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RESEARCH PAPER

Iowa gambling task impairment in Parkinson's disease can be normalised by reduction of dopaminergic medication after subthalamic stimulation

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ABSTRACT

Background Impulse control disorders (ICD), including pathological gambling, are common in Parkinson's disease (PD) and tend to improve after subthalamic (STN) stimulation after a marked reduction of dopaminergic medication. In order to investigate the effect of STN stimulation on impulsive decision making, we used the Iowa Gambling task (IGT).

Methods We investigated IGT performance in 20 patients with PD before STN surgery with and without dopaminergic treatment and in 24 age-matched controls. All patients underwent an extensive neuropsychological interview screening for behavioural disorders. Assessment in patients was repeated 3 months after surgery without dopaminergic treatment with and without stimulation.

Results Chronic antiparkinsonian treatment was drastically reduced after surgery (−74%). At baseline, on high chronic dopaminergic treatment 8/20 patients with PD presented with pathological hyperdopaminergic behaviours, which had resolved in 7/8 patients 3 months after surgery on low chronic dopaminergic treatment. Preoperative performance on the IGT was significantly impaired compared to after surgery.

Conclusions Dopaminergic medication likely contributes to the impairment in decision making underlying ICDs. Deep brain stimulation allows drastic reduction of dopaminergic medication and, thus, concomitant remediation of medication-induced impairment in decision making.

INTRODUCTION

Parkinson's disease (PD) can be considered as a neuropsychiatric disorder. Untreated or undertreated patients might suffer from hypodopaminergic symptoms, such as apathy, depression and anxiety. Conversely, patients with PD under dopamine replacement therapy (DRT) can develop a hyperdopaminergic syndrome, including impulse control disorders (ICD) and addictive behaviours.[1] Dysfunctioning of the mesocortical and mesolimbic dopaminergic projections, and of the orbitofrontal cortex is hypothesised to be implicated in the genesis of these disorders.[2 3]

Decision making is a complex process that requires the integrity of ventromedial frontal cortex.[4] Impairment in risky decision making, as assessed by the Iowa Gambling Task (IGT), has been shown in patients either with lesions in the ventromedial frontal cortex, or with orbitofrontal dysfunction in the context of drug and behavioural addictions, such as pathological gambling.[4 5] Several studies found impaired decision making also in PD.[6–14] This impairment is associated with dysfunction of the medial part of the orbitofrontal cortex, and of amygdala as shown by neuroimaging data.[7 11] Patients with PD with pathological gambling have poorer performance at the IGT than patients with PD without pathological gambling,[13] reinforcing the hypothesis that impaired decision making underpins pathological gambling and, more extensively, ICD and other behavioural addictions in PD. Recently, untreated patients with PD have been found to have intact decision making on the IGT.[15 16] Moreover, PD patients with apathy, which is at the opposite spectrum of ICD, performed at the IGT significantly better than patients with PD without apathy.[17] Altogether, these findings suggest that the impairment in decision making is related to dopaminergic replacement therapy rather than to the disease itself. Dopaminergic medication has been suggested to overdose the relatively intact mesocorticolimbic dopaminergic system, and thus, to induce impairment in decision making.[17–19]

Subthalamic nucleus deep brain stimulation (STN DBS) is an established treatment for motor fluctuations in PD and allows a marked reduction in dopaminergic treatment.[20 21] Its role in impulsive-compulsive behaviours in PD has been debated, with some retrospective studies using variable strategies of medication management reporting improvement and others worsening.[22 23] Recently, two prospective studies of STN DBS in PD[3 24] showed a recovery of preoperative behavioural addictions, with a shift from appetitive to apathetic behaviour after surgery.[3] These findings suggest that the improvement in appetitive behaviour seen after STN stimulation is related to the reduction of dopaminergic treatment.

To further examine this hypothesis, we retrospectively analysed performance on the IGT in a cohort of patients with PD, candidates for STN

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DBS, prospectively tested before and after surgery. We expected an improvement of performance after surgery. We also investigated the acute effects of both dopaminergic medication and STN DBS on the IGT performance.

METHODS

Subjects

Twenty patients with PD undergoing surgery for STN DBS at the University Hospital of Grenoble between 2001 and 2002 were prospectively included in this study. Inclusion criteria were a diagnosis of idiopathic PD suffering from disabling motor complications of levodopa therapy, absence of dementia, ongoing psychosis or severe depression, or surgical contraindications. Twenty-four age-matched healthy controls were recruited into the study.

All subjects gave informed consent to participate in the study, which was approved by the Grenoble University Hospital ethics committee.

Study design

Patients with PD were tested preoperatively and 3 months after surgery. Before surgery, patients were assessed under the off-medication condition (after a 12 h overnight withdrawal of all antiparkinsonian treatments) and under the on-medication condition (during the 'on-phase' after the intake of their usual antiparkinsonian drugs). Patients were assessed 3 months after surgery under the off-medication condition without and with stimulation. Postoperatively, the off-stimulation test began 20 min after turning off the stimulator. Both before and after surgery, tests were performed on two different days (one for the 'on' and the other for the 'off' condition) and the order of conditions was counterbalanced between patients. Controls were tested once.

Additionally, preoperative and postoperative levodopa equivalent daily doses were calculated as described elsewhere.[20] Patients also underwent neuropsychological evaluation preoperatively and postoperatively. Before surgery, the neuropsychological evaluation included the Mattis Dementia Rating Scale, to rule out dementia. A careful interview to detect any behavioural disorder as part of the disease, or as side effect of medication, was carried out by a neuropsychologist trained in PD, in routine presurgical and each postoperative follow-up assessment. The full details of these interviews are available as extensive written reports. This systematic interview has been used by our team as a routine procedure in the management of surgical patients.[3] For the purpose of the present study, diagnoses of hyperdopaminergic behavioural disorders were retrospectively made based on the written reports of these behavioural assessments.

Experimental procedure

To study decision making we used a computerised version of the IGT, which is a risk-taking task in which subjects have to balance immediate rewards with delayed losses.[25] The IGT requires 100 card selections from four decks of cards identical in appearance. Subjects are asked to maximise their profit starting from a loan of play money, selecting one card at a time from any deck. The goal of the game is to win as much money as possible by drawing cards from the four decks. After each draw, participants either win or lose money, and the cumulative sum of money is displayed on the screen after each draw. Two decks (A and B) are disadvantageous because alternation of high gains and high losses lead to an overall negative balance. The two other decks, C and D, with lower losses and lower gains are advantageous, because gains, although very low, are more frequent than losses, leading to an overall positive balance. Participants are not informed about the differences between decks. They need to (implicitly or non-implicitly) learn how to obtain overall benefit by trial and error. The test stops automatically after drawing a total of 100 cards.

Scores are calculated as the difference between the number of cards chosen from advantageous versus disadvantageous decks. One can compute an overall score and five serial scores for each consecutive series of 20 cards, in order to examine the evolution of performance over the test and, hence, the learning of the task.

Data analysis

Descriptive statistics were computed for the IGT total scores. Values are reported as means±SDs. The influence of surgery and treatment on the IGT total scores were first studied in the patients using a two-surgery (pre, post)-by-two condition (off, on) repeated measures analysis of variance. The total scores of patients were compared to those of controls in four independent analyses (presurgery off-medication, presurgery on-medication, postsurgery off-stimulation, postsurgery on-stimulation).

To examine the evolution of the patients' performance along the task we performed a two-surgery (pre, post)-by-two condition (off, on)-by-five (Series) repeated measures analysis of variance. The data were analysed using the software Statistica (Statsoft, France). A $p<0.05$ was considered significant.

RESULTS

Characteristics of patients and control participants are shown in table 1. Only the score on Mattis Dementia Rating Scale

Table 1 Characteristics of parkinsonian patients and controls before and 3 months after surgery (mean (SD))

	Before surgery	Three months after surgery	Controls
Number	20	20	24
Gender (female/male)	9/11	9/11	15/9
Age (years)	53.2 (6.6)	id.	54.9 (7.6)
Education (years)	13.1 (5.0)	id.	12.9 (3.8)
Mattis Dementia Rating Scale	137.6 (4.2)	id.	140.7 (2.4)*
Duration of the disease (years)	10.3 (3.8)	id.	–
Levodopa equivalent daily doses (mg)	1459 (657)	377 (403)	–
Levodopa daily doses (mg)	1003 (464)	219 (412)	
Dopamine agonist daily doses (mg)	458 (422)	158 (155)	
UPDRS III scores			
OFF L-dopa	42.6 (12.5)	–	–
ON L-dopa	12.3 (6.1)	–	–
OFF L-dopa/OFF STN stimulation	–	41.7 (14.4)	–
OFF L-dopa/ON STN stimulation	–	14.3 (8.8)	–
Parameters of STN monopolar stimulation (for both sides)			
Voltage (V)	–	2.8 (0.5)	–
Frequency (Hz)	–	132.4 (10.9)	–
Pulse width (μs)	–	60 (0)	–

*The patients' score on Mattis Dementia Rating Scale was significantly lower than those of the controls ($F(1,42)=8.12$, $p=0.007$).
STN, subthalamic nucleus.

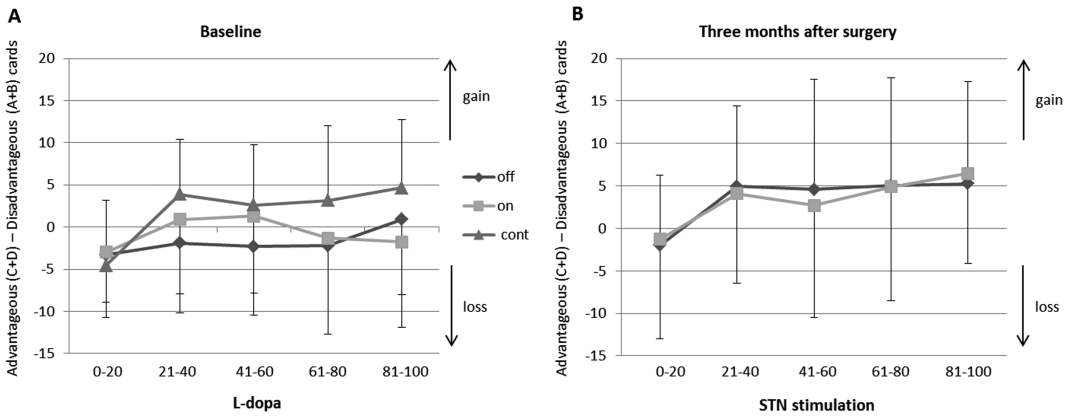

Figure 1 Iowa Gambling Task. Differences between the number of cards chosen in the advantageous desks (C+D) and the number of cards chosen in the disadvantageous decks (A+B), for the five series of 20 cards. (A) Preoperative evaluation ON and OFF L-dopa compared to controls in a population with high chronic dopaminergic replacement treatment (mean levodopa equivalent daily doses 1420 mg). (B) Evaluation 3 months after surgery, without medication ON and OFF subthalamic nucleus (STN) stimulation. Low chronic dopaminergic replacement treatment (mean levodopa equivalent daily doses 320 mg).

significantly differed between patients and controls, the patients' score being lower than those of the controls ($F(1,42)=8.12$, $p=0.007$). At 3 months after surgery, the daily dose of levodopa equivalents was significantly decreased by about 74% ($p<0.0001$). Preoperatively, eight patients presented with hyperdopaminergic disorders: pathological gambling (2), hypersexuality (4), compulsive eating (2), compulsive shopping (2), kleptomania (1), nocturnal hyperactivity (2). Three patients had ICD in more than one domain (eg, hypersexuality+kleptomania). Three months after surgery, hyperdopaminergic behaviour had disappeared in all patients, except in a patient with a 20-year history of pathological gambling, who continued to gamble, despite the drastic reduction of dopaminergic treatment and the interruption of dopamine agonist treatment.

IGT total scores

IGT total scores were significantly improved 3 months after surgery compared to before surgery (preoperative: −7.03 ±35.75; postoperative: 17.64±47.7; $F(1,18)=4.670$, $p=0.04$), but they were not influenced by condition (preoperative off-medication score: −10.2±38.3, preoperative on-medication score: −3.9±34.7, postoperative off-stimulation score: 17.9 ±46.5, postoperative on-stimulation score: 17.4±51.2).

Analyses further revealed that the patients' performance was significantly worse than that of controls (controls scores: 9.7 ±23.7) only before surgery under the off-medication condition ($F(1,42)=4.4361$, $p=0.04$).

IGT series' scores

The differences between the number of cards chosen from the advantageous decks and the number of cards chosen from the disadvantageous decks for all conditions are shown in figure 1.

The analysis of variance (ANOVA) revealed a main effect of series ($F(4,72)=5.97$, $p=0.0003$). Additionally, the effect of surgery was close to significance ($F(1,18)=4.26$, $p=0.054$), as were the interactions between series and surgery ($F(4,72)=2.41$, $p=0.057$), and between series, surgery and condition ($F(4,72)=2.44$, $p=0.054$). We further examined these effects based on our a priori hypothesis. Analyses showed that there was no difference between the series preoperatively whether off or on medication. By contrast, 3 months after surgery, the effect of series was significant ($p<0.05$). The score improved after the first series, so that the score of the first series was statistically different from the scores of the four following series. Additionally, the scores of the last two series 3 months after surgery were significantly greater (ie, improved) than any score before surgery ($p<0.05$).

Further analysis did not show any difference in the IGT performance between patients with and without hyperdopaminergic behaviour. Regression analysis showed a positive correlation between the postoperative improvement of the IGT scores (calculated as the difference between postoperative and preoperative scores) and the postoperative reduction in levodopa equivalent daily doses ($F(1,16)=5.59$; $r=0.51$; $R^2=0.26$; $p=0.031$).

DISCUSSION

Overall, the results showed that the performance of patients with PD on the IGT is improved 3 months after STN DBS, whatever the condition (off-/on-medication or off-/on-stimulation). Additionally, whereas before surgery patients' performance did not improve across the task, after 3 months of chronic STN DBS allowing for 74% reduction of dopaminergic treatment, their performance profile evidenced clear learning from the second series on. Dopaminergic medication or STN DBS did not have an acute effect on the IGT performance. Yet when compared with controls, patients' performance was significantly different before surgery only in the off-medication condition. After surgery, performance of patients was similar to that of controls.

Previous studies had shown impaired decision making in PD, which appears induced by dopaminergic treatment, since it is preserved in both de novo and apathetic patients with PD.[15 17] In this study, 3 months after surgery, allowing for drastic decrease of chronic dopaminergic treatment (−74%), decision making, as assessed by the IGT, had normalised. These data support the hypothesis that impaired impulsive decision making observed in PD could be related to chronic dopaminergic treatment.

In PD, dopamine depletion mainly occurs in the motor dorsal striatum, especially in early stages of disease, whereas it is relatively preserved in the ventral striatum.[26] Therefore, antiparkinsonian medications, assumed to compensate for dopamine depletion of the motor dorsal striatum, might 'over-dose' the limbic ventral striatum.[18 19 27] In our study, patients under high chronic dopaminergic treatment, who typically present with hyperdopaminergic behaviours,[3] performed more poorly and

tended to present with an impaired decision making. This impairment disappeared after chronic reduction of dopaminergic medication allowed by subthalamic stimulation, as reflected by a reversal both in hyperdopaminergic behaviours and a better performance in the IGT.

Patients with PD under dopaminergic treatment perform the IGT similarly to other types of patients with impulsive behaviours, for example, with drug addictions, or damage to the ventromedial prefrontal cortex (the medial part of the orbitofrontal cortex) lesion.[5 28 29] All these patients show a 'myopia for the future', being insensitive to the delayed consequences of their decision. Decision making is a complex process that requires the integration of different neural substrates, including the orbitofrontal cortex and the amygdala.[4 11 30 31] Dysfunction of the orbitofrontal cortex has been detected in patients with addiction,[32] with pathological gambling,[32] and in patients with PD with pathological gambling.[33–35]

In a previous study, comparing reward sensitivity under medical treatment and under STN stimulation, no differences were found in the total IGT between treatment groups.[36] However, analysis of learning curves was not performed. It has been already shown that patients with PD on dopaminergic medication tend to progressively choose disadvantageous cards over the task, contrarily to healthy subjects and untreated patients with PD, who tend to make more advantageous choices along the task.[10] Accordingly, in our study, patients with PD performed worse at the IGT under chronic high dopaminergic treatment, while this altered pattern was restored after surgery under chronic low dopaminergic medication independently of the stimulation state. This result also points at the role of the decrease in medication rather than an effect mediated by stimulation. The positive correlation between the postoperative IGT improvement and the reduction of dopaminergic medication supports this hypothesis. The finding that the IGT performance before surgery was not different between the off-medication and the on-medication conditions is not surprising. A previous study had already found no change in the IGT scores between the acute on-medication or off-medication conditions.[6] Dopaminergic medication has a long-duration effect.[37] Motor and non-motor complications of dopaminergic medications, such as dyskinesia and behavioural issues, are mediated by a chronic sensitisation, related to changes in synaptic plasticity.[2 38] These changes underlying behavioural issues, such as pathological gambling, obviously persist after an overnight withdrawal of medication. Hence, in the preoperative assessment, it is not surprising that there was no difference between the on and the off condition. Conversely, a marked chronic reduction of dopaminergic medication, allowed by chronic STN DBS, has been shown to induce a desensitisation of motor and psychotropic effects of dopaminergic treatment.[39 40] A too drastic postoperative medication reduction, and the non-motor desensitisation, might be associated with the occurrence of a hypodopaminergic syndrome, including apathy, anxiety and depression.[41 42]

The main drawback of this study is the fact that controls were tested only once, while patients were assessed four times. Therefore, a test-retest effect cannot be ruled out. However, the results of a recent study assessing IGT performance in patients with PD before and 2–4 weeks after STN stimulation do not support the hypothesis of a test-retest effect.[14] In this study, patients with PD undergoing STN stimulation were assessed before and after surgery on the same day with and without stimulation. A control group of non-operated patients with PD was included and assessed three times at the same intervals. In the control group, IGT scores did not improve with sessions, suggesting no test-retest effect. Contrary to our study, poorer performance in the last block with stimulation was found. This contradictory result might be explained by (1) the short delay after surgery, and (2) the less consistent reduction of dopaminergic therapy (−21%) compared to our study (−74%). Chronic dopaminergic reduction and its duration are key factors, which may be necessary to reverse hypersensitisation of mesocortical and mesolimbic systems.[39]

Only two of our patients had pathological gambling at baseline, but 8/20 had some type of hyperdopaminergic behaviours on retrospective evaluation. Although this study did not focus on behavioural disorders, we found hyperdopaminergic behaviours had disappeared in all patients but one after surgery. These observations are in line with the prevalence of hyperdopaminergic behaviours, which can typically be found in a PD population of surgical candidates with high-dose dopaminergic treatment and motor complications. In a prospective study with a systematic behavioural evaluation using the Ardouin scale, hyperdopaminergic behavioural disorders have been detected in half of the patients, typically presenting as behavioural addictions, which have common pathological mechanisms with ICD.[3] This study showed a reduction of all hyperdopaminergic behaviour including pathological gambling and other ICD, as well as behavioural addictions after STN stimulation in patients with marked reduction of dopaminergic treatment.[3] Chronic reduction of DRT along with the replacement of a pulsatile dopaminergic therapy with the continuous STN stimulation could account for a reversal of ventral striatum hypersensitivity and putative abnormal decision-making process.

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REFERENCES

1 Voon V, Sohr M, Lang AE, *et al*. Impulse control disorders in Parkinson disease: a multicenter case—control study. *Ann Neurol* 2011;69:986–96.
2 Evans AH, Pavese N, Lawrence AD, *et al*. Compulsive drug use linked to sensitized ventral striatal dopamine transmission. *Ann Neurol* 2006;59:852–8.
3 Lhommee E, Klinger H, Thobois S, *et al*. Subthalamic stimulation in Parkinson's disease: restoring the balance of motivated behaviours. *Brain* 2012;135:1463–77.
4 Bechara A. Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. *Nat Neurosci* 2005;8:1458–63.
5 Cavedini P, Riboldi G, Keller R, *et al*. Frontal lobe dysfunction in pathological gambling patients. *Biol Psychiatry* 2002;51:334–41.
6 Czernecki V, Pillon B, Houeto JL, *et al*. Motivation, reward, and Parkinson's disease: influence of dopatherapy. *Neuropsychologia* 2002;40:2257–67.
7 Thiel A, Hilker R, Kessler J, *et al*. Activation of basal ganglia loops in idiopathic Parkinson's disease: a PET study. *J Neural Transm* 2003;110:1289–301.
8 Mimura M, Oeda R, Kawamura M. Impaired decision-making in Parkinson's disease. *Parkinsonism Relat Disord* 2006;12:169–75.
9 Kobayakawa M, Koyama S, Mimura M, *et al*. Decision making in Parkinson's disease: analysis of behavioral and physiological patterns in the Iowa gambling task. *Mov Disord* 2008;23:547–52.
10 Pagonabarraga J, Garcia-Sanchez C, Llebaria G, *et al*. Controlled study of decision-making and cognitive impairment in Parkinson's disease. *Mov Disord* 2007;22:1430–5.
11 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;30:1162–71.
12 Delazer M, Sinz H, Zamarian L, *et al*. Decision making under risk and under ambiguity in Parkinson's disease. *Neuropsychologia* 2009;47:1901–8.
13 Rossi M, Gerschcovich ER, de Achaval D, *et al*. Decision-making in Parkinson's disease patients with and without pathological gambling. *Eur J Neurol* 2010;17:97–102.
14 Oyama G, Shimo Y, Natori S, *et al*. Acute effects of bilateral subthalamic stimulation on decision-making in Parkinson's disease. *Parkinsonism Relat Disord* 2011;17:189–93.
15 Poletti M, Frosini D, Lucetti C, *et al*. Decision making in de novo Parkinson's disease. *Mov Disord* 2010;25:1432–6.
16 Poletti M, Frosini D, Lucetti C, *et al*. Iowa Gambling Task in de novo Parkinson's disease: a comparison between good and poor performers. *Mov Disord* 2012;27:331–2.
17 Martinez-Horta S, Pagonabarraga J, Fernandez de Bobadilla R, *et al*. Apathy in Parkinson's disease: more than just executive dysfunction. *J Int Neuropsychol Soc* 2013;19:571–82.
18 Cools R, Altamirano L, D'Esposito M. Reversal learning in Parkinson's disease depends on medication status and outcome valence. *Neuropsychologia* 2006;44:1663–73.
19 Cools R, Barker RA, Sahakian BJ, *et al*. Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cereb Cortex* 2001;11:1136–43.
20 Krack P, Batir A, Van Blercom N, *et al*. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* 2003;349:1925–34.
21 Castrioto A, Lozano AM, Poon YY, *et al*. Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation. *Arch Neurol* 2011;68:1550–6.
22 Lim SY, O'Sullivan SS, Kotschet K, *et al*. Dopamine dysregulation syndrome, impulse control disorders and punding after deep brain stimulation surgery for Parkinson's disease. *J Clin Neurosci* 2009;16:1148–52.
23 Moum SJ, Price CC, Limotai N, *et al*. Effects of STN and GPi deep brain stimulation on impulse control disorders and dopamine dysregulation syndrome. *PLoS One* 2012;7:e29768.
24 Eusebio A, Witjas T, Cohen J, *et al*. Subthalamic nucleus stimulation and compulsive use of dopaminergic medication in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2013;84:868–74.
25 Bechara A, Damasio AR, Damasio H, *et al*. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 1994;50:7–15.
26 Kish SJ, Shannak K, Hornykiewicz O. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. *N Engl J Med* 1988;318:876–80.
27 Swainson R, Rogers RD, Sahakian BJ, *et al*. Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. *Neuropsychologia* 2000;38:596–612.
28 Dagher A, Robbins TW. Personality, addiction, dopamine: insights from Parkinson's disease. *Neuron* 2009;61:502–10.
29 Cavedini P, Riboldi G, D'Annucci A, *et al*. Decision-making heterogeneity in obsessive-compulsive disorder: ventromedial prefrontal cortex function predicts different treatment outcomes. *Neuropsychologia* 2002;40:205–11.
30 Clark L, Bechara A, Damasio H, *et al*. Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. *Brain* 2008;131:1311–22.
31 Zeeb FD, Winstanley CA. Lesions of the basolateral amygdala and orbitofrontal cortex differentially affect acquisition and performance of a rodent gambling task. *J Neurosci* 2011;31:2197–204.
32 Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology* 2010;35:217–38.
33 Cilia R, Siri C, Marotta G, *et al*. Functional abnormalities underlying pathological gambling in Parkinson disease. *Arch Neurol* 2008;65:1604–11.
34 van Eimeren T, Ballanger B, Pellecchia G, *et al*. Dopamine agonists diminish value sensitivity of the orbitofrontal cortex: a trigger for pathological gambling in Parkinson's disease? *Neuropsychopharmacology* 2009;34:2758–66.
35 van Eimeren T, Pellecchia G, Cilia R, *et al*. Drug-induced deactivation of inhibitory networks predicts pathological gambling in PD. *Neurology* 2010;75:1711–16.
36 Czernecki V, Pillon B, Houeto JL, *et al*. Does bilateral stimulation of the subthalamic nucleus aggravate apathy in Parkinson's disease? *J Neurol Neurosurg Psychiatry* 2005;76:775–9.
37 Fahn S, Oakes D, Shoulson I, *et al*. Levodopa and the progression of Parkinson's disease. *N Engl J Med* 2004;351:2498–508.
38 Calabresi P, Di Filippo M, Ghiglieri V, *et al*. Levodopa-induced dyskinesias in patients with Parkinson's disease: filling the bench-to-bedside gap. *Lancet Neurol* 2010;9:1106–17.
39 Castrioto A, Kistner A, Klinger H, *et al*. Psychostimulant effect of levodopa: reversing sensitisation is possible. *J Neurol Neurosurg Psychiatry* 2013;84:18–22.
40 Bejjani BP, Arnulf I, Demeret S, *et al*. Levodopa-induced dyskinesias in Parkinson's disease: is sensitization reversible? *Ann Neurol* 2000;47:655–8.
41 Thobois S, Ardouin C, Lhommee E, *et al*. Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation. *Brain* 2010;133:1111–27.
42 Thobois S, Lhommee E, Klinger H, *et al*. Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with piribedil. *Brain* 2013;136:1568–77.

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