European Journal of Neurology 2010, 17: 97–102 doi:10.1111/j.1468-1331.2009.02792.x

Decision-making in Parkinson's disease patients with and without pathological gambling

M. Rossi[a], E. R. Gerschcovich[b], D. de Achaval[b], S. Perez-Lloret[a], D. Cerquetti[a], A. Cammarota[a], M. Inés Nouzeilles[a], R. Fahrer[c], M. Merello[a] and R. Leiguarda[b]

[a]*Movement Disorders Section;* [b]*Cognitive Neurology Section; and* [c]*Psychiatry Section, Raul Carrea Institute for Neurological Research, FLENI, Buenos Aires, Argentina*

Keywords:
decision-making, impulse control disorders, Iowa gambling task, movement disorders, Parkinson's disease, pathological gambling, social behavior, ventromedial prefrontal cortex

Received 12 February 2009
Accepted 25 June 2009

Background and purpose: Pathological gambling (PG) in Parkinson's disease (PD) is a frequent impulse control disorder associated mainly with dopamine replacement therapy. As impairments in decision-making were described independently in PG and PD, the objective of this study was to assess decision-making processes in PD patients with and without PG.

Methods: Seven PD patients with PG and 13 age, sex, education and disease severity matched PD patients without gambling behavior were enrolled in the study. All patients were assessed with a comprehensive neuropsychiatric and cognitive evaluation, including tasks used to assess decision-making abilities under ambiguous or risky situations, like the Iowa Gambling Task (IGT), the Game of Dice Task and the Investment Task.

Results: Compared to PD patients without gambling behavior, those with PG obtained poorer scores in the IGT and in a rating scale of social behavior, but not in other decision-making and cognitive tasks.

Conclusions: Low performance in decision-making under ambiguity and abnormal social behavior distinguished PD patients with PG from those without this disorder. Dopamine replacement therapy may induce dysfunction of the ventromedial prefrontal cortex and amygdala-ventral striatum system, thus increasing the risk for developing PG.

Introduction

Pathological gambling (PG) is classified as an impulse control disorder and defined as a persistent and recurrent maladaptive gambling behavior that disrupts personal, family, or vocational pursuit [1]. Prevalence estimations in Parkinson's disease (PD) range from 3.4 to 8% [2,3]. It can occur in isolation or associated with other impulse control disorders, such as compulsive shopping, hypersexuality, and binge eating. Factors predisposing to PG are mainly male, sex, early PD onset, dopamine agonists, and psychiatric comorbidity [4]. Planning impairments and high novelty seeking traits were found to distinguish PD patients with PG from those not exhibiting this disorder [5]. However, underlying impairments of some aspects of decision-making might also be related to PG in PD.

Correspondence: Ramón Leiguarda, MD, Cognitive Neurology Section (FLENI), Montañeses 2325 (C1428AQK) Cdad, Aut, Buenos Aires, Argentina (tel.: +5411 5777-3200; fax: +5411 5777-3209; e-mail: rleiguarda@fleni.org.ar).

Decision-making connotes the process of choosing, under ambiguous or risky situations, the optimal selection in terms of rewarding or punishing outcomes between several alternative courses of action [6]. Decision-making impairments have been principally found in patients with focal lesions in the ventromedial prefrontal cortex (VMPFC), insula, amygdala, striatum, and parietal cortex [7,8] and also in many conditions, such as PG, PD, Huntington disease and drug addiction [6,9,10]. As decision-making processes were evaluated independently in PG and PD, the aim of this study was to investigate if PD patients exhibiting PG have poorer decision-making abilities than those patients without gambling behavior.

Methods

Study sample

Parkinson's disease patients attending at the Movement Disorders Section from a tertiary out-patient clinic were routinely inquired about any type of gambling

behavior. Positive answers from the patient or their relatives were followed by an evaluation for PG and other impulse control disorders. These evaluations included the DSM-IV-TR criteria for PG [1], the South Oaks Gambling Screen [11] and the Minnesota Impulsive Disorders Interview [12]. To be included in this study, patients had to fulfill the United Kingdom Parkinson's Disease Society Brain Bank criteria [13], show positive response to acute levodopa challenge [14] and a PG onset after the initiation of dopamine replacement therapy (DRT). Exclusion criteria included secondary parkinsonism, a Mini-Mental State Examination score < 24 points and mania symptoms, as maniac patients may show decision-making impairments [15]. A group of age, sex, education, and disease severity matched PD patients without gambling behavior served as control group. Controls had to fulfill all specified criteria except for those concerning PG. The protocol was approved by the local ethics committee and all subjects signed an informed consent.

PD evaluation

Motor status and disease severity were evaluated with the Unified Parkinson's Disease Rating Scale and with the Hoehn & Yahr scale. Patients exhibiting motor fluctuations were assessed during the 'on' state. Medication type and daily dosage were recorded and used to calculate levodopa equivalent daily dose applying the usual formula [16]. Compulsive dopaminergic medication use was examined according to Giovannoni *et al.* [17].

Neuropsychiatric and cognitive assessment

All patients were assessed with a comprehensive neuropsychiatric and cognitive evaluation including the Addenbrooke's Cognitive Examination, the Frontal Assessment Battery, the Montgomery-Asberg Depression Rating Scale and the Neuropsychiatric Inventory. Executive functions were evaluated with the modified version of the Wisconsin Card Sorting Test and the Stroop Color and Word Test. Sensation seeking was assessed with the reduced version of the Zuckerman–Kuhlman Personality Questionnaire [18] and response inhibition was evaluated with an adapted version of the Go/No-Go visual discrimination task [19]. Social cognition was examined with two tests: the Reading the Mind in the Eyes Test [20], which was conducted after excluding visual discrimination deficits [21] and the shortened version of the Social Behavior Questionnaire (SBQ) [22], which comprises the 12 questions that were found in a previous study [22] to be sensitive to VMPFC lesions. The SBQ was completed by patient's first-degree relatives. To investigate reversal and extinction learning, an adapted version of the stimulus reward learning, reversal and extinction task (SRL-RET) was employed [23].

Decision-making abilities were evaluated with the Iowa Gambling Task (IGT) [7], the Game of Dice Task (GDT) [24] and the Investment Task [25]. The IGT simulates real-life decision-making under ambiguity; this means the outcome probabilities are unknown. The GDT evaluates decision-making under risk, because the outcome probabilities are known or calculable. The Investment Task assesses if, under certain circumstances, subjects predisposed to taking risks make more advantageous decisions than subjects with risk aversion. These tasks were administered in a counterbalanced order. The complete evaluation was performed in 3–4 h, which varied depending on resting periods provided until fluctuating patient's motor status was 'on'.

Statistical analysis

Categorical data were compared using Chi-square test and continuous variables by Mann–Whitney *U*-test. IGT performance was analyzed as conventionally by dividing the task into five blocks of 20 consecutive card selections. An ANOVA with repeated measures was performed using 'group' as between factor, 'block' as within factor and the net score [(advantageous decks) – (disadvantageous decks)] as the dependent measure. GDT net score was calculated by subtracting number of risky selections from number of safety selections. Investment Task net score was defined as the mean number of rounds invested. Alfa error was set at 0.05. SPSS software version 13.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Demographic and clinical details of PD patients with and without PG

Seven consecutive PD patients satisfying DSM-IV-TR criteria for PG and 13 age, sex, education, and disease severity matched PD patients without gambling behavior participated in this study. All patients lacked of gambling history before developing PD, except for one patient who reported playing poker with friends for more than 30 years. However, his gambling behavior exacerbated after starting with DRT and included roulette and horse racing betting (Table 1). All patients had active PG; two of them had a reduction in their DRT before assessment, whereas five were switched to another dopamine agonist.

Table 1 Demographic and clinical features of PD patients with and without PG

	PD without PG (n = 13)	PD with PG (n = 7)
Demographic features		
Age (years)	65.1 (3.8)	61.4 (6.9)
Male (%)	10 (77%)	6 (86%)
Education (years)	11.9 (5.5)	13.8 (4.1)
Parkinson's disease features		
Age of PD diagnosis (years)	58.3 (6.9)	52.0 (5.6)*
UPDRS part 2	8.8 (4.7)	10.7 (5.7)
UPDRS part 3	14.7 (6.7)	17.0 (9.1)
Hoehn & Yahr	2.0 (0.7)	2.2 (0.7)
Motor fluctuations	8 (61%)	4 (57%)
LDED	698.2 (474.6)	935.9 (548.6)
LDED (agonists)	223.9 (136.8)	201.9 (78.0)
Anti-parkinsonian medication		
Combined levodopa/dopamine agonist therapy	9	6
Agonist alone	4	1
Compulsive dopaminergic medication use	0	2
Neuropsychiatric evaluation		
NPI	8.1 (5.9)	10.0 (7.1)
MADRS	14.1 (7.9)[a]	17.1 (6.5)[a]
Other ICD than PG		
Compulsive shopping	0	2
Hypersexuality	0	2
Preferred type of gambling		
Slot machines	0	6
Roulette	0	1
Horse racing betting	0	1

Values are mean (SD).

PD, Parkinson's disease; PG, pathological gambling; UPDRS, unified Parkinson's disease rating scale; LDED, levodopa equivalent daily dose; NPI, neuropsychiatric inventory; MADRS, montgomery-asberg depression rating scale; ICD, impulse control disorder.

*P < 0.05 PD without PG vs. PG with PG.

[a]Indicates impairment in relation to standardized scores derived from normal controls. Categorical data was analyzed by Chi-square test and continuous variables by Mann–Whitney U-test.

Decision-making

Decision-making analysis showed that patients exhibiting PG obtained a lower net score in the IGT than to those who were not gamblers (−20.3 ± 12.4 vs. 10.0 ± 16.7, P < 0.001). This score was under zero in patients with PG, indicating they selected disadvantageous alternatives more frequently than the advantageous, although this preference reached significance only for deck B (P < 0.001). A 2 (group) × 5 (block) ANOVA on the net scores revealed a significant main effect of group [F(1,18) = 17.6, P = 0.001], but no main effect of block [F(1,18) = 0.01, P = 0.9] nor interaction of group with block [F(1,18) = 2.5, P = 0.1] was found. However, single comparisons (2-tailed t-test for equality of means) between blocks revealed no differences for block 1 (t = 0.8, df = 12.9, P = 0.5), but achieved significance for block 2 (t = 2.8, df = 12.3, P = 0.015), block 3 (t = 2.6, df = 15.5, P = 0.020), block 4 (t = 3.6, df = 18.0, P = 0.002) and block 5 (t = 2.6, df = 8.4, P = 0.032), indicating that both groups developed opposed strategies throughout the task (Fig. 1). No differences between groups were found for the Investment Task (P = 0.3) and the GDT (P = 0.4).

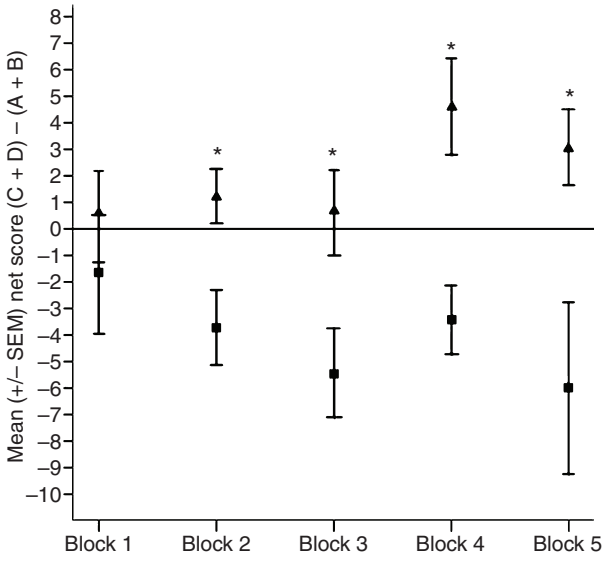

Figure 1 Mean (±SEM) Iowa Gambling Task net score from advantageous decks (C–D) minus disadvantageous decks (A–B) over the course of five blocks (each block represents 20 consecutive card selections) for PD patients with (■) and without PG (▲). *P < 0.05.

Performance on other cognitive functions

Patients with PG obtained a worse score only in a rating scale of social behavior, but there were no differences in the remaining cognitive tests, although many of them, such as the Wisconsin Card Sorting Test, the Stroop Color and Word Test, the SRLRET and the Reading the Mind in the Eyes Test were abnormal in both groups of PD patients according to standardized scores derived from normal controls (Table 2).

Discussion

In this study we examined different aspects of decision-making, as well as many other cognitive functions and neuropsychiatric features in PD patients with and without PG. Compared to PD patients without gambling behavior, those exhibiting PG obtained poorer scores in a rating scale of social behavior and in the IGT, but not in other decision-making tasks. Like

Table 2 Cognitive features of PD patients with and without PG

	PD without PG (n = 13)	PD with PG (n = 7)
Addenbrooke's cognitive examination	86.5 (10.0)	92.7 (3.0)
Mini-mental state examination	28.5 (2.0)	29.3 (0.7)
Frontal assessment battery	15.2 (3.0)	16.3 (1.7)
Executive functions		
Wisconsin card sorting test		
Categories achieved	4.3 (2.2)[a]	4.0 (2.6)[a]
Perseverations	5.1 (5.3)	4.8 (5.7)
Errors	6.5 (6.2)	8.3 (7.8)
Stroop color and word test		
Word score	92.8 (15.0)[a]	89.2 (13.3)[a]
Color score	63.4 (13.4)[a]	58.8 (10.5)[a]
Word-color score	38.5 (10.0)[a]	42.5 (2.9)
Interference	−1.1 (8.4)[a]	3.2 (2.6)
Social cognition		
Social behavior questionnaire	4.1 (0.6)	3.1 (0.5)*,[a]
Reading the mind in the eyes test	20.6 (7.1)[a]	21.3 (4.5)[a]
Sensation seeking	22.3 (6.9)	20.5 (7.5)
Response inhibition – Go/No-Go		
Omission errors	0.5 (0.9)	0.0 (0.0)
Commission errors	1.6 (2.1)	0.6 (0.8)
Reversal and extinction learning – SRLRET		
Reversal phase		
Reversals in last 30 trials	0.9 (0.9)[a]	1.0 (0.8)[a]
Omission errors	4.5 (4.1)	3.7 (2.7)
Commission errors	5.1 (4.5)	4.6 (4.5)
Total errors	9.6 (7.9)	8.3 (6.9)
Extinction phase		
Perseverative errors	5.6 (2.8)[a]	6.7 (3.2)[a]
Attribution errors	4.0 (3.5)[a]	4.0 (2.3)[a]
Total errors	9.6 (4.3)[a]	10.7 (5.0)[a]

Values are mean (SD).

PD, Parkinson's disease; PG, pathological gambling; SRLRET, stimulus reward learning, reversal and extinction task.

*$P < 0.01$, PD without PG vs. PG with PG.

[a]Indicates impairment in relation to standardized scores derived from normal controls. Data was analyzed by Mann–Whitney U-test.

previous studies [2,3], our sample of PD patients with PG were predominantly male, developed PD at a younger age than those without PG and exhibited, some of them, other impulse control disorders.

As mentioned above, patients with PG were rated by their family members as having worse social behavior. Particularly, they were found less co-operative with others, having difficulty in making or keeping close relationships and doing most of what they want without caring about other's opinions, which resembles the findings in subjects with frontal lesions [22].

Previous work found that PD patients without PG and pathological gamblers without PD were impaired on both IGT and GDT, relative to their healthy counterparts [9,10,24,26]. In the current study we observed that PD patients with and without PG were not different from each other in the GDT and the Investment Task, but those exhibiting PG achieved a poorer performance in the IGT than those who were not gamblers. Patients with PG developed a worst strategy, as they selected disadvantageous alternatives more frequently than the advantageous and did not shift to these later ones. In particular, they chose most frequently the disadvantageous deck B, which is associated with higher immediate gains than the other decks, but with a negative long-term outcome, regardless of the odds of winning. This disadvantageous strategy may be explained by a high-value and frequency gain preference amongst patients with PG, consistent with a failure to adequately process aversive outcomes and a hypersensitivity to reward [27,28].

However, this behavior seen in the IGT, which assess decision-making abilities under ambiguity, was not observed in tasks used to evaluate decision-making under risk, like the GDT and the Investment Task. In the GDT, PD patients with PG chose high-value risky options with similar frequency than the low-value safety alternatives. Likewise, in the Investment Task, PD patients with PG developed a conservative strategy, which resembles the findings in healthy subjects [25]. Therefore, the failure to adequately process aversive outcomes and the hypersensitivity to reward seen in PD patients with PG whilst performing the IGT, may apply only for decisions under ambiguous situations, in which the outcome probabilities are unknown, but not for decisions under risk, where outcome probabilities are known or calculable. As will be mentioned afterwards, the different behavior seen in these three kinds of decision-making tasks may result of the unequal involvement of the corticostriatal circuits in PD, as well as the different effects of DRT on cognitive functions.

Functional imaging studies in healthy subjects and studies in patients with focal lesions have allowed gaining insight into the neuronal circuits supporting different aspects of decision-making [28,29]. The circuit involved in affective decision-making is mainly composed by VMPFC, amygdala, striatum, insula, and somatosensory cortex. The VMPFC and other temporal-limbic cortical regions project to the ventromedial region of the striatum (limbic striatum), which has efferent connections with the ventral and rostrolateral globus pallidus and the rostrodorsal substantia nigra pars reticularis. These structures send projections to specific regions of the medial dorsal and ventral anterior thalamic nuclei, as well as to the ventral tegmental area, insula, habenula, hypothalamus, and amygdala. The ventral striatum also receives afferent projections from the insula, amygdala, and hippocampus. In turn, the dorsolateral-striatal circuit subserving executive functions is mainly related with decision-making under risk (GDT and Investment Task) [24,30].

Dysfunction of the VMPFC causes failure to process emotional feedback from rewards and punishments and render patients insensitive to future consequences ('myopia for the future'), whereas an excessive function of the amygdala-ventral striatum system may result in an exaggerated processing of the incentive value of the stimulus [27]. Furthermore, damage to the insular cortex causes deficits to adjust patient's bets by the odds of winning, consistent with the role in signaling the possibility of aversive consequences [8].

Dopamine replacement therapy in PD patients seems to have different effects on cognitive functions according to the unequal involvement of the corticostriatal circuits [31]. It may restore cognitive functions depending on the dorsolateral-striatal circuit, which undergoes dopamine depletion early in the disease process, but may impair those relying on the relatively spared mesolimbic circuit implicated in affective decision-making [32].

Decreased activation of VMPFC and ventral striatum was found in pathological gamblers without PD, [33] whereas PD patients showed a reduced activity in medial frontal regions whilst performing the IGT [34]. However, a recent SPECT study of 11 PD patients with active PG found overactivity in right orbitofrontal cortex, insula, hippocampus, amygdala, and ventral pallidum, consistent with a dysfunction by oversimulation of the relatively spared mesolimbic circuit [35]. Thus, dopamine induced dysfunction of this circuit, in particular the VMPFC, may led to improper adaptation of behavior towards obtaining future rewards and to an impaired ability to learn from negative decision outcomes; whereas a dysfunction of the amygdala may cause an exaggerated processing of the incentive value of the stimulus [27,36,37]. Furthermore, it is already well known the association of abnormal social behavior and damage to the VMPFC [22].

Therefore, the finding that some VMPFC related functions, like social behavior and decision-making under ambiguity distinguished PD patients with PG from those lacking this disorder, together with previous studies implicating dopamine agonists as a primary factor for PG in PD patients, [4,38] is in line with a DRT induced VMPFC and amygdala-ventral striatum dysfunction amongst a subgroup of PD patients [35]. However, a dysfunction of these areas and abnormal decision-making preceding the development of PG cannot be ruled out. Conversely, decision-making under risk (GDT and Investment task), whose underlying neural correlate is presumed to rely predominantly on the dorsolateral-striatal circuit, might be improved by DRT in both PD patients with and without PG, thus failing to find differences between groups.

The limitations of this study were two-fold. First, the small sample size of PD patients with PG might explain the absence of cognitive and neuropsychiatric features associated with PG in PD other than low performance in decision-making under ambiguity and abnormal social behavior. Secondly, patients were not tested off medication. However, this would have been hard to achieve due to long-lasting effects of levodopa or dopamine agonists and the confounding effects of the cognitive and clinical manifestations exhibited during the off state.

Furthermore, studies assessing patients recovering from PG would be needed to better understand the physiopathology of this impulse control disorder.

Acknowledgements

We are grateful to A. Bechara and M. Brand for providing the computerized version of the Iowa Gambling Task and the Game of Dice Task. We would also like to thank J. Grant and R. Stinchley for use of the Minnesota Impulsive Disorders Interview and are also particularly thankful to M. Zuckerman and A. Aluja for guidance regarding the Spanish version of the Zuckerman–Kuhlman Personality Questionnaire.

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed, Text Revision ed. Washington DC: American Psychiatric Association, 2000.
2. Grosset KA, Macphee G, Pal G, *et al*. Problematic gambling on dopamine agonists: not such a rarity. *Mov Disord* 2006; **21:** 2206–2208.
3. Voon V, Hassan K, Zurowski M, *et al*. Prospective prevalence of pathologic gambling and medication association in Parkinson disease. *Neurology* 2006; **66:** 1750–1752.
4. Gallagher DA, O'Sullivan SS, Evans AH, Lees AJ, Schrag A. Pathological gambling in Parkinson's disease: risk factors and differences from dopamine dysregulation. An analysis of published case series. *Mov Disord* 2007; **22:** 1757–1763.
5. Voon V, Thomsen T, Miyasaki JM, *et al*. Factors associated with dopaminergic drug-related pathological gambling in Parkinson disease. *Arch Neurol* 2007; **64:** 212–216.
6. Paulus MP. Neurobiology of decision-making: quo vadis? *Brain Res Cogn Brain Res* 2005; **23:** 2–10.
7. Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 1994; **50:** 7–15.
8. Clark L, Bechara A, Damasio H, Aitken MR, Sahakian BJ, Robbins TW. Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. *Brain* 2008; **131:** 1311–1322.
9. Cavedini P, Riboldi G, Keller R, D'Annucci A, Bellodi L. Frontal lobe dysfunction in pathological gambling patients. *Biol Psychiatry* 2002; **51:** 334–341.

10. Pagonabarraga J, Garcia-Sanchez C, Llebaria G, Pascual-Sedano B, Gironell A, Kulisevsky J. Controlled study of decision-making and cognitive impairment in Parkinson's disease. *Mov Disord* 2007; **22:** 1430–1435.
11. Lesieur HR, Blume SB. The South Oaks Gambling Screen (SOGS): a new instrument for the identification of pathological gamblers. *Am J Psychiatry* 1987; **144:** 1184–1188.
12. Christenson GA, Faber RJ, de Zwaan M, *et al.* Compulsive buying: descriptive characteristics and psychiatric comorbidity. *J Clin Psychiatry* 1994; **55:** 5–11.
13. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992; **55:** 181–184.
14. Merello M, Nouzeilles MI, Arce GP, Leiguarda R. Accuracy of acute levodopa challenge for clinical prediction of sustained long-term levodopa response as a major criterion for idiopathic Parkinson's disease diagnosis. *Mov Disord* 2002; **17:** 795–798.
15. Adida M, Clark L, Pomietto P, *et al.* Lack of insight may predict impaired decision making in manic patients. *Bipolar Disord* 2008; **10:** 829–837.
16. Hobson DE, Lang AE, Martin WR, *et al.* Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease: a survey by the Canadian Movement Disorders Group. *J Am Med Assoc* 2002; **287:** 455–463.
17. Giovannoni G, O'Sullivan JD, Turner K, Manson AJ, Lees AJ. Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. *J Neurol Neurosurg Psychiatry* 2000; **68:** 423–428.
18. Aluja A, Rossier J, Garcia LF, Angleitner A, Kuhlman DM, Zuckerman M. A cross-cultural shortened form of the ZKPQ (ZKPQ-50-cc) adapted to English, French, German, and Spanish languages. *Pers Individ Differ* 2006; **41:** 619–628.
19. Cooper JA, Sagar HJ, Tidswell P, Jordan N. Slowed central processing in simple and go/no-go reaction time tasks in Parkinson's disease. *Brain* 1994; **117:** 517–529.
20. Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I. The ''Reading the Mind in the Eyes'' Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. *J Child Psychol Psychiatry* 2001; **42:** 241–251.
21. Benton AL, Sivan AB, Hamsher K, Varney NR, Spreen O. *Contributions to Neurophsycological Assessment*, 2nd edn. New York: Oxford University Press, 1994.
22. Hornak J, Bramham J, Rolls ET, *et al.* Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. *Brain* 2003; **126:** 1691–1712.
23. Rolls ET, Hornak J, Wade D, McGrath J. Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. *J Neurol Neurosurg Psychiatry* 1994; **57:** 1518–1524.
24. Brand M, Kalbe E, Labudda K, Fujiwara E, Kessler J, Markowitsch HJ. Decision-making impairments in patients with pathological gambling. *Psychiatry Res* 2005; **133:** 91–99.
25. Shiv B, Loewenstein G, Bechara A, Damasio H, Damasio AR. Investment behavior and the negative side of emotion. *Psychol Sci* 2005; **16:** 435–439.
26. Brand M, Labudda K, Kalbe E, *et al.* Decision-making impairments in patients with Parkinson's disease. *Behav Neurol* 2004; **15:** 77–85.
27. Bechara A. Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. *Nat Neurosci* 2005; **8:** 1458–1463.
28. Bechara A, Tranel D, Damasio H. Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain* 2000; **123:** 2189–2202.
29. Fukui H, Murai T, Fukuyama H, Hayashi T, Hanakawa T. Functional activity related to risk anticipation during performance of the Iowa Gambling Task. *Neuroimage* 2005; **24:** 253–259.
30. Alexander GE, Crutcher MD, DeLong MR. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, ''prefrontal'' and ''limbic'' functions. *Prog Brain Res* 1990; **85:** 119–146.
31. 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:** 876–880.
32. Cools R, Barker RA, Sahakian BJ, Robbins TW. Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cereb Cortex* 2001; **11:** 1136–1143.
33. Reuter J, Raedler T, Rose M, Hand I, Gläscher J, Büchel C. Pathological gambling is linked to reduced activation of the mesolimbic reward system. *Nat Neurosci* 2005; **8:** 147–148.
34. Thiel A, Hilker R, Kessler J, Habedank B, Herholz K, Heiss WD. Activation of basal ganglia loops in idiopathic Parkinson's disease: a PET study. *J Neural Transm* 2003; **110:** 1289–1301.
35. Cilia R, Siri C, Marotta G, *et al.* Functional abnormalities underlying pathological gambling in Parkinson disease. *Arch Neurol* 2008; **65:** 1604–1611.
36. Frank MJ, Seeberger LC, O'Reilly RC. By carrot or by stick: cognitive reinforcement learning in parkinsonism. *Science* 2004; **306:** 1940–1943.
37. Everitt BJ, Parkinson JA, Olmstead MC, Arroyo M, Robledo P, Robbins TW. Associative processes in addiction and reward. The role of amygdala-ventral striatal subsystems. *Ann N Y Acad Sci* 1999; **877:** 412–438.
38. Driver-Dunckley E, Samanta J, Stacy M. Pathological gambling associated with dopamine agonist therapy in Parkinson's disease. *Neurology* 2003; **61:** 422–423.

