Neuropsychological effects of subthalamic nucleus stimulation in Parkinson's disease
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Pathological Gambling after bilateral STN stimulation in Parkinson disease

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Abstract

We describe a patient with advanced Parkinson’s disease who developed pathological gambling within a month after successful bilateral subthalamic nucleus (STN) stimulation. There was no history of gambling or psychiatric disturbances. On neuropsychological testing slight cognitive decline was evident a year after surgery. Stimulation of the most dorsal contact with and without medication induced worse performances on decision-making tests compared to the more ventral contact. Pathological gambling disappeared after discontinuation of pergolide and changing the stimulation parameters. Pathological gambling does not seem to be related to decision-making but appears to be related to a combination of bilateral STN stimulation and treatment with dopamine agonists.
Pathological gambling after STN DBS: a case study

Introduction

Pathological gambling in Parkinson disease (PD) is a behavioural complication, which has been related to the use of dopamine agonists\(^1,2\), but also to levodopa therapy\(^3\). Bilateral subthalamic nucleus (STN) stimulation has been shown to improve levodopa sensitive motor symptoms in PD, but negative effects have been reported on behaviour such as mania, depression, apathy, drug dependence, and compulsive self-stimulatory behaviour.\(^3-7\) Recently, improvement of pathological gambling after bilateral STN stimulation has been described.\(^8,9\) We report on a patient with advanced PD who developed pathological gambling within a few weeks after successful bilateral STN stimulation.

Patient

A 63-year-old, right-handed male with a 10 year history of PD underwent bilateral STN surgery for severe pharmaco-resistant response fluctuations. Before surgery, his medication consisted of 600 /150 mg levodopa/carbidopa slow release and pergolide 6-8 mg daily dose. He complained about slight forgetfulness, but neuropsychological evaluation was normal (see Table 1).

Surgery and postoperative management

In 2002, the patient underwent a one-stage bilateral stereotactic procedure using frame-based MRI visualizing the STN on T2-weighted images, verifying the atlas-based target (12 mm lateral (x), 2 mm posterior (y) and 6 mm inferior (z) to the midcommissural point (MCP), and macrostimulation to determine the final position for electrode placement.\(^10\) The electrodes (model 3389, Medtronic) were implanted with the deepest contact 8 mm below MCP on the right and 6 mm below MCP on the left. At discharge, monopolar stimulation at contact 1 was used on both sides with amplitude 1.9 V on the left and 2.4 V on the right, pulse width 60 \(\mu\)sec and frequency 185 Hz. There was a marked motor improvement with a reduction of the anti-PD medication to 400/100 mg levodopa/carbidopa slow release and pergolide 3mg daily dose.
# Table 1  Neuropsychological and neurological data at baseline and follow-up

<table>
<thead>
<tr>
<th>FU duration in weeks</th>
<th>Baseline 0</th>
<th>FU 1 26</th>
<th>FU 2 52</th>
<th>FU 3 156</th>
<th>FU 4 157</th>
<th>FU 5 163</th>
<th>FU 6 180</th>
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</thead>
<tbody>
<tr>
<td><strong>Stimulation parameters</strong></td>
<td>Contacts, right/left</td>
<td>1-/ 1-</td>
<td>1-/ 1-</td>
<td>1/- 1-2 Off</td>
<td>3/- 2-</td>
<td>3/- 2-</td>
<td></td>
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<tr>
<td></td>
<td>monopolar</td>
<td>1-2</td>
<td>1-2</td>
<td>2-</td>
<td>3-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>amplitude (V) right/left</td>
<td>3.2 /</td>
<td>3.2 /</td>
<td>3.2 /</td>
<td>2.6 /</td>
<td>2.6</td>
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</tr>
<tr>
<td></td>
<td>pulse width in μsec</td>
<td>60</td>
<td>60</td>
<td>60</td>
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<td></td>
<td>Frequency, Hz</td>
<td>185</td>
<td>185</td>
<td>185</td>
<td>130</td>
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<td></td>
<td>UPDRS-III off/on</td>
<td>56/34</td>
<td>21/1</td>
<td>21/13</td>
<td>3/14</td>
<td>22/18</td>
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<td></td>
<td>H &amp; Y off/on</td>
<td>3/3</td>
<td>3/2.5</td>
<td>3/2.5</td>
<td>2.5</td>
<td>3/2</td>
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<td>43</td>
<td>44</td>
<td>37</td>
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<td>33</td>
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<td>COWAT letter fluency (T)</td>
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<td>50</td>
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<td>Stroop color word (T)</td>
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<td>Trailmaking B (T)</td>
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<td><strong>Memory</strong></td>
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<td>37</td>
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<td>AVLT delayed recall(T)</td>
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<td>30</td>
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<td>31</td>
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<td><strong>Decision-making</strong></td>
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<td>56</td>
<td>78</td>
<td>70</td>
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<td></td>
<td>Go/no Go commission errors %</td>
<td>48</td>
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<td>68</td>
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<td><strong>Questionnaires</strong></td>
<td>DEX Questionnaire self/proxy</td>
<td>11/23</td>
<td>10/2</td>
<td>6/22</td>
<td>15/42</td>
<td>11/56</td>
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<td>71</td>
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<td>7</td>
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</tbody>
</table>

**FU** = Follow-up; **LEU** = Levodopa Equivalent Unit; **UPDRS** = Unified Parkinson disease rating scale; **H & Y** = Hoehn and Yahr scale; **COWAT** = Controlled Oral Word Association Test; **PASAT** = Paced Auditory Serial Addition Test; **AVLT** = Auditory Verbal Learning Test; **T** = normally distributed score with mean of 50 and standard deviation of 10, corrected for age and education; **IGT** = Iowa Gambling task; **DEX** = Dysexecutive questionnaire; **PDQL** = Parkinson’s disease Quality of Life; **MADRS** = Montgomery and Asberg Depression Rating Scale.

Significant changes in cognitive test scores (compared to baseline) are printed in bold typeface.
Follow-up
Six months postoperatively, the patient was satisfied with the results of surgery on motor functioning, although he noticed increased emotional lability. His wife reported memory decline, but she found this acceptable considering the large positive effect on motor functioning. Neuropsychological testing with stimulation on showed a significant decline in memory and in selective attention, compared to the preoperative status (table: FU 1).
Twelve months postoperatively, the patient complained of forgetfulness and word finding difficulties. His wife reported a decline in his cognitive functioning. She mentioned slight behaviour changes, namely increased lability, impulsivity and vivid dreams, but denied changes in hallucinations, apathy, irritability or euphoria. Neuropsychological functioning with stimulation on was fairly stable at 12 months compared to the 6 month follow-up, except for an improvement on the Stroop color-word card, which measures selective attention (Table 1: FU 2).

Figure 1 Advantageous minus disadvantageous decks, during five consecutive learning stages on the Iowa gambling task

FU # = follow-up number;
DBS = deep brain stimulation of STN; *data from: Goudriaan et al., 2005
Three years postoperatively, during a follow-up visit at the outpatient clinic for movement disorders, the patient informed the neurologist that he was suffering from pathological gambling with a preference for slot machines, which had started one month after surgery. Despite regular follow-up at the outpatient clinic over the preceding three years, the patient had never before mentioned pathological gambling. According to his wife and children, the patient used to be “as stingy as a Dutchman”. Because of increasing debts, the house had to be sold and his wife wanted a divorce. The patient had been admitted to a psychiatric institution because of a suicide attempt. Two more suicide attempts followed. Subsequently, the patient was admitted to the neurological ward. At this time neuropsychological evaluation was performed again, 156 weeks after STN implantation (FU 3). The patient now disclosed a history of alcohol abuse in his thirties, which he had overcome. His mood was characterised as slightly depressed. Compared to the 12 months follow-up, there was a decline in category fluency, and selected and divided attention. Two decision-making tests were added to the test battery: the Iowa gambling task (IGT) 11, an ecologically valid decision task involving weighing of immediate rewards against long-term losses, and a go/no-go discrimination task to investigate abnormal reward processing (for a description of both tasks as applied to pathological gambling, see Goudriaan et al.12). Parallel versions were used in each test session. Performance on the IGT was affected with 34% disadvantageous choices (see Figure 1 for performance curve), which is normal. Performance on the go/no-go task was at chance level.

One week after switching off the neurostimulation, the patient claimed to feel less urge to gamble. There was no change on the standard neuropsychological tests or on the go/no-go task (Table: FU 4). Performance on the IGT was worse compared to stimulation on, with 56% disadvantageous choices. There was a marked increase in motor impairment, necessitating the neurostimulation to be switched on. Because a chronic stimulation effect inducing the pathological gambling could not be excluded, monopolar stimulation at the most rostral contact point 3 was started. A CT-scan was performed and co-registered with the preoperative MRI using the ImageMerge module of Surgiplan (Elekta) to verify the position of the electrodes. On the left, the deepest contact (0) was 2mm higher than target. On the right, the deepest contact (0) was at target, within the limits of precision of this fusion technique.

One month later with stimulation at contact 3, his wife told that the patient had been buying scratch cards although his allowance had been restricted. The results
on standard neuropsychological testing were stable, but performance on the IGT and on the go/no-go task deteriorated (FU 5). Eventually, pergolide was tapered and stopped. The urge to gamble completely disappeared two days after the last dose. The patient was able to sit in a café with spare money in his pocket ignoring the slot machine. He regained his normal interest in family and hobbies. Emotional lability and vivid dreaming did not improve. There were no changes on standard neuropsychological testing. IGT or go/no-go task performance did not improve (FU 6).

Because of ongoing marital discord and severe financial problems, the patient was referred to social services for counselling.

Discussion

Our patient with PD developed pathological gambling shortly after bilateral STN stimulation despite reducing dopamine agonist medication. Slight cognitive decline and emotional lability were also present. Pathological gambling resolved suddenly after discontinuation of the pergolide, but the stimulation parameters had also been changed to a more rostral, i.e dorsal active contact point.

The association between pathological gambling and the use of dopamine agonists has been previously described.3;13;14 However in these studies, PD patients developed this behaviour disorder after the introduction or the increase of the dopamine agonist and not after reducing the daily dose. Moreover, pathological gambling after DBS STN has been recently reported in 5 out of 39 PD patients despite reduction or discontinuation of the dopamine agonists.14 This suggests the influence of chronic STN stimulation on the development of pathological gambling in PD. Stimulation seems to sensitise the brain to behavioural side effects of dopamine agonists, especially in patients like ours with a history of addictive behaviours. This explanation is in contrast to the one given by a recent study.8 who postulated desensitization of the limbic dopaminergic system after DBS STN and reduction of medication, leading to improvement of pre-existing pathological gambling.

Impaired decision-making has been reported in pathological gambling and in Parkinson’s disease.12;15 In pathological gambling research, diminished self-regulation, a neurocognitive function related to decision-making, has been
Chapter 6

associated with risk for developing gambling problems later in life. In PD, disadvantageous decision-making was highly correlated with executive dysfunction and has been associated with decreased dopaminergic transmission in fronto-striatal loops. In our patient, worse performance on decision-making tasks was seen with stimulation of the most dorsal contact compared to the ventral contact both with and without medication. This implies that bilateral STN stimulation directly influences decision-making. A previous report did not find any effects of bilateral STN stimulation on a similar gambling task. However, that study compared performance between on and off stimulation with stimulation switched off for only one hour.

Impaired decision-making does not seem to be directly related to the pathological gambling, because performance of our patient on the IGT was normal and performance on the go/no-go task did not improve when the pathological gambling disappeared. Perhaps the IGT is not as ecologically valid as it is claimed to be, since it does not predict real-world behaviour.

We conclude that pathological gambling may be induced by bilateral STN stimulation. Because of the known association between dopamine agonists and pathological gambling in PD, discontinuation of the dopamine agonist seems to be the first option of treatment before changing stimulation parameters. Because of the devastating effect of pathological gambling, physicians or neurologists should inform patients and their family about this risk of dopamine agonists and bilateral STN stimulation.
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References
