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Reversal learning in Parkinson's disease depends on medication status and outcome valence

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Abstract

We investigated the role of dopamine in distinct forms of reversal shifting by comparing two groups of patients with mild Parkinson's disease (PD), one ON and one OFF their normal dopaminergic medication. In accordance with our previous work, patients ON medication exhibited impaired reversal shifting relative to patients OFF medication. The present results extend previous studies by showing that the medication-induced deficit on reversal shifting was restricted to conditions where reversals were signaled by unexpected punishment. By contrast, patients ON medication performed as well as patients OFF medication and controls when the reversal was signaled by unexpected reward. The medication-induced deficit was particularly pronounced in patients on the dopamine D3 receptor agonist pramipexole. These data indicate that dopaminergic medication in PD impairs reversal shifting depending on the motivational valence of unexpected outcomes.

Keywords: Dopamine; Cognition; Reward; Punishment; Flexibility; Ventral striatum

1. Introduction

The mesocortical and nigrostriatal dopamine (DA) systems are well known to play a role in cognitive and reward-related processing (Brozoski, Brown, Rosvold, & Goldman, 1979; Castner, Williams, & Goldman-Rakic, 2000; Goldman-Rakic, 1992; Hollerman & Schultz, 1998). Human disorders that implicate the DA system, such as Parkinson's disease (PD), attention-deficit/hyperactivity disorder (ADHD) and schizophrenia, are associated with a variety of cognitive deficits, ranging from impulsivity to inflexibility. Treatment with dopaminergic medication may alleviate some of these deficits. However, the relationship between DA and cognitive performance is complex (Arnsten, 1998; Williams & Goldman-Rakic, 1995; Zahrt, Taylor, Mathew, & Arnsten, 1997): Dopaminergic medication may improve or impair cognitive function depending on a number of factors, such as task demands and baseline DA levels in underlying neural circuitry (Arnsten, 1998; Cools, Barker, Sahakian, & Robbins, 2001; Kimberg, D'Esposito, & Farah, 1997; Mattay et al., 2003).

PD is associated with nigrostriatal, and to a lesser extent mesocorticolimbic DA depletion and subtle cognitive impairments even in the early disease stages (Owen et al., 1992; Taylor, Saint-Cyr, & Lang, 1986). Recent evidence indicates that administration of dopaminergic medication, which is known to ameliorate the motor deficits in PD, has more complex effects on cognitive function: Both beneficial and detrimental effects have been observed (Cools et al., 2001; Cools, Barker, Sahakian, & Robbins, 2003; Frank, 2005; Frank, Seeberger, & O'Reilly, 2004; Shohamy, Myers, Geghman, Sage, & Gluck, 2005; Shohamy, Myers, Grossman, Sage, & Gluck, 2005; Swainson et al., 2000). It has been hypothesized that these contrasting effects reflect an imbalance of DA in distinct regions of the striatum (Cools et al., 2001; Gotham, Brown, & Marsden, 1988; Swainson et al., 2000). In early PD, DA depletion is restricted to the dorsal striatum, whereas the ventral striatum is relatively intact (Farley, Price, & Hornykiewicz, 1977; Kish, Shannak, & Hornykiewicz, 1988). Thus, medication doses necessary to remedy depleted DA levels in the dorsal striatum may detrimentally 'over-dose' DA levels in the relatively intact ventral striatum. To test this, we have assessed performance of patients ON and

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OFF L-Dopa medication on two tasks associated with the dorsal and ventral striatum, respectively (Cools et al., 2001). Consistent with the hypothesis, we found that dopaminergic medication in mild PD remedied impairments in task-switching, associated with the lateral prefrontal cortex and its connections with the severely depleted dorsal striatum (Brass et al., 2003; Meyer et al., 1998; Sohn, Ursu, Anderson, Stenger, & Carter, 2000). Conversely, medication impaired probabilistic reversal learning (Cools et al., 2001; Swainson et al., 2000), associated with the relatively intact ventral striatum and its connections with the ventral prefrontal cortex (Cools, Clark, Owen, & Robbins, 2002; Dias, Robbins, & Roberts, 1996; Divac, Rosvold, & Szwarcbart, 1967; Iversen & Mishkin, 1970). A follow-up functional imaging study in mild PD patients has strengthened this 'over-dose' hypothesis by showing that dopaminergic medication modulated the ventral striatum (i.e. the nucleus accumbens), but not the dorsal striatum during the performance of a probabilistic reversal shifting paradigm (Cools et al., submitted for publication). The findings are consistent with observations from animal studies suggesting that the dopaminergic modulation of cognitive function adheres to an 'inverted U' function whereby excessive, as well as insufficient DA receptor stimulation impairs cognitive performance (Arnsten, 1998; Williams & Goldman-Rakic, 1995; Zahrt et al., 1997).

A recent study by Frank et al. (2004) extended the above-described contrasting effects of dopaminergic medication on cognitive flexibility to the domain of outcome-based learning.[1] Frank et al. (2004) showed that relative to PD patients ON medication, PD patients OFF medication were better at learning from negative outcomes than at learning from positive outcomes. Thus, patients OFF medication exhibited an increased tendency towards 'not-choosing' (i.e. avoiding) a previously punished stimulus (an increased 'NoGO' bias) relative to patients ON medication. By contrast, patients ON medication learned more from positive than negative outcomes and accordingly, exhibited an increased 'GO' tendency towards choosing a previously rewarded stimulus (Frank et al., 2004). This profile was predicted by their computational model, which simulated transient changes in DA following positive and negative outcomes, and subsequent contrasting effects on the direct and indirect pathways within the basal ganglia system: DA was thought to excite the direct or 'GO' pathway, which facilitates rewarded responding, while inhibiting the indirect or 'NoGO' pathway, which suppresses non-rewarded responding. It was proposed that DA bursts, which occur when animals receive unexpected reward, increase plasticity in the direct pathway (supporting 'GO' learning). Conversely, plasticity in the indirect pathway (supporting 'NoGO' or avoidance learning) was proposed to be increased by DA dips, which occur when an expected reward is omitted. In the model, elevated (tonic) levels of DA following dopaminergic medication blocked the effects of normal phasic 'DA dips', which are thought to occur following reward omission (i.e. a form of punishment) (Hollerman & Schultz, 1998). The medication-induced attenuation of phasic 'DA dips' impaired reversal learning by diminishing the normal 'NoGO' bias in learning from punishment (Frank, 2005). Although this model did not explicitly take into account the spatiotemporal progression of DA depletion from the dorsal to the ventral striatum in PD, it did provide a mechanistic account of the detrimental effect of dopaminergic medication on outcome-related functioning associated with relatively intact ventral fronto-striatal circuitry.

These data raise the question whether the previously observed medication-induced deficit on reversal shifting is valence-specific; that is, restricted to conditions where the reversal is signaled by an unexpected negative outcome. The specific aim of the present study was to examine the hypothesis that dopaminergic medication in mild PD impairs reversal shifting based on unexpected negative, but not positive outcomes. Such a selective punishment-based reversal deficit would support the existence of different representations of reward- and punishment-based learning signals (Daw, Kakade, & Dayan, 2002; Frank et al., 2004; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001; Seymour et al., 2005). We examined performance of 2 groups of 10 patients with mild PD, 1 ON medication and 1 OFF medication, as well as 12 control subjects using a novel paradigm that enabled the separate investigation of learning reversals, signaled by either negative or positive outcomes.

2. Methods

2.1. Patients

The study was approved by the UC Berkeley Committee for the Protection of Human Subjects and all subjects gave written informed consent.

Twenty-eight patients with mild PD were recruited from the movement disorders clinics at the Northern California Veterans Administration Medical Center and the University of California, San Francisco. All patients were diagnosed by a neurologist. Selected patients were contacted and a medical history was obtained. Patients with a significant neurological history not related directly to PD (e.g. stroke, head injury) as well as dementia (as measured with the Montreal Cognitive Assessment; MoCA; scores < 24; Nasreddine et al., 2005) or depression (as measured with the Beck Depression Inventory; BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) were excluded from the study. The MoCA and BDI were administered on the same test session on which the here-presented data were obtained (except for one patient from the ON group who was tested on a subsequent OFF session and one patient from the OFF group who tested on a subsequent ON session). Following MoCA and BDI testing, six patients were excluded based on MoCA scores below 24 and one patient based on an abnormally high BDI score (above 20). One additional patient, tested ON medication, was unable to understand the instructions of the task. The mean MoCA score of the remaining 20 patients was 26.4 (S.E.M. = 0.4) and the mean BDI score was within the normal range (mean = 8.0, S.E.M. = 0.9). 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, & Members of the UPDRS Development Committee, 1987). Hoehn and Yahr ratings ranged between I and III. The average disease duration was 9.6 years (S.E.M. = 1.7). All, but two patients included in the study were receiving daily L-Dopa preparations. The two patients that were not receiving L-Dopa preparations were receiving mirapex only, a DA D3 receptor agonist. Other dopaminergic and non-dopaminergic medications are summarized in Table 1. All patients were on stable medication for at least 2 months prior to the study. Patients were

[1] The term cognitive flexibility refers here to the ability to rapidly change previously relevant responding in response to a change in the environment. Conversely, the term learning is used to refer to the ability to gradually acquire newly relevant responding in order to adapt to the environment.

Table 1
Medications

	PD ON	PD OFF
Sinemet	9	9
Pramipexole (D3 agonist)	6	7
Pergolide (D1/D2 agonist)	1	0
Amantadine	2	3
Comtan (COMT inhibitor)	3	2
Methylphenidate	0	1
Modafinil	0	1
Namenda (NMDA antagonist)	0	1
Anti-depressants (SSRIs)	3	4

tested either ON or OFF their dopaminergic medication. The patients OFF medication were asked to abstain from their medication for at least 16 h prior to the experiment. The other patients ON medication were taking their medication as normal. Demographics and clinical characteristics are summarized in Table 2.

2.2. Controls

Twelve neurologically healthy, age- and education-matched control subjects were recruited from the surrounding Berkeley community. There were no differences between the control group and the patient groups in terms of age ($F_{2,29} = 1.0$) or premorbid IQ (as measured with the North American version of the National Adult Reading Test (NAART; Nelson, 1982; $F_{2,29} < 0.1$). Other details are summarized in Table 3.

2.3. Background neuropsychological tests

In addition to the experimental tasks, all patients and controls were also given a paper and pen version of the Stroop task (Stroop, 1935) as well as letter and semantic fluency tasks (Benton, 1968). There were no significant differences between the ON, the OFF and the control groups on any of these, or the BDI, MoCA and NAART measures as revealed by one-way ANOVAs (see Tables 2 and 3). This background profile enabled us to evaluate the DA-dependent cognitive deficits against a background of relatively preserved basic cognitive abilities.

In order to ensure that our two patient groups did not differ in their baseline sensitivity to reward and punishment, we obtained self-report data from all subjects on the BIS/BAS Scales (Carver & White, 1994), developed to measure individual differences in the sensitivity of a behavioral inhibition system (BIS) and a behavioral activation system (BAS), as proposed by McNaughton and Gray (2000). More specifically, the BIS (Carver & White, 1994) is a seven-item questionnaire designed to reflect dispositional variation in aversive motivation, i.e. sensitivity to anxiety-provoking stimuli (e.g. "even if something bad is about to happen to me, I rarely experience fear or nervousness") followed by a 4-point scale to rate agreement. The BAS is a 13-item questionnaire designed to reflect dispositional variation in appetitive motivation. Carver and White (1994) demonstrated that the BIS is a reliable predictor of vulnerability to nervousness as a function of exposure to cues of impending punishment and that the BAS is a reliable predictor of happiness in response to impending reward.

2.4. Task design (see Figs. 1 and 2)

2.4.1. General description

Subjects were presented with a series of pairs of stimuli, and on each trial one of the two stimuli was highlighted. Subjects were required to predict whether the highlighted stimulus would lead to reward or punishment. The outcome was presented after subjects made their prediction and was deterministic: Outcomes were not contingent upon the responses, but rather depended on which stimulus was highlighted. During the task, the stimulus-outcome contingencies reversed multiple times (provided attainment of learning criteria), and these reversals were signaled to subjects by either unexpected reward or unexpected punishment.

Subjects were given the following instructions:

> "Imagine that you are the boss of a casino and that you are watching the casino floor through a camera from your office. You are looking at a very simple card-game played by one of your customers. The card-game consists

Table 2
Demographics and clinical characteristics

	Age	Dis dur	NAART	Edu	BDI	L-Dopa	Updrs ON	Updrs at test	Hours since last dose
OFF ($n = 10$)	64.6 (8.5)	11.0 (8.8)	122.9 (11.9)	17.5 (2.9)	8.4 (4.8)	640.0 (450.6)	22.4 (15.1)	32.1 (17.0)	19.2 (2.1)
ON ($n = 10$)	68.9 (8.7)	8.1 (5.8)	122.8 (5.8)	17.9 (2.4)	7.7 (3.6)	835.8 (924.7)	25.4 (16.2)	25.4 (16.2)	1.85 (1.2)
CS ($n = 12$)	67.8 (8.2)	Na	122.6 (6.2)	17.2 (3.4)	5.7 (4.7)				
P	0.4	0.4	0.9	0.8	0.3	0.6	0.7	0.3	0.0001

Values represent means (standard deviations). Dis dur: disease duration from diagnosis; NAART: American version of the National Adult Reading Test; Edu: the number of years of education including primary school; BDI: Beck Depression Inventory; L-Dopa: L-Dopa equivalent dosages were calculated according to Simuni et al. (2002): 100 mg standard levodopa = 130 CS levodopa = 10 mg bromo = 1 mg pergolide = 1.5 mg pramipexole = 3 mg cabergoline = 9 mg ropinirole. Nondopaminergic therapy, amantadine, entacapone (COMT inhibitors) and selegiline were not included in the calculation.

Table 3
Background neuropsychology

	MoCA	FAS	Semflu	Str-words	Str-colors	Str-interf	Str-err-words	Str-err-colors	Str-err-interf
OFF	27.1 (2.2)	41.7 (12.6)	34.7 (11.4)	92.5 (20.4)	60.6 (11.3)	31.6 (8.5)	0.3 (0.7)	0.2 (0.4)	0.6 (0.8)
ON	25.7 (1.5)	36.9 (8.8)	31.5 (8.4)	91.3 (14.3)	53.1 (16.6)	30.1 (12.7)	0.8 (2.2)	1.8 (3.0)	1.7 (2.1)
CS	26.7 (2.0)	43.8 (12.7)	36.3 (12.4)	92.8 (17.4)	61.3 (9.0)	34.1 (10.7)	0.1 (0.3)	0.9 (2.3)	1.1 (1.6)
P	0.3	0.4	0.6	0.9	0.3	0.7	0.4	0.3	0.3

Values represent means (standard deviations). *Abbreviations*: MoCA, Montreal Cognitive Assessment; FAS, letter fluency (number of words generated in 60 s for the letters F, A and S); Semflu, semantic fluency (number of words generated for the categories animals and fruit); Str-words, the number of (black ink) words read in 45 s; Str-colors, the number of colors named in 45 s of colored crosses; Str-interf, the number of colors named in 45 s of colored words; Str-err-words, the number of errors made for black ink words; Str-err-colors, the number errors made for colored crosses; Str-err-interf, the number of errors made for colored words.

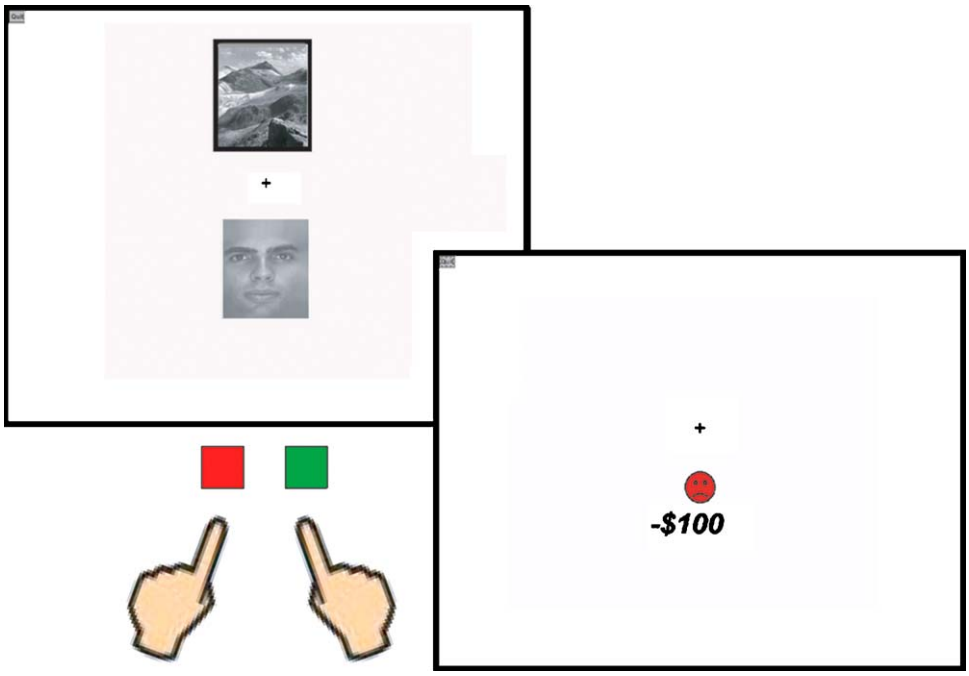

Fig. 1. Sample trial-event. Subjects were presented with two stimuli, one of which was highlighted (here, the landscape). They pressed a red or green button according to whether they predicted reward or punishment. Following the response, the outcome was presented (here, punishment). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

of only two cards: One card has a picture of a face; the other card has a picture of a landscape. In each game, the dealer shuffles the cards and the customer has to choose one of the two cards. The customer cannot see the front of the cards and so his choice is completely random. However, you are the boss of the casino and you can see which picture he chooses. The customer's choice is indicated by a black box.

Prior to each game, the dealer has decided which of the two cards wins and which card loses. Depending on the dealer's decision, the customer wins $100 or loses $100. You are the boss of the casino and your task is to observe the game, and discover which card is the winning card and which is the losing card.

You will notice that the dealer may change his mind about which card is the winning card and which is the losing card now and then, although not very often.

Try to predict whether the customer will lose or win. Press LEFT if you predict that the customer will lose $100; press RIGHT if you predict that the customer will win $100. Your response DOES NOT AFFECT whether the customer will win or lose. You can only OBSERVE and PREDICT."

2.4.2. Trial details

A sample trial-event is shown in Fig. 1. On each trial subjects were presented with two vertically adjacent stimuli at about 19 in. viewing distance (subtending about 3° horizontally and 3.5° vertically), one scene and one face (location randomized). These two stimuli were the same throughout the experiment. On each trial, one of the two stimuli was highlighted by a black border surrounding the stimulus. Subjects were asked to attend to the highlighted stimulus and to predict whether that stimulus would lead to reward or punishment. Responses were made by pressing, with the right or left finger, one of two colored buttons (2 in. high and 2.5 in. wide) on a button-box (Cedrus Response Pad, Model RB-834, San Pedro, California, see www.cedrus.com/support/rb_series). They were asked to press the green button if they predicted reward and to press the red button if they predicted punishment. The outcome-response contingencies (i.e. the right/left location of the green/red buttons) were counterbalanced between subjects; the green button was the right button in four patients ON medication, five patients OFF medication and five controls. Following an interval of 1000 ms after the (self-paced) response, during which the screen was cleared, the outcome was presented for 500 ms in the location of the highlighted stimulus. The response-outcome interval was introduced to minimize the intuitive tendency to perceive the outcome as response-contingent. Reward consisted of a green smiley face, a "+$100" sign and a high-frequency jingle tone. Punishment consisted of a red sad face, a "−$100" sign and a single low-frequency tone.[2] Following the outcome, the screen was cleared for 500 ms, after which the next stimuli were presented. Stimuli stayed on the screen until subjects made a response. A black fixation cross was presented in the middle of the screen throughout the experiment.

2.4.3. Procedure

Each subject consecutively performed one practice block (see below), two experimental blocks, another practice block and a final two experimental blocks. The experimental blocks were divided into two valence conditions: an unexpected punishment and an unexpected reward condition. Subjects were not made aware of this difference. On the reversal trials of the unexpected punishment condition, the previously rewarded stimulus was highlighted and followed unexpectedly by punishment. On the reversal trials of the unexpected reward condition, the previously punished stimulus was highlighted and followed unexpectedly by reward. The order of conditions was approximately counterbalanced between groups (four patients OFF, six patients ON and five controls received the unexpected punishment condition first). There were 2 blocks per condition, with 120 trials per block, so that each subject performed 4 blocks and 480 trials per experimental session. A schematic of sample trial-sequences for each condition is shown in Fig. 2.

Each set of experimental blocks was preceded by a practice block, which consisted of two stages, one initial acquisition stage and one reversal stage. Following attainment of an initial learning criterion of 20 correct trials the practice block proceeded to the reversal stage (or terminated if a maximum of 80 trials was performed). The practice block was terminated if the subject reached a learning criterion of 20 correct trials in the reversal stage or if a maximum of 80

[2] The term 'punishment' refers here to a negative outcome, which may be perceived either as an actively aversive punishment, or more likely as reward omission.

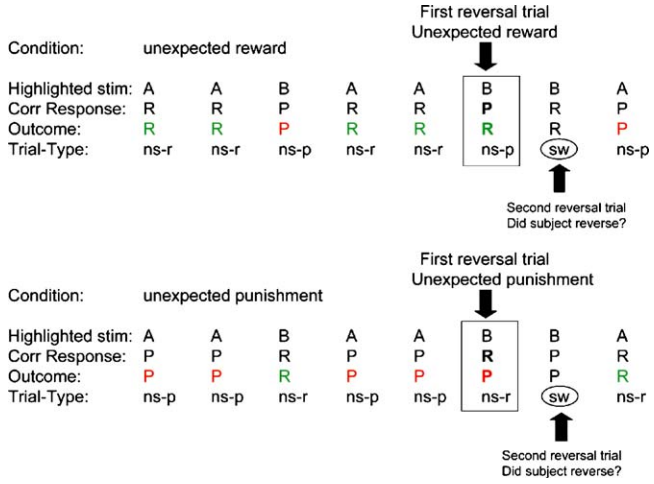

Fig. 2. Schematic of sample trial-sequences from the unexpected reward and punishment conditions. Subjects were presented with two stimuli (A and B). One of these two stimuli was highlighted (Highlighted stim: A or B). Subjects were required to press a red or green button according to whether they predicted reward (R) or punishment (P) (Corr Response: R or P). Following the response, the outcome was presented (Outcome: R or P). Subjects had to predict reward on nonswitch-reward trials (ns-r) and punishment on nonswitch-punishment trials (ns-p). On the first trial of a reversal stage (indicated here by a box), subjects were presented with an unexpected outcome (R in the unexpected reward and P in the unexpected punishment condition). The critical measure of interest was whether or not subjects reversed stimulus-outcome contingencies on the second trial of the reversal stages (i.e. the switch trial, 'sw'). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

trials was performed. The reversals in the practice blocks were signaled by either unexpected punishment or unexpected reward, depending on which experimental valence condition followed the practice block. Other details (event-timing and outcomes) were identical to those in the experimental blocks. All subjects attained the learning criterion of 20 correct trials in both stages of the practice blocks and displayed understanding of the task instructions (which are counter to the intuitive tendency to work for and obtain as many rewards as possible).

2.4.4. Block and trial-sequence details

Each block of the experimental session consisted of an initial acquisition stage and a variable number of reversal stages (see below). In the initial acquisition stage, one of the two stimuli was followed by reward, while the other stimulus was followed by punishment. Subjects learned to predict which of the two stimuli was associated with reward and which was associated with punishment. Following a number of consecutive correct trials (determined by the pre-set learning criterion, see below) in this initial acquisition stage, the task proceeded to the first reversal stage. On the first trial of this reversal stage, the stimulus-outcome contingencies changed so that the previously rewarded picture was presented and followed unexpectedly by punishment or the previously punished picture was presented and followed unexpectedly by reward (depending on the valence condition, see above and Fig. 1). Following attainment of another learning criterion, the task proceeded to the next reversal stage. The maximum number of reversal stages per block was 14, although the block terminated automatically after completion of 120 trials (~6.6 min). Learning criteria (i.e. the number of consecutive correct trials following which the contingencies changed) varied between stages (but not between conditions or subjects, see below) according to a pre-set fixed pseudorandom sequence (mean = 6.9; S.D. = 1.8; range from 5 to 9), in order to prevent predictability of reversals.

The highlighted stimulus, the outcome contingencies and the learning criteria were determined a priori according to a fixed pseudorandom sequence. This sequence was the same for the two valence conditions and for all subjects. If subjects made an incorrect prediction, then the same stimulus was highlighted again on the next trial. Each block terminated automatically after 120 trials. For this reason, the number of completed stages varied between blocks, conditions and subjects. However, relevant trial-sequence features (i.e. which stimulus was highlighted, which stimulus was rewarded and punished, learning criteria, etc.) were matched exactly between conditions and subjects.

The stimulus that was highlighted on the first trial of the reversal stage (on which the unexpected outcome was presented) was always highlighted again on the second trial of the reversal stage (on which the subject was required to reverse their responding) (see Fig. 1). For example, if the previously rewarded stimulus A was highlighted on the first trial of a reversal stage and followed by unexpected punishment, then stimulus A was highlighted again on the second trial of that reversal stage. The fixed response alternation requirement was unknown to the subject and ensured that a correct stimulus-outcome reversal always required response alternation. Therefore, the below-reported valence effect cannot be due to effects of medication on response alternation. This design feature minimized the need, on switch trials, to generalize the new stimulus-outcome contingency to the other stimulus. That is, switch trials only required the ability to learn, for example, that stimulus A was no longer associated with reward, but instead with punishment. Switch trials did not require the ability to transfer this new information about stimulus A to stimulus B which was now no longer associated with punishment but instead with reward.

2.5. Data analysis

A first measure of interest was the number of stages performed by the different groups as a function of valence: Good performance would lead to few trials to criterion and a large number of stages performed within the maximum of 120 trials. This total number of stages was analyzed with ANOVA with one between-subjects factor (group) and one within-subjects factor (valence).

Subsequently, the data were decomposed in the following way: the critical measure of interest was the proportion of errors on switch trials (i.e. the second trial in the reversal stages), which were defined as those trials following unexpected reward or punishment (see Fig. 2). Performance on such switch trials indicated the efficacy of reversal learning from unexpected reward or punishment. We also recorded accuracy on nonswitch trials, which were defined as those trials following expected outcomes. These nonswitch trials did not include trials from the initial acquisition stage, because those acquisition trials did not differ between valence conditions (which only varied in terms of the valence of unexpected outcomes on reversal trials). The nonswitch trials were analyzed according to whether subjects were required to predict reward or punishment (i.e. press the green or the red button). 'Green' trials were referred to as nonswitch-reward trials and 'red' trials were referred to as nonswitch-punishment trials (see Fig. 2). Only those trials were included that followed correct responses.

Mean proportions of errors were analyzed using repeated measures ANOVAs (SPSS 11, Chicago, IL) with one between-subjects factor (group) and two within-subjects factors: valence (two levels: unexpected punishment versus unexpected reward) and trial-type (three levels: switch, nonswitch-reward and nonswitch-punishment). Strong a priori predictions allowed us to report one-tailed P-values. Greenhouse–Geisser corrections were applied when the sphericity assumption was violated (Howell, 1997).

3. Results

3.1. Effects of medication withdrawal

Fig. 3 presents the total number of stages performed as a function of valence and group. Patients OFF medication and control subjects completed approximately the same number of stages in the unexpected punishment and the unexpected reward condition. By contrast, patients ON medication completed fewer stages in the unexpected punishment condition relative to the unexpected reward condition. While the omnibus ANOVA with a three-level group factor revealed a trend towards an interaction between valence and group (comparing controls, patients ON and patients OFF medication) ($F_{2,29} = 1.9$, $P = 0.08$), simple effects analyses confirmed that patients ON medication com-

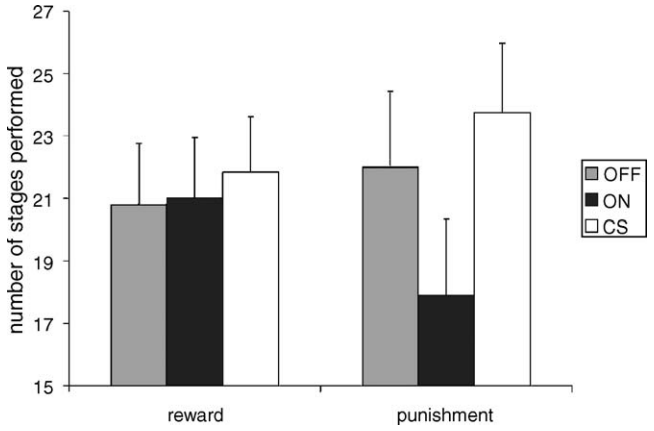

Fig. 3. Number of stages performed as a function of group and valence. Error bars represent standard errors of the mean.

pleted significantly fewer stages in the unexpected punishment condition relative to the unexpected reward condition ($F_{1,9} = 3.7$, $P = 0.04$). There was no difference between the two valence conditions for the OFF or control groups ($P > 0.4$).

Further simple effects analyses revealed a trend towards a main effect of group in the unexpected punishment condition ($F_{2,29} = 1.6$, $P = 0.1$), which was due to patients ON medication completing significantly fewer blocks than controls ($F_{1,20} = 3.1$, $P = 0.05$). The difference between the two patient groups did not reach significance ($F_{1,18} = 1.1$). However, we argue that the most meaningful comparisons are the within-subjects effects of valence. These effects are not biased by between-subject variability of no interest and address directly our research question which relates to valence. Indeed, a post hoc ANOVA confirmed a significant interaction between group and valence when patients ON medication were compared with patients OFF medication ($F_{1,18} = 3.0$, $P = 0.05$).

Decomposition of the data by trial-type revealed that the deficit in the ON group was particularly pronounced on punishment-induced switch trials. Fig. 4 presents the mean error rates for each of the two valence conditions as a function of group and trial-type. Patients ON medication made considerably more errors on switch trials in the unexpected punishment condition than in the unexpected reward condition. Conversely, patients OFF medication and control subjects made approximately the same number of errors in the two valence conditions. ANOVAs confirmed the statistical significance of these observations: There was a significant three-way interaction between group (PD ON, PD OFF and controls), valence and trial-type ($F_{4,58} = 2.7$, $P = 0.02$) in addition to a significant two-way interaction between group and valence ($F_{2,29} = 3.7$, $P = 0.02$). Decomposition of the significant omnibus three-way interaction into simple interaction effects revealed a significant group by valence interaction for switch trials ($F_{2,29} = 4.1$, $P = 0.01$), but not for nonswitch-reward trials ($F_{2,29} = 1.1$) or nonswitch-punishment trials ($F_{2,29} = 2.2$). Further analyses of simple effects showed a significant main effect of group for switch trials from the unexpected punishment condition ($F_{2,29} = 2.7$, $P = 0.04$), but not for switch trials from the unexpected reward condition ($F_{2,29} = 1.0$). The main group effect for switch trials from the unexpected punishment condition was due to patients ON medication making significantly more errors than patients OFF medication ($F_{1,18} = 4.2$, $P = 0.03$). The difference between patients ON medication and controls was also marginally significant ($F_{1,20} = 2.2$, $P = 0.07$). Conversely, the number of errors on switch trials in the unexpected punishment condition in patients OFF medication was statistically indistinguishable from that of controls ($F_{1,20} = 0.08$).

A post hoc ANOVA revealed a highly significant group by valence effect for switch trials, when patients ON medication were compared with patients OFF medication ($F_{1,18} = 7.9$, $P = 0.006$). For patients ON medication, there was a significant main effect of valence for switch trials ($T_9 = 2.5$, $P = 0.02$), which was due to higher error rate in the unexpected punishment condition than in the unexpected reward condition. For patients OFF medication, there was a trend towards a main effect of valence for switch trials in the opposite direction, with a higher error rate in the unexpected reward condition than in the unexpected punishment condition ($T_9 = -1.4$, $P = 0.1$). However, this effect did not reach significance. For control subjects, there was no significant effect of valence for switch trials ($T_{11} = 0.7$).

The deficit in the ON group on punishment-induced switch trials was not due to a deficit in predicting punishment per se, but rather due to a selective difficulty with adapting responding following unexpected punishment. This was evidenced by statistically indistinguishable error rates on nonswitch-punishment trials across conditions (main effect of group: $F_{2,29} = 0.7$).

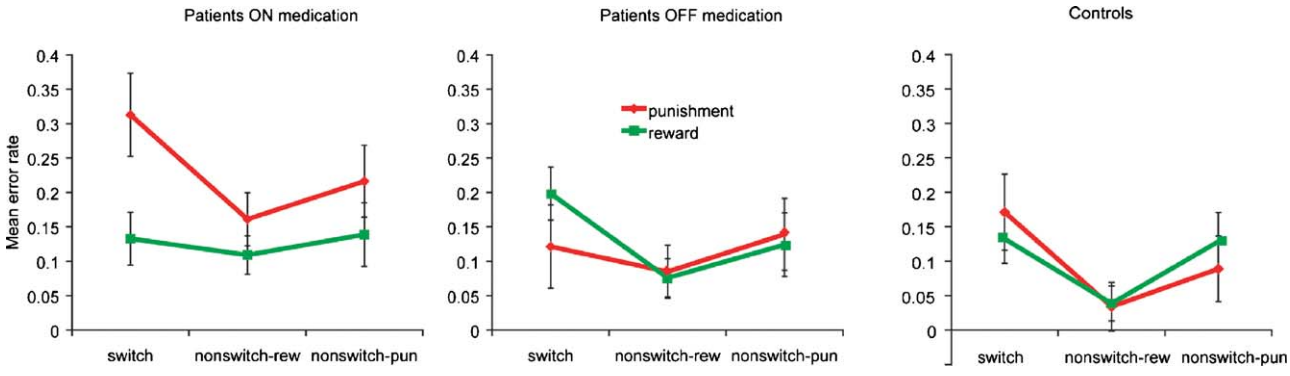

Fig. 4. Proportions of errors as a function of group, valence and trial-type. Error bars represent standard errors of the mean.

The testing order of valence conditions could not account for the data, as revealed by additional analyses evidencing that the significant three-way interaction between group (ON, OFF versus CTR), trial-type and valence remained significant following correction for testing order ($F_{4,56} = 2.6$, $P = 0.03$) as did the two-way interaction between group and valence when switch trials only were analyzed ($F_{2,28} = 3.6$, $P = 0.02$).

We observed no significant difference between any of the groups in terms of BIS ($F_{2,29} = 0.6$) or BAS scores ($F_{2,39} = 0.7$). Moreover, the three-way interaction between group, valence condition and trial-type remained significant even after correcting for BIS ($F_{4,56} = 2.6$, $P = 0.03$) or BAS scores ($F_{4,56} = 2.7$, $P = 0.03$), as revealed by repeated measures ANCOVAs with BIS and BAS scores as covariates.

3.2. Effects of pramipexole

A recent report has suggested that activation at DA D3 receptors by pramipexole (mirapex) may play a particularly important role in the generation of medication-induced cognitive impairment in PD (Dodd et al., 2005). In the present study, 6 out of 10 patients ON medication were also receiving pramipexole (and 7 out of 10 patients OFF medication). In order to test the hypothesis that pramipexole played a role in the medication-induced reversal learning impairment, we conducted additional post hoc analyses comparing patients from the ON group who took pramipexole ($n = 6$) with patients from the ON group who did not take pramipexole ($n = 4$; see Table 4). These two groups did not differ in terms of age, disease duration, NAART IQ, UPDRS/Hoehn and Yahr scores or L-Dopa dose ($P > 0.2$).

A repeated measures ANOVA with group (pramipexole) as the between-subjects factor and valence and trial-type as the within-subjects factors revealed a significant main effect of group ($F_{1,8} = 4.7$, $P = 0.03$) as well as significant group by valence interaction ($F_{1,8} = 10.0$, $P = 0.007$). These effects were due to patients-on-pramipexole being impaired in the punishment condition relative to patients-not-on-pramipexole ($F_{1,8} = 6.5$, $P = 0.02$). A similar group effect was not found in the reward condition ($F_{1,8} = 1.9$, $P = 0.1$). There was no evidence for a three-way interaction between group, valence and trial-type ($F_{2,16} = 1.0$) and the simple group by valence interactions were significant for switch trials ($F_{1,8} = 5.4$, $P = 0.03$) and nonswitch-punishment trials ($F_{1,8} = 6.5$, $P = 0.02$). These interactions were due to significant valence effects for patients-on-pramipexole, but not for patients-not-on-pramipexole, on both switch trials ($F_{1,5} = 11.6$, $P = 0.01$) and nonswitch-punishment trials ($F_{1,5} = 7.9$, $P = 0.02$). Thus, pramipexole critically contributed to the medication-induced impairment seen in the unexpected punishment condition.

Table 4
Performance as a function of pramipexole use

	Switch	Nonswitch-reward	Nonswitch-punishment
Patients-not-on-pramipexole			
Punishment	0.12 (0.09)	0.04 (0.07)	0.03 (0.08)
Reward	0.11 (0.07)	0.05 (0.05)	0.06 (0.06)
Patients-on-pramipexole			
Punishment	0.44 (0.07)	0.24 (0.06)	0.34 (0.07)
Reward	0.15 (0.06)	0.15 (0.04)	0.19 (0.05)

Values represent means (standard errors of the mean).

In sum, our data indicate that, relative to patients OFF medication and controls, patients ON medication were selectively impaired on reversal shifting, but only when the reversal was signaled by unexpected punishment, and not when the reversal was signaled by unexpected reward. These differences were observed despite similar trait-sensitivities to reward and punishment. Supplementary analysis revealed that pramipexole may play a particularly important role in the generation of these medication-induced impairments.

4. Discussion

The present findings concur with previous observations indicating that dopaminergic medication in mild PD patients impaired probabilistic and concurrent reversal learning in tasks where reversals were signaled by unexpected punishment (Cools et al., 2001; Swainson et al., 2000). Our results significantly extend these previous findings by showing that the medication-induced deficit on reversal shifting was restricted to conditions where reversals were signaled by unexpected punishment and did not extend to conditions where reversals were signaled by unexpected reward. This observation is consistent with the theoretical model proposed by Frank (2005), who has suggested that phasic 'DA dips', associated with punishment are particularly vulnerable to the excessive DA levels following dopaminergic medication. Specifically, in their model, bad choices that do not lead to reward are associated with 'DA dips' that drop below baseline DA levels. These dips are critical for 'NoGO' learning, i.e. they support subsequent avoidance of bad choices. It is these 'DA dips' that are thought to be blocked by dopaminergic medication, leading to a selective impairment in learning from punishment.

Our data indicate a critical role for pramipexole in the punishment-based reversal learning impairment. This finding is remarkable in the context of disproportionate representation of pramipexole in recent case reports of pathological gambling in PD patients (Driver-Dunckley, Samanta, & Stacy, 2003). For example, Dodd et al. (2005) reported that pramipexole was taken by 82% of their sample of patients who had recently developed pathological gambling. Pathological gambling has been associated with a failure to adequately process negative consequences of behavior (Bechara, 2005). The presently observed impairment in punishment-based reversal learning may well relate to the phenomenon of pathological gambling in patients on pramipexole. Pramipexole is an unusual DA receptor agonist in that it is highly selective for the DA D3 receptor: Its affinity for the D3 receptor is at least two orders of magnitude greater than that for other receptors (Dodd et al., 2005). Unlike D1 and D2 receptors, D3 receptors are predominantly localized in the ventral striatum (the nucleus accumbens and ventral putamen), but not the dorsal striatum (Gerlach et al., 2003; Murray, Ryoo, Gurevich, & Joyce, 1994; Sokoloff, Giros, Martres, Bouthenet, & Schwartz, 1990). Therefore, this observation strengthens the hypothesis that functions associated with the

relatively intact ventral striatum are particularly vulnerable to the detrimental side effects of dopaminergic medication in PD. Previous studies on medication-induced cognitive changes (Cools et al., 2001, 2003; Frank et al., 2004; Swainson et al., 2000) have not included patients on pramipexole, although significant correlations between DA receptor agonist doses and reversal learning impairments have been noted (Swainson et al., 2000). Future studies with larger samples of patients with and without pramipexole are necessary to confirm that pramipexole underlies the reversal learning impairment.

The present study revealed a significant effect of dopaminergic medication, but failed to reveal a significant effect of disease. Thus, despite the well-recognized role of striatal DA in learning (Berger et al., 2004; Shohamy, Myers, Grossman et al., 2005), patients OFF medication did not show a statistically significant learning deficit in the current task. The present study may have lacked statistical power to detect a significant impairment in patients OFF medication, specifically in the unexpected reward condition. Nevertheless, the unimpaired performance of patients OFF medication in the current study in the context of significant impairment in the ON group as well as significant impairments in patients OFF medication on other learning tasks (Shohamy, Myers, Grossman et al., 2005) highlights the multifaceted nature of learning. The lack of a significant disease effect may relate to the fact that outcomes in our paradigm did not depend on the subjects responses, but rather on the highlighted stimuli. Functional imaging studies as well as work with experimental animals has revealed that response-outcome and stimulus-outcome learning implicate distinct neural systems (O'Doherty et al., 2004; Reading, Dunnett, & Robbins, 1991; Yin, Knowlton, & Balleine, 2004), which are differentially depleted in the early stages of PD (Kish et al., 1988). Specifically, whereas instrumental response-outcome learning is thought to involve the severely depleted dorsal striatum, stimulus-outcome learning (as measured here) has been associated with the relatively intact ventral striatum. Alternatively, the lack of significant impairment in patients OFF medication (in the unexpected reward condition) may relate to the fact that the present paradigm required simple as opposed to multi-dimensional or probabilistic discriminations (Frank et al., 2004; Shohamy et al., 2004). This is unlikely, however, given recent data that have specifically implicated dopaminergic medication (rather than the disease itself) in parkinsonian deficits on tasks requiring multi-dimensional discriminations (Swainson et al., 2006). A third possibility is that a significant impairment in patients OFF medication would have surfaced if we had increased the magnitude or salience of the rewards. Indeed, based on prospect theory, losses loom larger than gains and brain activity in the striatum differentiates between rewards and punishments of distinct magnitude (Breiter, Aharon, Kahneman, Dale, & Shizgal, 2001; Delgado, Nystrom, Fissell, Noll, & Fiez, 2000).

Our pattern of results is very similar to the data reported by Frank et al. (2004). These authors showed that PD patients OFF medication were better at avoiding a stimulus that had been previously associated with a negative outcome than at choosing a reward-associated stimulus. By contrast, patients ON medication learned more from positive than negative outcomes (Frank et al., 2004). Frank et al. (2004) also observed, early in learning, a reduced tendency to switch responding following negative feedback in patients ON medication relative to patients OFF medication. The present findings concur with these observations and reveal detrimental effects of medication on rapid, punishment-based cognitive flexibility. Whereas the probabilistic learning tasks used previously loaded highly on the ability to gradually form new associations, the present task required more readily the ability to rapidly change previously relevant responding. We found that the effect of medication was particularly pronounced on switch trials, when outcomes were unexpected and when they led to shifting. This suggests that the effect of dopaminergic medication in PD on gradual learning about punishment relative to reward may be related to, or may even be due to effects on the rapid (one-trial based) switching following unexpected punishment. However, this conclusion must be considered cautiously, given that supplementary analysis (albeit with small sample sizes) revealed that the effect of pramipexole was not disproportionately larger on switch trials than on nonswitch trials. Thus, the punishment-based deficit following pramipexole extended to nonswitch trials, suggesting that pramipexole had a more pervasive effect leading to difficulty also with the more gradual integration of the unexpected punishment in subsequent (post-switch trial) responding.

Our findings speak directly to our previous observation that patients ON medication were significantly impaired on reversal learning relative to control subjects (Cools et al., 2001). The results from the Frank et al. study were less clear in this respect: While their patients ON medication performed better than patients OFF medication when learning about negative outcomes, they did not actually perform more poorly than controls. By contrast, the present study showed significant medication-induced impairment relative to controls. Therefore, our data help to further define the nature of the detrimental 'over-dose' effect of medication on cognitive function in mild PD. Specifically, the present data suggest that the detrimental effect of medication is restricted to shifting based on punishment and does not extend to shifting based on reward.

Finally, the presently observed interaction between medication status and outcome valence considerably strengthens the previous observation and its construct validity by replicating and generalizing the finding to an entirely different paradigm. In particular, our results show that patients ON medication had selective difficulty with learning from negative, but not positive outcomes, even when the reward- and punishment-associated stimuli were equally relevant for responding. Thus, the learning deficit cannot be solely due to differential processing of behaviorally irrelevant information or response suppression, but rather must be due to specific difficulty with the processing of unexpected negative outcomes.

Our findings extend brain imaging and computational work suggesting different, possibly opponent representations of reward- and punishment-based learning signals (Daw et al., 2002; Delgado et al., 2000; Frank et al., 2004; O'Doherty et al., 2001; Seymour et al., 2005). The learning signal in these studies is the prediction error, which records changes from expected outcomes, thereby driving new learning (and flexibility). A negative

prediction error occurs when an outcome is worse than expected, whereas a positive prediction error occurs when an outcome is better than expected. The unexpected punishment in the present experiment constitutes a negative prediction error, while the unexpected reward serves as a positive prediction error. The prediction error signals have been suggested to be conveyed by phasic neuronal activity of DA neurons (Hollerman & Schultz, 1998). Specifically, phasic bursts of DA activity are thought to signal positive prediction errors, whereas phasic depressions ('dips') of tonic DA activity are thought to signal negative prediction errors (Hollerman & Schultz, 1998). In keeping with previous theorizing (Frank, 2005), we hypothesize that dopaminergic medication impaired punishment-based reversal shifting in the current study by blocking phasic 'DA dips' and attenuating associated negative prediction error signals. Based on our previous finding that dopaminergic medication in PD modulated the nucleus accumbens during reversal learning, we hypothesize that this attenuation occurs by dopaminergic modulation of the relatively intact nucleus accumbens (Cools et al., submitted for publication). This hypothesis is strengthened by the observation that the deficit is particularly pronounced in patients on pramipexole, which has high affinity for DA D3 receptors that are abundant in the ventral but not the dorsal striatum.

Although the hypothesis that dopaminergic medication attenuates the negative prediction error by blocking phasic 'DA dips' is parsimonious, several questions remain. First, the effects of dopaminergic medication on phasic DA bursts and, by inference, positive prediction errors are unclear. Some have argued that the increases in tonic DA levels should also block the phasic DA bursts and associated positive prediction errors (Shohamy, Myers, Geghman et al., 2005). Particularly in the face of this uncertainty, one might consider the alternative hypothesis that the medication-induced impairments relate to non-dopaminergic mechanisms. Of particular interest is the serotonergic neurotransmitter system, which has been implicated in negative processing biases seen in anxiety/depression and punishment-processing (Abrams, Johnson, Hollis, & Lowry, 2004; Fallgatter et al., 2004; Harmer, Shelley, Cowen, & Goodwin, 2004; Moresco et al., 2002). Critically, L-Dopa may inhibit the activity of tryptophan hydroxylase and interfere with serotonin synthesis (Arai, Karasawa, Geffard, & Nagatsu, 1995; Kuhn, 1999; Maruyama et al., 1992; Naoi, Maruyama, Takahashi, Ota, & Parvez, 1994). Similarly, DA D3 receptor agonists may decrease 5-HT turn-over (Lynch, 1997). Moreover, the aversive, negative prediction error has been proposed to be mediated by DA-opponent activity of serotonin-releasing neurons which also project to the ventral striatum (Daw et al., 2002). Accordingly, the medication-induced impairment in punishment-based reversal learning may relate to medication-induced central serotonin depletion, biasing processing away from non-rewarded or punished events. Although the present study cannot refute this alternative hypothesis, it may be noted that this hypothesis cannot easily account for the abnormal trend towards poorer performance of patients OFF medication in the reward condition relative to the punishment condition.

Regardless of the precise pharmacological mechanism underlying the medication-induced deficits, the reduced impact of unexpected punishment is a robust phenomenon (Frank et al., 2004; current data). The same dopaminergic medication that is accepted to remediate the frequently observed motor and cognitive inflexibility (Cools et al., 2001, 2003) impairs ventral striatal function by attenuating healthy punishment-induced control over inappropriate behavior. This deficit may well contribute to the impulsive behaviors seen in certain PD patients following medication, such as pathological gambling and addiction to medication intake (Dodd et al., 2005; Lawrence, Evans, & Lees, 2003; Seedat, Kesler, Niehaus, & Stein, 2000). In keeping with this hypothesis, impulsive decision making and drug addiction have been hypothesized to reflect myopia for future negative consequences (Bechara, 2005).

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