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## Pathological Gambling in Parkinson's Disease Improves on Chronic Subthalamic Nucleus Stimulation

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**Abstract:** Pathological gambling (PG) related to dopaminergic treatment in Parkinson's disease (PD) is part of a spectrum of behavioral disorders called the dopamine dysregulation syndrome (DDS). We describe a series of PD patients with preoperative active PG due to dopaminergic treatment from a total of 598 patients who have undergone surgery for subthalamic nucleus stimulation for disabling motor fluctuations. The patients had systematic open assessment of behavioral symptoms and standardized assessments of motor symptoms, mood, and apathy. Seven patients (6 men, 1 woman; age,  $54 \pm 9$  years; levodopa equivalent dose,  $1,390 \pm 350$  mg/day) had preoperative PG over a mean of 7 years, intolerant to reduction in medication. Six had nonmotor fluctuations and four had other behavioral symptoms consistent with a diagnosis of the DDS. After surgery, motor symptoms improved, allowing for 74% reduction of dopaminergic treatment, below the dosage of

gambling onset. In all patients, PG resolved postoperatively after 18 months on average (range, 0–48), although transient worsening occurred in two. Improvement paralleled the time course and degree of reduction in dopaminergic treatment. Nonmotor fluctuations, off period dysphoria, and other symptoms of the DDS improved. Two patients developed persistent apathy. In conclusion, PG and other symptoms of the DDS-associated dopaminergic treatment improved in our patients following surgery. Dopaminergic dysregulation commonly attributed to pulsatile overstimulation of the limbic dopaminergic system may be subject to desensitization on chronic subthalamic stimulation, which has a relative motor selectivity and allows for decrease in dopaminergic treatment. © 2006 Movement Disorder Society

**Key words:** Parkinson's disease; deep brain stimulation; pathological gambling; dopamine; subthalamic nucleus

Psychiatric symptoms related to Parkinson's disease (PD) or dopaminergic treatment include mood disorders, psychotic symptoms, apathy, anxiety,<sup>1</sup> the recently recognized dopamine dysregulation syndrome,<sup>2,3</sup> and impulse control disorders.<sup>4–7</sup> Dopamine dysregulation syndrome is defined as compulsive use of dopaminergic treatment with secondary cognitive and behavioral disturbances.<sup>2,3</sup> The range of reported impulse control behaviors includes pathological gambling (PG), hypersexuality, compulsive shop-

ping, pathological overeating, hobbyism, and other repetitive, purposeless behaviors ("punding").

PG has been conceptualized within the impulsive-compulsive spectrum disorders and also as a behavioral addiction with overlaps with substance use disorders.<sup>8</sup> Subthalamic nucleus (STN) deep brain stimulation (DBS) is a treatment for advanced PD with demonstrated efficacy on levodopa-sensitive motor symptoms.<sup>9</sup> However, there are limited data available on the effects of STN DBS on preoperative psychiatric symptoms in PD. Postoperative amplification or decompensation of previously existing psychiatric disorders has been reported<sup>10</sup> and behavioral problems therefore are generally considered as a contraindication for STN DBS. The objective of this study was to describe the outcomes of a series of PD patients with active preoperative medication-related PG who have undergone STN DBS.

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## PATIENTS AND METHODS

The databases of four participating neurological centers (Grenoble, Creteil/Paris, Salpêtrière/Paris, Toronto) were reviewed, which included a total of 598 idiopathic PD patients who underwent bilateral STN DBS surgery using previously published procedures.<sup>9,11,12</sup> The main selection criteria for surgery were the presence of disabling motor complications of dopaminergic treatment in patients younger than 70 years, the absence of dementia, and severe depression with suicidal intention. Patients with DSM IV-defined PG before surgery were included in the study.

Motor symptoms were assessed before and after surgery using the Unified Parkinson's Disease Rating Scale III (UPDRS III).<sup>13</sup> The levodopa equivalent dosage (LED) = dosage of agonist + levodopa was calculated according to established protocols.<sup>14</sup> Behavioral symptoms were assessed with an exhaustive systematic open interview performed before and after surgery by a neuropsychologist or psychiatrist familiar with PD. Diagnosis of dopamine dysregulation syndrome and related behaviors was retrospectively based on the documentation of the behavioral assessment using recently published criteria.<sup>2,3,15</sup> Apathy was assessed using the Starkstein apathy scale<sup>16</sup> (14 items; score range, 0–42; cutoff score of > 14 used for the diagnosis of apathy). Depression was assessed using the Beck Depression Inventory (BDI), which has been validated in the PD population<sup>17</sup> (21 items; score range, 0–63). Neuropsychological assessment varied between centers, but 6/7 patients had global cognitive evaluation based on the Mattis Dementia Rating Scale (range, 0–144; cutoff for dementia < 130).<sup>18</sup> Wilcoxon rank test was used for statistical comparison between long-term evaluation and preoperative scores. The mood, motivational and behavioral changes, their temporal course, and their relationship to treatment are illustrated with a representative case report.

## RESULTS

Seven patients (six men, one woman) had DSM IV-defined preoperative PG,<sup>19</sup> which had developed de novo on dopaminergic treatment. At onset of PG, patients were on levodopa monotherapy ( $n = 1$ ) or on an association of levodopa and dopamine agonist (bromocriptine,  $n = 5$ ; ropinirole,  $n = 1$ ). PG started after a mean of 4.6 (range, 1–8) years on a mean LED of  $968 \pm 409$  mg/day. All patients had active PG at the time of surgery as attempted medication changes or decreases were either not successful in treating the PG or were not tolerated by the patient. Prominent social and occupational dysfunction occurred as a result of the PG symptoms in all patients. Behavioral therapy ( $n = 4$ ) and treatment with clozapine ( $n = 1$ ) were ineffective. The mean

duration of PG was 7 years. The main mode of PG was slot machines in five and lottery scratch cards in two patients. All patients were on a combination of levodopa and a dopamine agonist at the time of surgery (LED  $1,395 \pm 342$  mg/day). Six patients had nonmotor fluctuations with *on* period euphoria and *off* period dysphoria and gambled while *on* drug only. In four patients, following primary PG symptoms, excessive dopaminergic medication use developed with other behavioral symptoms, consistent with a diagnosis of dopamine dysregulation syndrome. One patient had a premorbid history of alcohol abuse in remission and one had childhood-onset obsessive-compulsive disease. None was demented.

No permanent side effects from surgery occurred. Two patients had transient postoperative worsening of manic symptoms not requiring specific pharmacological intervention or hospitalization. Patient 3 had to be reoperated bilaterally due to limited motor response and in this patient dopaminergic treatment could only be reduced after the second surgery. Patient 6 had a two-stage operation, whereas all other patients were operated bilaterally during the same intervention.

The mean long-term follow-up was 3.4 (range, 2–6) years after surgery. Changes in treatment (medication, stimulation parameters), neuropsychological evaluation, and motor assessment at 3 month and at maximal follow-up compared to baseline are summarized in Table 1. Dopamine agonists were stopped in three patients. Mean dopamine equivalent dose was decreased by 74% 3 months after surgery, well below the mean dosage at which patients had started PG. Stimulation parameters are typical for those used in PD and *off* period motor symptoms and dyskinesia duration were improved. There was no change in global cognitive function as assessed by the Mattis Dementia Rating Scale and no change in mood as assessed by the Beck depression inventory. The motivational state tended to change with a small increase in apathy scores. While there was no change in mood and apathy scales reflecting a longer time period, the individual short-term fluctuations in mood and motivation paralleling the motor fluctuations did change, however, as well as overall judgment as illustrated in the case report of Patient 2. Several months after surgery, three patients had a transient episode of depression. Depressive symptoms acted as triggers to their gambling behaviors. However, the patients were not able to experience the same intense pleasure during gambling as before.

Figure 1 schematically represents the relative changes in gambling behavior over time in a semiquantitative manner in the individual patients, together with individual changes in dopaminergic treatment. PG disappeared after surgery in all patients. The delay was quite variable,

**TABLE 1.** Changes in treatment (medication, stimulation parameters), neuropsychological evaluation, and motor assessment at 3-month and at maximal follow-up compared to baseline

	STN Surgery	3-month follow-up	Last follow-up (2-6 years)	P
Dopamine equivalent dose (mg/day)	1395 ± 342	368 ± 204 <sup>b</sup>	571 ± 402	<0.05
Mean DBS voltage (60 µs/130 Hz/monopolar)		2.8 ± 0.7 <sup>a</sup>	2.9 ± 0.7	
UPDRS III/108, <i>Off</i> drug	37.9 ± 19.4	15.3 ± 11.6 <sup>a</sup>	19.6 ± 12.5	<0.05
UPDRS III/108, <i>On</i> drug	9.9 ± 6.7	13.7 ± 7.1 <sup>a</sup>	14.9 ± 9.2	0.05
Dyskinesia duration (item 32/4)	1.4 ± 1.0	0.5 ± 0.5 <sup>a</sup>	0.1 ± 0.4	<0.05
Dyskinesia disability (item 33/4)	1.0 ± 1.3	0.2 ± 0.4 <sup>a</sup>	0.1 ± 0.4	NS
Mattis Dementia Rating Scale/144	138.2 ± 3.5 <sup>a</sup>	NA	139 ± 4.1	NS <sup>a</sup>
Apathy (Starkstein scale/42)	9.5 ± 3.0 <sup>b</sup>	9.8 ± 6.3 <sup>a</sup>	14.3 ± 2.2	0.07 <sup>b</sup>
Depression (BDI-II/63)	15.3 ± 4.0	9.5 ± 5.3 <sup>a</sup>	14.3 ± 8.4	NS

After surgery patients were evaluated ON stimulation. The right column shows statistical significance comparing last follow-up with baseline evaluations.

<sup>a</sup>Data available on six patients.

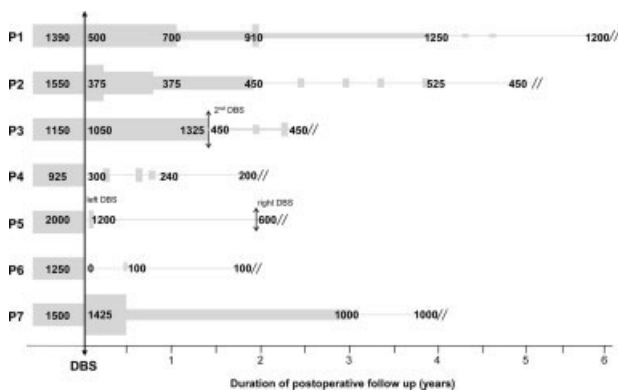
<sup>b</sup>Data available on five patients.

NA, not applicable

being shortest if medication could be drastically reduced. In Patient 6, dopaminergic treatment was stopped and PG disappeared immediately after surgery. In Patient 3, PG improved only after a second operation, the first one not allowing a reduction in medication. Patient 5 had staged surgery. After the first unilateral operation, the dopamine agonist (3 mg of pergolide) was stopped altogether and levodopa was reduced by 500 mg/day. With the exception of a single visit to the casino, the patient immediately stopped PG. In Patients 1 and 7, medication was reduced less drastically and these patients continued their PG much longer. In Patients 2 and 7, there was a transient worsening of PG immediately after surgery in the

context of exacerbation of preoperative manic symptoms. Although some patients did not completely stop, they gambled in a controlled manner and criteria for PG were not fulfilled anymore. Patient 1, e.g., visited a free online casino on the Internet; he was debt-free but continued to accept financial control. This patient was on the same agonist dosage than before surgery.

Nonmotor fluctuations improved in all patients. This improvement relates not only to *on* period euphoria or hypomania, but also to *off* period-related nonmotor symptom such as anxiety, feeling of oppression, sadness, absence of motivation, summarized as dysphoria in Table 2. Nonmotor fluctuations with mild *off* period dysphoria reappeared in the long-term in two patients (Table 2). In the long term, there was a trend in increase in apathy. Two patients developed persistent mild apathy in the long term, but this was well accepted as illustrated in the case report of Patient 2. Apathy was improved in these patients compared to baseline *off* period apathy. All pathological behaviors out of spectrum of dopamine dysregulation syndrome improved and none of the patients



**FIG. 1.** Severity of PG and its evolution over time in parallel with changes in dopaminergic treatment. The thickness of the gray bars represent severity of PG in a semiquantitative way in the individual patients. Baseline severity before surgery is set at 100% to allow an illustration of individual changes over time. The black figures represent the levodopa equivalent daily dosage in mg/day. Note that Patient 3 had a second bilateral surgical intervention as the first one was a failure. Patient 5 had a staged intervention with surgery of the left STN first and then the right STN 2 years later.

**TABLE 2.** Follow-up of behavioral characteristics

	STN surgery	3-month follow-up	Last follow-up (2-6 years)
<i>Off</i> period dysphoria	6/7	0/7	2/7
Apathy	0/7	0/7	2/7
<i>On</i> period hypomania	4/7	2/6	0/7
Hypersexuality	5/7	1/6	0/7
Insomnia	3/7	2/6	0/7
Addiction to levodopa	4/7	0/6	0/7
Compulsive shopping	3/7	1/6	1/7
Risk behavior	2/7	1/6	0/7
Binge eating	2/7	3/6	1/7

fulfilled diagnostic criteria for dopamine dysregulation syndrome in the long term (Table 2).

### Illustrative Case Report: Patient 2

A 59-year-old man with PD onset in 1984 with no prior psychiatric history and no history of substance abuse started to buy lottery cards in 1986 while on levodopa 300 mg/day and bromocriptine 30 mg/day. In 1989, treatment was increased to 700 mg levodopa and 50 mg bromocriptine. In addition, the patient took higher doses than prescribed. Although he had no previous tendency to gamble, he began to visit casinos almost on a daily basis. He felt a thrill when entering the casino ("it's like sexual arousal . . . I feel in love with slot machines"). He went into debt. In 1991, he divorced and left his family of three children for a love affair with a young woman. In 1992, he was put under financial guardianship and had behavioral therapy. He was banned from the casino but then started buying scratch cards. In 1998, a worsening of his motor symptoms led to increasing his treatment to levodopa 1,000 mg and bromocriptine 45 mg and apomorphine injections 3.5 mg on demand several times a day. This was associated with an increase in his "urge" to play the slot machines. He had to sell his house and was eventually bankrupted. In 2000, surgery was proposed for his severe motor fluctuations (UPDRS III 50/108 *off* drug, 12/108 *on* drug). In parallel, he had marked fluctuations in mood (BDI: 29 *off* drug, 15 *on* drug) and motivation (Starkstein: 31 *off* drug, 7 *on* drug). He felt intense pleasure at the moment of switching *on*, and he was gambling in the *on* drug condition only. Surgery was successful and STN DBS allowed a decrease of treatment to 225 mg levodopa and 15 mg bromocriptine. Stimulation parameters were monopolar 60  $\mu$ s, 130 Hz, 3.3 V on both sides. With this treatment, he felt "in a state of grace," with disappearance of both motor and nonmotor fluctuations, a feeling of constant euphoria, and a transient exacerbation of PG. Three months after surgery, the motor score was 9/108 with STN stimulation whether *on* or *off* Levodopa. BDI score was 4 and Starkstein apathy score was 4, with no fluctuations of either mood or motivation. Six months after surgery, while still on the same treatment, he gradually became depressed and apathetic with a progressive decrease of PG. Antidepressive treatment trials with 20 mg paroxetine and 50 venlafaxine over several months failed to improve mood or motivation. One year after surgery, he was depressed (BDI 25, no feeling of sadness, no suicidal ideas) and apathetic (Starkstein 18). He went back to the casino several times trying to fight his depression, but he did not experience pleasure on gambling anymore and eventually gave up gambling, with a last

visit to the casino 2 years after surgery. Antiparkinsonian medication and stimulation parameters had not been changed and the motor state was stable. In 2005, depression was only mild (BDI 14) but he still complained of apathy (Starkstein apathy score 15), which he accepted, however, because he felt that apathy had both decreased the "urge" to gamble and facilitated resisting to this "urge." He had no mood fluctuations. He had lost the addictive behavior not only to gambling but also to dopaminergic treatment. He felt that he had found back his premorbid "serene judgment" again.

### DISCUSSION

We describe seven PD patients from four neurological centers with preoperative histories of dopaminergic medication-related active PG who underwent STN DBS surgery. PG developed after 1 to 8 years of dopaminergic treatment while on a combination of levodopa and a dopamine agonist (bromocriptine,  $n = 5$ ; ropinirole,  $n = 1$ ). Prominent social and occupational dysfunction occurred as a result of the PG symptoms in all patients. In all patients, PG was the primary behavioral disorder. Six patients had marked nonmotor fluctuations and experienced *off* period dysphoria. In four patients, other associated behavioral symptoms were consistent with a diagnosis of dopamine dysregulation syndrome. Following STN DBS surgery, PG symptoms eventually resolved. The mean dopamine equivalent daily dose after surgery was lower than the dose at onset of PG. Improvement was progressive and closely matched the time course of decreases in dopaminergic medications. In the immediate postoperative period, however, pathological gambling exacerbated in two patients in a context of transient postoperative mania. Several months after surgery, three patients had a transient episode of depression. Depressive symptoms acted as triggers to their gambling behaviors. However, the patients were not able to experience the same intense pleasure during gambling as before. Apathy scores tended to increase systematically after surgery and two had a pathological score on the apathy scale in the long term. In the long term, the craving for both dopaminergic medication and gambling urges improved in parallel with an increase in apathy. *Off* period dysphoria related to PD and pathological behaviors associated with dopaminergic treatment improved in keeping with a previous report describing improvement in dopamine dysregulation syndrome in two patients post-STN DBS.<sup>20</sup> Preoperative nonmotor fluctuations disappeared.

In the following, we discuss potential pathophysiological mechanisms underlying the improvement of PG following STN DBS.

### Mechanisms of Pathological Gambling

The two primary anatomical regions potentially implicated in PG include the ventral striatum and ventral prefrontal cortex, areas implicated in reinforcement learning and reward processing.<sup>21</sup> The neurodegenerative process in PD patients affects primarily the substantia nigra pars compacta and can also variably affect the ventral tegmental area, which projects to the ventral striatum, mesolimbic, and prefrontal regions. D3 receptors of the limbic areas of the brain have been suggested as the pharmacological substrate of gambling behavior.<sup>6</sup> The development of PG in PD patients may be compatible with overstimulation of dopamine receptors receiving their projections from the relatively spared ventral tegmental area.<sup>22</sup> The dopaminergic ventral tegmental area projections to the ventral striatum are believed to be involved in motivation and reward prediction as demonstrated by animal studies of microrecordings from mid-brain dopamine neurons in nonhuman primates.<sup>23,24</sup>

A decrease in activity in orbitofrontal cortex was found during gambling urges in PG.<sup>25</sup> From a behavioral point of view, patients with pathological gambling<sup>26</sup> or with substance addiction<sup>27</sup> share certain characteristics with patients with neurological damage to the ventromedial prefrontal cortex.<sup>28</sup>

### Why Do Gambling Behavior and Dopamine Dysregulation Syndrome in PD Patients Improve on STN Stimulation?

The improvement of PG symptoms and associated behavioral problems following STN DBS surgery may be related to the following factors.

First, STN DBS allows for a marked decrease of total dopaminergic medications.<sup>9,11</sup> Thus, either a discontinuation or a decrease of levodopa and even more importantly in dopamine agonists may play a role in the improvement of PG symptoms. That the region of stimulation associated with STN DBS is relatively circumscribed to the motor regions rather than the nonspecific stimulation of limbic or prefrontal regions from dopaminergic medications may allow for an improvement of behavioral symptoms related to a hyperdopaminergic state and explain an unmasking of disease-related apathy<sup>29</sup> reflecting a hypodopaminergic state that can occur in some patients after a delay of several months, once the long-term effects of dopaminergic treatment have vanished.<sup>9,30,31</sup> This increase in apathy seems to help both the craving for the dopaminergic treatment and the gambling urges. On the behavioral spectrum, apathy is the exact opposite of the dopamine dysregulation syndrome.

Second, the decrease in single doses of levodopa and/or dopamine agonists resulting in a less pulsatile and nonsu-

prathreshold dopaminergic stimulation may also play a role in the improvement of symptoms. PG symptoms in the reported patients improved in parallel to decreases in both total and single dopaminergic medication doses. Whether this observation is a dose-related effect, or an effect of decreases in the pulsatile administration of levodopa, is therefore not known. With respect to the latter hypothesis, medication-induced dyskinesias may represent a potential analogous model. Both symptoms of the dopamine dysregulation syndrome<sup>3</sup> and dyskinesias in PD<sup>32,33</sup> are favored by a pulsatile and suprathreshold administration of levodopa. STN stimulation is presumed to improve dyskinesias through the replacement of pulsatile suprathreshold dopaminergic medications with chronic subthalamic stimulation.<sup>34,35</sup> Plasticity of corticostriatal synapses in PD<sup>36</sup> and the sensitization phenomenon resulting from long-term intermittent levodopa administration are partially reversible.<sup>37</sup> The behavior of PG and other behaviors related to a hyperdopaminergic state may have similarities to such a model.

Third, STN stimulation may also have a specific effect on the limbic part of the STN<sup>38</sup> and it has been suggested that this may explain postoperative apathy.<sup>39</sup> However, acute subthalamic stimulation has been shown to have positive psychotropic effects in PD patients mimicking those of levodopa.<sup>40–42</sup> Neuronal activity in the STN in the nonparkinsonian monkey is modulated by reward<sup>43</sup> and STN lesions in a nonparkinsonian rat model can enhance behavioral motivation.<sup>44</sup> Indeed, as illustrated in the case report, we observed improvement in *off* period-related apathy scores with chronic subthalamic stimulation, likely explained by current diffusion to the limbic STN.

In conclusion, patients with active PG and other symptoms of the dopamine dysregulation syndrome—associated dopaminergic treatment in PD do not necessarily constitute a contraindication for surgery. On the contrary, this dopaminergic dysregulation attributed to pulsatile overstimulation of the limbic dopaminergic system may be subject to desensitization on chronic subthalamic stimulation, which has a relative motor selectivity and allows for decrease in dopaminergic treatment. However, patients with active symptoms at the time of surgery are at risk for postoperative decompensation of PG in the immediate postoperative period. Moreover, in the long term, these patients can develop apathy corresponding to a hypodopaminergic state. These patients therefore need a very close long-term follow-up of their motivational state.

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