



## Full-length Article

# Aberrant reward processing in Parkinson's disease is associated with dopamine cell loss

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## ARTICLE INFO

## Article history:

Received 3 August 2011

Revised 14 November 2011

Accepted 24 November 2011

Available online 6 December 2011

## Keywords:

Impulsivity

Dopamine

SPECT

Flexibility

Reward

Parkinson's disease

## ABSTRACT

Dopamine has been implicated in reward-related impulsivity, but the exact relationship between dopamine, reward and impulsivity in humans remains unknown. We address this question in Parkinson's disease (PD), which is characterized by severe dopamine depletion. PD is associated primarily with motor and cognitive inflexibility, but can also be accompanied by reward-related impulsivity. This paradoxical symptom of PD has often been attributed to dopaminergic overstimulation by antiparkinson medication, which is necessary to relieve the motor and cognitive inflexibility. However, factors other than medication may also contribute to aberrant impact of reward. Here we assess whether cognitive inflexibility and aberrant reward impact in PD are two sides of the same coin, namely dopamine cell loss. To measure dopamine cell loss, we employed <sup>123</sup>I-FP-CIT Single Photon Emission Computed Tomography (SPECT) in 32 PD patients (10 never-medicated patients and 22 patients after withdrawal of all medication for > 12 h) and related the values to behavior on a rewarded task-switching paradigm. Dopamine cell loss was associated not only with cognitive inflexibility (under low reward), but also with aberrant impact of reward. These effects could not be attributed to medication use. Relative to controls ( $n = 26$ ), aberrant reward processing in PD was particularly expressed as reduced capacity to maintain (i.e., repeat) the current task-set under high reward. Our findings demonstrate that factors intrinsically related to PD may underlie the paradoxical symptoms of inflexibility and reward-related impulsivity in PD. The present results concur with observations that low baseline dopamine states predispose to drug and other addictions.

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## Introduction

Dopamine has long been implicated in reward motivation and impulsivity. However, the precise nature of the relationship between dopamine, reward and impulsivity remains unclear. Here we address this issue by assessing reward processing in Parkinson's disease (PD), a neurodegenerative disorder characterized by severe dopamine loss. PD can be accompanied by compulsive drug taking (i.e., dopamine dysregulation syndrome) and/or impulse control problems, such as pathological gambling, compulsive shopping, and hyper-sexuality (Evans et al., 2009; Voon et al., 2011; Weintraub et al., 2010). According to

recent understanding, such impulsive–compulsive behavior may result from the common dopaminergic medication that is prescribed to treat the motor and cognitive symptoms of PD, such as the D2/3 receptor agonists and levodopa (Gallagher et al., 2007; Pontone et al., 2006; Weintraub et al., 2010). In particular, we and others have put forward the dopamine overdose hypothesis, stating that medication doses that are necessary to remedy severe dopamine depletion in the dorsal striatum might detrimentally overdose relatively intact dopamine levels in the ventral striatum (Cools et al., 2001a, 2003; Cools et al., 2007a; Swainson et al., 2000). Remediation of dorsal striatal dopamine would lead to restoration of motor and cognitive inflexibility, whereas overdosing of ventral striatal dopamine would contribute to aberrant reward sensitivity and impulsivity. This theory concurs with the implication of dopamine in reward and incentive motivation (Dagher and Robbins, 2009), and with the well-known dopamine-releasing properties of drugs and other rewards of abuse (Boileau et al., 2006; Di Chiara and Imperato, 1988; Leyton et al., 2002).

However, factors unrelated to medication have also been implicated in aberrant reward sensitivity and impulsivity in PD, for instance

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premorbid personality and genetic vulnerability (Dagher and Robbins, 2009; Evans et al., 2009). Furthermore, in apparent contradiction to the overdose hypothesis, trait impulsivity has been associated with low dopamine function (Buckholz et al., 2010; Cools et al., 2007b; Dalley et al., 2007). Specifically, pathological gambling and other addictions have been hypothesized to reflect self-medication of a reward-deficient state (Blum et al., 2000; Reuter et al., 2005). If true, then the aberrant impact of reward in PD might be related, at least in part, to degeneration of dopamine cells. This implies that the dopamine-depleted state of PD should be accompanied not only by motor and cognitive inflexibility, but also by aberrant impact of reward.

Here we investigated associations between, on the one hand, cognitive inflexibility and reward impact, and on the other hand, the degree of dopamine cell loss of mild PD patients. Cognitive inflexibility was anticipated to be positively associated with dopamine cell loss. Furthermore, aberrant reward impact was hypothesized to be greatest in patients with the greatest dopamine cell loss. To test this hypothesis, dopamine cell loss was quantified using pre-synaptic dopamine transporter (DaT) imaging with  $^{123}\text{I}$ -FP-CIT Single Photon Emission Computed Tomography (SPECT). Patients performed a behavioral task that allowed us to quantify cognitive inflexibility as well as the impact of reward. Specifically, we used a task-switching paradigm where each trial was preceded by either a high or low reward cue (Aarts et al., 2010). Cognitive inflexibility was indexed by the ability to switch between tasks under low reward. Previous task-set switching studies in PD have found that switch deficits were restricted to switching between well-established sets, and did not extend to new, to-be-learned sets (Cools et al., 2001b; Lewis et al., 2005; Slabosz et al., 2006). Because the best established task (here, the arrow task) is known to evoke larger switch costs than the least established task (here, the word task) (Wylie and Allport, 2000), we expected cognitive inflexibility in PD to be most pronounced in the arrow task.

## Materials and methods

### Participants

We included 32 early- to moderate-stage PD patients (withdrawn from their dopaminergic medication or never medicated) and 26 matched controls (Table 1). All participants gave written informed consent according to institutional guidelines of the local ethics committee (CMO region Arnhem-Nijmegen, The Netherlands). All participants

**Table 1**  
Patient and control group characteristics.

	Parkinson's disease <sup>a</sup> ( <i>n</i> = 32)	Control ( <i>n</i> = 26)
Gender, men	23 (72%)	15 (58%)
Age, years	57.7 (10.0)	59.6 (7.1)
Age range, years	40–74	42–69
Education level	5.9 (0.7) <sup>b</sup>	6.2 (0.6)
BIS	19.2 (3.7)	18.8 (3.2)
BAS – reward <sup>c</sup>	16.3 (1.8)	15.3 (1.6)
BAS – drive	12.6 (1.7)	13.0 (1.6)
BAS – fun	11.9 (2.0)	11.5 (2.2)
BAS – TOTAL	40.8 (4.1)	39.8 (3.7)
UPDRS-III	26.3 (7.6)	
Hoehn and Yahr	2.0 (0.2)	
Disease duration, years <sup>d</sup>	4.1 (2.2)	

Values represent mean (SD). Education level on a range from 1 to 7. BIS = Behavioral Inhibition System (here, a high score means a high trait); BAS = Behavioral Approach System (here, a high score means a high trait); UPDRS-III = motor section of the Unified Parkinson's Disease Rating Scale.

<sup>a</sup> Patients were never-medicated or tested in a practically defined OFF state.

<sup>b</sup> 1 missing data point in patient group.

<sup>c</sup>  $p < .05$  (2-tailed independent-samples *t*-test).

<sup>d</sup> Defined as the time since the patient subjectively noticed the first symptoms.

were native Dutch speakers. They were paid for participation according to institutional guidelines. 31 PD patients were included in the SPECT analyses, because DaT binding values of one patient were unavailable.

Patients were recruited from the Parkinson Centre at the Radboud University Nijmegen Medical Centre. Patients were included when they had idiopathic PD, diagnosed according to the UK Brain Bank criteria by an experienced movement disorders specialist (B.R.B.). Exclusion criteria were cognitive dysfunction (mnemonic or frontal executive problems) and other neurological or psychiatric diseases (including impulse control disorders, compulsive medication intake, and depression), as assessed by the movement disorder specialist during the clinical consults. Executive functioning in PD was also tested with the frontal assessment battery (FAB, Dubois et al., 2000), on which none of the patients scored lower than 14 (avg: 17; SD: 1.2). Ten patients had never used any anti-Parkinson medication; six used levodopa, four dopamine receptor agonists, ten a combination of levodopa and dopamine receptor agonists, and two MAO-B inhibitors. The experiments were carried out in the morning, at least 12 h after the last dose of dopaminergic medication.

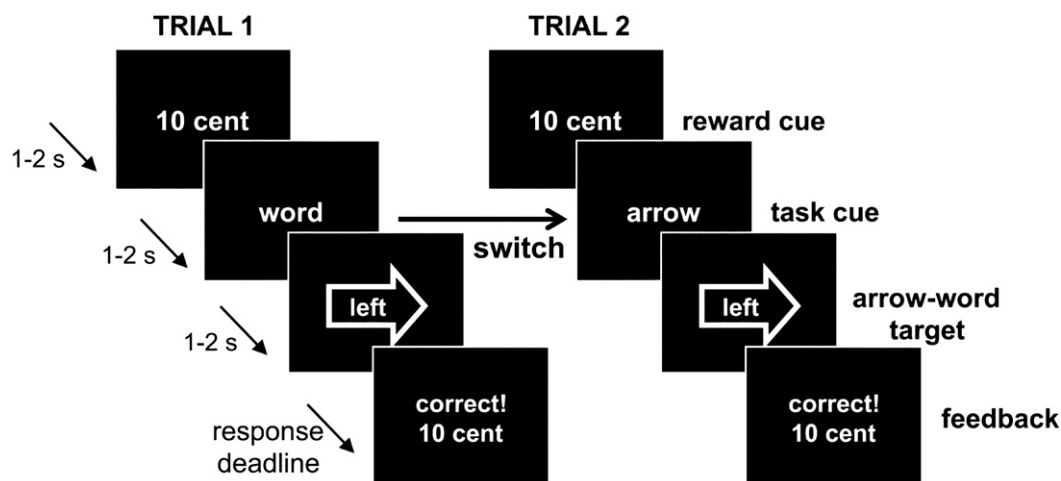
None of the controls had current major health problems or history of neurological/psychiatric illness. Patients and controls were matched on gender, age, and education level (Table 1).

### General procedure

Measurements in PD patients were performed on two separate occasions, separated by less than three months. On day 1, each patient received a structural MRI scan, and disease severity and FAB were assessed clinically. Each patient's disease severity was measured using the Hoehn & Yahr stages and the Unified Parkinson's Disease Rating Scale (UPDRS). On day 2, patients performed a computerized rewarded switching task (see below) and they received a  $^{123}\text{I}$ -FP-CIT SPECT scan to measure the amount of presynaptic dopamine transporter (DaT) binding. Patients performed the behavioral experiment approximately 30 min after the injection of  $^{123}\text{I}$ -FP-CIT, and before the actual SPECT scan (which was performed three hours after injection of the isotope). All patients also completed the Dutch version of the Behavioral Inhibition System and Behavioral Activation System (BIS/BAS) scales (Carver and White, 1994; Franken et al., 2005), a questionnaire that assesses two aspects of personality; one related to reward sensitivity (BAS) and one related to behavioral inhibition/anxiety (BIS). The BAS scales include positive affect and excitability (BAS reward responsiveness) (e.g., "When good things happen to me, it affects me strongly"). Measurements in healthy controls were performed on one day: subjects completed the same behavioral task and BIS-BAS questionnaire as the PD group. Healthy control subjects did not undergo SPECT or structural MRI, because in this project we aimed to relate the expected behavioral changes in PD patients to the pathological substrate of PD (striatal dopamine loss).

### Rewarded task-switching paradigm

Participants performed a pre-cued task-switching task designed to measure effects of reward on cognitive performance (Fig. 1). Participants switched between responding according to the direction of the arrow (task A) and responding according to the direction indicated by the word (task B) of a series of incongruent Stroop-like arrow-word targets (consisting of the words "left" or "right" in a left or right pointing arrow, with the meaning of the word and direction of the arrow always in conflict). Repetitions or switches of task-set were pseudo-randomly preceded by high (10 cents) or low (1 cent) reward cues. In a previous fMRI study with the same paradigm in healthy young adults (Aarts et al., 2010), the reward cues evoked differential incentive motivation, both behaviorally and in terms of brain activity (e.g., in ventral striatum). The task was identical to the one described previously (Aarts et al., 2010), with the exception of



**Fig. 1.** In both of these example trials from the experimental paradigm, the reward-cue indicated that the participant could earn 10 cents with a correct and sufficiently quick response (as opposed to 1 cent in the low reward condition). The task-cue told the participant to respond to the word of the incongruent arrow-word Stroop-like target in the first trial (correct response: button press with the left index finger), but to the arrow of the incongruent arrow-word Stroop-like target in the second trial (correct response: button press with the right index finger). Hence, the second trial is an example of a switch of the task relative to the previous trial (as opposed to a repetition of the same task, independent of a left or right button press). Immediately after the response, feedback was given with the amount of reward the participant had earned for this specific trial. There was a variable delay of one to two seconds between cues and targets in which participants had to fixate on an asterisk in the middle of the screen. The whole experiment lasted about 30 min with a self-paced break after every 40 trials. In the break, the amount of money the participant had earned thus far in the experiment was displayed on the screen.

shorter inter-trial and inter-stimulus intervals (1–2 s instead of 2–6 s) and more trials (240 instead of 160).

#### Striatal regions of interest

We used an automated segmentation procedure implemented in FSL to define the putamen, caudate and nucleus accumbens in each individual patient (FIRST v1.1; see [www.fmrib.ox.ac.uk/fsl/first](http://www.fmrib.ox.ac.uk/fsl/first) and Patenaude et al., 2011 for details). FIRST is a model-based segmentation and registration tool. The shape/appearance models are constructed from 336 manually segmented T1-weighted MR images. FIRST searches through linear combinations of shape modes of variation for the most probable shape instance given the observed intensities in the T1 images. This results in subject-specific images centered in MNI space, including the putamen, caudate and nucleus accumbens. Subsequently, we separated the putamen into a posterior and an anterior part, to account for the well-known functional differences between these regions (Lehericy et al., 2005; Postuma and Dagher, 2006), and to account for the uneven amount of dopamine depletion between these regions in PD, which is most severe in the posterior putamen (Kish et al., 1988). The border between these two regions was defined as the line passing through the anterior commissure, following previous studies (Helmich et al., 2010; Postuma and Dagher, 2006). To avoid partial volume effects (i.e. averaging of signals from two functional compartments into one voxel), we left a gap of 3 mm between the posterior ( $y < -1$ ;  $32 \pm 1\%$  of total volume) and anterior ( $y > +1$ ;  $68.2 \pm 1\%$  of total volume) subdivisions of the putamen. Voxels in this gap were excluded. This procedure resulted in eight subject-specific striatal ROIs: the left and right posterior putamen (3.9 ml), anterior putamen (5.0 ml), caudate nucleus (5.4 ml) and nucleus accumbens (1.2 ml) (Fig. 2A).

#### SPECT measurements

Thirty one PD patients received a presynaptic dopamine transporter (DaT) scan, using  $^{123}\text{I}$ -FP-CIT. See Supplement 1b for details. Briefly, each subject's SPECT scan was coregistered to his or her anatomical MRI scan using SPM5. This procedure allowed us to calculate average DaT binding in the subject-specific basal ganglia ROIs (see Striatal regions of interest).  $^{123}\text{I}$ -FP-CIT binding in the basal ganglia was normalized with respect to the visual cortex. DaT density was estimated by computing the

specific-to-non-displaceable equilibrium partition coefficient ( $V''_3$ ) (Scherfler et al., 2005). Differences in DaT binding were assessed between the different striatal sub-regions. We also computed associations between regional DaT binding and clinical measures of disease severity.

#### Data analysis

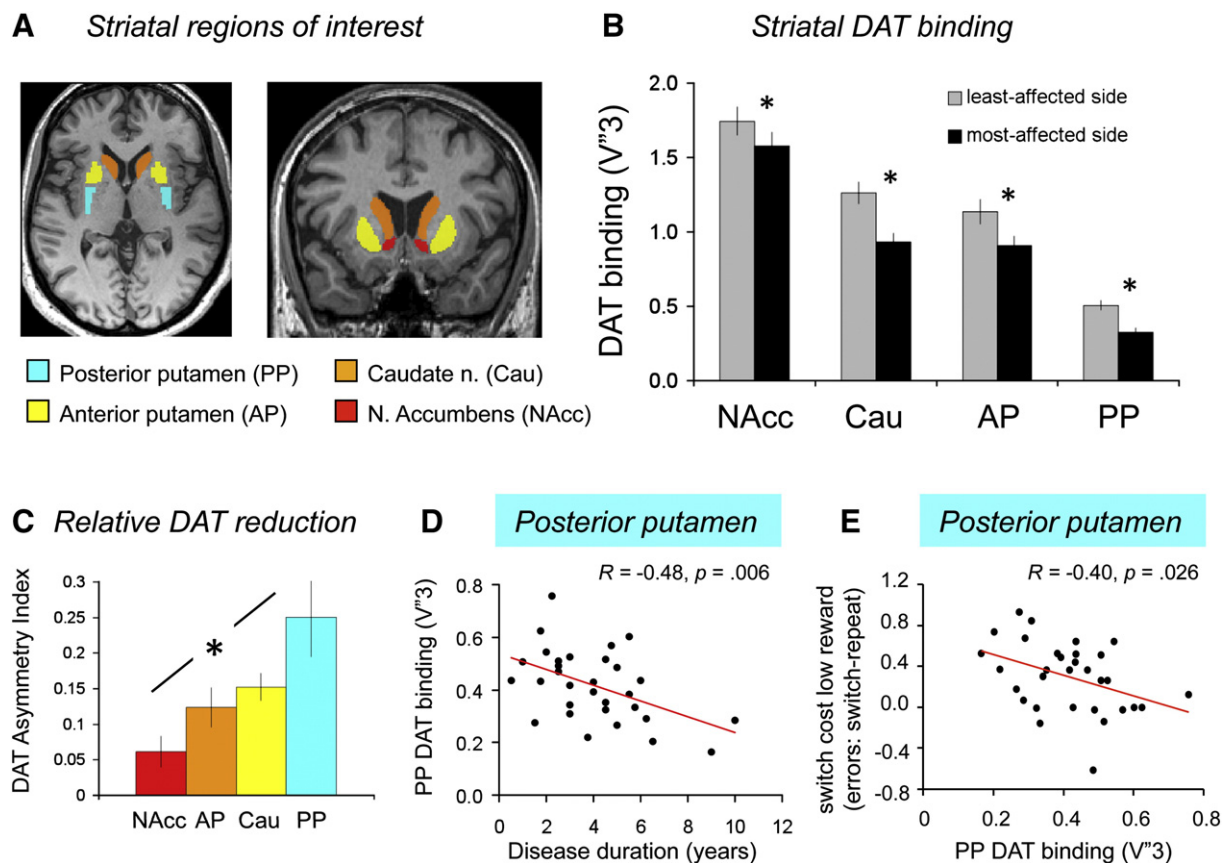
##### PD patients

Reaction times (RTs) and error rates were analyzed with SPSS 15.0 (SPSS Inc., Chicago, IL, USA). We used an analysis of variance (ANOVA) with within-subjects factors REWARD (high, low), TASK (arrow, word), and TRIAL-TYPE (repeat, switch), and DaT binding ( $V''_3$ , averaged across hemispheres; see SPECT measurements) in the four different striatal sub-regions as covariates of interest. Levodopa equivalent daily dose (Wenzelburger et al., 2002) (LEDD, in mg) was added as a covariate of non-interest to control for long-term medication effects. Upon significant effects, post-hoc simple Pearson's correlations were calculated between DaT binding and behavioral measures. Multiple regression analyses were performed to validate the specificity of the results (Supplement 2d). Given the large age range, age was added as another covariate of non-interest in a supplementary ANOVA. Moreover, multiple regression analyses were performed to demonstrate the specific contribution of DaT binding versus age in explaining the observed effects (Supplement 2d).

##### Patients versus controls

Additionally, we compared patients' behavior with that of controls. We performed an ANOVA with the within-subjects factors REWARD (high, low), TASK (arrow, word), TRIAL-TYPE (repeat, switch) and the between-subjects factor DIAGNOSIS (Parkinson's disease, healthy controls). Gender was taken as a covariate of non-interest in the between-subject analyses, because reward anticipation can differ depending on gender (Spreckelmeyer et al., 2009). Similar to the within-patient ANOVA mentioned above, age was added as another covariate of non-interest in a supplementary analysis.

For statistical purposes, a natural logarithm (LN) transformation was applied to the RTs, to maximize homogeneity of variances between groups. Levene's test of homogeneity of variances revealed that this transformation was successful in equalizing variance between groups (all  $P$ s > .1). The mean proportions of incorrect responses were transformed with the following formula:  $2 \arcsin \sqrt{x}$



**Fig. 2.** Dopaminergic imaging results. The amount of presynaptic dopamine transporter binding (using 123-I-FP-CIT SPECT) across four striatal regions of interest (ROI): the posterior putamen (in cyan), anterior putamen (in yellow), caudate nucleus (in orange), and the nucleus accumbens (in red). (A) For each patient, these four ROIs were defined based on the structural MRI scan, and then overlaid on that subject's co-registered and normalized SPECT scan. (B) In each ROI, dopamine transporter (DaT) binding ( $V''3$ ; averaged across the ROI) was calculated and averaged ( $\pm$  SEM) across the group (separately for the most- and least-affected hemispheres (black and gray bars, respectively)). (C) Hemispheric DaT asymmetry ( $V''3$  asymmetry index: (least – most) / (least + most), on the y-axis), for different portions of the striatum (x-axis). (D) Correlation between disease severity (in years, on the x-axis) and DaT binding ( $V''3$ , averaged across both hemispheres, on the y-axis) in the posterior putamen. (E) Correlation between DaT binding in the posterior putamen and the behavioral switch cost (transformed error rates, arrow task: switch trials – repeat trials, on the y-axis) following low reward cues. The results show regionally distinct patterns of dopamine depletion in PD (panels B, C), and significant associations between dopamine depletion in posterior putamen and disease severity as well as cognitive rigidity when anticipated reward was minimal (panels D, E). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(Sheskin, 2003). Levene's test of homogeneity of variances revealed that this error rate transformation was successful in equalizing variance between groups (all  $P$ s > .1).

## Results

### Patients: regional DaT binding

Consistent with prior evidence (Kish et al., 1988), analyses of DaT binding in the different striatal sub-regions demonstrated a spatial gradient, with DaT reduction being highest in the posterior putamen, followed by the anterior putamen, the caudate nucleus, and the nucleus accumbens (Fig. 2A–C and Supplement 2b). In line with these and previous results (Brooks and Piccini, 2006; Spiegel et al., 2007), we found that DaT binding in the posterior putamen predicted disease severity (Fig. 2D), whereas similar associations were not found with DaT binding in other striatal sub-regions (Supplement 2c). These data indicate that dopamine depletion in the posterior putamen was relatively severe compared to other striatal sub-regions, and that it was the best predictor of the patients' clinical status.

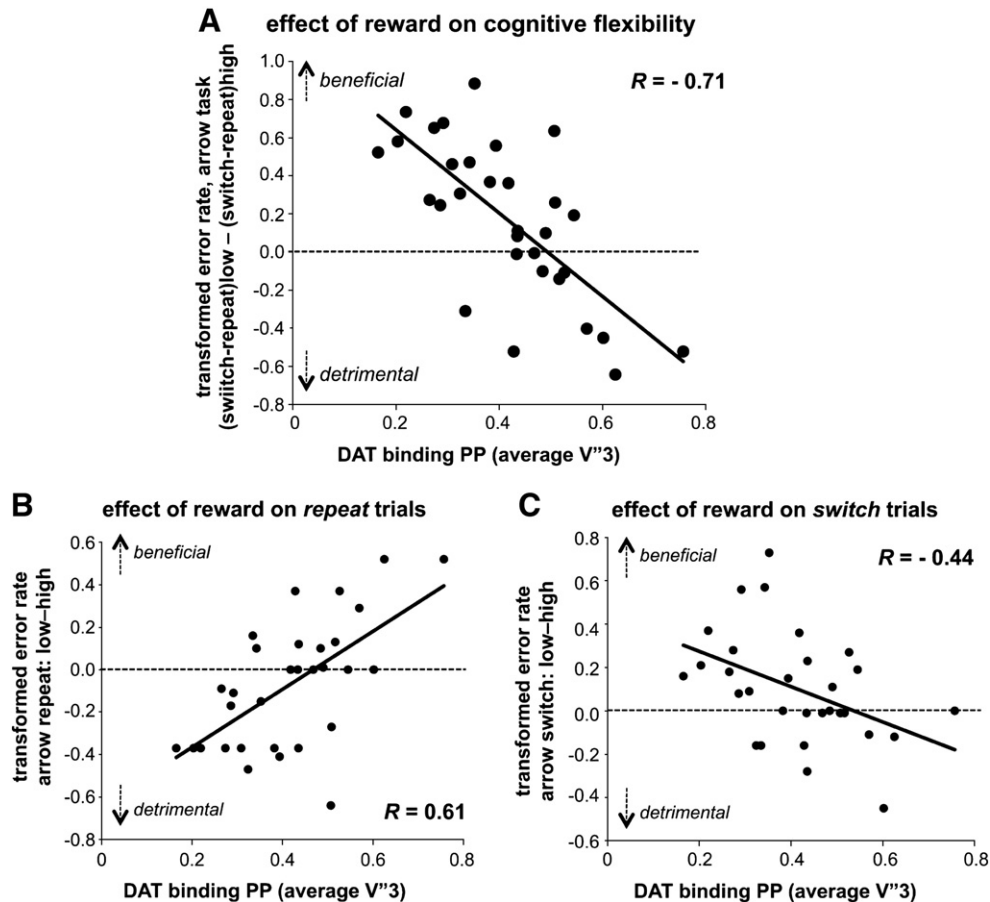
### Patients: DaT binding and rewarded task-performance

Patients with more severe dopamine depletion in the most affected striatal sub-region (i.e., posterior putamen) showed greater reward-induced changes in task performance. Specifically, ANOVA of the error

rates with DaT binding ( $V''3$  values, see [SPECT measurements](#)) in the different striatal sub-regions as covariates revealed a significant interaction between REWARD, TRIAL-TYPE, TASK and DaT binding in posterior putamen, DaT-PP ( $F(1,25) = 6.16, p = .020$ ). We also observed an interaction between REWARD, TRIAL-TYPE, and DaT-PP independent of TASK ( $F(1,25) = 8.49, p = .007$ ), as well as a REWARD  $\times$  TRIAL-TYPE interaction independent of both TASK and DaT binding ( $F(1,25) = 5.27, p = .030$ ). No other interactions were significant.

Breakdown of the 4-way interaction into two 3-way REWARD, TRIAL-TYPE, and DaT-PP interactions for each TASK separately demonstrated a 3-way interaction for the arrow task ( $F(1,25) = 25.82, p < .001$ ; also 2-way REWARD  $\times$  TRIAL-TYPE:  $F(1,25) = 15.87, p = .001$ ), but not the word task ( $F(1,25) < 1$ ). These results show that effects of reward on performance of the most pre-potent arrow task (Supplement 2e) depended on DaT binding in the posterior putamen as well as on TRIAL-TYPE: greater reduction in DaT binding in posterior putamen was associated with greater reward-induced increases in performance on switch relative to repeat trials ( $R = -0.71$ ; Fig. 3A). The nature of this relationship between the reward effect and DaT-PP binding was different for the switch and repeat trials. For repeat trials, we found a strong REWARD  $\times$  DaT-PP binding interaction ( $F(1,25) = 13.53, p = .001$ ) on the error rates. This was due to a positive relationship between DaT-PP binding and the reward-associated performance: Lower DaT-PP binding predicted a greater detrimental effect of reward on repeat trials, thus more instead of less reward-induced errors ( $R = 0.61$ ; Fig. 3B). There was also a main (detrimental) effect of reward





**Fig. 3.** Correlations between DaT binding in the posterior putamen and the effects of anticipated reward on task performance. (A) Specific dopamine transporter binding in posterior putamen, averaged across both hemispheres (see Supplement 1b), correlated negatively with the effects of reward on task-switch performance [transformed error rates, arrow task: (switch-repeat) low – (switch-repeat) high, on the y-axis]. This effect was driven by (B) a strong positive correlation between DaT binding and the effect of reward (low–high) on repeating the arrow task and, conversely, (C) a negative correlation between DaT binding and the effect of reward (low–high) on switching to the arrow task.

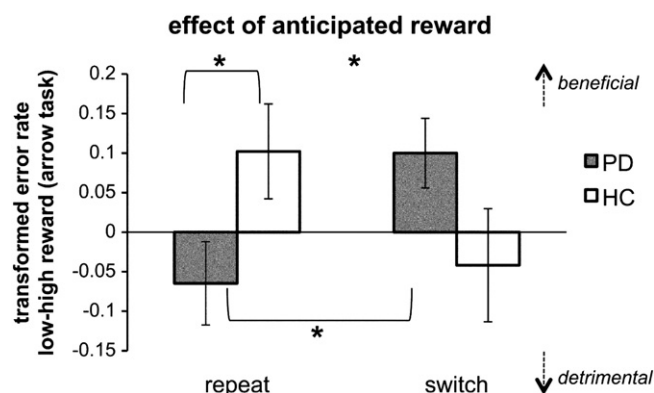
on repeat trials ( $F(1,25) = 4.71, p = .040$ ). Conversely, DaT-PP binding was negatively associated with the effect of reward on switch trials ( $F(1,25) = 7.44, p = .011$ ): greater reduction in DaT-PP binding predicted reward-induced decreases in error rates on switch trials ( $R = -0.44$ ; Fig. 3C). The main (beneficial) effect of reward on switch trials was also significant ( $F(1,25) = 8.29, p = .008$ ). In sum, reduced DaT binding in posterior putamen was associated with greater beneficial effects of reward on switch trials, but greater detrimental effects on repeat trials. None of these effects co-varied with DaT binding in other striatal sub-regions. We verified this unique contribution of DaT-PP binding to task behavior with multiple regression analyses in Supplement 2d.

Importantly, in contrast to DaT binding in posterior putamen, long-term medication use as indexed by the LEDD did not co-vary with any of the results. Additionally, when taking medication as a between-group factor in the design (medicated vs. never-medicated, or agonist vs. other medication), we did not observe any effects of medication either (see Supplement 2f). This suggests that our findings are not driven by persistent medication-related effects in the medication-withdrawn patients ( $n = 21$ ) of our PD group. No significant effects were observed in terms of RTs either. Adding age as a covariate to the statistical model did not yield qualitatively different effects (see also Supplement 2d); and age did not interact with any factor itself.

#### Patients vs. controls: rewarded task-performance

Consistent with the hypothesis that reward-induced changes might reflect disease pathology, we observed that rewarded task-

performance was abnormal in the (non-medicated) patient group as a whole relative to controls. There was a significant 3-way interaction between REWARD, TRIAL-TYPE, and DIAGNOSIS in terms of error rates ( $F(1,55) = 4.32, p = .042$ ) and a trend for a 4-way interaction between TASK, REWARD, TRIAL-TYPE, and DIAGNOSIS ( $F(1,55) = 2.34, p = .1$ ). Given the observed associations within the patient group, and given a priori reasons to anticipate the greatest effects in the dominant arrow task (see Introduction), we tested simple interaction analyses for each task separately. This showed that the 3-way interaction between REWARD, TRIAL-TYPE and DIAGNOSIS for error rates was driven by an effect in the arrow task ( $F(1,55) = 5.87, p = .019$ ; Fig. 4), not in the word task ( $F(1,55) < 1$ ), comparable with the effects within the PD group (described in Patients: DaT binding and rewarded task-performance). Further breakdown of this interaction revealed that the differences between patients and controls were due to differential effects of reward on repeating the arrow task (REWARD  $\times$  DIAGNOSIS:  $F(1,55) = 4.60, p = .036$ ; Fig. 4), not on switching to the arrow task (REWARD  $\times$  DIAGNOSIS:  $F(1,55) = 2.15, p > .1$ ). Post-hoc t-tests demonstrated that the group differences in the reward effect (low vs. high) on repeat trials were attributable to more errors on high-reward repeat trials for PD relative to HC ( $t(56) = 2.30, p = .025$ ; Table 2) rather than to an effect in low-reward repeat trials ( $t(56) = .45, p > .6$ ). Similar effects were obtained when looking across tasks (REWARD  $\times$  DIAGNOSIS, repeat trials:  $F(1,55) = 5.47, p = .023$ ; REWARD  $\times$  DIAGNOSIS, switch trials:  $F(1,55) < 1$ ). Specifically, anticipated reward was beneficial for performance on repeat trials in controls, whereas it was detrimental in patients (Fig. 4).



**Fig. 4.** Main effects of anticipated reward in transformed error rates of arrow repeat and arrow switch trials in the Parkinson's disease (PD) group and the healthy control (HC) group. Differences between patients and controls in the effects of reward on different trial-types (repeat, switch) were driven by differential effects of reward (low vs. high reward, but driven by high reward in particular) on repeat trials. That is, anticipated reward was detrimental for performance on repeat trials in PD, whereas it was beneficial in controls. Overall, anticipated reward had differential effects depending on trial-type in the PD group, but these effects were not significant in the HC group. Significant effects ( $p < .05$ ) are indicated with an asterisk.

As a result, we also observed a smaller switch cost (switch-repeat) on high-reward relative to low-reward arrow trials for patients (REWARD  $\times$  TRIAL-TYPE:  $F(1,31) = 5.19$ ,  $p = .030$ ; Fig. 4), but not for controls (REWARD  $\times$  TRIAL-TYPE:  $F(1,25) = 2.22$ ,  $p > .1$ ). Patients demonstrated not only increased reward effects on repeat trials, but also a switch deficit, i.e., enlarged switch cost compared with controls, on low-reward trials (TRIAL-TYPE  $\times$  DIAGNOSIS:  $F(1,55) = 5.63$ ,  $p = .021$ ), but not on high-reward trials (TRIAL-TYPE  $\times$  DIAGNOSIS:  $F(1,55) < 1$ ). The switch deficit was caused by increased error rates on low-reward switch trials for the PD relative to the HC group ( $t(56) = 3.11$ ,  $p = .003$ ; Table 2), and not by reduced error rates on low-reward repeat trials (see above). This cognitive inflexibility (switch-repeat) on low-reward trials also correlated with DaT binding in the posterior putamen in patients (Fig. 2E), indicating that greater reduction in DaT binding is associated not only with greater impact of reward, but also with greater cognitive inflexibility when the potential for reward is minimal.

None of the above effects interacted with GENDER, and no significant effects were observed in terms of RTs (see Table 2 for raw error + RT data). Adding age as covariate to the statistical model did not yield qualitatively different effects; and age did not interact with any factor itself.

**Table 2**  
Raw (untransformed) data on the rewarded task-switching paradigm.

	Error rates (%)				Response times (ms)			
	Arrow task		Word task		Arrow task		Word task	
	Low reward	High reward	Low reward	High reward	Low reward	High reward	Low reward	High reward
<i>Parkinson's disease (n = 32)</i>								
Repeat	6.9 (2.0)	8.1 (2.0)	3.2 (0.9)	3.3 (0.7)	525.2 (21.9)	532.6 (22.7)	585.5 (18.2)	575.0 (18.3)
Switch	13.4 (2.0)	10.1 (1.4)	5.4 (0.9)	5.8 (1.2)	556.9 (24.7)	537.2 (22.2)	618.2 (21.5)	607.1 (21.2)
<i>Healthy controls (n = 26)</i>								
Repeat	4.8 (1.4)	3.1 (0.8)	2.3 (0.8)	2.1 (0.8)	470.3 (23.3)	463.1 (22.1)	539.1 (15.1)	526.6 (16.1)
Switch	6.8 (1.6)	7.3 (1.3)	5.5 (1.6)	5.4 (1.4)	498.6 (26.6)	487.8 (27.2)	566.3 (19.6)	560.0 (22.2)

Values represent mean proportion of incorrect responses in % and mean response times in ms (standard errors of the mean).

### Patients vs. controls: trait reward sensitivity

Relative to controls, PD patients exhibited increased subjective reward responsiveness, as measured with the reward scale of the behavioral activation system (BAS)/behavioral inhibition system (BIS) questionnaire ( $t(56) = 2.21$ ,  $p = .031$ ; Table 1). The score on this reward scale did not correlate with task performance or DaT binding in posterior putamen. Patients and controls did not differ on the other BAS subscales, BAS drive and BAS fun, total BAS or total BIS scores (all  $t(56) < 1$  and  $> 0$ ; Table 1).

### Discussion

The present data show that the impact of reward on cognitive performance in non-medicated PD patients is predicted by reduced DaT binding, likely reflecting severe dopamine cell loss. In particular, we demonstrate that lower DaT binding in the most affected striatal sub-region, posterior putamen, is associated not only with greater disease severity and greater cognitive inflexibility (for a review, see Cools, 2006), but also with greater (beneficial as well as detrimental) impact of reward. This conclusion from the within-patient analysis was substantiated by the between-groups analysis, showing that patients exhibited more errors in high- than in low-reward trials relative to controls when a task-set had to be maintained. Finally, enhanced reward responsiveness in PD versus controls was also evident by increased trait reward-sensitivity on a self-report questionnaire.

In line with the observed cognitive inflexibility or perseveration in PD when switching between well-established sets (Cools et al., 2001b; Lewis et al., 2005; Slabosz et al., 2006), patients demonstrated a particular difficulty switching to the best-established arrow task under low reward, in a way that was proportional to the degree of dopamine cell loss in posterior putamen. The DaT-dependent detrimental effect of reward was also task-specific, i.e. particularly pronounced in the most pre-potent arrow task. In light of the role of striatal dopamine in both reward motivation and habit-like flexibility (e.g., drug seeking habits) (for a review, see Aarts et al., 2011), it is perhaps no surprise that the DaT-dependent effects of both anticipated reward and task-switching were most visible in the best established, most 'habitized' stimulus-response set.

Intriguingly, under high reward PD patients no longer demonstrated a switch deficit compared with controls. Instead, under high reward they demonstrated a 'repeat deficit'. This reward-induced failure to persist with current task representations likely also underlies the beneficial effect on switch trials observed in PD, perhaps reflecting reduced need to overcome suppression (Wylie and Allport, 2000) of the dominant arrow task on preceding trials. Reduced perseverance in the face of reward is reminiscent of ideas that reward may interfere with the robust maintenance of current working memory representations by promoting striatal dopamine-dependent updating (Hazy et al., 2006). Reduced working memory maintenance has been related to reward-induced impulsive decision-making in the context of delay discounting (Hinson et al., 2003; Shamosh et al., 2008). Delay discounting, i.e., the preference of immediate reward over delayed reward, is suggested to be a trait marker in impulsivity-related psychopathologies like addiction (for a review, see Peters and Buchel, 2011), and accordingly observed in PD patients with impulsive-compulsive behavior (Housden et al., 2010). Here, we show that increased motivation in the face of reward can reduce maintenance processes in the domain of task switching, reversing the tendency to persevere in PD patients off medication and without impulsive-compulsive problems.

The aberrant reward processing observed currently in PD reflected dopamine cell loss. This finding is in line with previous studies showing that a low baseline dopamine state predisposes to impulsivity and addictions (Buckholtz et al., 2010; Dalley et al., 2007; Nader et al., 2006). These studies have revealed that addiction-prone individuals

exhibit abnormally low dopamine D2/D3 (auto)receptor availability. Low D2/D3 (pre-synaptic) autoreceptor availability in particular is accompanied by potentiated dopamine release (see Buckholtz et al., 2010). In PD, dopamine cell loss might well be associated with reduced D2/D3 autoreceptor availability in the remaining intact neurons, resulting in increased dopamine release in response to rewarding stimuli. Positron emission tomography (PET) studies have indeed revealed increased (stimulus-evoked) dopamine release in the ventral striatum of patients with impulsive–compulsive behavior relative to those without (Evans et al., 2006; O'Sullivan et al., 2011; Steeves et al., 2009). Here, we measured dopamine cell integrity rather than dopamine release in striatal target regions. As such, associations between DaT binding and task performance were most pronounced in the posterior putamen, which showed most severe dopamine cell loss and was best associated with disease severity (see Fig. 2 and Supplement 2b and e). However, we anticipate, based on previous fMRI work with the same design in healthy participants (Aarts et al., 2010), that future PET displacement studies will reveal a similar link between ventral striatal dopamine release and the presently observed aberrant reward processing in patients without impulse control disorders. This is likely given that ventral striatal dopamine neurons are still relatively intact early in PD (Braak et al., 2003; Kish et al., 1988), as also revealed by our supplementary SPECT results and as suggested by the observation of relatively intact reward-based learning in patients OFF medication relative to controls (Cools et al., 2006; Cools et al., 2001a; Frank et al., 2007; Frank et al., 2004; Rutledge et al., 2009; Shohamy et al., 2006). In particular, as was observed in Parkinsonian rats (van Oosten et al., 2005), when dopamine levels in more dorsal regions of the striatum are depleted, extracellular ventral striatal dopamine levels are increased. The above mentioned reduced auto-regulatory mechanisms (by D2/D3 receptors for example) might provide the basis for such (over)compensation in intact striatal neurons in PD, with reward-induced impulsivity as a result.

Reward-related impulsivity in the present study was observed in a patient group that was not medicated with dopaminergic drugs. Instead, we report evidence that aberrant reward processing was related to dopamine depletion in the striatum, and unrelated to long-term medication use. This is particularly striking because accumulating evidence indicates that abnormal reward-related behavior in PD might be due to levodopa or dopamine agonist therapy (Cools et al., 2006; Cools et al., 2003; Cools et al., 2007a; Dagher and Robbins, 2009; Evans et al., 2009). The present data do not speak directly to effects of medication because we did not compare patients ON and OFF their dopaminergic medication. However, importantly, we report that the aberrant impact of reward in PD is directly related to the degree of dopamine neuron loss, i.e. the disease pathology itself, and can also be observed in non-medicated patients. Accordingly, using quantitative neurocognitive measures, this is the first study to demonstrate that other factors than medication, including the disease pathology itself, likely contribute to impulsive–compulsive disorders in PD. This was also suggested by the finding that patients exhibited increased self-reported *trait* reward sensitivity, a finding possibly related to observations that certain premorbid personalities and genetic variations in regulatory dopamine mechanisms (e.g. DaT and D2 receptor function) can confer risk factors for impulsive–compulsive behavior (Comings and Blum, 2000; Lott et al., 2005; Shahmoradgoli Najafabadi et al., 2005). Long-term use of dopaminergic medication might well exacerbate the aberrant impact of reward and represent the critical trigger of impulsive–compulsive disorder (ICD) in PD. One such mechanism by which long-term use of dopaminergic medication could contribute to ICD in PD is by inducing neuroadaptations in the form of downregulation of D2/D3 (auto)receptors (Thobois et al., 2004). The detrimental effect of these adaptations in terms of impulsivity and compulsivity might be particularly evident in patients with genetically determined low levels of D2 receptor density, associated with poor auto-regulation at baseline (Buckholtz et al., 2010; Dalley et al., 2007).

## Conclusions

Dopamine depletion in PD is accompanied by both cognitive inflexibility (on low reward trials) as well as aberrant impact of reward. The finding that aberrant reward processing in PD is proportional to dopamine cell loss suggests that a low baseline dopamine state contributes to impulsive–compulsive behavior. Here, reward-related impulsivity was associated with detrimental effects of anticipated reward on the persistence of current task representations, but beneficial effects on task-switching.

## Acknowledgments

This work was supported by a fellowship of the Hersenstichting Nederland to support dementia research to R.C. (F2008 (1)–01), a VIDI grant of The Netherlands Organisation for Scientific Research (NWO) to R.C. (016.095.340), the Niels Stensen foundation to E.A., the Alkemade–Keuls foundation to B.R.B. and a VIDI grant of The Netherlands Organisation for Scientific Research (NWO) to B.R.B. (91776352). The funding sources had no involvement in acquisition, analysis, interpretation, or reporting of the data. We would like to thank Marieke van der Schaaf and Matthias Wilde for their help with data acquisition.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2011.11.073.

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