, Pezzoli, Antonini, and De Gaspari); Department of Neurology, University of Milan-Bicocca, San Gerardo Hospital, Monza (Drs Cilia and Isaias); and Nuclear Medicine, IRCCS-Ospedale Maggiore, Milan (Dr Marotta), Italy.
Clinical and Gambling-Related Features of 11 PD Patients With Pathological Gambling

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age, y</th>
<th>Disease Duration, y</th>
<th>PG Duration, mo</th>
<th>Disease Duration at PG Onset, y</th>
<th>DRT, mg/d</th>
<th>Other ICDS</th>
<th>Subtype of PG</th>
<th>Losses, Mean, $e^{a}$</th>
<th>Score, Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/55</td>
<td>10</td>
<td>31</td>
<td>7</td>
<td>LD/C, 500; PPX, 1.4</td>
<td>None</td>
<td>Slot machines, scratch/lotto cards, casino, horse/dog racing betting, stock market</td>
<td>&gt;50 000 (64 390)</td>
<td>28.3</td>
</tr>
<tr>
<td>2/M/46</td>
<td>2</td>
<td>10</td>
<td>1</td>
<td>LD/C, 400; ROP, 9</td>
<td>BE, HS, IA, CS</td>
<td>Scratch/lotto cards, playing cards, stock market</td>
<td>&gt;50 000 (64 390)</td>
<td>28</td>
</tr>
<tr>
<td>3/M/56</td>
<td>7</td>
<td>9</td>
<td>6</td>
<td>LD/C, 300; PPX, 2.1</td>
<td>HS, BE</td>
<td>Slot machines, playing cards</td>
<td>&gt;10 000 (12 921)</td>
<td>29.4</td>
</tr>
<tr>
<td>4/M/66</td>
<td>13</td>
<td>29</td>
<td>11</td>
<td>LD/B, 750; LD/C, 200; PPX, 2.1</td>
<td>HS, BE</td>
<td>Slot machines, lotto cards</td>
<td>&gt;50 000 (64 390)</td>
<td>30</td>
</tr>
<tr>
<td>5/M/59</td>
<td>13</td>
<td>8</td>
<td>12</td>
<td>LD/B, 750; PPX, 2.1</td>
<td>HS, CS</td>
<td>Scratch/lotto cards</td>
<td>NA</td>
<td>28.5</td>
</tr>
<tr>
<td>6/M/54</td>
<td>5</td>
<td>21</td>
<td>3</td>
<td>LD/C, 300; PRG, 3</td>
<td>None</td>
<td>Slot machines, scratch/lotto cards</td>
<td>10 000 (12 921)</td>
<td>29</td>
</tr>
<tr>
<td>7/M/55</td>
<td>9</td>
<td>51</td>
<td>5</td>
<td>LD/B, 300; PRG, 3</td>
<td>HS, BE</td>
<td>Casino, slot machines, playing cards, scratch/lotto cards</td>
<td>65 000 (83 954)</td>
<td>28</td>
</tr>
<tr>
<td>8/M/67</td>
<td>7</td>
<td>32</td>
<td>4</td>
<td>LD/C, 400; PPX, 2.1</td>
<td>HS, BE</td>
<td>Scratch/lotto cards</td>
<td>50 000 (64 390)</td>
<td>28.5</td>
</tr>
<tr>
<td>9/M/58</td>
<td>11</td>
<td>10</td>
<td>10</td>
<td>LD/B, 650; PRG, 3</td>
<td>HS, CS, IA</td>
<td>Lotto cards, slot machines</td>
<td>15 000 (19 374)</td>
<td>30</td>
</tr>
<tr>
<td>10/M/55</td>
<td>6</td>
<td>19</td>
<td>4</td>
<td>LD/B, 600; ROP, 20</td>
<td>LD/B, 600; PPX, 2.1</td>
<td>Slot machines, scratch cards</td>
<td>NA</td>
<td>28.9</td>
</tr>
<tr>
<td>11/F/60</td>
<td>9</td>
<td>4</td>
<td>9</td>
<td>None</td>
<td>None</td>
<td>Slot machines</td>
<td>10 000 (12 921)</td>
<td>29.2</td>
</tr>
</tbody>
</table>

Abbreviations: BE, binge eating; CS, compulsive shopping; DRT, dopamine replacement therapy; FAB, Frontal Assessment Battery; GDS, Geriatric Depression Scale; HS, hypersexuality; IA, Internet addiction; ICDS, impulse control disorders; LD/B, levodopa + benserazide; LD/C, levodopa + carbidopa; MMSE, Mini-Mental State Examination; NA, not available; PD, Parkinson disease; PG, pathological gambling; PPX, pramipexole; PRG, pergolide; ROP, ropinirole; RPM, Raven Colored Progressive Matrices; SOGS, South Oaks Gambling Screen.

*aActual total losses (US dollars) during the whole period of active PG.*
The SPECT images were reconstructed by means of an iterative algorithm (ordered subset expectation-maximization, 20 iterations and 15 subsets), filtered using a 3-dimensional Butterworth filter (order, 5; cutoff frequency, 0.31 cycles/pixel). Attenuation was corrected by means of the Chang method (attenuation coefficient, µ=0.1 cm⁻¹) for Statistical Parametric Mapping (SPM2; Wellcome Department of Imaging Neuroscience, London, England). The SPECTs of PD patients and healthy controls were spatially normalized to the standard SPECT template embedded in SPM2. All of the images were then smoothed using a full-width half-maximum 12-mm gaussian kernel to increase the signal-to-noise ratio and to account for subtle variations in anatomical structures.

The level of significance of cerebral areas with regional cerebral blood flow (rCBF) changes was assessed by means of the spatial extent and the peak height (z score) of their clusters using estimations based on the theory of random gaussian fields.

A general linear model was used to perform the appropriate voxel-by-voxel statistics using SPM2 in whole brain of all the participants. The analysis was applied to SPECT images by means of single-subject: conditions and covariates design: the 3 groups of PD gamblers, PD controls, and healthy controls were modeled as conditions, with age as the nuisance variable. The effect of global differences in blood flow was removed by using the proportional scaling global mean to

Table 2. Clinical Features of PD Gamblers, PD Controls, and Healthy Controls

<table>
<thead>
<tr>
<th></th>
<th>PD Gamblers (n=11)</th>
<th>PD Controls (n=40)</th>
<th>Healthy Controls (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>57.4 (5.8)</td>
<td>55 (7)</td>
<td>56 (6)</td>
</tr>
<tr>
<td>Age at PD onset, mean (SD), y</td>
<td>49.5 (4.7)</td>
<td>46.4 (7.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Male/female, No.</td>
<td>10/1</td>
<td>27/13</td>
<td>14/15</td>
</tr>
<tr>
<td>Side of symptom onset, No. (%)</td>
<td>Right 7 (64)</td>
<td>23 (57)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Left 4 (36)</td>
<td>17 (43)</td>
<td>NA</td>
</tr>
<tr>
<td>Disease duration, mean (SD), y</td>
<td>8.4 (3.4)</td>
<td>8.4 (5.1)</td>
<td>NA</td>
</tr>
<tr>
<td>MMSE score, mean (SD)</td>
<td>28.9 (0.8)</td>
<td>28.6 (1.6)</td>
<td>28.7 (1.7)</td>
</tr>
<tr>
<td>SOGS score, mean (SD)</td>
<td>7.6 (2.8)a</td>
<td>1.1 (0.4)</td>
<td>0.8 (0.3)</td>
</tr>
<tr>
<td>FAB score, corrected, mean (SD)</td>
<td>15.3 (1.4)</td>
<td>15.1 (2.7)</td>
<td>NA</td>
</tr>
<tr>
<td>RPM score, mean (SD)</td>
<td>28.3 (3.8)</td>
<td>29.6 (4.1)</td>
<td>NA</td>
</tr>
<tr>
<td>GDS score, mean (SD)</td>
<td>8.1 (4.0)</td>
<td>8.5 (3.8)</td>
<td>7.4 (4.2)</td>
</tr>
<tr>
<td>PD duration, mean (SD), mo</td>
<td>20.4 (14.2)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Other ICDs, No.</td>
<td>HS, 5; BE, 2; CS, 2; IA, 1</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Total LEDD, mean (SD), mg</td>
<td>811.8 (229.0)</td>
<td>877.3 (289.3)</td>
<td>NA</td>
</tr>
<tr>
<td>DA daily dosage, mean (SD), mg</td>
<td>289.1 (57.5)</td>
<td>340.1 (157.2)</td>
<td>NA</td>
</tr>
<tr>
<td>DA, % of total LEDD</td>
<td>35.6</td>
<td>38.8</td>
<td>NA</td>
</tr>
<tr>
<td>Type of DA, No. (%)</td>
<td>PPX, 6 (55); PRG, 3 (27); ROP, 2 (18); CBG, 0</td>
<td>PPX, 20 (50); PRG, 10 (25); ROP, 7 (17); CBG, 3 (8)</td>
<td>NA</td>
</tr>
<tr>
<td>UPDRS Part III, mean (SD)</td>
<td>18.0 (11.0)</td>
<td>19.1 (8.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Hoehn and Yahr stage, mean (SD)</td>
<td>2.1 (0.6)</td>
<td>2.3 (0.8)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: BE, binge eating; CBG, cabergoline; CS, compulsive shopping; DA, dopamine; FAB, Frontal Assessment Battery; GDS, Geriatric Depression Scale; HS, hypersexuality; IA, Internet addiction; ICDs, impulse control disorders; LEDD, levodopa-equivalent daily dose; MMSE, Mini-Mental State Examination; NA, not applicable; PD, Parkinson disease; PG, pathological gambling; PPX, pramipexole; PRG, pergolide; ROP, ropinirole; RPM, Raven Colored Progressive Matrices; SOGS, South Oaks Gambling Screen; UPDRS III, Unified Parkinson Disease Rating Scale motor score.

aP < .05, PD gamblers vs PD controls and PD gamblers vs healthy controls.
50, with the threshold masking relative to the default value of 0.8. All voxel-based statistical analyses were performed by applying a threshold of $P < .005$, corrected for false discovery rate, for significance and considering clusters of at least 50 voxels. The coordinates of the most significant voxel in a cluster were converted from the Montreal Neurological Institute standard coordinates used by SPM to Talairach coordinates, and their location was investigated using Talairach Daemon software.17

Comparisons between continuous variables in PD gamblers, PD controls, and healthy controls were performed using the unpaired $t$ test ($P < .05$), and the $\chi^2$ test was used for categorical variables ($P < .05$). Statistical analysis was performed using a software program (SPSS for Windows Release 10.0; SPSS Inc, Chicago, Illinois).

RESULTS

We investigated 11 selected PD patients (mean [SD] age, 57 [6] years; age range, 46-67 years) with active PG according to the inclusion criteria. All identified patients were high-frequency gamblers (more than 1 gambling episode per week), and neuropsychological assessment excluded significant frontal lobe dysfunction or depression. Detailed features of each PD gambler are reported in Table 1. There were no differences between PD gamblers and both control groups for all of the demographic and clinical features listed in Table 2, except for higher SOGS scores ($P < .001$).

PD GAMBLERS VS PD CONTROLS

SPM$_2$ analysis showed several clusters of increased perfusion in PD gamblers, mainly in the right hemisphere, but no area of relative reduced perfusion (Figure 1, Figure 2, and Table 3). We found a cluster of 557 voxels with a peak located in the right lateral orbitofrontal cortex (OFC) and extended to the insula. There were rCBF increases in the right hippo-

Figure 2. Areas of significantly increased blood flow in Parkinson disease (PD) patients with pathological gambling vs PD controls obtained from whole-brain Statistical Parametric Mapping analysis ($P < .005$, false discovery rate corrected). The crossbars indicate the voxel with the peak of significance in the ventral pallidum cluster, extending to the nucleus accumbens. The cluster of increased perfusion in the right insula is also present on axial view. L indicates left; R, right.
campus extended to the parahippocampal gyrus and also encompassing the amygdala (Figure 1A). Moreover, there were increases in a cluster located in the ventral basal ganglia on the right hemisphere, with a peak in the globus pallidus, and extended to the nucleus accumbens (Figure 1B). Enhanced rCBF was also found in the left insula and in the bilateral precuneus, extending to the cuneus and the posterior cingulate cortex.

PD GAMBLERS VS HEALTHY CONTROLS

SPM analysis detected 2 large clusters of increased perfusion in the right hemisphere without areas of reduced perfusion (Figure 3 and Table 3). We found a large cluster (955 voxels) with a peak in the insular cortex extended to the lateral OFC and also involving the putamen and the caudate nucleus. Another cluster (163 voxels) was present in the right hippocampus extending to the parahippocampal gyrus.

PD CONTROLS VS HEALTHY CONTROLS

Nongambling PD controls showed reduced perfusion in the frontal lobe bilaterally, the right parietooccipital cortical areas, and the left thalamus compared with age-matched healthy controls. Clusters of increased rCBF were found in the cerebellum bilaterally (Table 3).

This is the first investigation, to our knowledge, of resting cerebral perfusion in a selected cohort of PD patients with active PG. We previously demonstrated the reliability of this approach in assessing cerebral activity in PD. The PDGamblers showed significant overactivity in brain areas critically involved in reward and reward-based learning, motivation, impulse control, decision making, and memory processing, namely, the basal ganglia, the OFC, the hippocampus, the amygdala, and the insula. This pattern of activity increments is similar in PD gamblers and in the PD and non-PD control groups and suggests specific functional abnormalities in the mesocorticolimbic network.

The lack of significant rCBF decrements in PD gamblers is an intriguing finding given that perfusion reductions in the cortical areas found in PD controls vs healthy individuals have been described as a result of the neurodegenerative process. In the present study, we applied strict inclusion criteria, and PD controls were selected to have similar demographic characteristics, disease-related features, cognitive function, dose range, and type of medication use to those of the PG cohort to minimize possible confounding effects. Therefore, the absence of a significant cerebral activity decrement in PD gamblers suggests relatively preserved neuronal systems in the presence of nigrostriatal impairment similar to PD con-
Pathological gambling may develop as a consequence of an abnormal drug-induced overstimulation in PD individuals with a relatively spared mesocorticolimbic network. This hypothesis would be consistent with reports of PG in patients without neurodegenerative diseases (e.g., restless legs syndrome) treated with low doses of dopamine agonists.

Patients with PD taking dopaminergic medications commonly experience a mild to moderate nonpathological increment of the physiologic drive toward natural rewards, but only some individuals eventually develop ICDs. It is likely that common predisposing factors between ICDs and substance use disorders favor switching from occasional to compulsive reward-seeking addictive behaviors. Indeed, differences in trait reward sensitivity and motivation levels in individuals with other ICDs and substance use disorders are associated with activation of the OFC, hippocampus, and amygdala, insula, and ventral pallidum. Two dominant descriptive models of PG have been proposed so far, one considering it among obsessive-compulsive-spectrum disorders and another in the context of behavioral addictions. Increased resting state activity of the OFC is reported in obsessive-compulsive disorder and substance use disorders during early withdrawal. Therefore, the present findings further support the hypothesis of OFC dysfunction as a common neurobiological substrate underlying disorders characterized by poor impulse control and compulsive behaviors. The abnormally increased perfusion in limbic and paralimbic areas in PD gamblers might suggest a medication-induced enhancement of lower-level impulsive drive rather than a primary dysfunction of the lateral prefrontal cortex with subsequent impairment of higher-level top-down supervisory cognitive control. This hypothesis would also be consistent with the lack of executive dysfunction in PD patients with ICDs. Indeed, in this study and in a previous, more...
general study on ICDs, we found normal frontal lobe function in most PG patients.

We found significant activity changes in the ventral pallidum and not in the nucleus accumbens per se. The ventral pallidum is implicated in the modulation of hedonic responses to natural and drug rewards, and subsequent reward seeking–motivated drive by reciprocal connections with limbic areas. The OFC function is critical in establishing the motivational value of a stimulus based on its potential reward, with a specific right-sided lateralization of conditioned responses to salient stimuli, and once activated by reward-related internal (memories) or environmental stimuli, it induces an intense urge (craving) even without activation of the nucleus accumbens. Craving for gambling is often reported by PD gamblers, in particular when exposed to gambling-related external stimuli or memories. The hippocampus, parahippocampal gyrus, amygdala, precuneus, and posterior cingulate cortex are all brain regions involved in memory retrieval based on previous rewarding experience, and the insula is implicated in the processing and recall of the emotional relevance of stimuli through its reciprocal connections with the OFC, the hippocampus, and the amygdala. The baseline overactivity we found in brain areas related to memory processing and conditioned responses may underlie craving responses and the subsequent high risk of relapse in PG, as previously reported in substance use disorders. Moreover, OFC dysfunction is associated with impaired use of information from previous rewarding and punishing outcomes to modulate behavioral responses.

In the present PG cohort, there was a high predominance of men, consistent with other reported case series. The mechanisms of male preponderance are unclear, but imaging studies have shown a stronger functional connectivity and responsiveness to rewards of the mesocorticolimbic system in males compared with females, suggesting increased vulnerability to addictive disorders.

In conclusion, we hypothesize that PG occurs in PD as a result of DRT-induced overstimulation of a relatively preserved mesocorticolimbic dopamine pathway in patients with individual predisposition. The occurrence of PG may be associated with abnormal reward-based learning processes combined with reduced inhibition of impulsive drives and impaired ability to evaluate the negative consequences of financial losses. The present imaging findings support the proposal to group PG together with addictive disorders in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders. Further prospective controlled studies in larger cohorts are needed to investigate the predisposing factors to the development of ICDs in patients with PD undergoing DRT (including neurobiological features and premorbid personality traits) and the clinical-functional correlates of lowering DRT.

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Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Cilia, Siri, Isaias, and Antonini. Acquisition of data: Cilia, Siri, Marotta, De Gaspari, Canesi, and Antonini. Analysis and interpretation of data: Cilia, Siri, Marotta, Pezzoli, and Antonini. Drafting of the manuscript: Cilia, Siri, and Antonini. Critical revision of the manuscript for important intellectual content: Cilia, Siri, Marotta, Isaias, De Gaspari, Canesi, Pezzoli, and Antonini. Statistical analysis: Siri and Marotta. Study supervision: Siri, Marotta, Isaias, De Gaspari, Canesi, Pezzoli, and Antonini.

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REFERENCES

19. Tippmann-Peikert M, Park JS, Boeve BF, Shepard JW, Silber MH. Pathologic gam-