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SYMPOSIUM

Dissecting the Effects of Disease and Treatment on Impulsivity in Parkinson's Disease

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Abstract

Converging evidence, including observations in patients with Parkinson's disease (PD), suggests that dopamine plays a role in impulsivity. This multi-faceted construct includes considerations of both time and risk; determining how these more specific processes are affected by PD and dopaminergic treatment can inform neurobiological models. We examined the effects of PD and its treatment on temporal discounting and risky decision-making in a cohort of 23 mild-moderate PD patients and 20 healthy participants. Patients completed the Balloon Analogue Risk Task and a temporal discounting paradigm both on and off their usual dopamine replacement therapy. PD patients did not differ from controls in their initial risk-taking on the Balloon Analogue Risk Task, but took progressively more risks across trials when on medication. A subset of patients and controls was tested again, 1.5–3 years later, to explore the effects of disease progression. On follow-up, baseline risk-taking diminished in patients, but the tendency to take increasing risks across trials persisted. Neither disease progression nor its treatment affected the temporal discounting rate. These findings suggest a different neural basis for temporal discounting and risk-taking, and demonstrate that risk-taking can be further decomposed into initial and trial-by-trial effects, with dopamine affecting only the latter. (*JINS*, 2012, *18*, 942–951)

Keywords: Decision-making, Reinforcement learning, Self-control, Risk-taking, Human, Dopamine

INTRODUCTION

Impulsivity is broadly defined as action without foresight (Winstanley, Eagle, & Robbins, 2006); a definition that encompasses processes ranging from myopia for the future, to seeking potential rewards despite potential hazards (Bechara, Damasio, Damasio, & Anderson, 1994; Lejuez et al., 2002). While impulsivity may be adaptive in some situations, overly impulsive choices can threaten personal health and safety, as in clinical conditions like addiction, pathological gambling, and dopamine dysregulation syndrome in Parkinson's disease (PD) (Dagher & Robbins, 2009; Kirby & Petry, 2004; Voon & Fox, 2007).

While the neurobiology of impulsivity is not fully established, dopamine seems to play a central role. PD, a neurodegenerative disorder characterized by a loss of nigrostriatal dopamine neurons (Bruck et al., 2006; Kish, Shannak, & Hornykiewicz, 1988), provides an important model for studying these issues in humans. The loss of dopaminergic neurons in PD results in aberrant functioning of fronto-striatal circuitry (Albin, Young, & Penney, 1989; Cools, 2006; Frank, 2005) and has been associated with risk aversion and reduced reward seeking behavior (Evans et al., 2006; Menza, Golbe, Cody, & Forman, 1993; Ondo & Lai, 2008; Ragonese et al., 2003; Tomer & Aharon-Peretz, 2004). In contrast, in a small subset of PD patients, dopamine replacement therapy (DRT) can lead to impulse control disorders (Dagher & Robbins, 2009; Driver-Dunckley, Samanta, & Stacy, 2003; Seedat, Kesler, Niehaus, & Stein, 2000; Voon & Fox, 2007; Weintraub et al., 2010). Although causality has yet to be unequivocally established, it is thought these disorders result from interactions between DRT and intrinsic vulnerabilities to such behaviors in individual patients (van Eimeren, Monchi, Ballanger, & Strafella, 2009; Voon et al., 2010). A separate line of work has shown that PD and DRT influence feedback-driven learning (Cools, Altamirano, & D'Esposito, 2006; Frank, Samanta, Moustafa, & Sherman, 2007; Frank, Seeberger, & O'Reilly, 2004; Shohamy, Myers, Kalanithi, & Gluck, 2008; van Wouwe, Ridderinkhof, Band, van den Wildenberg, & Wylie, 2012). In principle, learning mechanisms could moderate maladaptive impulsivity in situations where choices can be repeated.

Research on the risk-taking aspect of impulsivity in Parkinson's patients has focused on lab-based gambling

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tasks. The most widely used task, the Iowa gambling task (Bechara et al., 1994) is complex (Dunn, Dalgleish, & Lawrence, 2006), and results to date are variable. Both impaired (Kobayakawa, Koyama, Mimura, & Kawamura, 2008; Mimura, Oeda, & Kawamura, 2006; Pagonabarraga et al., 2007; Perretta, Pari, & Beninger, 2005) and intact (Euteneuer et al., 2009; Stout, Rodawalt, & Siemers, 2001; Thiel et al., 2003) Iowa gambling task performance have been reported in PD. Small samples and between-group designs likely contribute to this variability. PD patients on DRT have shown greater risk-taking in a more specific risk-taking task, the Game of Dice, compared to healthy control subjects (Brand et al., 2004; Euteneuer et al., 2009), but this does not establish whether the effect is due to PD or its treatment.

Here, we used the Balloon Analog Risk Task (BART) to examine the effects of DRT and PD on baseline risk-taking and on risk-taking over repeated gambles, with feedback. The BART is a widely used measure of risk-taking with ecological validity, showing associations with real-world risk-taking such as alcohol and drug use, cigarette smoking, risky-sexual behaviors, and self-reported impulsivity (Aklin, Lejuez, Zvolensky, Kahler, & Gwadz, 2005; Bornovalova et al., 2009; Crowley et al., 2009; Hopko et al., 2006; Hunt, Hopko, Bare, Lejuez, & Robinson, 2005; Lejuez et al., 2002, 2003; Lejuez, Simmons, Aklin, Daughters, & Dvir, 2004). The task requires participants to pump up virtual balloons on a computer screen, gaining more money with each pump. Participants can collect their earnings at any time, but they also risk "losing it all," as each pump is associated with a monotonically increasing chance of balloon explosion with loss of the money earned up to that point on that trial. Thus, as the balloon inflates and potential winnings accumulate, the risk of explosion (and so monetary loss) also increases. The task provides feedback in the form of wins or explosions (losses), providing an opportunity for participants to learn about the riskiness of subsequent choices (Bishara et al., 2009). In principle, the task can thus distinguish initial risk-taking propensity from how risk-taking is influenced by feedback across repeated trials (Lejuez et al., 2003). Two recent studies using variations of this task in PD focused only on overall risk-taking: one found that DRT does not affect overall BART performance (van Eimeren, Ballanger, et al., 2009), and another suggested DRT increases overall risk-taking only in PD patients with impulse control disorders (Claassen et al., 2011). We pursue this issue in more detail, in patients without impulse control disorders, aiming to disentangle initial risk-taking from the effects of experience on repeated risk-taking.

Temporal discounting, the preference for smaller immediate rewards over larger delayed rewards, is a second impulsivity-related phenomenon (Ainslie, 2001). The rate at which a reward loses its subjective value across delay can be described by a hyperbolic or exponential function, the steepness of which varies across individuals (Ainslie, 2001; Kirby & Herrnstein, 1995; Madden, Begotka, Raiff, & Kastern, 2003), and is relatively stable over time, at least in healthy subjects (Kirby, 2009). Populations with impulse control problems, such as substance abusers, pathological gamblers and those with attention deficit/hyperactivity disorder, reliably show steeper discounting functions than healthy controls (Bickel & Marsch, 2001; Coffey, Gudleski, Saladin, & Brady, 2003; Housden, O'Sullivan, Joyce, Lees, & Roiser, 2010; Petry, 2002; Reynolds, 2006; Voon et al., 2010; Vuchinich & Simpson, 1998; Winstanley et al., 2006).

The dopamine-rich ventral striatum is among the brain regions implicated in temporal discounting (Cardinal, Winstanley, Robbins, & Everitt, 2004; Kable & Glimcher, 2007; McClure, Ericson, Laibson, Loewenstein, & Cohen, 2007; McClure, Laibson, Loewenstein, & Cohen, 2004; Peters & Buchel, 2009; Pine et al., 2009; Weber & Huettel, 2008; Xu, Liang, Wang, Li, & Jiang, 2009). Amphetamine and methylphenidate decrease discounting rates in healthy subjects (de Wit, Enggasser, & Richards, 2002; Pietras, Cherek, Lane, Tcheremissine, & Steinberg, 2003). The picture in PD is less clear, with medicated PD patients having discounting rates either similar to (Housden et al., 2010), or steeper than (Milenkova et al., 2011) those of healthy controls. DRT may increase discounting only in PD patients with impulse control disorders (Voon et al., 2010).

Heterogeneity of PD and baseline individual differences in impulsivity may explain the conflicting findings. Here, we used within-subject designs to examine the effects of DRT on risk-taking and temporal discounting in mild-moderate PD patients. The effects of PD progression were explored in a subset of PD patients and controls tested again 1.5–3 years later. To avoid complex interactions between pre-existing risk-taking tendencies, disease and treatment, we excluded patients with impulse control disorders.

MATERIALS AND METHODS

Subjects

Twenty-three patients with mild-moderate idiopathic Parkinson's disease (mean age, 65 years; *SD* 8.6) and 20 demographically matched healthy control subjects (HCTL) (mean age, 63 years; *SD* 7.4) participated in this study. Patients were recruited from the McGill University Health Centre Movement Disorders clinic. Healthy controls were recruited from the local community. Demographic and clinical data are shown in Tables 1 and 2. Experienced movement disorder neurologists identified PD patients without dementia or impulse control disorders for this study, based on comprehensive clinical assessment. All patients scored $\geq$24/30 on the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), a screening test for mild cognitive impairment, and were free of pathological gambling, confirmed by an average score of 0.04 ($SD = 0.2$) (range, 0–1) on the South Oaks Gambling Screen (SOGS; scores >5 suggest pathological gambling) (Lesieur & Blume, 1987). Patients with other neurological diagnoses that might affect cognition or overt clinical depression were excluded. Controls were excluded if they had a history of neurologic or psychiatric disease, closed head injury, or were taking psychoactive medication. They scored at

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Table 1. Characteristics of subjects (mean (*SD*))

Group	*N*	Education (years)	H & Y	Disease duration (years)	Estimated IQ	BDI	MoCA
PD	23	14.8 (4.2)	2.3 (0.5)	6.3 (6.1)	116.8 (9.1)	9.5 (4.4)**	26.6 (1.9)
HCTL	20	15.1 (3.1)	–	–	120.3 (11.5)	3.8 (3.9)	28.1 (1.4)

BDI, Beck Depression Inventory; MoCa, Montreal Cognitive Assessment.
**$p < .01$, PD-HCTL.

least 28/30 on the Folstein Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975). There was no significant difference between patients and controls with regard to age or education (*t* test, *p*'s $> .4$). PD patients had higher BDI scores ($t(44) = -3.07$, $p < .01$) compared to controls, although patient's scores were still well below the usual thresholds for depression on this scale.

The severity of motor signs was rated using Part III of the unified Parkinson's disease rating scale, UPDRS (Fahn & Elton, 1987), and motor function was assessed with the Purdue Pegboard (Lafayette Instrument Co). The mean onset of PD symptoms, by patient report, was 7.0 (5.9) years, and from diagnosis was 6.3 (6.1) years before enrollment. Hoehn and Yahr ratings (Hoehn & Yahr, 1967) ranged from 1.5 to 3. Seventeen patients were taking L-dopa/carbidopa, and 10 were taking dopaminergic agonists (ropinirole or pramipexole) in isolation or in combination with L-dopa therapy. Six patients were taking a COMT inhibitor (entacapone), 3 were taking MAO B inhibitors (selegiline or rasagiline) and 3 were taking amantadine. Additional medications included venlaflaxine (in 3 patients, none of whom were depressed at the time of testing) and trihexyphenidyl in 1 patient. All patients were on stable medication for at least 3 months before the study. Levodopa Equivalent Daily Dosage (LEDD) and Dopamine Agonist Levodopa Equivalent Daily Dosage (DA LEDD) calculated according to Pahwa et al. (1997) are shown in Table 2.

All participants completed two morning testing sessions, once while taking their usual medications, and once after an overnight (minimum 18 h) washout of their DRT, in a randomized order, at least 2 weeks apart. Participants continued all other medications as usual in the washout condition.

In the longitudinal portion of the study, all available PD subjects ($N = 12$) were tested again 1.5–3 years later. A demographically similar subset of the healthy controls ($N = 8$) was also re-tested longitudinally (L-HCTL), after the same interval. The longitudinal PD sub-group (L-PD) is likely biased toward subjects with slower disease progression; common reasons for non-participation in this portion of the study included emergence of mild dementia (as assessed by their neurologist) or severe motor disability (i.e., Hoehn and Yahr [H&Y] score ≥ 4).

At follow-up, patients showed evidence of disease progression with increasing DRT doses and H&Y staging (Table 3). BDI scores remained unchanged. At re-testing, 9 patients were taking L-dopa, and 5 were taking a dopaminergic agonist (pramipexole) in isolation or in combination with L-dopa therapy. Six were taking a COMT inhibitor (entacapone), 6 were taking an MAO B inhibitor (rasagiline) and 2 were taking amantadine. One was taking an antidepressant (venlafaxine) but was not depressed at time of testing. All participants gave written informed consent and were compensated for their time, in addition to receiving their winnings from the BART. The local research ethics committee approved the study.

Tasks

The BART involves pumping up a virtual balloon on a computer screen. Participants were given the following verbal instructions. "Throughout the task you will see 30 balloons, one at a time. For each balloon, you can press this button to increase the size of the balloon. You will get 1 cent in a temporary bank for each pump. You will not be shown the amount of money in your temporary bank. At any point, you can stop pumping up the balloon and press this button to collect your earnings. Pressing this button will start you on the next balloon and will transfer the money you have won from your temporary bank to your permanent bank. It is your choice to determine how much to pump up the balloon, but be aware at some point the balloon will explode. The explosion point varies across balloons, ranging from the first pump to enough pumps to make the balloon fill the entire computer screen. If the balloon explodes before you collect your earnings, then you move on to your next balloon and all the money in your temporary bank is lost.

Table 2. Motor symptom and treatment characteristics of Parkinson's patients (mean (*SD*))

			Purdue pegboard (# pins)					
	UPDRS (motor)		On		Off			
N	On	Off	RH	LH	RH	LH	LEDD (mg)	DA LEDD (mg)
23	12.0 (5.5)	15.2 (6.3)***	10.6 (2.3)	10.4 (1.8)	9.8 (2.3)*	10.0 (2.3)	541.6 (357.3)	79.7 (102.6)

RH, Right hand; LH, Left hand; LEDD, Levodopa equivalent daily dose; DA, Dopamine agonist.
***$p < .001$, On-Off; *$p < .05$, RH On-Off.

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Table 3. Clinical characteristics of longitudinal Parkinson's patients at initial testing and at follow-up (1.5–3 years later) (mean (S.D))

					Purdue pegboard (# pins)					
			UPDRS (motor)		On		Off			
Time	H & Y	Disease duration (years)	On	Off	RH	LH	RH	LH	LEDD (mg)	DA LEDD (mg)
Initial	2.2 (0.5)	6.3 (3.5)	13.0 (6.2)	18.3 (7.3)	10.7 (1.7)	10.4 (1.8)	10.0 (2.1)	9.7 (2.4)	586.7 (408.0)	163.3 (95.1)
Follow-up	2.6 (0.5)**	8.4 (3.3)	12.4 (6.1)	19.2 (9.0)	10.3 (1.4)	9.7 (2.6)	9.8 (2.0)	9.4 (2.0)	821.0 (460.9)*	164.2 (112.6)

RH, Right hand; LH, Left hand; LEDD, Levodopa equivalent daily dose; DA, Dopamine agonist.
$^{**}p < .01$; $^{*}p < .05$, Initial-Follow-up.

Exploded balloons do not affect the money accumulated in your permanent bank. At the end of the task, you will receive the money you earned in your permanent bank."

Participants completed a one-balloon practice trial (with no explosion) to ensure they understood the task. During the task, the probability that a balloon would explode was 1/128 for the first pump, 1/127 for the second and so on. Thus, after 64 pumps, the risk of loss begins to outweigh the chance of gains. The task involved 30 trials grouped into 3 blocks of 10 for the analysis, in keeping with prior work (Fecteau et al., 2007; Lejuez et al., 2003). The dependent measure was the average number of adjusted pumps for each block (the average number of pumps on trials when the balloon did not explode). Higher values reflect greater risk-taking. The average number of exploded balloons and earnings per block were also examined, as was the effect of a monetary loss (exploded balloon) on adjusted pumps in the subsequent trial, similar to recent work (Claassen et al., 2011). At the end of the session, participants received their earnings ($\leq$$11.00 CDN).

Temporal discounting rate was estimated with a widely used, computerized temporal discounting task (Fellows & Farah, 2005; Kirby & Marakovic, 1996; Kirby, Petry, & Bickel, 1999). In this task, subjects are asked to make hypothetical choices between various amounts of money now, and larger amounts delayed by 7–180 days. The task assumes a hyperbolic discounting function ($V = v/(1 + kD)$, where V is the current (subjective) value, v the absolute value, and D the delay), offering 27 choices across 9 values of k (k = 0.00016; 0.00040; 0.0010; 0.0025; 0.0060; 0.016; 0.041; 0.10; 0.25). By definition, choices should consistently favor the "now" option for k values less than the indifference curve, and the "later" option for k values larger than the indifference curve. Participants' choices are not always perfectly consistent; the best fitting k value was determined for each participant following published methods (Kirby et al., 1999). When more than one k value provided an equally good fit, the geometric mean of these values was used. We also report the number of inconsistent choices as a metric of "goodness of fit."

Statistical Analysis

Raw data from the BART were normally distributed. The k values and temporal discounting inconsistencies approximated normal distributions following logarithmic or square root transformations, respectively. All data were analyzed using analysis of variance (ANOVA) followed by *post hoc* pair-wise *t* tests where appropriate. Effect size, Cohen's d (Cohen, 1988), was calculated for contrasts of interest, using the Morris and DeShon (2002) equation to account for within-subject measures.

RESULTS

Effects of DRT and Parkinson's disease on Risk-Taking as Captured by the BART

Figure 1 shows the BART performance of the PD group both on and off DRT, as well as that of the HCTL group tested twice. There was a significant treatment by block interaction in the PD group ($F(2,44) = 8.75$; $p < .01$). Simple main effects analysis comparing performance in each block in on *versus* off DRT conditions revealed patients pumped significantly more on the last block of trials on DRT compared to off ($p < .05$; $d = 0.63$). There was a similar trend in the second block ($p = .07$). Similarly, simple main effects analysis comparing performance in each block, within treatment conditions, showed only medicated patients pumped significantly more across blocks. Tukey's HSD test revealed medicated patients pumped more on the second and third blocks, relative to their own performance on the first block (all p's $< .01$; d's = 1.1; 1.5, respectively). Patients off DRT showed stable performance across blocks. When medicated

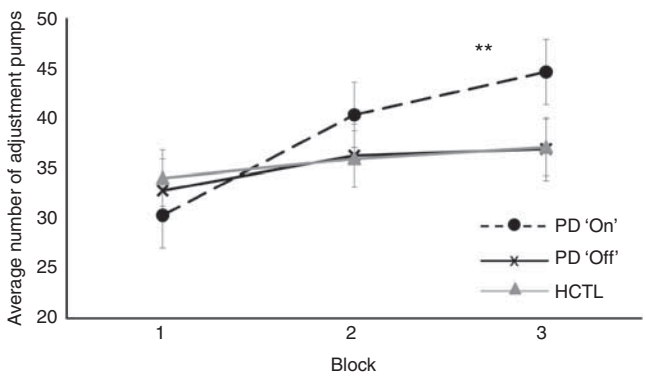

Fig. 1. Average number of adjusted pumps on the BART for Parkinson's patients (PD; on and off dopamine replacement therapy) and healthy control subjects (HCTL). Error bars indicate *SEM*. $^{**}p < .01$, treatment by block interaction for Parkinson's patients.

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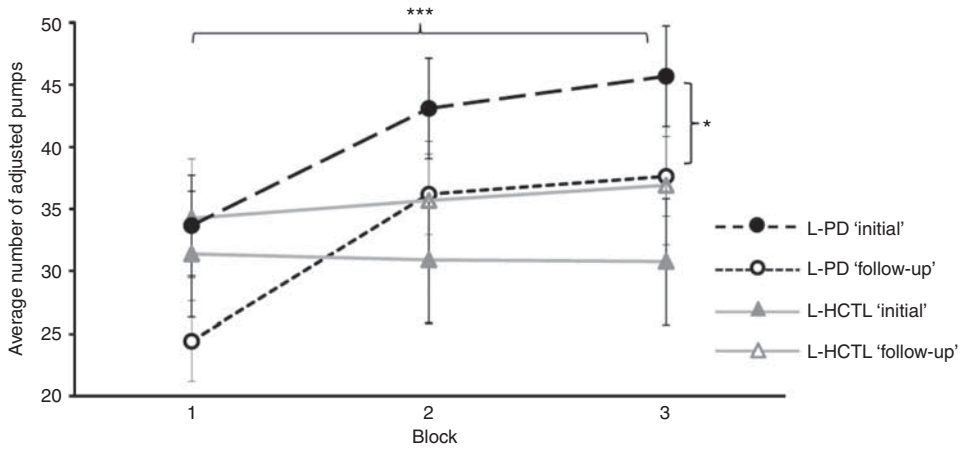

Fig. 2. Average number of adjusted pumps on the Balloon Analog Risk Task (BART) for Parkinson's patients and healthy control subjects, at initial testing and at follow-up (longitudinally). Errors bars indicate *SEM*. *$p < .05$, main effect of time for Parkinson's patients; ***$p < .001$, main effect of block for Parkinson's patients. L-PD = longitudinal Parkinson's disease sub-group; L-HCTL = healthy controls re-tested longitudinally.

PD patients were compared to HCTL, there was again a significant interaction of group by block ($F(2,82) = 6.0$; $p < .01$), driven by the increasing number of pumps made by the PD group across blocks, compared to the stable performance of HCTL. There was no significant interaction or main effects when PD patients off DRT were compared to HCTL. The total number of adjusted pumps was similar in all groups (t tests, all p's $> .05$): [mean, (*SD*)], PD "on" 38.43 (13.0); PD "off" 35.31 (11.7), HCTL 35.67 (9.7)].

As expected, the number of exploded balloons for each block was closely correlated with adjusted pumps ($r = 0.91$) and showed exactly the same pattern of significant effects when entered into the statistical analysis described above. The total number of explosions was similar across groups (t tests, all p's $> .05$): [mean, (*SD*)]: PD "on" 9.14 (3.9); PD "off" 8.48 (4.3); HCTL 8.34 (3.0). The money earned in the task is a coarser, more integrative measure of performance. All groups earned more money across blocks (effect of block, all p's $< .05$). There were no significant interactions of group or treatment with block, and overall, total earnings were similar in all groups (t tests, all p's $> .05$): [mean, (*SD*)], PD "on" $7.43 (1.50); PD "off" $7.27 (1.51); HCTL $7.35 (1.53).

Effects of Disease Progression on Risk-Taking as Captured by the BART

As shown in Figure 2, disease progression in the L-PD group was associated with a reduction in the average number of adjusted pumps (effect of time, $F(1,11) = 6.09$; $p < .05$; $d = 0.8$), nevertheless, the pattern of increasing pumps across blocks persisted (effect of block, $F(2,22) = 32.23$; $p < .001$). In contrast, the L-HCTL group showed stable performance across time points and across blocks. In line with these within-subject findings, there were significant interactions between group (L-PD *vs.* L-HCTL) and block, at initial testing ($F(2,36) = 6.00$; $p < .01$), and at follow-up ($F(2,36) = 4.38$; $p < .05$). The total number of adjusted pumps was similar between groups at initial testing and at follow-up (t tests, all p's $> .05$): [mean, (*SD*)], L-PD "initial" 40.8 (12.2); L-HCTL "initial" 31.0 (10.9); L-PD "follow-up" 32.7 (8.8); L-HCTL "follow-up" 35.6 (8.8).

The explosion analysis again showed the same pattern of significant effects as for pumps. The total number of explosions was similar between groups at initial testing and at follow-up (t tests, all p's $> .05$): [mean, (*SD*)], L-PD "initial" 9.7 (3.4); L-HCTL "initial" 7.5 (3.7); L-PD "follow-up" 7.2 (2.8); L-HCTL "follow-up" 8.8 (4.2).

Finally, earnings also dropped with disease progression in the L-PD group (effect of time, $F(1,11) = 4.91$; $p < .05$), but continued to increase across blocks (effect of block $F(2,22) = 8.66$; $p < .01$). The L-HCTL group's overall earnings remained stable across time, and increased across blocks as well. Overall earnings were similar between groups at initial testing and at follow-up (t tests, all p's $> .05$): [mean, (*SD*)], L-PD "initial" $7.83 (1.17); L-HCTL "initial" $7.49 (1.21); L-PD "follow-up" $7.14 (1.29); L-HCTL "follow-up" $7.54 (1.13).

Effect of a Loss on Risk-Taking in the Subsequent Trial

When the average number of adjusted pumps on post-explosion trials was compared to that on all other trials, for each block, we found a significant effect of trial type within each group. PD patients "on" ($F(1,19) = 12.11$; $p < .01$, d = 3.2) and "off" DRT ($F(1,17) = 6.29$; $p < .05$; $d = 2.9$), as well as healthy controls ($F(1,19) = 11.25$; $p < .01$; $d = 4.1$), made significantly fewer pumps on trials immediately following a monetary loss (explosion). Only medicated PD patients showed an effect of block ($F(2,38) = 18.44$; $p < .01$), pumping more across blocks in both trial types. There was no effect of treatment in the PD patients ($F(1,22) = 0.35$; $p > .05$), nor effect of group in the PD ("on"; "off") *versus* HCTL comparisons (all p's $> .05$).

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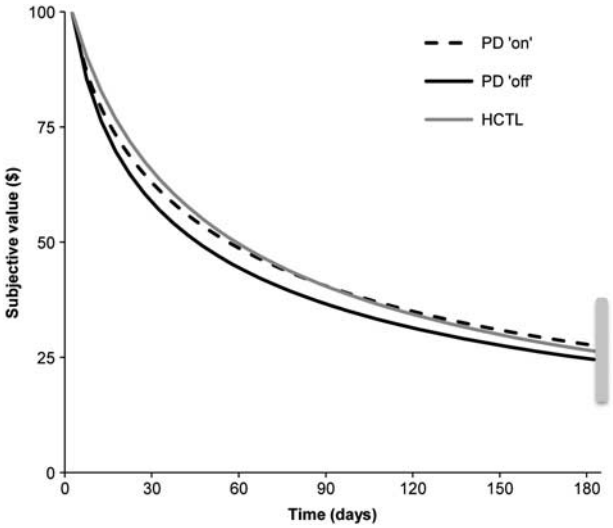

Fig. 3. Temporal discounting curves illustrating the average temporal discounting rate for Parkinson's disease (PD) patients on and off dopamine replacement therapy (DRT), and for healthy control subjects, for a hypothetical $100 CDN. The gray bar indicates the 95% confidence interval for the control group (HCTL). There was no significant difference between groups, or significant medication effect in the PD group.

A similar pattern of significantly reduced risk-taking on the trial immediately following an explosion was found in the patients and healthy controls tested longitudinally.

BART performance, measured by overall score and mean difference between the first and last block, was not significantly related to DRT dose (LEDD and DA LEDD), age, age at onset, BDI score, duration of illness at enrollment, or gender (all p's $> .05$).

Effects of DRT and Parkinson's Disease on Temporal Discounting

The mean discounting rates were similar in the "on" and "off" conditions ($t(22) = 0.24$; $p > .05$) and comparable to that of healthy controls in both conditions (all p's $> .05$). The (geometric) mean discounting coefficient, k (*SD*), for each group, was: PD "on" 0.009 (0.066); PD "off" 0.012 (0.059); HCTL 0.013 (0.023). In other words, $100 CDN in 6 months would be of subjectively equal value to $38 now for PD "on," $31 for PD "off" and $30 for HCTL. Figure 3 shows prototypic temporal discounting curves for the 3 groups.

We performed an additional analysis to explore the mean number of inconsistent responses. Choices that differed from those predicted by the overall best fitting discounting function for each subject, on each testing occasion, were counted as inconsistencies. These could be considered deviations from subjective value maximization (Camille, Griffiths, Vo, Fellows, & Kable, 2011; Fellows & Farah, 2007), or could result from systematic departures from the presumptive hyperbolic discounting function. The mean number of inconsistencies in each group was small [mean (*SD*)]: PD "on" 1.3 (1.2); PD "off" 0.6 (0.9); HCTL 1.0 (1.1). This value was significantly greater for PD patients on DRT relative to "off" (paired t test, $t(22) = 2.24$; $p < .05$; $d = 1.2$). There were no between group differences. All subjects were as likely to make inconsistent choices for "now" or "later" options, suggesting these inconsistencies reflected "noisy" choices rather than systematic changes in the discounting function.

Effects of Disease Progression on Temporal Discounting

Progression of PD was not associated with a change in temporal discounting rate, $t(11) = 0.65$; $p > .05$. L-HCTL subjects also showed stable discounting on follow-up. There were no significant differences between groups either initially or at follow-up. The (geometric) mean discounting constant, k (*SD*), for each group was: L-PD "initial" 0.010 (0.087); L-PD "follow-up" 0.013 (0.063); L-HCTL "initial" 0.011 (0.031); L-HCTL "follow-up" 0.015 (0.030).

Temporal discounting was not significantly related to DRT dose (LEDD and DA LEDD), age, age at onset, BDI score, duration of illness at enrollment, or gender (p's $> .05$).

DISCUSSION

We used laboratory measures of risk-taking and temporal discounting with established real-world validity to assess the effects of DRT on risky and impulsive decision-making, in a cohort of mild-moderate PD patients free of clinical impulse control disorders. We found DRT did not affect global measures of impulsivity: overall risk-taking as measured by the BART, or temporal discounting rate. Furthermore, mild-moderate PD did not substantially affect these measures compared to healthy controls. However, DRT did affect BART performance across blocks, arguing DRT affects how experience influences repeated risky choices.

A single prior study administered the BART to PD patients on and off DRT (van Eimeren, Ballanger, et al., 2009), while another examined the effects of pramipexole, a D2/D3 agonist, on BART performance in healthy subjects (Hamidovic, Kang, & de Wit, 2008). These studies agree with our findings of no significant effects of dopamine manipulation on overall task performance, but neither examined the dynamics of risky choice across trials. Here, we show risk-taking as measured by the BART can be decomposed into initial tendencies and block-wise effects, with DRT affecting only the latter.

People generally err on the side of caution in risky situations. This was evident here: the average number of adjusted pumps (overall and across blocks) for all groups was well below what would have yielded maximal earnings, as is typical for healthy subjects and even clinical populations in other studies using this task (Lejuez et al., 2003; van Eimeren, Ballanger, et al., 2009). While the medicated PD group made increasingly risky choices over the course of the task, they approached more optimal performance. Thus DRT yielded adaptive changes in risk-taking in this particular context. Whether this tendency would lead to harmful consequences in other risk settings, or with more trials in the present task, remains an open question.

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These observations provide a novel perspective on risk-taking related to PD, emphasizing the influence of experience and learning on risk-taking in situations where gambles are repeated, with feedback. We speculate this relates to the growing evidence that DRT has specific effects on reinforcement learning in PD (Cools et al., 2006; Frank et al., 2007; Jahanshahi, Wilkinson, Gahir, Dharminda, & Lagnado, 2010). In animals, rewards are associated with phasic increases, and punishment or reward omission is associated with dips in dopamine firing; these changes are thought to serve as teaching signals underlying reinforcement learning. Phasic dopamine increases are thought to act preferentially on D1 receptors, and via the direct basal ganglia pathway, supporting "go" learning. Dopamine dips may act more through a D2 receptor mechanism, via the indirect pathway, reducing the likelihood of subsequent responses (Frank, 2005). Consistent with this model, PD patients show relatively enhanced learning from reward compared to punishment when on DRT (Frank et al., 2004, 2007). In line with these findings, we propose here that DRT shifts the balance toward learning more from gains than losses in the BART, leading to the tendency to take increasing risks across trials when on DRT. At the trial-by-trial level, DRT did not detectably affect behaviour immediately following a loss: whether on or off medication, PD patients were more cautious on post-explosion trials, as were controls. However, this immediate reaction did not translate into more global tendencies toward caution, to the extent this can be detected in this task. Future work might fruitfully apply tasks better suited to measuring distinct effects of reward and punishment in risky contexts to follow-up on this idea.

At the least, this work suggests that models of risk-taking in PD would benefit from looking beyond "one shot" risk-taking contexts. DRT effects on learning, particularly from reward, may be a critical factor in the repeated, cumulative risk-taking that is often seen in everyday settings such as casinos or shopping centers.

The longitudinal portion of this study, while including only part of the original cohort, offered a unique opportunity to explore the effects of PD progression on impulsivity. The longitudinally followed control group showed no change in overall risk-taking or temporal discounting, but the PD patients were more risk-averse compared to their own performance 1.5–3 years earlier. Of interest, even though they were more risk-averse overall, these DRT-treated patients continued to take increasing risks across blocks of the BART, different from the stable performance of the control group.

In contrast to the clear effects of PD and DRT on these two different aspects of risk-taking, we found no consistent effect of either disease or treatment on temporal discounting. The widely used measure of temporal discounting we used has previously detected group differences in a variety of clinical populations. Only one prior study applied the same task we used to PD patients on and off DRT. Milenkova et al. (2011) reported no significant effect of dopamine manipulation on discounting rates, consistent with our finding, but found steeper discounting in PD patients relative to healthy controls, whether the patients were on or off DRT. Here, we show PD patients do not differ from healthy controls on this measure, consistent with findings from Housden et al. (2010) who reported steeper discounting only in PD patients with impulse control disorders but not in otherwise healthy medicated PD patients. Given the wide variability in temporal discounting in healthy subjects, any between group differences detected with such designs in PD likely reflect sampling biases or chance rather than disease or dopamine related influences.

This task has been successfully applied to measure changes in temporal discounting within-subject in other contexts: temporal discounting rates were reduced by d-amphetamine and methylphenidate in healthy subjects (de Wit et al., 2002; Pietras et al., 2003). However, recent work by Hamidovic et al. (2008) failed to find an effect of acute low (0.25 mg) and medium (0.50 mg) doses of the D2/D3 agonist pramipexole in healthy subjects with this task. An effect of DRT in PD patients has been reported with a different temporal discounting task involving experienced (much briefer) delays, but again, only in those with clinically evident impulse control disorders (Voon et al., 2010).

The findings we report suggest a distinction between risk-taking and temporal discounting, in terms of the effects of DRT and disease progression, arguing for different neurobiological (likely non-dopaminergic) contributions to these two aspects of behavior. As with any complex behavioral measures, it is difficult to fully exclude the alternative explanation that there are differences in the measurement properties of the tasks. We think this is less likely: neither task was at floor or ceiling, the measures were remarkably stable over time in the control group, and, as reviewed above, at least some prior work using these tasks in other conditions has shown detectable differences.

Although DRT and PD were not associated with changes in the steepness of temporal discounting, a secondary analysis revealed that DRT did affect decision-making in the temporal discounting task. Patients made more inconsistent choices while on DRT compared to off. One potential explanation for this observation is that DRT impaired the ability to consistently estimate the subjective value of relative reward. There was no bias in the direction of this inconsistency; patients were as likely to make inconsistent choices for "now" or "later" options. Damage to the orbitofrontal cortex has shown similar effects on other kinds of preference judgments (Camille et al., 2011; Fellows & Farah, 2007; Henri-Bhargava, Simioni, & Fellows, 2012), raising the possibility that changes in dopamine modulation within orbitofrontal cortex may have mediated this effect.

In conclusion, PD patients on DRT showed increasing risk-taking across trials of the BART, which was not present when they were off DRT, or in healthy controls. This effect was distinct from initial risk-taking in this task, which resembled that seen in controls, but declined as the disease advanced. We speculate that the tendency of PD patients to learn more from reward on DRT, and more from punishment off DRT (Frank et al., 2004) may underpin this risk-taking

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momentum in conditions where gambles are repeated. That is, dopamine may have a particular role in "knowing when to walk away" from risky choices.

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