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L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease

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Abstract

In the current study we investigated the role of dopamine in attentional and socio-emotional functioning by examining effects of withdrawing dopaminergic medication in patients with Parkinson's disease (PD). Patients 'on' medication exhibited abnormal betting strategies on a task of decision-making, reflecting impulsive behaviour and/or delay aversion, whilst the same patients 'off' medication exhibited abnormally increased switch costs when switching between two tasks, reflecting attentional inflexibility. Hence, these data replicate and extend previous findings that dopaminergic medication improves or impairs cognitive performance depending on the nature of the task and the basal level of dopamine function in underlying cortico-striatal circuitry.

Keywords: Task-switching; Decision-making; Dopamine; Prefrontal cortex; Basal ganglia

1. Introduction

The dopamine (DA) system is known to affect cognitive and reward-related processing. For example, behavioural studies with rats and non-human primates support a role for DA in working memory (Brozoski, Brown, Rosvold, & Goldman, 1979; Castner, Williams, & Goldman-Rakic, 2000; Goldman-Rakic, 1992) and reward-related learning (Hollerman & Schultz, 1998; Schultz, Tremblay, & Hollerman, 2000). In keeping with these observations, abnormal cognitive and/or reward-mediated processing is frequently observed in human disorders that implicate the nigrostriatal and/or mesolimbic DA system, such as Parkinson's disease (PD), Attention Deficit Hyperactivity Disorder (ADHD), drug addiction and schizophrenia.

PD, associated with nigrostriatal and, to a lesser extent, mesocorticolimbic DA depletion, is accompanied by subtle cognitive impairments even in the early stages, resembling those seen in frontal lobe patients (Owen et al., 1995; Taylor, Saint-Cyr, & Lang, 1986). Recent evidence suggests that administration of L-Dopa medication, known to ameliorate the motor deficits in PD, can both improve and impair cognitive function, depending on the nature of the task and basal levels of DA in underlying cortico-striatal circuitry (Cools, Barker, Sahakian, & Robbins, 2001; Gotham, Brown, & Marsden, 1988; Swainson et al., 2000). Thus, L-Dopa medication in these patients ameliorates deficits on task-switching, associated with *dorsal* striatal-dorsolateral prefrontal cortex circuitry (e.g. Sohn, Ursu, Anderson, Stenger, & Carter, 2000), but, in contrast, impairs performance on probabilistic reversal learning, associated with *ventral* fronto-striatal circuitry in both animals and humans (Cools, Clark, Owen, & Robbins, 2002; Dias, Robbins, & Roberts, 1996; Divac, Rosvold, & Szwarcbart, 1967; Iversen & Mishkin, 1970). In early PD, DA depletion is restricted to the putamen and the dorsal caudate nucleus, only later progressing to the more ventral parts of the striatum and the mesocorticolimbic DA system (Agid et al., 1993; Kish, Shannak, & Hornykiewicz, 1988). Thus, we hypothesized that L-Dopa normalizes DA levels in severely depleted areas in the parkinsonian brain, such as the dorsal striatum and its connections to the dorsolateral prefrontal cortex, whilst detrimentally 'overdosing' the relatively intact ventral striatum and its connections to the ventral prefrontal cortex. These data are consistent with findings from animal studies suggesting that the modulation by DA of cognitive function adheres to an 'inverted U' function whereby excessive, as well as insufficient DA

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D1 receptor stimulation in the prefrontal cortex (PFC) impairs working memory (Arnsten, 1998; Williams & Goldman-Rakic, 1995; Zahrt, Taylor, Mathew, & Arnsten, 1997).

The current study was designed to test the above 'DA overdose hypothesis' further by investigating other tasks known to be associated with ventral fronto-striatal brain systems. Reversal learning deficits were previously interpreted to reflect losses of inhibitory control in 'affective' processing, thus, 'impairing the ability to alter behaviour in response to changes in the emotional significance of stimuli' (Dias et al., 1996). Consistent with this interpretation, L-Dopa administration in PD has been reported to induce abnormalities in 'affect-related' or socio-emotional behaviours, such as pathological gambling (Geschwandtner, Aston, Renaud, & Fuhr, 2001; Molina et al., 2000; Seedat, Kesler, Niehaus, & Stein, 2000), presumably reflecting poor 'impulse control', and psychotic symptoms (Jenner, 2002; Starkstein & Merello, 2002). We examined performance of 12 patients with mild PD on two occasions, once 'on' medication and once 'off' medication, using the following two paradigms: (i) a task-switching paradigm to replicate our previous data (Cools et al., 2001) and to evaluate the hypothesized detrimental effects of L-Dopa in the context of improved function associated with the more dorsal fronto-striatal brain systems; (ii) a task of decision-making, measuring rational decision-making, risk taking and impulsivity, recently developed by Rogers et al. (1999a). The task is a refinement of the Iowa Gambling task (Bechara, Damasio, Damasio, & Anderson, 1994), and accumulating evidence from both functional imaging and patient studies indicates that orbital and ventromedial prefrontal cortices are important for accurate performance on such tasks (Bechara et al., 1994; Bechara, Damasio, Tranel, & Anderson, 1998; Bechara, Damasio, & Damasio, 2000a; Bechara, Tranel, & Damasio, 2000b; Rahman, Sahakian, Hodges, Rogers, & Robbins, 1999; Rahman, Sahakian, Cardinal, Rogers, & Robbins, 2001; Rogers et al., 1999a; Manes et al., 2002; Mavaddat, Kirkpartick, Rogers, & Sahakian, 2000; Tranel, Bechara, & Denburg, 2002).

In keeping with earlier work, we predicted detrimental effects of L-Dopa administration on decision-making, but beneficial effects on the task-switching paradigm. We also aimed to extend these task-switching findings by showing that the switching deficit is restricted to certain conditions, in which patients cannot rely on strong external cues. In order to test this, cue–stimulus intervals (CSI) were manipulated to encourage preparation processes in advance of task-switches. Thus, in addition to showing a DA-induced deficit on the gambling task, we aimed to show that the DA-dependent task-switching deficit parallels the commonly observed motor abnormality in PD, known as 'paradoxical kinesia'. This phenomenon describes the situation in which patients can paradoxically overcome their motor akinesia during stressful circumstance or when guided by salient external cues.

2. Methods

2.1. Subjects

These studies were approved by the Cambridge Local Research Ethics committee and all subjects gave informed consent.

2.1.1. Patients

Twelve PD patients participated in the study. All patients were diagnosed by a Consultant Neurologist (RAB) as having idiopathic PD according to UK PDS brain bank criteria. Patients with a significant medical (or neurological) history not related directly to PD (e.g. stroke, head injury) as well as dementia (Mini Mental State Examination) (Folstein, Folstein, & McHugh, 1975; MMSE $=< 24$) or depression were excluded from the study. The mean MMSE score was 29.5 (S.E.M. $= 0.15$) and the mean score on the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) was within the normal range (mean $= 7.7$, S.E.M. $= 1.1$). The severity of clinical symptoms was assessed according to the Hoehn and Yahr rating scale (Hoehn & Yahr, 1967) and the Unified PD (44-item) Rating Scale (UPDRS) (Fahn, Elton, & Committee, 1987). Hoehn and Yahr ratings ranged between I and III. The average disease duration was 6.5 years (S.E.M. $= 1.4$). All 12 patients included in the study were receiving daily L-Dopa preparations, and 4 were also taking dopamine receptor agonists and/or selegiline. All patients were on stable medication for at least 3 months prior to the study. One patient was on a long term antidepressant and another on a betablocker. Analysis of the data when these 2 patients were excluded revealed the same results as presented in this paper (for the whole group of 12). All patients were assessed on two occasions. For one occasion they were asked to abstain from their medication the night before the assessment was scheduled to take place, at least 18 h prior to the experiment. On the other occasion they were taking their medication as normal. The order of testing was counterbalanced so that five patients were 'on' medication and seven patients were 'off' medication during their first visit. Two further patients who were tested 'on' medication during their first visit were excluded from the study due to subsequent comorbid diagnoses (multiple sclerosis and corticobasal degeneration, respectively). Other demographics are summarized in Tables 1 and 2.

2.1.2. Controls

Twelve age and NART IQ (Nelson, 1982) matched control subjects were tested on the task-switching paradigm. In addition, 12 elderly control subjects were selected from a large sample of previously collected data (by J. Deakin, see Deakin, Aitkin, Robbins, & Sahakian, 2003) to provide individual matches in terms of age and NART IQ to the patient group. These data were used to compare patients' performance on the decision-making task to baseline levels. There was no difference between any of the control groups and the

Table 1
Clinical characteristics of patients

	Hoehn and Yahr	UPDRS	Pattern recognition memory (mean number correct)	Spatial recognition memory (mean number correct)
PD 'on'	1.9 (0.2)	30.9 (6.8)	21.4 (0.6)	14.9 (0.8)
PD 'off'	2.3 (0.2)*	47.1 (7.7)*	21.4 (0.7)	15.3 (0.9)

Values represent mean (S.E.M.). Motor symptoms were significantly worsened after withdrawal of medication as measured with the UPDRS and the Hoehn and Yahr rating scale at the time of testing.
* Significantly different from PD 'on' at the 0.05 level.

patient group in terms of age or premorbid IQ. Other details are summarized in Table 2.

In addition to the experimental tasks, all patients were also given the CANTAB tests of pattern and spatial recognition memory. There was no significant difference between the 'on' and the 'off' state (pattern: $P = 1.0$; spatial: $P = 0.8$), or between patients (data averaged across sessions) and task-switching controls (pattern: $P = 0.8$; spatial: $P = 0.4$). Data on these tests from the decision-making controls were not available. This background profile, together with normal MMSE and BDI scores, enabled us to evaluate the DA-dependent cognitive deficits and benefits against a background of relatively preserved basic cognitive abilities.

2.2. Cognitive tasks

2.2.1. Task-switching

Subjects were shown a display with a letter and a number and were required to name the letter or digit as fast as possible without making a mistake. Subjects switched between (A) letter and (B) digit-naming tasks on every second trial, so that switch and non-switch trials alternated in a predictable way. Thus, the sequence of trials employed was AABBAA and so on, which enabled the measurement of switching (i.e. A to B or B to A) against a baseline of non-switching (i.e. A to A or B to B). The colour of the border of the stimulus window (the cue) indicated which task was to be performed. If the cue was green, then subjects had to name the letter. If the cue was red, then subjects had to name the number. Switch costs were calculated by subtracting performance (i.e. reaction times (RTs) and proportion of errors) on non-switch trials from performance on switch trials. Two conditions were distinguished. In the '*long* cue–stimulus interval (CSI)' condition, the CSI was 1100 ms, so that subjects were able to prepare for the next trial (or task) by making use of the cue. In the '*short* CSI' the CSI was 150 ms, so that subjects could not prepare for the upcoming task beforehand. The short CSI was set to 150 ms rather than 0 ms (i.e. simultaneous presentation of cue and stimulus) to ensure that preparation effects were not confounded by interference with perceptual encoding (see also Meiran, 1996). 'Long CSI' and 'short CSI' trials were administered in blocks rather than at random, because previous work has shown that subjects are better able to use preparation intervals when trials are blocked (Rogers & Monsell, 1995). The stimulus–stimulus interval was held constant to 2700 ms to ensure that the effects of preparation interval were not contaminated by effects of remoteness from the previous trial (or dissipating proactive task–set interference) (Meiran, 1996).

Subjects were encouraged to respond as fast as possible without making too many mistakes and in the 'long CSI' blocks to make use of the cue and prepare themselves for the upcoming task. The task started with two practice blocks of 20 trials (one 'long CSI' and one 'short CSI' switch block). The training session was followed by the actual experiment, consisting of four blocks of 40 trials (two 'long CSI' and two 'short CSI' blocks, always administered in the following order: long–short–long–short). After each block the mean RT was displayed on the screen and the number of errors was given by the experimenter. Following this feedback, the instruction for the next block was presented to the subject.

A Toshiba Intel Notebook was used as a testing machine, a small throat-microphone was used to record reaction times and the program, written in Experimental Run Time System (ERTS, Berisoft Corporation, Frankfurt, Germany), ensured that reaction times were measured to millisecond accuracy.

Stimuli were presented on a black background within a stimulus window (height: 65 mm; width: 85 mm) with either a red or a green border (thickness: 3 mm). Each stimulus consisted of two closely adjacent characters (separated by 20 mm; each character 16 mm wide and 20 mm high)

Table 2
Demographic subject characteristics

	N	NART IQ	Age (years)	Sex ratio (f:m)	L-Dopa dose (daily)
PD patients	12	115.0 (2.2)	64.6 (1.5)	7:5	552 (60)
CS task-switching	12	115.9 (2.0)	62.7 (1.8)	6:6	Na
CS decision-making	12	114.9 (1.9)	64.2 (1.0)	2:10	Na

Values represent mean (S.E.M.); no group differences were found in terms of age or premorbid IQ. Abbreviations: PD, Parkinson's disease; CS, control subjects; *n*, sample size; NART IQ, premorbid IQ as estimated with the National Adult Reading Test; f:m, female:male.

presented side by side. The characters were randomly presented on the left or the right of the stimulus pair. Letters were sampled randomly from the set {G, K, M, P, R, A, E, U} and digits from the set {2, 3, 4, 5, 6, 7, 8, 9}. Stimulus sequences were generated randomly for each subject with the restriction that the same character did not appear on two successive trials. Each character pair was displayed in an uppercase upright Arial font (colour: yellow), and remained on the screen until the subject responded by naming one of the two characters.

At the start of each trial a fixation cross was presented for either 100 ms in the 'long CSI' condition or 1050 ms in the 'short CSI' condition. Following this, the stimulus window was presented for 1100 ms (in the 'long CSI' condition) or 150 ms (in the 'short CSI' condition). Then the stimulus was presented for a maximum of 1500 ms, within which the subjects had to respond. The fixation cross for the next trial was presented as soon as the subject responded or after 1500 ms (in the latter case, a 'too late' response was recorded). The inter-trial interval was 2700 ms.

Median RTs were analysed using repeated measures ANOVAs. The main analysis was performed, on patients' data only, with three within-subject factors: drug ('on' versus 'off'), trial-type (switch versus non-switch) and preparation (short versus long CSI). Additional analyses are described in Section 3. The first three trials of each block, invalid trials (such as 'lip-pops'), trials on which an error was made and trials following such error–trials were excluded from the RT analyses. None of the subjects made more than 5% errors. Proportions of errors were arcsin-transformed (Howell, 1997) ($2 \arcsin \sqrt{x}$). In case the assumption of homogeneity of covariance matrices in repeated measures ANOVA was violated, the degrees of freedom were adjusted by the Greenhouse–Geisser epsilon. The significance threshold was set at $P = 0.05$.

2.3. Decision-making (Rogers et al., 1999b)

The decision-making task was administered using an Advantech computer with a touch sensitive screen for recording responses. On each trial, 10 red or blue boxes were displayed at the top of the screen. Subjects were told that the computer had randomly hidden a yellow token in one of the 10 boxes. The ratio of red and blue boxes varied from trial to trial (ratios could be 6:4, 7:3, 8:2 or 9:1) and subjects were asked to decide whether the token was hidden under a blue or a red box. After they had made their choice, by touching either the box with the word 'red' or the box with the word 'blue' presented at the bottom of the screen, subjects were invited to make a 'bet' on whether or not they believed that their decision was correct. After selecting a bet, one of the boxes at the top of the display opened up to reveal the actual location of the yellow token, accompanied by either a 'You win!' message and a short rising musical scale, or a 'You lose!' messsage and a low tone. The chosen bet was then added to or subtracted from the total point score, which was presented below the 10 red or blue boxes, according to whether or not the red/blue decision was correct. No monetary significance was attached to the total points accumulated at the end of the task.

The task consisted of two conditions, that affected the way subjects placed their bets. In the 'ascending' condition, a box towards the centre of the screen, initially containing 5% of the total points score (presented to the subject in a box positioned next to the 'bet' box), gradually filled up with points until it contained 95% of the total points score. Points in the 'bet' box increased in a stepwise manner through 5, 25, 50, 75 and then 95% of the total score. Each bet was displayed for 5 s before it was replaced by its successor and each bet was presented with a short tone whose pitch corresponded to the size of the bet. Subjects touched this 'bet' box as soon as it contained the desirable amount of points. Conversely, in the 'descending' condition, the 'bet' box initially contained 95% of the total score and the bet then gradually decreased until the box contained 5% of the total score. Thus, if subjects wished to make a large bet in the 'ascending' condition, they had to wait until the box contained the desired amount of points. In contrast, if subjects wished to make a large bet in the 'descending' condition, a fast response was required. The order of conditions was counterbalanced across the 'on' and 'off' conditions. Each condition consisted of four blocks of nine trials (eight trials of each ratio plus four trials of a 5:5 ratio). At the start of each trial, subjects were given 100 points and were asked to increase this total by as much as possible. If a score fell below 1 point, the task proceeded to the next trial.

Four measures were taken from this experiment. First, the quality of decision-making was measured by calculating the proportion of rational decisions, that is, the proportion of trials on which subjects chose the most likely outcome (the colour with the most number of boxes). Second, the mean *deliberation time* before subjects made their red/blue decision was measured. Third, *risk taking* was measured by calculating the rate at which subjects increased their bets in response to higher ratios of coloured boxes (e.g. 9 red:1 blue versus 6 red:4 blue). Fourth, a difference score was calculated by subtracting the proportion of bets placed in the 'ascending' condition from the proportion of bets placed in the 'descending' condition. This provided an index of *impulsivity*, which would manifest itself by a relatively high difference score, i.e. by small bets in the 'ascending' condition and large bets in the 'descending' conditions.

To prevent skew and unequal variances in the data, proportions of rational decisions and proportions of bets placed were arcsin-transformed (Howell, 1997) ($2 \arcsin \sqrt{x}$). Deliberation times were log 10-transformed. The main repeated measures ANOVA was performed with three within-subject factors (drug ('on' versus 'off'), ratio (9:1, 8:2, 7:3, 6:4) and condition ('ascending' versus 'descending')) and three dependent measures proportion of rational choices, proportion of bets and deliberation times. Other analyses are described in Section 3. Greenhouse–Geisser corrected statistics are

reported when the assumption of homogeneity of covariance matrices was violated. The significance threshold was set at $P = 0.05$.

3. Results

3.1. The task-switching paradigm

Mean RTs for the 'long CSI' and the 'short CSI' conditions are presented in Table 3 as a function of trial-type and group.

A preliminary analysis of control data confirmed the usual predictions of the paradigm. Significant effects of switch ($F(1, 11) = 4.9$, $P = 0.05$) and preparation × switch ($F(1, 11) = 5.6$, $P = 0.04$) were observed, indicating that switch costs were reduced when the CSI was long, i.e. that subjects made use of the cue when intervals were long to prepare themselves for the upcoming task.

Consistent with our prediction, patients 'off' medication exhibited increased switch costs relative to patients 'on' medication, but only in the 'short CSI' condition (a significant drug × switch × preparation interaction: $F(1, 11) = 5.2$, $P = 0.04$; see Fig. 1a). Simple interaction effect analyses confirmed that the switch × drug interaction was significant only in the 'short CSI' condition ($F(1, 11) = 5.2$, $P = 0.04$) and not in the 'long CSI' condition ($F(1, 11) = 0.3$, $P = 0.6$). Thus, patients 'on' and 'off' medication did not exhibit differential switch costs when there was a possibility of utilizing an external cue.

Supplementary analyses revealed that this effect is not contaminated by (i) general slowing of cognitive processes, (ii) 'on'–'off' testing order and (iii) differential practice or fatigue effects in the 'off' state compared with the 'on' state. (i) First, the switching deficit was specific to certain conditions of the experiment. Second, baseline non-switch RTs were higher in the 'off' state than the 'on' state in the 'long CSI' condition relative to the 'short CSI' condition and third, patients 'off' medication also exhibited significantly increased proportional switch costs, which were calculated by dividing the actual switch cost by the mean baseline non-switch reaction time for each individual subject. Proportional switch costs were increased in the 'short CSI' condition and not in the 'long CSI' condition (as confirmed by a significant drug × preparation effect when proportional switch costs were analysed: $F(1, 11) = 4.7$, $P = 0.05$). Proportional switch costs are corrected for the baseline RT and are therefore unlikely to be solely due to differences in baseline RT. (ii) An analysis with the between-subject factor 'on'–'off' testing order showed that there was no difference between the patient group that was tested 'on' medication on the first visit and the patient group that was tested 'off' medication on the first visit. The other effects reported above remained significant when this factor was added to the model. Finally, (iii) an analysis with the within-subject factor 'block' (two levels; data collapsed over the first two blocks and the last two blocks) confirmed that the observed effects are not confounded by practice or fatigue effects. Thus, there was no drug × switch × block interaction ($F(1, 11) = 0.2$, $P = 0.6$), or a drug × block interaction ($F(1, 11) = 2.5$, $P = 0.14$) indicating that practice and/or fatigue effects were similar in the 'off' and the 'on' state.

A separate orthogonal analysis including control subjects revealed that switch costs did not differ between patients (*averaged* across the 'on' and 'off' sessions) and controls. However, inspection of the data revealed that, in the critical 'short CSI' condition, patients' switch costs were similar to those of controls when they were 'on' medication, but not when they were 'off' medication. A post hoc analysis comparing the data from control subjects and data from patients 'off' medication confirmed these observations (for the 'short CSI': group × switch $F(1, 22) = 5.24$, $P = 0.03$; for the 'long CSI': group × switch $F(1, 22) = 0.9$, $P = 0.4$). The complementary comparison confirmed that switch

Table 3
Task-switching data

	Short CSI		Long CSI	
	RT (ms)	Errors (%)	RT (ms)	Errors (%)
Control subjects				
Switch trials	653.1 (33.4)	0.5 (0.2)	604.8 (33.5)	0.4 (0.1)
Non-switch trials	616.2 (31.0)	0.2 (0.09)	593.0 (30.8)	0.2 (0.1)
Switch costs	36.9	0.3	11.8	0.2
Patients 'on'				
Switch trials	686.4 (26.5)	0.3 (0.20)	658.0 (27.1)	0.4 (0.2)
Non-switch trials	640.0 (18.4)	0.2 (0.01)	621.8 (18.1)	0.1 (0.06)
Switch costs	46.4	0.1	36.2	0.3
Patients 'off'				
Switch trials	744.0 (39.9)	0.6 (0.20)	681.9 (22.2)	0.7 (0.2)
Non-switch trials	662.3 (22.3)	0.1 (0.08)	651.53 (20.1)	0.3 (0.2)
Switch costs	81.6	0.5	30.4	0.4

Values represent mean (S.E.M.).

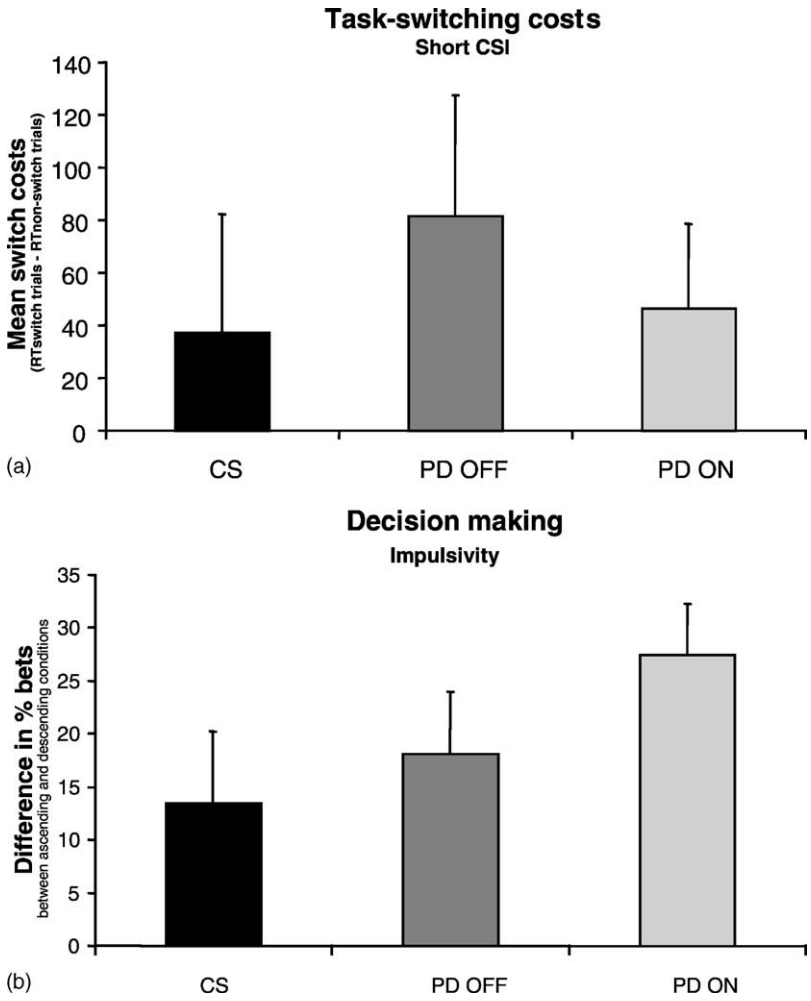

Fig. 1. (a) Task-switching costs in the 'short CSI' condition. Patients exhibited increased switch costs when they were 'off' medication (PD off) relative to when they were 'on' medication (PD on) and relative to control subjects (CS), but only in the 'short CSI' condition ('on' vs. 'off': $F(1, 11) = 5.2$, $P = 0.04$; controls vs. 'off': switch $F(1, 22) = 5.2$, $P = 0.03$). Error bars represent standard errors of the difference. See Section 3 for further details; (b) betting strategy on the decision-making task. Data shown are the difference scores in terms of proportions of bets placed between the 'ascending' and 'descending' conditions. Patients placed larger bets in the 'descending' condition, but smaller bets in the 'ascending' condition when they were 'on' medication compared with when they were 'off' medication ($F(1, 11) = 5.9$, $P = 0.03$) and compared with control subjects ($F(1, 22) = 5.4$, $P = 0.03$). Error bars represent standard errors of the difference.

costs were similar in controls and patients 'on' medication in both conditions (for the 'short CSI': switch × group $F(1, 22) = 0.3$, $P = 0.6$; for the 'long CSI': switch × group $F(1, 22) = 2.0$, $P = 0.2$).

Analysis of proportions of errors revealed that subjects made more errors on switch trials than on non-switch trials ($F(1, 22) = 15.8$, $P = 0.001$). Patients made more errors when they were 'off' medication than when they were 'on' medication ($F(1, 11) = 20.5$, $P = 0.001$). No other significant effects were observed.

3.2. The decision-making task

Analysis of the proportions of bets made revealed a significant drug × condition interaction ($F(1, 11) = 5.9$, $P = 0.03$), indicating that patients placed greater bets in the 'descending' condition, but smaller bets in the 'ascending' condition when they were 'on' medication compared with when they were 'off' medication (see Fig. 1b). Thus, when they were 'on' medication, patients placed their bets significantly more quickly than when they were 'off' medication.

Supplementary analyses revealed that this effect was not contaminated by 'on'–'off' testing order. Thus, an analysis with the between-subject factor 'testing order' showed that there was no difference between the patient group that was tested 'on' medication on the first visit and the patient group that was tested 'off' medication on the first visit. The drug × condition effect reported above remained significant when this factor was added to the model ($F(1, 10) = 5.3$, $P = 0.045$).

An orthogonal analysis comparing patients (data averaged across sessions) with control subjects did not reveal any

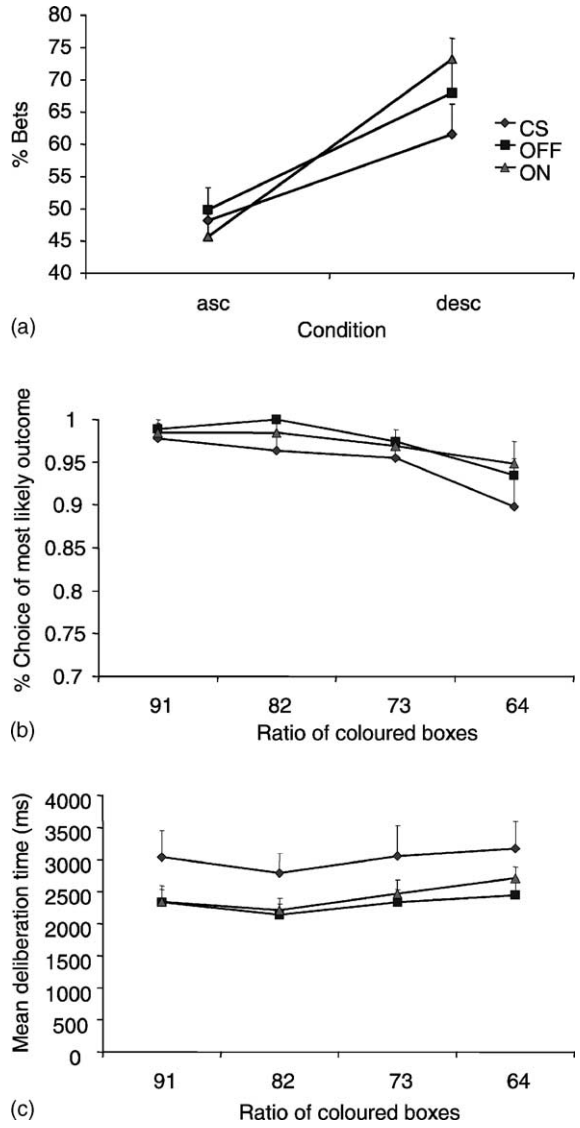

Fig. 2. Performance on the decision-making task. (a) Percentage of bets placed in the 'ascending' and 'descending' conditions. (b) Probability of choosing the most likely outcome as a function of the ratio of red and blue boxes. (c) Deliberation times to choosing a red or blue box.

significant between-group differences. However, data inspection (see Figs. 1b and 2a) revealed that patients' betting strategy was particularly different from that seen in control subjects when they were 'on' medication, but not when they were 'off' medication. In keeping with this observation, direct comparison of patients 'on' medication and control subjects confirmed that there was a significant group × condition interaction ($F(1, 22) = 5.4$, $P = 0.03$). The complementary analysis confirmed that betting strategies did not differ between patients 'off' medication and control subjects (group × condition interaction: $F(1, 22) = 0.8$, $P = 0.4$).

The analysis comparing patients (data averaged across sessions) with controls revealed a significant main effect of ratio ($F(3, 66) = 28.7$, $P < 0.0001$), indicating that subjects (across groups) placed greater bets when the ratio of coloured boxes was greater than when the ratio was smaller (9:1 rather than 6:4), and a main effect of condition ($F(1, 22) = 46.3$, $P < 0.0001$), indicating that subjects (across groups) placed greater bets in the 'descending' than the 'ascending' condition.

In terms of choosing the most likely outcome (i.e. making rational decisions) and deliberation times patients did not perform significantly different from controls (percent choice: $F(1, 22) = 0.9$, $P = 0.4$; times: $F(1, 22) = 1.3$, $P = 0.3$) (see Fig. 2b and c). A significant main effect of ratio was observed ($F(3, 66) = 8.3$, $P = 0.001$), indicating that subjects (across groups) chose the most likely outcome more often when the ratio of coloured boxes was greater than when it was smaller. Analysis of log 10-transformed deliberation times also revealed a main effect of ratio ($F(3, 66) = 3.4$, $P = 0.03$), indicating that subjects responded faster when the ratio of coloured boxes was greater than when it was small. No other significant effects of making rational decisions or deliberation times were observed.

No significant correlations were observed between the following selected task measures: (i) the difference in percent bets between the 'ascending' and 'descending' conditions (both 'on' and 'off' medication) and (ii) switch costs from the 'long CSI' and 'short CSI' conditions (both 'on' and 'off' medication).

3.3. Summary

In summary, patients 'off' L-Dopa medication exhibited abnormally increased switch costs when switching between two tasks, but *only* when subjects could not, and were not encouraged to rely on strong, external cues. This specific deficit was remediated by L-Dopa medication. In contrast, the same medication increased abnormal betting strategy on the decision-making task, whilst preserving normal, rational decision-making.

4. Discussion

Results from the present study revealed that whilst L-Dopa medication in PD remediated cognitive inflexibility on a task-switching paradigm, it induced impulsive behaviour on a task of decision-making in the context of normal reasoning. These data extend and replicate previous findings that L-Dopa medication can have contrasting effects on cognitive processing in patients with mild PD, depending on task demands and the basal level of DA in underlying cortico-striatal brain circuitry (Cools et al., 2001).

The effects of DA on inflexibility and impulsivity concur with previous work. Thus, two previous studies revealed that L-Dopa medication in mild patients with PD ameliorated a significant switching deficit on a similar paradigm, associated with dorsolateral fronto-parieto-striatal circuitry (e.g. Cools et al., 2001; Hayes, Davidson, & Keele, 1998; Sohn et al., 2000). The current findings extend these earlier

reports by showing that the switching deficit in patients 'off' L-Dopa was specific to conditions in which cue–stimulus intervals were short (150 ms), where subjects had no opportunity and were not encouraged to make use of an external cue. There was no significant difference between patients' and controls' performance in conditions where cue–stimulus intervals were long, i.e. when the experiment allowed enough time to make use of the external cue to prepare for task-switches. Cue–stimulus intervals were not confounded with the remoteness from the previous trial, because stimulus–stimulus intervals were held constant. Hence, the effects are not contaminated by task difficulty and, critically, the effects are also not confounded by passively dissipating proactive interference effects (see also Meiran, 1996). This finding indicates that cognitive inflexibility in PD can be largely overcome when patients are encouraged to carry out executive control processes in advance of task switches. Therefore, the task-switching deficit parallels the parkinsonian motor phenomenon of 'paradoxical kinesia', that is, the symptom that patients can overcome their brady or akinesia by effort or when aroused by a strong stimulus. The finding is also in keeping with a growing experimental literature on the increased reliance of patients with PD on external cues for both movement and cognitive intitiation as a compensatory strategy (e.g. Brown & Marsden, 1988; Cools, Van Den Bercken, Horstink, Van Spaendonck, & Berger, 1984; Haslinger et al., 2001; Praamstra, Stegeman, Cools, & Horstink, 1998; Sabatini et al., 2000; Van Spaendonck, Berger, Horstink, Borm, & Cools, 1995).

The impulsive betting strategy in patients 'on' medication on the decision-making task was accompanied by normal or rational decision-making (in terms of proportions of choice of the most likely outcome) and, critically, by deliberation times that were not significantly different from control values. Thus, their impulsive responding was specific to the placement of bets and did not affect accuracy on the task. Previously, normal rational decision-making in PD has been shown by both Stout, Rodawalt, and Seimers (2001) and Czernecki et al. (2002) using the Iowa Gambling task (Bechara et al., 1994), although Czernecki et al. did find some evidence for poor performance on a second session which was interpreted to reflect impaired reinforcement learning.

In view of evidence for normal decision-making in PD, it is notable that several studies have reported increased incidence of pathological gambling in PD (e.g. Molina et al., 2000; Seedat et al., 2000). For example, Seedat et al. (2000) presented a case study in which the administration of a DA receptor antagonist was used to control abnormal gambling behaviour secondary to DA-ergic treatment in PD patients. Molina et al. (2000) reported markedly increased psychopathology in the spectrum of impulse control disorder and gambling during the 'on' periods of motor fluctuations in patients with PD. These results strongly suggest that DA may induce abnormal gambling behaviour in patients with predispositions. The current data provide the first neuropsychological evidence that L-Dopa can induce abnormal impulse control, whilst leaving normal reasoning intact, in patients with mild PD. The findings suggest that decreasing the L-Dopa dose may improve such abnormal behaviour.

The pattern of performance on the decision-making task observed in patients when 'on' medication is similar to that seen in patients with first-episode schizophrenia (Hutton et al., 2002). Thus, like medicated PD patients, patients with schizophrenia exhibit normal quality of decision-making, but abnormal betting strategies. Similarities between cognitive patterns in PD patients 'on' medication and (non-medicated) patients with schizophrenia are relevant in the context of a hypothesized overactive mesolimbic DA system in both schizophrenia (Carlsson, 1978) and early medicated PD (Cools et al., 2001; Swainson et al., 2000). Conversely, the observed abnormal pattern of performance on the decision-making task is qualitatively different from that seen in some other patient groups. Thus, chronic amphetamine abusers, opiate abusers and acutely tryptophan depleted normal volunteers exhibit slowed deliberation times and/or choose the least likely outcome more often than controls, but are not more impulsive than normal controls (Rogers et al., 1999a). Non-medicated, patients with early Huntington's disease exhibit a similar profile to control subjects in terms of both choosing the most likely outcome (albeit responding more slowly) and betting (Watkins et al., 2000) and are also not abnormally impulsive. Notably, this relatively intact performance on the decision-making task in these patients is accompanied by an impairment on the Tower of London planning task, which has been associated with more dorsal fronto-parietal brain circuitry (Owen, Doyon, Petrides, & Evans, 1996). Finally, patients with frontotemporal dementia, characterised by prefrontal cortex neurodegeneration (Rahman et al., 1999), patients with ruptured aneurysms of the anterior communicating artery, supplying mainly the orbitofrontal cortex (Mavaddat et al., 2000), and patients with large (mainly right-sided) prefrontal lesions (Manes et al., 2002) exhibit increased risk taking, exemplified by increased proportions of bets made on both 'ascending' and 'descending' conditions of the decision-making task. However, these patients are not more impulsive in terms of placing their bets *more quickly* than control subjects. Thus, the present results are the exact mirror image of these previous findings in disorders with structural prefrontal or striatal damage, showing normal risk taking, but abnormal impulsivity in patients with PD when 'on' medication relative to when 'off' medication. These qualitatively distinct performance patterns may reflect dissociable manifestations of losses of impulse control in different disorders (see also Bechara, 2003).

The present data reveal a double dissociation, that is evident within the same group of patients and predicted a priori by the 'DA overdose hypothesis' (Swainson et al., 2000;

Gotham et al., 1988). The effects cannot be explained by general changes in motor symptoms or generalized slowing of cognitive processes. Thus, the increased switch costs in patients 'off' medication were observed even when the data were corrected for baseline slowing. Moreover, the fastening of response latencies when placing bets in patients 'on' medication did not extend to faster deliberation times relative to patients 'off' medication. Furthermore, the abnormal betting strategy in the 'on' medication state cannot be attributed to impaired comprehension of the task, because patients (both 'on' and 'off' medication) and controls were equally sensitive to the different ratios of red and blue boxes (as evidenced by the absence of significant group × ratio effects on all measures).

We hypothesize that the abnormal betting strategy indicates either a form of motor impulsivity or delay aversion, i.e. an intolerance for waiting, that can manifest as a tendency to select an immediate reward over a delayed reward (see, e.g. Castellanos & Tannock, 2002). This form of impulsivity has frequently been associated with Attention Deficit Hyperactivity Disorder and Sonuga-Barke (2002) has argued that delay aversion in ADHD is based on more fundamental abnormalities in reward mechanisms, which in turn have been associated with limbic-striatal circuitry, including the nucleus accumbens and the ventral prefrontal cortex (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000; Knutson, Adams, Fong, & Hommer, 2001; Mogenson, 1987; Robbins, Cador, Taylor, & Everitt, 1989; Rolls, 1999; Schultz, Apicella, Scarnati, & Ljungberg, 1992). Consistent with this hypothesis, Cardinal, Pennicott, Sugathapala, Robbins, and Everitt (2001) showed that selective lesions of the rat nucleus accumbens core induced persistent impulsive choice on a delayed reinforcement task. In addition, converging lines of evidence suggest that dysfunction of brain serotonergic systems may underlie impulsive behaviours. Thus, 5-HT depletion following lesions of the ascending serotonergic projections in the rat increased impulsive behaviour on both a five-choice reaction time task (Harrison, Everitt, & Robbins, 1997a; Harrison, Everitt, & Robbins, 1997b) (but see Dalley, Theobald, Eagle, Passetti, & Robbins, 2002; Passetti, Dalley, & Robbins, 2002) and a delayed reward procedure (Mobini, Chiang, Ho, Bradshaw, & Szabadi, 2000). Harrison et al. (1997a) emphasized the similarities between the effects of 5-HT depletion and amphetamine administration and suggested that the effects of serotonin depletion may be due to the removal of an inhibitory influence on DA-ergic transmission. Consistent with this hypothesis, accumulating evidence indicates that 5-HT receptor stimulation inhibits the activity of mesocorticolimbic DA-ergic neurons as well as reducing DA release in the frontal cortex and nucleus accumbens (Millan, Dekeyne, & Gobert, 1998; Passetti et al., 2002). In keeping with these findings, Harrison et al. (1997a) found that the effects of 5-HT depletion could be antagonised by administration of the DA-agonist SCH 23390. Thus, this literature concurs with the hypothesis that dysfunctioning 5-HT and DA neurotransmitter systems, particularly in ventral striatal-orbitofrontal circuitries, may underlie impulsivity.

DA is not the only neurotransmitter affected in Parkinson's disease. Cell groups, such as the A10 DA-ergic cells in the ventral tegmental area, the noradrenergic neurons in the locus coeruleus, the serotonergic neurons in the dorsal raphe and the cholinergic neurons in the substantia innominata (particularly the basal nucleus of Meijnert) may also be affected. However, the effect of L-Dopa stems mainly from its ability to elevate DA levels (Maruyama, Naoi, & Narabayashi, 1996) in the striatum (Hornykiewicz, 1974), and therefore the observed effects on attentional inflexibility on the task-switching paradigm and impulse control in the decision-making task are most likely due to effects of DA in dorsal and the ventral striatum respectively (or strongly connected ventral and dorsal prefrontal cortices (Alexander, DeLong, & Stuck, 1986)). The detrimental effect of L-Dopa on impulse control parallel findings from a recent study (Cools et al., 2001) in which L-Dopa induced a reversal learning deficit, which was previously interpreted to reflect an impairment in the inhibitory control of affective information (Dias et al., 1996). The dual cognitive effects of DA-ergic medication in PD patients are consistent with recent proposals that segregated prefrontal areas underlie distinct mechanisms of attentional and affective inhibitory control (e.g. Bechara, 2003; Dias et al., 1996; Yamasaki, LaBar, & McCarthy, 2002).

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