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# Greater striatal responses to medication in Parkinson's disease are associated with better task-switching but worse reward performance

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ABSTRACT

Dopaminergic medication in Parkinson's disease has been proposed to improve cognitive processing by modulating the severely depleted dorsal striatum, while impairing reward processing by modulating the relatively intact ventral striatum. However, there is no direct (neural) evidence for this hypothesis. Here we fill this gap by scanning Parkinson's disease patients ($n=15$) ON and relatively OFF their dopaminergic medication using functional magnetic resonance imaging. During scanning, patients performed a task that enabled the simultaneous measurement of task-switching and reward-related processing. Brain–behavior correlations revealed that medication-related increases (ON–OFF) in switch-related BOLD signal (switch-repeat) in the dorsomedial striatum were associated, on an individual basis, with *improvements* in task-switching (i.e. a decreased switch cost). Conversely, medication-related increases (ON–OFF) in reward-related BOLD signal (high–low) in the ventromedial striatum were associated, on an individual basis, with *impairments* in performance in anticipation of reward (i.e. an increased reward cost). Linear regression analyses demonstrated that the positive relationship between medication-related changes in BOLD and the reward cost was unique to the ventromedial striatum, whereas the negative relationship between medication-related changes in BOLD and the switch cost was not unique to the dorsomedial striatum. These findings extend the dopamine overdose hypothesis, according to which dopamine-induced changes in dorsal and ventral striatal processing lead to cognitive improvement and impairment respectively.



## 1. Introduction

Parkinson's disease (PD) is accompanied by motor deficits such as tremor, rigidity and bradykinesia, as well as cognitive deficits. Dopaminergic medication therapy (i.e. levodopa or dopamine receptor agonists) remediates the motor deficits, but the effects on cognition are more complex. Based on the spatiotemporal progression of dopamine depletion in PD (Fearnley & Lees, 1991; Kish, Shannak, & Hornykiewicz, 1988), it has been suggested that medication doses that are needed to remedy dopamine levels in the severely depleted dorsal striatum can detrimentally overdose dopamine levels in the relatively intact ventral striatum (Cools, Barker, Sahakian, & Robbins, 2001; Gotham, Brown, & Marsden, 1988; Swainson et al., 2000). There is ample neuropsychological evidence in support of this dopamine overdose hypothesis (Cools, 2006). For example, medication improves cognitive functions associated with the dorsal striatum, such as task-switching, but impairs cognitive functions associated with the ventral striatum, such as (reward-based) learning and decision-making (Cools et al., 2001; Cools, Barker, Sahakian, & Robbins, 2003; Gotham et al., 1988; MacDonald et al., 2011; Swainson et al., 2000). However, neural responses were not assessed in these studies. The studies that did assess effects of dopaminergic medication on neural responses in PD investigated either only dorsal frontostriatal function (Cools, Stefanova, Barker, Robbins, & Owen, 2002; Mattay et al., 2002), or only ventral frontostriatal function (Argyelan et al., 2008; Cools, Lewis, Clark, Barker, & Robbins, 2007; van Eimeren et al., 2009; Voon et al., 2010). Therefore, there is no direct evidence for the hypothesis that the contrasting effects of dopaminergic medication on different cognitive functions are

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accompanied by modulation of distinct ventral and dorsal subregions of the striatum. Here, we used fMRI in mildly affected PD patients (tested ON and relatively OFF medication) to assess medication effects on brain and behavior using a task that measured both task-switching as well as reward processing (i.e. performance in anticipation of reward). Previous fMRI work with this task in healthy young adults has demonstrated dopamine-dependent effects of reward anticipation in the ventromedial striatum, and dopamine-dependent task-switching effects in the dorsomedial striatum (i.e., caudate nucleus) (Aarts et al., 2010). Accordingly, this paradigm was anticipated to be sensitive to dopaminergic medication withdrawal effects in PD patients. We predicted that dopaminergic medication would improve task-switching performance (i.e. decreasing the switch cost) in PD (Cools et al., 2001, 2003) and increase BOLD responses in the dorsomedial striatum. In contrast, we predicted medication-induced impairments in reward processing (i.e. an increased reward cost) in PD and decreased BOLD in the ventromedial striatum (Cools et al., 2001, 2003, 2007). We assessed both medication effects across the group as well as brain–behavior correlations between the medication-induced striatal BOLD effects and the switch cost and reward cost respectively.

## 2. Material and methods

### 2.1. Patients

Analyses were performed on data from 15 PD patients. We initially scanned 16 patients, but one was excluded due to excessive error rate in both sessions (overall error percentage day 1: 46% and day 2: 29%) resulting in cells of the factorial design with less than 10 trials. All patients gave written informed consent and were paid for participation according to institutional guidelines of the local ethics committee (CMO region Arnhem-Nijmegen, The Netherlands; nr. 2008/159). Patients were native Dutch speakers, right-handed, and had normal or corrected-to-normal vision. Patients were recruited from the Parkinson Centre at the Radboud University Nijmegen Medical Centre. They were included if they had idiopathic PD, diagnosed according to the UK Brain Bank criteria by a neurologist specialized in movement disorders (B.R.B. or Dr. R. Esselink), showed all three cardinal symptoms of PD (rest tremor, rigidity, and bradykinesia), and reported a reduction in the severity of their symptoms when using dopaminergic medication. Exclusion criteria assessed by the neurologists were: neurological and/or psychiatric co-morbidity, including stroke, severe head trauma, hallucinations, impulse control disorders and compulsive medication intake. Furthermore, we screened patients (Table 1) on clinical dementia (mini mental state examination (Folstein, Folstein, & McHugh, 1975), MMSE < 24); frontal executive problems (frontal assessment battery (Dubois, Slachevsky, Litvan, & Pillon, 2000), FAB < 13); moderate to severe depression (Beck depression inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), BDI > 20); and general exclusion criteria for MRI scanning (e.g., claustrophobia, metal parts in the body, vascular disease). Using paired-samples $t$ tests, we assessed differences ON vs. relative OFF medication on motor functioning (Unified PD Rating Scale (Fahn, Elton, & MotUD, 1987), UPDRS-III; timed motor test (Haaxma, Bloem, Borm, & Horstink, 2008), TMT), on global executive functioning (FAB), on visuo-motor speed (box completion and number cancellation), on subjective mood ratings (VAS; Bond & Lader, 1974), and on bonus money earned on the task (Table 2).

### 2.2. General procedure

Patients were assessed on two occasions, both starting at 9 a.m. All PD patients received levodopa ($n=3$), dopamine receptor agonists ($n=5$), or both ($n=7$) (Table 1). Patients were asked to take their normal dopaminergic medication at 8:30 a.m. on one occasion ('ON'), and to abstain from this medication ('relative OFF') for at least 18 h prior to testing on the other occasion (48 h for ropinirole prolonged release tablets to ensure adequate wash-out). The sequence of these ON and relative OFF sessions was counterbalanced (8 patients were ON medication in the first session). Both sessions were separated by at least 1 week and maximally 1 month (mean: 17 days, SD: 5.8 days). Before MR scanning on both sessions, the severity of patients' clinical symptoms was assessed using the UPDRS-III (Fahn et al., 1987) (Table 2). After MR scanning, the patients performed a value-based decision-making task reported elsewhere (Smittenaar et al., 2012).

**Table 1**
Demographics of PD patients ($n=15$).

| | |
|---|---|
| Gender, men ($n$) | 9 |
| Age (yr) | 54.1 (9.7) |
| Level of education[a] | 5.2 (.86) |
| MMSE | 28.7 (1.2) |
| NART-IQ | 99 (14) |
| BDI | 8.2 (4.4) |
| Response hand, left[b] | 7 |
| BIS-11, total | 60.9 (6.0) |
| Disease duration (yr) | 5.5 (3.2) |
| LEDD (mg/day) | 449.9 (381.1) |
| Medication ($n$)[c] | 3; 4; 3; 1; 4 |

Values represent mean (SD). MMSE = mini mental state examination (Folstein et al., 1975); NART = Dutch version of the national adult reading test (Nelson & O'Connell, 1978; Schmand, Bakker, Saan, & Louman, 1991); BDI = Beck depression inventory (Beck et al., 1961); BIS-11 = Barratt impulsiveness scale (Patton, Stanford, & Barratt, 1995); LEDD = levodopa-equivalent daily dose (Wenzelburger et al., 2002).

[a] Level of education was measured on a scale from 1 to 7, with 5 means lower general secondary education or vocational education and 6 means higher general secondary education or higher vocational education.

[b] Response hand on the fMRI task was the least affected hand in patients (all patients were right-handed).

[c] The dopaminergic medication used to calculate the LEDD is mentioned in the following order: L-dopa; L-dopa + pramipexole; L-dopa + ropinirole; Pramipexole; Ropinirole. L-dopa (levodopa) is a dopamine precursor (L-dopa was always administered with a DOPA decarboxylase inhibitor); Ropinirole and pramipexole are dopamine receptor agonists with affinity for D2, D3, and D4 receptors (Millan et al., 2002).

**Table 2**
Neuropsychological tests: medication effects in PD.

| | Relative OFF | ON | $p$ value ON–OFF |
|---|---|---|---|
| UPDRS-III | 29.3 (8.9) | 20.5 (7.6) | < .001 |
| FAB | 16.7 (1.3) | 17.4 (1.1) | .036 |
| TMT, s | | | |
| Right hand | 30.8 (10.4) | 28.2 (7.4) | ns |
| Left hand | 40.3 (29.4) | 37.9 (25.0) | ns |
| Most affected hand | 45.3 (28.1) | 40.3 (24.1) | .045 |
| Least affected hand | 25.8 (5.3) | 25.7 (5.7) | ns |
| Box completion[a] | 116 (33) | 115 (23) | ns |
| Number cancellation[a] | 317 (53) | 314 (66) | ns |
| VAS | | | |
| Alertness | 6.3 (1.6) | 7.3 (1.2) | .016 |
| Calmness | 6.5 (1.4) | 7.7 (1.4) | .006 |
| Contentedness | 7.3 (1.2) | 7.7 (1.0) | ns |
| Bonus in fMRI task, € | 10.8 (1.7) | 11.1 (1.2) | ns |

Values represent mean (SD). UPDRS-III = motor examination with the Unified PD Rating Scale (Fahn et al., 1987); FAB = frontal assessment battery (Dubois et al., 2000); TMT = timed motor test (Haaxma et al., 2008); ns = not significant, $p > .05$; VAS = visual analog scales for subjective mood ratings (Bond & Lader, 1974), which comprised a total of 16 100-mm lines anchored at either end by antonyms. Patients marked their current subjective state between the antonyms on the line. The 16 scales were reduced to 3 factors (Bond & Lader, 1974): 'alertness' (represented by lines anchored by alert–drowsy, attentive–dreamy, lethargic–energetic, fuzzy–clearheaded, well-coordinated–clumsy, mentally slow–quick witted, strong–feeble, interested–bored, incompetent–proficient); 'calmness' (calm–excited, tense–relaxed); 'contentedness' (contented–discontented, troubled–tranquil, happy–sad, antagonistic–friendly, withdrawn–sociable). Scores for each factor represent the average distance in mm between the mark and the positive antonym.

[a] Box completion and number cancellation tasks were performed with the least affected hand to measure visuo-motor speed in seconds (Lewis & Kupke, 1977).

### 2.3. Rewarded task-switching paradigm

In the scanner, brain and behavioral responses were assessed with a pre-cued task-switching paradigm designed to measure effects of reward anticipation, associated with the ventromedial striatum, and of task-switching, associated with the dorsomedial striatum, as well as their interaction (Aarts et al., 2010) (Fig. 1). Subjects 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 arrow–word targets (consisting of the words 'left' or 'right' in a left or right pointing arrow). Repetitions or switches of task-set were pseudo-randomly preceded by high or low reward cues, resulting in 40 trials per condition (high_-repeat, high_switch, low_repeat, low_switch). The amount of switches between the left and right *response* did not differ between the task switch and task repeat conditions. Cues and targets remained on the screen for 600 ms. The task was identical to one described previously (Aarts et al., 2010), with the exception of a smaller fixed (1 s) interval between task cues and arrow–word targets (but jittered, 2–6 s intervals before and after reward cues), one task cue per task (Dutch word for 'word' or Dutch word for 'arrow'), and 15 instead of 10 cents bonus for high reward trials (low reward bonus was kept at 1 cent). Patients responded manually to the arrow–word targets, which were always incongruent, by pressing a left or right button with the index and middle finger of their least affected hand (Table 1).

### 2.4. Behavioral analysis

We were interested in a measure of overall performance, without having a priori hypotheses about either RTs or error rates separately. Therefore, we computed a composite score of the response times (on correct trials) and error rates by z-scoring both measures and dividing their sum by two ((RTz+ERRz)/2). This overall performance measure takes into account any speed–accuracy trade-offs (Salthouse & Hedden, 2002), and reduces the multiple comparison problem. The composite z-scores were analyzed with SPSS 16.0 (Inc., Chicago, IL, USA). We used an analysis of variance (ANOVA) with within-subjects factors REWARD (high, low) and TRIAL-TYPE (repeat, switch), and MEDICATION (ON, OFF). The absence of SESSION ORDER effects allowed us to assess effects of medication in PD (ON vs. OFF) across first and second sessions (8 patients were ON medication in the first session; 7 patients were ON medication in the second session).

### 2.5. EMG

During MR scanning, we measured muscle activity in the most affected arm of PD patients with electromyography (EMG) to account for tremor-related activity. EMG electrodes were placed on the hand that was not used for responding (i.e. the most affected hand). Carbon wired MR compatible electrodes were placed 3 cm apart along the muscle bellies of the flexor and extensor in the forearm muscle, and a neutral electrode was placed on the head of the ulna. The EMG signals obtained during scanning were processed in accordance with previous studies (Helmich et al., 2010; Helmich, Janssen, Oyen, Bloem, & Toni, 2011). Vision Analyzer (Brain Products GmBH, Gilching, Germany) was used for signal preprocessing, including MR artifact correction, down-sampling (from 5000 to 1000 Hz), band-pass filtering (allowing frequencies between 25 and 250 Hz), and rectification to enhance information on tremor bursts. Using the FieldTrip toolbox (http://fieldtrip.fcdonders.nl/) in Matlab (MathWorks, Natick, MA), scan-by-scan EMG power at the patient's tremor frequency was determined for the muscle with the clearest peak in the power spectrum (either flexor or extensor). To control for BOLD responses related to (changes in) the tremor amplitude, both an EMG amplitude regressor and an EMG first derivative regressor were convolved with the HRF and added as nuisance regressors to the first level model of all PD patients (Helmich et al., 2011).

### 2.6. fMRI

#### 2.6.1. Data acquisition

Whole-brain imaging was performed on a 3 T MR scanner (Magnetom Trio Tim, Siemens Medical Systems, Erlangen, Germany) using an eight-channel head coil. BOLD sensitive functional images were acquired using a T2*-weighted multi-echo EPI sequence (TR: 2.44 s; TEs for 5 echoes: 9.4 ms, 21.2 ms, 33.0 ms, 45.0 ms, and 56.0 ms). We used a multi-echo EPI sequence to reduce image distortion and increase BOLD sensitivity in our regions of interest which are typically affected by strong susceptibility artifacts, such as the ventral striatum (Poser, Versluis, Hoogduin, & Norris, 2006). One volume consisted of 31 axial slices (voxel size, $3.5 \times 3.5 \times 3.0$ mm$^3$; interslice gap, .5 mm; field of view, 224 mm; flip angle, 90°). All images were acquired in a single run comprising ~32 min. Visual stimuli were projected on a screen and were viewed through a mirror attached to the head coil. Before the acquisition of functional images, a high-resolution T1-weighted MP-RAGE anatomical scan was obtained (192 sagittal slices, repetition time = 2300 ms, echo time = 3.03 ms, voxel size = $1.0 \times 1.0 \times 1.0$ mm$^3$, field of view = 256 mm).

#### 2.6.2. Preprocessing

All data were pre-processed and analyzed with SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). The first 4 volumes were discarded from analysis as dummy scans to allow for magnetization to reach steady state. Realignment parameters were estimated from the shortest TE-images and applied to all echoes of a given excitation (Poser et al., 2006) using a least squares approach and a 6 parameter (rigid body) spatial transformation (Friston et al., 1995). Thirty volumes, acquired before the start of the actual experiment, were used to estimate weights for a BOLD contrast-to-noise ratio map (CNR map) for each echo. Weighted summation was then used to combine all five echoes into a single data set (Poser et al., 2006). During slice timing correction, the time-series for each voxel were realigned temporally to acquisition of the middle slice. Anatomical images were spatially coregistered to the mean of the functional images and segmented using a unified segmentation approach. The resulting transformation matrix was then used to normalize the anatomical and functional images. Normalized images were spatially smoothed with an isotropic 8 mm full-width-half-maximum (FWHM) Gaussian kernel.

#### 2.6.3. First level analysis

For each subject and session the resulting pre-processed fMRI time-series were analyzed at the first level using an event-related approach in the context of the general linear model (GLM). The first level model included regressors for all phases of a trial: reward cue, task cue-target combinations (onset at task cue), and feedback, resulting in 14 regressors: 2 for reward cues (high/low), 8 regressors for targets (reward [high/low] × task [arrow/word] × trial-type [switch/repeat]), and 4 regressors for feedback (1 cent/15 cents/miss/error). All regressors of interest were modeled as an impulse response function (duration = 0) convolved with a canonical haemodynamic response function (HRF). Regressors of non-interest included: the 30-s breaks, missed targets (no button response), and the EMG signal. Also, to optimally control for motion effects, 36 motion parameters were added to the model: the linear, quadratic and cubic effects of *x*, *y*, *z*, pitch, roll, and yaw movement. None of the patients moved more than the voxel size, in either ON or relative OFF state. Furthermore, to remove non-neuronal fluctuations from the data, we added time courses to our model describing compartment signals for cerebrospinal fluid (CSF) and out-of-brain signal (OOB). Both regressors of interest

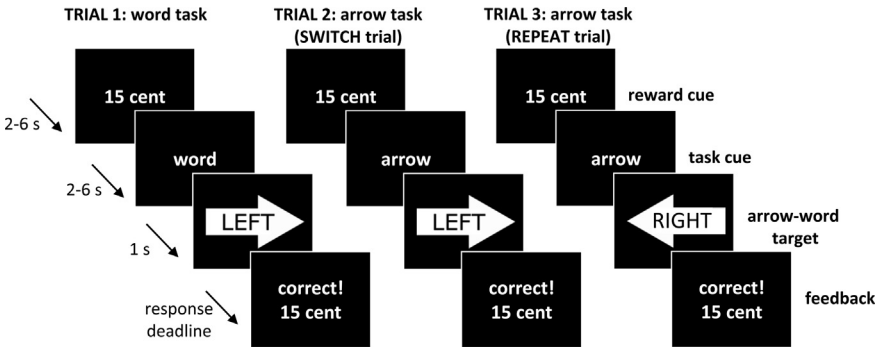


**Fig. 1.** The rewarded task-switching paradigm: in these example trials from the experimental paradigm, the reward cue indicated that the patient could earn 15 cents (as opposed to 1 cent in the low reward condition) with a correct and sufficiently quick response. Thus, all three trials are examples of 'high reward' trials. The response deadline per condition was individually determined in a practice block preceding the main experiment during the anatomical scan in each scan session. The task cue told the patient to respond to the word of the incongruent arrow–word Stroop-like target in the first trial (correct response: left button press), but to the arrow of the incongruent arrow–word Stroop-like target in the second trial (correct response: right button press). Hence, the second trial is an example of a 'switch trial', i.e. a switch of the task relative to the previous trial (independent of a left or right button press). In contrast, in the third trial, the same task (i.e. arrow task) is repeated, hence representing a 'repeat' trial. Immediately after the response, feedback was given with the amount of reward the patient had earned for this specific trial. In the inter-stimulus intervals, patients had to fixate on an asterisk in the middle of the screen. The whole experiment lasted about 32 min with a break after every 32 trials (160 trials in total). In the break, the amount of money the patient had earned thus far in the experiment was displayed on the screen.

and regressors of non-interest (except CSF and OOB compartment regressors) were convolved with their temporal derivative to account for variance due to different slice timings as well as to different HRF delays of different regions. Functional scans were high-pass filtered (128 s) to remove low-frequency confounds such as scanner drifts. Parameter estimates for all regressors were obtained by maximum-likelihood estimation, modeling temporal autocorrelation as an AR(1) process.

#### 2.6.4. Second level analysis

Contrast images from the first level were entered into second level random effects analyses. One full factorial model was estimated to investigate reward anticipation effects, with the within-subject factors REWARD anticipation (high vs. low reward cues) and MEDICATION (ON vs. OFF). Another full factorial model was estimated to investigate the processing of the targets, with the within-subject factors REWARD (high vs. low reward targets), TRIAL-TYPE (switch vs. repeat targets), and MEDICATION (ON vs. OFF). All reported results are corrected for multiple comparisons ($p < .05$ at family wise error [FWE] correction) at the whole brain level.

#### 2.6.5. Regions-of-interest (ROIs)

Our *a priori* hypotheses allowed us to investigate the effects of medication on reward processing and task-switching in pre-defined regions in the striatum. We expected medication effects on reward anticipation in the ventromedial striatum (nucleus accumbens), but medication effects on task-switching in the dorsomedial striatum (dorsal caudate nucleus). The 'automated anatomical labeling' interface (Tzourio-Mazoyer et al., 2002) with SPM was used to select the anatomically defined caudate nucleus (left and right combined) in MNI space (across subjects). Only the dorsal part (from $z > 0$) of the anatomically defined caudate nucleus was used (Fig. 2A, right). We chose a bilateral ventromedial striatum region in MNI space from an independent study that demonstrated effects of dopaminergic medication in PD on reward-related processing (Cools et al., 2007) (Fig. 2A, left), because the ventromedial striatum is difficult to define anatomically. The ventromedial and dorsomedial striatum regions were used as ROIs for the effects of medication on the REWARD contrast (high vs. low reward cues) and for the effects of medication on the TRIAL-TYPE contrast (switch vs. repeat targets). We extracted the mean beta weights (betas) from our bilateral ROIs with MarsBar (Brett, Anton, Valabregue, & Poline, 2002) for every patient, session and condition. The regionally averaged betas were also used for our other measure of interest, i.e. the brain–behavior correlations described below.

#### 2.6.6. Brain–behavior correlations

Brain–behavior correlations were calculated by correlating the parameter estimates extracted from the ventromedial striatal (VMS) ROI or the dorsomedial striatal (DMS) ROI with reward- or switch-related performance. To this end, we calculated the reward cost (composite z-score of error rates+RTs; see Section 2.4) by computing differences between high vs. low reward trials (collapsed across switch and repeat trials), and we calculated the switch cost (composite z-score of error rates+RTs; see Section 2.4) by computing differences between switch and repeat trials (collapsed across low and high reward trials). We were interested in inter-individual variability in the effects of medication, which is why we used the subtraction [(high–low reward)ON–(high–low reward)OFF] for the medication-induced reward effects, and the subtraction [(switch–repeat)ON–(switch–repeat) OFF] for the medication-induced switch effects. The medication-induced reward and switch effects in brain and behavior were also correlated with medication dose (LEDD) and disease severity (UPDRS-III). We report Pearson's *r* for the measures that were normally distributed. In addition, we performed linear regression analyses to assess the unique contribution of the medication-induced changes in the reward- or switch-related signal in the ventromedial and the dorsomedial striatal ROIs to the medication-induced changes in the performance reward cost or switch cost respectively.

## 3. Results

### 3.1. Neuropsychological tests

Performance ON and relative OFF medication on neurological and neuropsychological tests are presented in Table 2. Patients improved in the ON compared with the relative OFF state on motor functioning (UPDRS-III and timed motor test) and global executive functioning (FAB). Patients relatively OFF medication indicated on the visual analog scales that they felt less alert and less calm than ON medication. These subjective effects, however, cannot account for the effect of primary interest, which represents opposite medication effects.

### 3.2. Performance

The error rates and response times (RT) on the rewarded task-switching paradigm (Fig. 1) are displayed in Table 3, as well as composite z-scores of both measures. Patients performed more poorly on switch trials than on repeat trials (main effect TRIAL-TYPE: $F(1,14) = 17.52$, $p = .001$).[1] There were no main or interaction effects with the factors REWARD or MEDICATION across the patient group. Significant brain–behavior correlations are reported below.

### 3.3. Imaging data

Main effects of task are presented in Table 4. We did not observe effects of medication in the striatum on our stringent threshold of $P_{FWE} < .05$. Below, we report medication effects in our striatal ROIs, and associations between medication effects on brain and behavior. To this end, brain–behavior correlations were calculated between the averaged reward- or switch-related signal per bilateral striatal ROI and the reward cost or switch cost in performance (composite z-scores).

We observed an interaction between reward anticipation and medication in the bilateral ventromedial striatal ROI ($F(1,14) = 5.61$, $p = .033$), with patients relatively OFF medication demonstrating greater responses for reward anticipation than when ON medication. The dorsomedial striatal ROI did not show such an interaction between reward anticipation and medication ($F(1,14) = 1.44$, $p > .1$). We were also interested in the individual differences in medication effects and their relation to behavior. The effect of medication on reward-related signal in the ventromedial striatum correlated significantly with the effect of medication on the behavioral reward cost (high–low reward) ($r = .54$, $p = .039$; Fig. 2A left).[2] Medication-induced increases (ON > OFF) in reward-related ventromedial striatum signal were associated with medication-induced increases in the behavioral reward cost, thus with diminished behavioral performance in anticipation of reward. This brain–behavior correlation with the reward cost was not significant in the dorsomedial striatum ($r = -.054$, $p > .8$).[3] When comparing the effects in the two striatal regions on the reward cost in a linear regression analysis, only the medication-induced reward effect in the ventromedial striatal region contributed to the medication-induced reward cost difference (beta = .58, $p = .037$); the reward effect in the dorsomedial striatum did not (beta = −.18, $p > .4$) (Fig. 2B left).

We did not observe an interaction between task-switching and medication in either the bilateral dorsomedial striatal ROI ($F(1,14) < 1$) or the ventromedial striatal ROI ($F(1,14) = 1.40$, $p > .1$) across the patient group. However, the task-switch analyses revealed a negative correlation between medication-induced differences in switch-related signal in the dorsomedial striatum and medication-induced differences in the behavioral switch cost (switch–repeat) ($r = -.53$, $p = .045$; Fig. 2A right).[4] Medication-induced increases (ON > OFF) in switch-related signal in the dorsomedial striatum were associated with medication-induced reductions in the behavioral switch cost, thus with better task-switching performance. This brain–behavior correlation with the switch cost was not significant for the ventromedial striatum ($r = -.38$, $p > .15$).[5] However, a linear regression analysis did not show a unique

[1] A main effect of TRIAL-TYPE was present in both error rates ($F(1,14) = 14.84$, $p = .002$) and RTs ($F(1,14) = 15.95$, $p = .001$).

[2] This correlation was significant with error rates ($r = .56$, $p = .031$), but not with RTs ($r = .21$, $p > .4$).

[3] This correlation was neither significant with error rates ($r = -.18$, $p > .5$) nor with RTs ($r = .29$, $p > .3$).

[4] This correlation was significant with error rates ($r = -.51$, $p = .05$), but not with RTs ($r = -.12$, $p > .6$).

[5] This correlation was neither significant with error rates ($r = -.37$, $p > .15$) nor with RTs ($r = -.11$, $p > .7$).

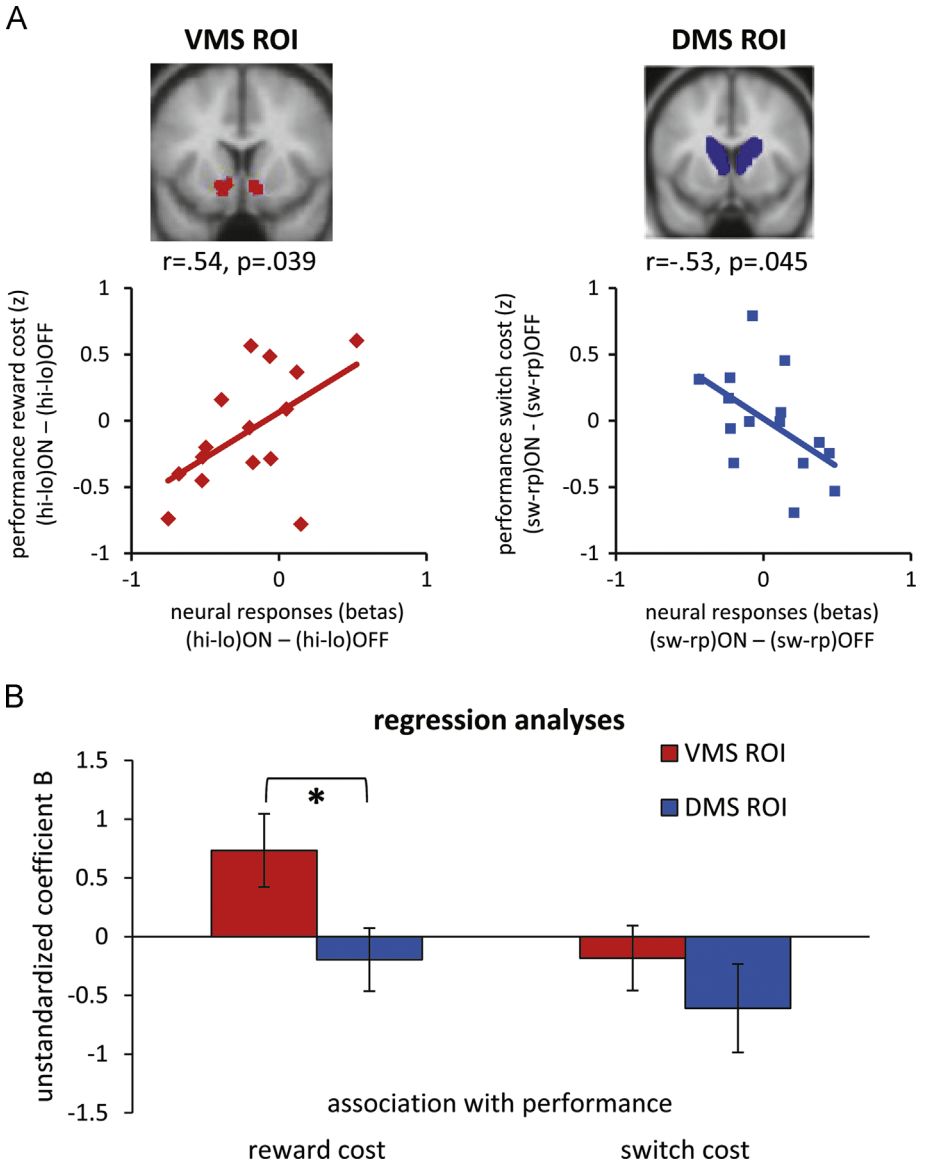


**Fig. 2.** Opposing effects of dopaminergic medication via distinct striatal subregions in PD. (A) Brain–behavior correlations showing that medication-induced increases in reward-related BOLD signal in the pre-defined bilateral ventromedial striatum (VMS) predicted a medication-induced increase in the behavioral reward cost (left), whereas medication-induced increases in switch-related signal in the pre-defined bilateral dorsomedial striatum (DMS) predicted a medication-induced decrease in the behavioral switch cost (right). (B) Linear regression analyses demonstrated that medication-induced changes in the ventromedial striatum uniquely contributed to changes in the reward cost (left). On the left, we plotted the reward-related signal (ON > OFF medication) from both bilateral striatal ROIs as predictors and the behavioral reward cost (ON > OFF medication) as dependent variable. On the right, we plotted the switch-related signal (ON > OFF medication) from both bilateral striatal ROIs as predictors and the behavioral switch cost (ON > OFF medication) as dependent variable. Error bars are standard errors of the unstandardized coefficients B. VMS = ventromedial striatum; DMS = dorsomedial striatum; hi = high reward; lo = low reward; sw = switch; rp = repeat.

contribution of the medication-induced switch effect in the dorsomedial striatal region to the medication-induced switch cost difference (beta: −.44, $p$ = .13) when including the switch effect in the ventromedial striatal region (beta = −.18, $p > .5$) in the same model (Fig. 2B right). Thus, the correlation during task-switching in the dorsomedial striatum did not differ significantly from that in the ventromedial striatum. This was in contrast to the unique contribution of the ventromedial striatum to the medication-induced reward cost, which differed significantly from that of the dorsomedial striatum.

Medication dose (LEDD) and disease severity (UPDRS-III) did not co-vary with the medication effects on the reward or switch cost or the BOLD differences in our striatal ROIs.

In sum, brain–behavior correlations revealed that medication-induced increases in switch-related dorsomedial striatal signal (non-uniquely) resulted in improved task-switching (i.e. reduced switch costs), whereas medication-induced increases in reward-related ventromedial striatal signal uniquely resulted in diminished reward processing (i.e. increased reward costs).

## 4. Discussion

The present study revealed that positive and negative effects of dopaminergic medication in PD are accompanied, on an individual basis, by medication-related increases in BOLD signal in the dorsal and ventral striatum respectively. Although the patient group as a whole did not show opposite medication effects, the brain–behavior correlations constitute direct evidence that contrasting effects of dopaminergic medication in PD reflect modulation of

**Table 3**
Raw behavioral data on the rewarded task-switching paradigm.

| | Error rates (%) | | Response times (ms) | | Composite z-score | |
|---|---|---|---|---|---|---|
| | Repeat | Switch | Repeat | Switch | Repeat | Switch |
| ***Parkinson's disease—relative OFF*** | | | | | | |
| Low reward | 4.6 (1.7) | 10.7 (2.4) | 550 (36) | 581 (40) | −.11 (.20) | .46 (.28) |
| High reward | 6.6 (1.6) | 8.9 (2.4) | 546 (33) | 569 (40) | .02 (.15) | .28 (.26) |
| ***Parkinson's disease—ON*** | | | | | | |
| Low reward | 5.5 (1.9) | 8.9 (2.1) | 519 (20) | 555 (27) | −.18 (.15) | .22 (.21) |
| High reward | 3.7 (1.1) | 8.2 (1.6) | 521 (21) | 542 (28) | −.29 (.10) | .11 (.19) |

Values represent mean percentage of incorrect responses, mean response times of correct responses in ms, and an overall performance score (composite of z-scores of the error rates and response times). The numbers between brackets are the standard errors of the mean. Session order (1/2) did not interact with medication state (ON/OFF).

**Table 4**
MNI stereotactic coordinates of local BOLD maxima across medication sessions at $P_{FWE} < .05$.

| Region | | Voxel $P_{FWE}$ | Voxel T | *x*, *y*, *z* (mm) |
|---|---|---|---|---|
| *Reward anticipation (high–low reward cues)* | | | | |
| Sup front g | L | .021 | 5.56 | 0, −14, 46 |
| Mid front g | L | .041 | 5.36 | −24, 8, 64 |
| *Task-switching (switch-repeat targets)* | | | | |
| Suppl motor area | L | .000 | 6.6 | −2, 16, 52 |
| Inf par lobe | L | .000 | 6.41 | −34, −46, 40 |
| Ant cing cortex | R | .001 | 5.88 | 6, 26, 32 |
| Inf front g | L | .001 | 5.86 | −52, 6, 34 |
| Inf front g | R | .004 | 5.61 | 52, 16, −4 |
| Precuneus | L | .005 | 5.58 | −14, −62, 56 |
| Mid front g | R | .006 | 5.53 | 44, 6, 54 |
| Inf front g | L | .007 | 5.45 | −50, 18, −4 |
| Inf front g | L | .017 | 5.24 | −34, 22, 0 |
| Precuneus | L | .024 | 5.15 | −10, −66, 42 |
| Inf par lobe | L | .044 | 4.98 | −52, −48, 44 |
| Suppl motor area | R | .046 | 4.96 | 12, 6, 68 |

*Note*: The opposite contrasts (low–high reward cues and repeat–switch targets) did not yield any suprathreshold voxels.
sup=superior; front=frontal; g=gyrus; mid=middle; suppl=supplementary; inf=inferior; par=parietal; ant=anterior; cing=cingulate.
At our stringent threshold ($P_{FWE} < .05$), we did not find any effects of the factor REWARD during *target* processing across or between medication states.

distinct dorsal and ventral striatal regions. The present data can be reconciled with the dopamine overdose hypothesis, which states that dopaminergic medication may improve cognitive functions by remediating severely depleted brain areas (i.e., dorsomedial striatum) while impairing cognitive functions by detrimentally overdosing relatively intact or up-regulated brain areas, such as the ventromedial striatum (Cools et al., 2007; Gotham et al., 1988; Swainson et al., 2000). The dissociation was most pronounced in terms of reward-related performance, which was uniquely associated with medication-related changes in the ventromedial striatum. Such a dissociation was not observed for switch-related performance, which is perhaps unsurprising given the ascending anatomical connections between the ventral and dorsal parts of the striatum (Haber, Fudge, & McFarland, 2000). Importantly, however, the brain–behavior correlations were functionally in an opposite direction. Specifically, PD patients whose dopaminergic medication increased signal in the ventromedial striatum demonstrated decreased performance (i.e. reward processing), whereas medication-induced increases in dorsomedial striatal signal resulted in increased performance (i.e. task-switching).

The finding that medication-induced increases in switch-related signal in the dorsomedial striatum were associated with medication-induced improvement in task-switching in PD establishes a critical role for dopamine in the dorsomedial striatum in the well-known parkinsonian task-switching deficit (Cools et al., 2001, 2003). Although the medication-induced effects during task-switching were not necessarily specific to the dorsomedial striatum (relative to the ventromedial striatum), our findings generally concur with the suggestion that (dorsal) striatal dopamine is important for cognitive switching (Cools 2006, 2011; Cools & D'Esposito, 2011). They are also in accordance with previous observations that the caudate nucleus is underactive in PD during processes that depend on cognitive flexibility, such as working memory updating (Marklund et al., 2009), planning (Dagher, Owen, Boecker, & Brooks, 2001) and motor switching (Holden, Wilman, Wieler, & Martin, 2006; Spraker, Prodoehl, Corcos, Comella, & Vaillancourt, 2010). Remarkably there was no main effect of dopaminergic medication on task-switching performance when averaged across the group as a whole. This is particularly surprising in the context of previous work showing a robust beneficial effect of dopaminergic medication on task-switching in PD (Cools et al., 2001, 2003; Hayes, Davidson, Keele, & Rafal, 1998; Shook, Franz, Higginson, Wheelock, & Sigvardt, 2005). We argue that this might reflect individual variability in the degree of dopamine depletion in the dorsal striatum. Thus, some patients might exhibit medication-induced reductions rather than increases in task-switching performance due to relatively modest dopamine depletion in the caudate nucleus, the striatal region most strongly associated with task-switching in this paradigm (Aarts et al., 2010).

In agreement with previous studies (Cools et al., 2007; van Eimeren et al., 2009), we observed medication-induced decreases in ventromedial striatal BOLD responses during reward processing across the patient group. However, in contrast to our prediction, medication-induced decreases in striatal BOLD were associated with better reward-related performance (i.e. a decreased reward cost). How can this be reconciled with the dopamine overdose hypothesis? A number of recent studies have observed positive associations between striatal BOLD signal and dopamine release (Buckholtz et al., 2010; Duzel et al., 2009; Knutson & Gibbs, 2007; Schott et al., 2008). This observation chimes well with the current finding that medication-induced increases in striatal BOLD signal are accompanied by positive effects on task-switching, associated with the severely depleted dorsal striatum, but negative effects in anticipation of reward, associated with the relatively intact ventral striatum. According to this reasoning, a medication-related increase instead of a decrease in ventral striatal BOLD would be detrimental for performance. Nevertheless, our finding that medication-induced *increases* in BOLD signal were accompanied by medication-induced *decreases* in performance does not obviously concur with some previous findings (Cools et al., 2007; van Eimeren et al., 2009). For example, our findings are apparently not consistent with those of Van Eimeren and colleagues (2009), who found that dopamine agonist-induced decreases of reward-related orbitofrontal cortex responses (i.e. correlations with reward prediction error values) were associated with increased (off-line) risk taking. An important point here is that the present paradigm provides a measure of reward motivation whereas previous studies employed tasks that relied on prediction error coding and (reward) learning (see also Kwak, Muller, Bohnen, Dayalu, & Seidler (2012)). These distinct processes might well be associated with distinct (tonic vs. phasic) modes of dopamine transmission (Niv, Daw, Joel, & Dayan, 2007; Schultz, 2002). As such, detrimental overdosing of intact baseline levels of dopamine might have a differential impact on these distinct (tonic vs. phasic) modes of dopamine transmission and might surface as differential effects on BOLD signal. This hypothesis could be tested in future (animal) studies combining neuroimaging with optogenetics and/or voltammetry.

We are left with one important puzzle: in the patient group as a whole, dopaminergic medication reduced rather than increased ventral striatal BOLD signal. The decrease in ventral striatal BOLD signal was accompanied, on a subject by subject basis, by positive effects in anticipation of reward. This is not consistent with the original dopamine overdose hypothesis, according to which dopaminergic medication should impair ventral striatal (reward) function across the group. One, albeit speculative possibility is that, in our patient group, dopaminergic medication acts primarily on presynaptic dopamine receptors in the ventral striatum leading to a paradoxical net reduction in dopamine release and reduction of reward motivation. Indeed we have previously shown that mild PD patients, relative to healthy controls, can exhibit 'excessively' high levels of reward motivation in the baseline OFF state, perhaps due to relatively high (possibly up-regulated) levels of dopamine in the ventral striatum (Aarts et al., 2012). According to this hypothesis, which needs further testing, dopaminergic medication might normalize aberrant reward motivation by reducing dopamine release in the ventral striatum. Detrimental overdosing of reward motivation by dopaminergic medication would then be restricted to those patients whose auto-regulatory (presynaptic) dopamine system is dysfunctional, either due to long-term exposure to excessive doses of medication in the ON state and/or genetic predisposition. Accordingly, the average medication dose (LEDD) was higher in most previous studies that have demonstrated medication-induced decreases in reward-related performance or BOLD than in the current study (e.g. Cools et al., 2001, 2003, 2007; Gotham et al., 1988; MacDonald et al., 2011; van Eimeren et al., 2009). Medication doses likely interact with genetic predisposition to determine vulnerability to over-dosing, an observation that might explain why LEDD did not co-vary with the observed medication effects in the current study. An autoregulatory mechanism has also been invoked to explain impulse control disorders in PD (Cilia et al., 2010; Vriend et al., 2014). Thus patients with impulse control disorder, who suffer particular vulnerability to excessive reward motivation after dopaminergic medication (Voon et al., 2011; Weintraub et al., 2010), differ from patients without impulse control disorder already prior to disease onset, for example in terms of genetically determined baseline dopamine levels (Dagher & Robbins, 2009; Evans, Strafella, Weintraub, & Stacy, 2009). It should be noted that the finding that overdosing was not seen in the patient group as a whole, but only in a few patients (i.e. those in which medication-related increases in BOLD were associated with increases in a behavioral cost; the right upper quadrant of the scatter plots in Fig. 2A), is not necessarily inconsistent with the overdose hypothesis. Thus, the overdose hypothesis does not state that overdosing should be seen in all patients, but rather states that if detrimental effects of medication are seen, then they reflect overdosing of brain regions that are relatively unaffected early on the disease. Our results show that medication-induced increases in ventromedial striatal BOLD responses are accompanied by detrimental effects of medication on reward motivation. The proposal outlined suggests that overdosing is seen only in those patients whose autoregulatory systems are dysfunctional (e.g. as a function of genetic predisposition). Future studies should reveal the mechanisms underlying the individual differences observed in the current study and extend the present results to patients with premorbid psychiatric abnormalities such as impulse control disorder.

### 4.1. Limitations and future directions

Our conclusions are based on brain–behavior correlations in 15 PD patients. Future studies should include more patients to enable replication of the present results. Such future work with larger sample sizes will also enable us to begin elucidating the factors that contribute to the individual variability in the medication effects in PD. For example, with large sample sizes we can consider taking into account individual genetic differences in presynaptic dopamine (receptor) function. This will allow elucidation of medication effects as a function of (genetic) group rather than individual differences in performance. Furthermore, larger sample sizes might result in robust brain–behavior correlations in either error rate or RTs that withstand a multiple comparison test (in addition to the composite measure of the two). Although the observed brain–behavior correlations in PD are meaningful, we cannot conclude that the medication-related changes lead to (ab) normality relative to healthy controls. Future work may consider assessing medication effects across the PD group relative to a matched control group to address this issue.

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