Motivational Compensation of Cognitive Decline in Parkinson's Disease: Preliminary Results from a Pharmacological fMRI Study

Master Thesis Cognitive Neuroscience

Drs. A.A.M. Nusselein, s0826812

Institute Supervisors:

Dr. R. Cools (PI)

Dr. E. Aarts

Second reader:

Dr. I. Toni

Radboud University Nijmegen, Donders Centre for Cognitive Neuroimaging

ABSTRACT

Dopamine (DA) depletion in Parkinson's disease (PD) not only affects motor function, but also cognitive flexibility, associated with the DA-depleted dorsolateral (DL) circuitry, while relatively sparing the separate ventromedial (VM) frontostriatal circuitry necessary for reward processing. We employed a rewarded switching task and fMRI to assess whether early PD patients OFF medication can compensate for switch deficits with anticipated monetary reward. Furthermore, we investigated the effects of DA medication on this motivation-cognition interface. Results showed that PD patients OFF medication exhibit a task-switching deficit in the proportion of errors on low reward trials, but not on high reward trials, accompanied by an increase of switch-related BOLD signal in the dorsal anterior cingulate cortex (dACC) on high relative to low reward targets. PD patients ON medication did not show abnormal cognitive inflexibility, and did not use anticipated reward to reduce their switch cost. These findings concur with our hypothesis that motivational processing can be used by PD patient OFF medication to overcome cognitive inflexibility, and implicate a crucial role of the dACC in this compensation process.

Keywords: Parkinson's disease, dopamine, task switching, flexibility, reward, fMRI

INTRODUCTION

Although the exact causes of Parkinson's disease (PD) are unknown, the pathophysiology involves the loss of dopamine (DA) producing neurons in the substantia nigra. The resulting DA depletion affects the activity of several brain regions that are normally modulated by DA and that are implicated in motor control, reward processing and cognition (Rodriguez-Oroz *et al.*, 2009). One such region is the striatum, which in turn connects with many other parts of the brain, in particular the prefrontal cortex (PFC). Low levels of DA disrupt information-processing between the striatum and the PFC which are strongly connected in so-called frontostriatal circuits (Alexander, DeLong &

Strick, 1986). Besides motor deficits, symptoms include cognitive and motivational problems. These cognitive deficits make it difficult for PD patients to adapt their behavior to the ever changing environment we live in. The cognitive decline experienced by PD patients greatly contributes to a decrease in their quality of life (Schrag, Jahanshahi & Quinn, 2000).

There is increasing evidence for the existence of several parallel frontostriatal circuits involved in different aspects of behavior that interact with each other (Haber, 2003). The dorsolateral (DL) frontostriatal circuit includes the dorsal parts of the striatum (i.e., the caudate nucleus) and the dorsolateral prefrontal cortex (DLPFC), and is associated with cognitive flexibility and working memory (Levy *et al.*, 1997; Fuster, 2000). The ventromedial (VM) frontostriatal circuit includes the ventral parts of the striatum (i.e. nucleus accumbens), areas in (ventro)medial PFC like the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC), and is associated with motivational functions and sensitivity to rewards (Cardinal *et al.*, 2002; O'Doherty, 2004). PD is characterized by a spatiotemporal progression of DA depletion, so that DA levels in the ventral part of the striatum are relatively intact in the early stage of the disease, while the dorsal striatum is already severely depleted of DA (Kish, Shannak & Hornykiewicz, 1988). Brain functions associated with the DL frontostriatal circuit are therefore disrupted in early PD, while those associated with the VM frontostriatal circuit remain relatively unaffected at this stage (Cools *et al.*, 2003).

Previous studies suggest that DA medication can alleviate deficits in task switching associated with the dopaminergic dysfunction of the DL frontostriatal circuit (Cools *et al.*, 2001; Gotham, Brown & Marsden, 1988), presumably by bringing DA in the dorsal striatum back to optimal levels. On the other hand, the same medication has detrimental effects on task performance during reward learning which relies on proper functioning of the VM frontostriatal circuit (Cools *et al.*, 2001; Cools *et al.*, 2007). These latter findings suggest that dopaminergic medication can actually overdose the ventral striatum in early PD by increasing the levels of DA in an area that still exhibits baseline dopaminergic function under normal conditions (the 'dopamine overdose' hypothesis; Gotham, Brown & Marsden, 1988). Overstimulation of the reward system by DA medication could be at the basis of several impulse control disorders prevalent in PD

patients, such as pathological gambling and addiction to medication (Dagher & Robbins, 2009).

In the present study we employ a controlled medication withdrawal procedure in which we assess PD patients in an early stage of the disease both ON and OFF their DA medication in two separate sessions using fMRI. We compare these data with those of healthy controls who also have been scanned on two occasions.

Our first goal is to test the hypothesis that motivational processing (reward anticipation) associated with the relatively intact VM frontostriatal circuit can compensate for cognitive inflexibility associated with DA depletion in the DL frontostriatal circuit. Work with experimental rodents has shown that an induced lowering of DA levels in the DL striatum can lead to an increase in DA levels in the VM striatum (van Oosten, Verheij & Cools, 2005). Such a mechanism could also apply to early PD in which there is a depletion of DA in the DL circuit. A previous fMRI study on the effects of reward and task switching in young adults as a function of expression of the gene coding for the DA transporter (DAT1) showed a stronger interaction between reward mechanisms and task switching with increased amounts of DA in the striatum (Aarts *et al.*, 2010), suggesting that DA plays a key role in the interaction between reward processing and task switching. A follow-up study in PD patients by Aarts *et al.* (in preparation) provided direct evidence for this hypothesis by showing that the task switching deficit in PD patients OFF their normal DA medication was correlated with DA depletion in the dorsal striatum as measured with DaT (DA transporter) single photon emission computed tomography (SPECT). Aarts *et al.* found that patients with more decreased levels of DA in the posterior putamen could increasingly use reward to compensate for their switch deficit. This observation concurs with anatomical evidence from tracer studies in primates, which implicates that the interaction of the VM and DL frontostriatal circuits could come about by spiraling connections between functional regions of the striatum via DA midbrain cells (Haber, Fudge & McFarland, 2000). We investigate the compensation hypothesis by assessing both behavioral and blood oxygenation level-dependent (BOLD) data from PD patients OFF their normal DA medication. We predict that patients OFF DA medication show intact task switching due to compensation by the relatively intact VM circuit in a high reward condition, but not in

a low reward condition, as we have shown previously on a behavioral level (Aarts *et al.*, in preparation). In terms of the BOLD signal, we expect to find a decrease in task switching-related activity in the dorsal striatum and connected cortical structures in patients OFF medication compared to healthy controls in a low reward condition, but a restoration of this activity to normal in a high reward condition. Thus, we expect to find an increased effect of high relative to low reward on functional activity related to task-switching

Our second goal is to obtain definitive evidence for the neurobiological basis of the paradoxical effects of dopaminergic medication on cognitive functioning in PD. Earlier studies investigating the 'dopamine overdose' hypothesis (Gotham *et al.*, 1988; Cools *et al.*, 2001; Cools *et al.*, 2003) did not provide evidence for a double dissociation in terms of brain activity in the DL frontostriatal and VM frontostriatal circuits. The aim of the current study is to obtain such a double dissociation using a single task in which task switching and reward sensitivity are measured simultaneously. We predict that PD patients OFF their normal DA medication will show a decrease in performance on task switching and reduced activity in DL circuitry related to task switching in a low reward condition but not in a high reward condition. For PD patients ON DA medication we predict that they will show intact task switching in a low reward condition, but show premature (i.e. too fast, incorrect) task switching in a high reward condition. In terms of the BOLD signal, we expect to find that switch-related activity in DL circuitry is normalized under low reward, but abnormally enhanced reward-related activity in the ventral striatum and connected cortical structures, due to medication-induced oversensitivity to reward.

METHODS

Participants

Twelve PD patients (7 males) and thirteen matched control subjects (10 males) participated in the study. All participants were native Dutch speakers, right-handed, and had normal or corrected to normal vision. Participants were assessed on two occasions, both starting at 09:00 h in the morning. All PD patients included in the study were

receiving levodopa preparations and/or dopamine-agonists (see Table 1) on a daily basis. Patients were asked to take their normal DA medication at 08:30 h on one occasion, and to abstain from their normal DA medication at least 18 h prior to the other occasion (48 h for Requip Modutab prolonged release tablets to ensure complete wash-out). The sequence of these ON and OFF sessions, respectively, was pseudo-randomized (7 PD patients were ON medication in the first session). Control subjects were also tested on two separate sessions to allow for assessment of test-retest effects.

PD patients were diagnosed by a neurologist specialized in movement disorders (BRB or RAE) as having idiopathic PD according to the UK PD Society Brain Bank criteria. Patients showed all three cardinal symptoms of PD (rest tremor, rigidity and bradykinesia) and reported a reduction in severity of their symptoms when using DA medication. Exclusion criteria were: neurological and/or psychiatric co-morbidity (e.g. stroke, severe head trauma, hallucinations), use of substances acting on the central nervous system other than anti-Parkinson medication (e.g. anti-cholinergics, benzodiazepines; one PD patient in our study did use an SSRI, but was not withdrawn from it in the OFF session), clinical dementia (Mini Mental State Examination < 24; Folstein, Folstein & McHugh, 1975), moderate to severe depression (Beck Depression Inventory scores > 20; Beck *et al.*, 1961; Kendall *et al.*, 1987) and general exclusion criteria for MRI scanning (e.g. claustrophobia, metal parts in the body). The severity of clinical symptoms was assessed according to the Unified PD Rating Scale (part III motor examination, consisting of 14 items measuring severity of the cardinal symptoms of Parkinson's disease; Fahn *et al.*, 1987). Healthy control subjects were recruited from an existing subject data base at the Donders Institute for Cognitive Neuroimaging, Nijmegen, The Netherlands. See Tables 2 and 3 for demographics, symptoms and test scores of both PD patients and healthy controls.

The protocol included additional assessment of participants on several neuropsychological tests (Tables 2 & 3): We employed the Dutch Reading Test for Adults, which consists of a series of words with an irregular pronunciation and is a good predictor of premorbid intelligence level (Schmand et al, 1991), to assess whether PD patients and control subjects differed on premorbid IQ. To assess possible differences between PD patients and control subjects on frontal lobe functioning, we used the Frontal

Assessment Battery, consisting of six subtests exploring conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy (Dubois *et al.*, 2000). In addition to the UPDRS motor examination, we further characterized severity of motor dysfunction with the Timed Motor Test, which measures the time needed to displace wooden pegs on a pegboard with the right hand, left hand, and both hands simultaneously (Haaxma *et al.*, 2008). Both PD patients and the control group were furthermore tested on visuomotor speed with the Box Completion Task (measuring time to draw a missing axis for 100 squares; Lewis & Kupke, 1977) and Digit Vigilance Test (measuring completion time and accuracy on crossing out the numbers 6 and 9 amongst 28 rows of randomly ordered numbers ranging from 0 to 9; Lewis & Kupke, 1977). Participants completed the Barratt Impulsiveness Scale-11, a self-report questionnaire measuring trait impulsivity (Patton *et al.*, 1995), to assess possible differences between groups in impulsivity. Subjective mood was measured on both sessions with 16 visual analogue scales (Bond & Lader, 1974)**.**

This study was approved by the local research ethics committee (CMO region Arnhem-Nijmegen, The Netherlands). All participants gave written informed consent.

Task Description

Participants were scanned while performing a rewarded switching task designed to measure both reward sensitivity and cognitive flexibility (Fig. 1). Before scanning, the task was practiced extensively (see below) to ensure optimal performance during scanning. The targets to which participants had to respond were incongruent arrow-word combinations (see Aarts, Roelofs & van Turenhout, 2008). Targets consisted of written Dutch words for “left” or “right” (“links” or “rechts”) within arrows that were always pointing in the opposite direction of what the word indicated. Stimuli were presented in white on a black background. Patients responded manually to the incongruent targets by pressing a left or right button with the index finger and middle finger of the hand that was least affected (7 PD patients responded with their left hand, as did 5 control subjects). Participants responded either to the direction the arrow indicated (arrow task) or to the direction the word indicated (word task). A task cue indicated which task to perform: “arrow ” (“pijl”) for the arrow task and “word” (“woord”) for the word task. The task

switched in a pseudo-random order such that half of the trials were repetitions of the task in the previous trial and half of the trials were switches compared with the task on the previous trial.

A reward cue (reward anticipation) preceded the task cue, informing the participant whether 1 cent (low reward) or 15 cents (high reward) could be earned with a quick and correct response, denoted by the words “1 cent” or “15 cent”. Additionally, participants received feedback after their response (reward receipt). Positive feedback was given for a correct response and depended on the preceding reward cue at the beginning of the trial: “correct! 1 cent” or “correct! 15 cent”. Negative feedback was given for an incorrect response, “wrong! 0 cent” (“fout! 0 cent”), or for a missed response, “too late! 0 cent” (“te laat! 0 cent”). Feedback for correct responses was given in the color green, feedback for incorrect responses in red, and feedback for misses in yellow. A white asterisk was displayed in the center of the screen between the reward cue and task cue, and between the task cue and the target. In the inter-trial interval, a blue asterisk was displayed.

The duration of the interval between task cue and target was 1 s. The intervals between reward cue and task cue, and feedback and the reward cue of the following trial were jittered with a variable delay between 2 to 6 s. Feedback was given immediately after the participant’s response. Cues and feedback were displayed on screen for 600 ms. Targets remained on screen either until a response was made by the participant or until the end of the response window. This response window was individually calculated for each participant based on their mean response times (RT) of the correct trials per trial-type in a practice block during a T1-weighted anatomical scan in the first session and during a MR spectroscopy scan in the second session. The individually calculated response deadline was implemented to ensure fast responding of participants and was not used in the analysis, i.e. all RTs for both correct and incorrect responses were used regardless of whether responses fell inside or outside the response window. The practice block lasted for ~5 minutes, and consisted of 16 word-task trials and 16 arrow-task trials, half of which were repeat trials and half of which were switch trials. No reward cues or feedback appeared on screen during this last practice block.

The main experiment consisted of 160 trials and lasted ~ 32 min. The factors reward (high/low), task (arrow/word), trial-type (switch/repeat), and response (right/left) were equally distributed over trials in a random fashion, resulting in 40 trials per condition when taking reward and trial-type into account. Participants received a 30 s break after 32 trials. During this break, the amount of money earned in the preceding 32 trials, the amount of money that could have been earned in the preceding 32 trials, and the total amount of money earned until thus far were displayed on screen. Furthermore, a message was displayed below these money statistics encouraging the participant to earn as much money as possible and indicating how much blocks were remaining until the end of the experiment. The maximum amount of money a participant was able to earn was 12.80 euros. The total amount of awarded money was shown on screen at the end of the experiment and was transferred to the participant's bank account, along with a standard compensation for participation in the experiment (30 euros) and a compensation for travel expenses.

Switch-related behavioral performance (RT and error-rate) on targets (i.e., switch cost = switch – repeat trials) and switch-related BOLD changes during task cues and targets (switch – repeat) were taken as correlates of cognitive flexibility, while reward-related performance (RT and error-rate; reward benefit = low rewarded – high rewarded trials) and BOLD signal during reward anticipation (high – low reward) were taken as correlates of reward processing.

Image acquisition

Whole-brain imaging was performed on a 3 Tesla MRI system (Magnetom Trio Tim, Siemens Medical Systems, Erlangen, Germany) using an eight-channel head coil. High-resolution anatomical images were acquired using a T1-weighted MP-RAGE sequence (192 saggital slices; TR, 2.3s; TE, 3.03 ms; voxel size, 1.0 x 1.0 x 1.0 mm; field of view, 256 mm) over ~5 minutes. BOLD sensitive functional images were acquired using a T2*-weighted multi-echo EPI sequence (TR, 2.44 s; TEs for 5 echos, 9.4 ms, 21.2 ms, 33.0 ms, 45.0 ms, 56.0 ms). We used a multi-echo EPI sequence to reduce image distortion and thereby increase BOLD sensitivity in our regions of interest which are typically affected by strong susceptibility artifacts, such as the ventral striatum,

ventromedial PFC and orbitofrontal cortex (OFC) (Poser *et al.*, 2006). One volume consisted of thirty-one axial slices (voxel size, 3.5 x 3.5 x 3.0 mm; interslice gap, 0.5 mm; field of view, 244 mm; flip angle, 90°). All images were acquired in a single run comprising ~32 minutes.

To control for possible BOLD signal changes in PD patients due to parkinsonian tremor, muscle activity in the most-affected forearm was sampled with electromyography (EMG) during the scanning procedure (see below). EMG measurements were also taken from the forearm (of the non-responding hand) of control subjects. In addition, heart rate and respiratory rate were monitored using a pulse oximeter and respiratory belt, respectively. To minimize head movement, all subjects were stabilized with tightly packed foam padding surrounding the head. Visual stimuli were projected on a screen at the back of the scanner and were viewed through a mirror mounted on the head coil.

Preprocessing of imaging data

All data were pre-processed and analyzed with SPM5 (Statistical Parametric Mapping, Welcome Department of Cognitive Neurology, London, UK). 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 echos into a single data set (Poser *et al.*, 2006). Subsequently, the time-series for each voxel was realigned temporally to acquisition of the middle slice. Anatomical images and the mean of the functional images were first spatially coregistered to their respective templates before being coregistered to each other. Structural images were segmented into grey matter, white matter and cerebro-spinal fluid compartments using standard templates for these compartments in Talairach space. The parameters from this segmentation step were used for normalization of the functional images. Normalized images were spatially smoothed with an isotropic 8 mm full-width-half-maximum (FWHM) Gaussian kernel.

Behavioral statistical analyses

Dependent measures were mean response latencies for correct manual responses (including correct responses on 'too late' trials) and the proportion of errors (incorrect responses on all trials, including 'too late' trials). These were analyzed using a repeated measures GLM with factors medication session (ON/OFF), reward (high/low), task (arrow/word), trial-type (repeat/switch). Furthermore, we performed planned comparisons between controls and patients ON medication, and between controls and patients OFF medication with the same within-subjects factors. For all comparisons the two sessions of controls were averaged. Specific effects were tested using paired *t*-tests (ON versus OFF sessions) or independent sample *t*-tests (PD versus controls). Since PD and control groups significantly differed in terms of age ($F_{(1,23)} = 10.1$; $p < 0.001$), age was used as a covariate of non-interest in the statistical comparisons. Session number (first session ON, first session OFF) was used as a covariate in statistical analysis between ON and OFF in order to control for possible session effects (7 PD patients were ON medication in the first session compared with 5 PD patients being OFF medication in the first session). An effect was significant when $p < .05$ (two-tailed).

fMRI statistical analyses

For each subject and medication session the resulting pre-processed fMRI time-series was 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, and feedback, resulting in 14 regressors: 2 for reward cues (high/low), 8 regressors for targets (reward [high/low] x task [arrow/word] x trial-type [switch/repeat]), and 4 regressors for feedback (1cent/15cent/miss/error). All regressors of interest were modeled as an impulse response function (duration = 0) convolved with a canonical haemodynamic response function (HRF) (Friston *et al.*, 1998). Regressors of non-interest were: the 30-second breaks, missed targets (no response at all for a target) 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. To remove non-

neuronal fluctuations from the data, we added time courses to our model describing compartment signals for cerebro-spinal fluid (CSF) and out-of-brain signal (OOB). Both regressors of interest 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 and/or shapes 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.

We used contrasts images from the first level to calculate different *t*-tests at the second level, dividing participants into three groups: PD patients OFF medication, PD patients ON medication and controls. Contrast images were averaged over sessions for the control group. Second level designs consisted of two-sample *t*-tests comparing either PD ON or PD OFF with control groups, including age as a covariate of non-interest, and paired-sample *t*-tests comparing ON and OFF sessions, including session as covariate of non-interest. To measure reward anticipation, we included contrast images for high versus low reward-cues for each participant (high > low reward-cues). To measure cognitive flexibility, we included contrast images for switch versus repeat targets for each participant (switch > repeat targets). Finally, in order to measure the interaction between reward anticipation and cognitive flexibility, contrast images for switch versus repeat targets on low- versus high-reward trials were included for each participant ((switch-repeat)high – (switch-repeat)low).

First, we assessed the main effects of task (reward anticipation, switch effect and the reward x switch effect) across groups, as well as the task by group and task by medication interaction effects at whole brain level corrected for multiple comparisons (**$p_{FWE} < .05$**).

Secondly, we used two regions of interest (ROIs) from the study by Aarts *et al.* (2010) to further investigate the BOLD signal during reward anticipation and the reward x switch interaction. In their study, Aarts and colleagues found activation of the bilateral nucleus accumbens (peak voxels: x = 10, y = 8, z = -2, and x = -12, y = 8, z = 8) during reward anticipation on a similar task as used in the current study. This activity was *DAT1*-dependent, suggesting that activation of this ventral striatal region during reward

anticipation is dependent on DA. In the same study, Aarts *et al.* found switch-related activation of the left caudate nucleus (peak voxel: x = -12, y = 18, z = 8) on high relative to low reward targets, which again varied as a function of *DAT1* genotype, suggesting that the amount of DA in the dorsomedial striatum mediates the interaction between reward anticipation and cognitive flexibility. In the current study, we assessed functional activation of the same striatal regions with a similar task, this time manipulating DA levels by testing PD patients ON and OFF their normal DA medication. For both the bilateral nucleus accumbens and left caudate nucleus, we constructed a 6 mm sphere around the peak voxels as reported in the experiment by Aarts *et al.* (Fig. 3) and extracted the mean beta weights from these regions with MarsBar (Brett *et al.*, 2002). These regionally averaged beta weights were analyzed using a repeated-measures GLM to assess main and interaction effects during reward-cues and targets.

To further explore our a priori hypotheses, we also selected ROIs from the main task effect contrasts, containing activation patterns averaged over the two sessions of both PD and control groups combined for reward anticipation and cognitive flexibility. Extracted mean beta weights from all voxels within clusters located in the VM or DL frontostriatal circuits (clusters selected based on **$p < 0.001$**, **uncorrected for multiple comparisons**; cluster extent: 50 voxels; y-coordinate > 1) were analyzed using a repeated-measures GLM to assess main and interaction effects during reward-cues and targets.

EMG analysis

Parkinsonian tremor might fluctuate with high relative to low reward and thereby provide a trivial source of differences in BOLD signal between patient and control groups For instance, this might cause us to attribute tremor-related functional activity in motor cortex and cerebellum (Helmich *et al.*, 2010) to reward-related functional activity. Therefore, we controlled for this factor by measuring muscle activity during MR scanning in the most-affected arm of PD patients with EMG. The same measurement was taken in the control group to ensure that PD patients and controls experienced similar conditions in the scanner. However, since the EMG signals of healthy controls contained no tremor activity, these signals were not included in the first-level analyses. Carbon

wired MRI 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. Vision Analyzer (Brain Products GmBH, Gilching, Germany) was used for signal preprocessing: MR artifact correction followed the method described in Allen *et al.* (2000) and van Duinen *et al.* (2005), which included down-sampling (From 5000 to 1000 Hz), band-pass filtering to remove possible motion artifacts (allowing frequencies between 25 and 250 Hz) and rectification to enhance information on tremor bursts (Myers *et al.*, 2003). After preprocessing, the time-series was segmented into one segment for each volume. Subsequent analyses were performed in Matlab (MathWorks, Natick, MA) using the FieldTrip toolbox for EEG/MEG analysis (http://fieldtrip.fcdonders.nl/). Peak frequency of the parkinsonian tremor was determined for each PD patient individually by visual inspection of the average power spectrum across segments, calculated in steps of 0.5 s. For the muscle with the clearest peak in the power spectrum (either flexor or extensor), the power at the peak tremor frequency was extracted and log-transformed to remove outliers. To capture functional activation related to changes in tremor amplitude (e.g. in the pallidum; Helmich *et al.*, in preparation), we calculated the first derivative of the EMG amplitude regressor. Lastly, a z-transformation was applied to both the EMG amplitude regressor and the EMG first derivative regressor. Both regressors were then convolved with the HRF and added to the first level model of all PD patients.

RESULTS

Demographics and neuropsychological assessment

In Table 2, we show that PD patients and healthy controls did not differ in terms of educational level, general mental status, impulsivity or reward sensitivity. However, PD patients reported significantly more symptoms of depression, had lower premorbid IQ, and were younger than healthy controls. As data collection for the current study is still in progress, we hope to resolve these differences between groups in the near future.

In Table 3, we show that PD patients and healthy controls did not differ on frontal executive functioning, working memory or accuracy on the Digit Vigilance Test. As

expected, PD patients exhibited significantly more PD related motor symptoms on the UPDRS when they were OFF their normal DA medication than when they were ON their medication, showing that the pharmacological manipulation in our study was successful. This was confirmed by results from the Timed Motor Test showing that there were no significant differences in performance during the ON session between least and most impaired hand, while there was a significant difference between least and most impaired hand during the OFF session. Furthermore, patients were less accurate on the Digit Vigilance test in the OFF relative to the ON state. The PD patient group also performed worse than controls on tasks measuring visuomotor speed.

Effects of reward on behavioral switch cost

Our prediction was that patients OFF their normal DA medication would show a decrease in performance on task switching in a low reward condition, but not in a high reward condition. As expected, the analysis of the proportion of errors revealed a significant interaction effect of reward x switch x group in the HC versus PD OFF comparison ($F_{(1,22)} = 5.2$; $p < .05$; Fig. 2a). Further simple effect analyses showed that switch cost for the PD OFF group in the low reward condition was significantly greater compared to the control group ($F_{(1,22)} = 8.5$; $p < .01$). Switch cost did not differ between the PD OFF group and the healthy control group in the high reward condition ($F_{(1,22)} < 1$). These results demonstrate the predicted switch cost deficit in the low reward condition, but, critically, not in the high reward condition in PD patients OFF their normal DA medication compared to healthy controls. We hereby replicate the behavioral results found in the study by Aarts *et al.* (in preparation).

PD patients ON medication did not demonstrate a switch deficit in the low reward condition compared with controls ($F_{(1,10)} = 1.9$; $p > .1$), nor did the PD ON group exhibit an effect of anticipated reward on switching ($F_{(1,11)} < 1$; $p > .9$).

For mean response latencies, the reward x switch x group interaction was not significant in any of the group comparisons (Fig. 2b).

Neural correlates of the reward x switch interaction

We first assessed the main effects of task across groups at whole brain level corrected for multiple comparisons ($p_{FWE} < .05$): reward anticipation (high > low reward-cues), the switch effect (switch > repeat targets) and the reward x switch effect ((switch-repeat)high – (switch-repeat)low). Analyses of the task effects at this stringent statistical threshold did not show any significant effects across groups. We also did not find any differences, at this stringent statistical threshold, between healthy controls and PD patients OFF their DA medication, nor between the ON and OFF sessions. Note that tasks effects at $p < 0.001$, uncorrected for multiple comparisons, are reported in Tables 4 and 5. At this more liberal threshold, we observed several regions within the VM and DL frontostriatal circuits to be activated, with the dorsal ACC specifically showing the reward x switch interaction (fig. 4; see below).

Secondly, we used the two ROIs from the study by Aarts *et al.* (2010) to further investigate the BOLD signal during reward anticipation and the reward x switch interaction (as described above under fMRI statistical analyses). Statistical analyses of the mean beta weights extracted from the ventral striatum ROI did not show any differences between groups or as a function of medication in functional activity during reward anticipation at $p < 0.05$. Similarly, the signal extracted from the dorsomedial striatal ROI did not show significant differences for the reward x switch interaction for any of the group or medication comparisons. This analysis suggests that the behavioural differences observed between the OFF medication and control group were not accompanied by differences in striatal activity. Exploration of the relevant task by group and task by medication brain maps at a more liberal threshold of $P_{uncorrected} < 0.001$ confirmed this observation:

Our a priori hypotheses allowed us to further investigate the influence of reward on cognitive flexibility in regions of the DL and VM frontostriatal circuitry, and therefore we selected ROIs from the main task effect contrasts, containing activation patterns averaged over the two sessions for both PD and control groups combined: reward anticipation (associated with the VM frontostriatal circuitry) and task-switching (associated with the DL frontostriatal circuitry). For the main effect of reward (Table 4),

we found no significant differences between groups in functional activity during reward anticipation in any of the group comparisons. For the main effect of switch (Table 5), the dorsal ACC (dACC; Fig. 4) showed a significant reward x switch effect when comparing the PD OFF versus the control group ($F_{(1,22)} = 4.4$; $p < 0.05$). Simple effect analyses for the separate reward conditions revealed a significant switch x group interaction for high reward trials only, with PD patients OFF their normal DA medication showing more switch-related activity compared to healthy control subjects ($F(1,22) = 5.0$; $p < 0.05$). No differences between these groups were found on low reward trials. Furthermore, no reward x switch interactions were found in any of the other group comparisons for dACC activity, nor in any of the other regions selected from the main effect of switch.

DISCUSSION

The current study establishes a key role of DA in the modulation of motivational compensation of cognitive deficits, by demonstrating that PD patients OFF their normal DA medication exhibit a potentiation of the reward effect on behavioral switch cost, in line with earlier findings by Aarts and colleagues (in preparation). Importantly, we also show the neural correlates of this behavioral effect, by demonstrating that it is accompanied by a potentiation of the reward effect on switch-related BOLD signal in the dACC. Thus, PD patients OFF medication show a task-switching deficit in the proportion of errors on low reward trials, but not on high reward trials, accompanied by an increase of switch-related BOLD signal in the dACC on high relative to low reward targets. These findings concur with our hypothesis that motivational processing can be used by PD patient OFF medication to overcome cognitive inflexibility, and implicate a crucial role of the dACC in this compensation process.

Compensation of the switch deficit by monetary reward in PD patients OFF medication might be driven by intact or up-regulated DA levels in the ventral striatum, which could normalize DA levels in the DA-depleted dorsal striatum (Aarts *et al.*, in preparation). An interaction of motivation and cognition, two functions linked to distinct VM and DL frontostriatal circuits (Alexander *et al.*, 1986; Hoover & Strick, 1993), could come about by spiraling connections between functional regions of the striatum via DA

midbrain cells (Haber *et al.*, 2000). Although we did not find an interaction of reward x switch in activity of the DMS, as shown in healthy subjects by Aarts and colleagues (2010), our BOLD data suggests that, on a cortical level, such an interaction of motivation and cognition does take place in the dACC for PD patients OFF their DA medication. Compensation mechanisms in PD patients have previously been shown to occur more strongly on a cortical level, in comparison to healthy controls that rely more on striatal regions (Helmich *et al.*, 2009; Monchi *et al.*, 2004). Lack of functional activity for a motivation and cognition interaction in the DMS might be due to the fact that this region is depleted of DA in PD patients in contrast to healthy individuals who do show activity in the DMS during this interaction (Aarts *et al.*, 2010). The ACC, specifically, can become hyperactive in early PD patients (Kaasinen *et al.*, 2000), with findings by Bruck *et al.* (2005) suggesting that activity within the ACC may be important in resolving conflict during a Stroop task in PD. Therefore, we argue that in PD patients, the dACC might serve as a nexus between the two separate frontostriatal circuits in PD patients OFF medication on a cortical level, as does the DMS in young healthy controls on a subcortical level. The ACC seems to be particularly suitable for this function, as it is one of the parts of the frontal cortex most richly innervated by DA neurons from the midbrain ventral tegmental area (VTA; Williams & Goldman-Rakic, 1998), which are still intact in early PD. The ACC has also repeatedly been found to be activated during tasks requiring cognitive flexibility in neuroimaging studies (Botvinick *et al.*, 2004). Importantly, the ACC has been suggested to use motivational input to guide decision making (Amiez *et al.*, 2006; Rushworth & Behrens, 2008), and could be a region where motor control, drive and cognition interface, with DA modulating the interaction between cognition and motor control in relation to changes in emotional and motivational states (Paus, 2001). Our current study provides further evidence for such a role of the ACC, and in addition implicates that the region becomes specifically important in compensation of cognitive deficits associated with DA depletion in PD patients.

Using the same experimental design as we employed, Aarts *et al.* (2010) found an increased reward benefit on task-switching in individuals with genetically-determined higher DA levels accompanied by elevated BOLD signal within the bilateral nucleus accumbens. We did not observe supra-threshold activations of ventral striatal areas in the

main effect of reward, nor an effect of reward-cues in beta weights extracted from the bilateral nucleus accumbens ROI used by Aarts and colleagues. However, the mean age of healthy young volunteers in their study was 21.6 years, and a reason for not finding similar effects in the current experiment might be due to the effects of ageing on activation of reward-processing regions in the older subjects who participated in our study. It has been shown that various alternations take place in components of the DA system with ageing, such as decreases in number of dopamine receptors (DaT; Seeman *et* al, 2004) and dopamine transporters in the striatum (Volkow *et al.*, 1996). Alternations in the DA system might contribute to insufficient information processing in the reward system for elderly individuals (Mell *et al.*, 2009; Dreher *et al.*, 2008)

Furthermore, the pattern of DA cell loss in the pars compacta of the substantia nigra (SN_c) in normal ageing shows a dorsal-to-ventral gradient (Fearnley & Lees, 1991), opposite to the pattern found in PD patients (Kish *et al.*, 1988), implicating differences in ventral striatal function between healthy elderly and PD patients. We speculate that due to relatively more DA-ergic cell loss in the ventral compared to the dorsal striatum, healthy elderly might also be less able to use reward to compensate for possible cognitive decline. As we demonstrate in this study, PD patients OFF their DA medication can still use reward to alleviate their switching deficit, suggesting that they recruit the ventral striatum more strongly than healthy controls, despite possible effects of age, as this region is relatively intact compared to the already severely depleted dorsal striatum in early PD. Unfortunately, we were not able to show such differences between the PD OFF and control group in activation of the ventral striatum in the current analyses of the BOLD signal, and the mechanism mentioned above remains speculation.

Besides investigating the compensation hypothesis in the current study (discussed above), we also set out to find evidence for the overdose hypothesis (Gotham *et al.*, 1988; Cools *et al.*, 2001; Cools *et al.*, 2003): We predicted that PD patients ON their normal DA medication would show intact task switching in a low reward condition, but show premature task switching in a high reward condition. In terms of the BOLD signal, we expected abnormal functional activity in the ventral striatum and connected cortical structures, due to medication-induced oversensitivity to reward in PD patients ON medication compared to healthy control subjects. However, we did not find any

differences between the PD ON and control group in both behavioral and functional activity data. We were only able to demonstrate that the interaction of reward x switch was not significant in PD patients ON medication, whereas it was significant in PD patient OFF medication. Thus, it is unclear whether either the DA-rich ACC (Williams & Goldman-Rakic, 1998) was overdosed in PD patients ON medication, and therefore they could no longer use reward to compensate their switch deficit, or the PD ON group simply did not use reward since there was no switch deficit to compensate for in the first place, likely because DA medication normalized DA levels in the DL frontostriatal circuitry associated with switching. Earlier studies investigating the DA overdose hypothesis (Cools *et al.*, 2001; Cools *et al.*, 2003), used separate tasks to look into switch deficits (Letter-number switching; Task-set switching by Rogers *et al.*, 1998) and reward sensitivity (probabilistic reversal learning task by Lawrence *et al.*, 1999; decision-making task by Rogers *et al.*, 1999). In the rewarded switching task employed in the current experiment, on the other hand, both reward processing and switching were intrinsically linked to each other. This allowed us to uniquely test the interaction between the two cognitive processes, but might have made it more difficult to selectively assess overdosing effects of DA medication. A separate reward sensitivity paradigm might have been needed to further test our overdose hypothesis. Fortunately, a study employing such a paradigm is currently being conducted within the same PD patients and control subjects who participated in our study (Smittenaar, in preparation).

Future studies into motivational compensation of cognitive decline in Parkinson's disease might also be extended by including measures of genetic polymorphisms. The relation of genetic variations in DA transmission (e.g. *DAT1* gene polymorphisms: Aarts *et al.*, 2010; or *DRD2* gene polymorphisms: Kirsch *et al.*, 2006) to the extent to which PD patients can make use of reward for compensating cognitive deficits could then be investigated. For example, recent evidence suggests that down-regulation of DaT might underlie increased DA release in the ventral striatum of PD patients with pathological gambling in comparison to those without impulse control disorders (Cilia *et al*, 2010). Inter-individual differences in *DAT* expression might therefore mediate the ability to reduce cognitive inflexibility with reward due to different degrees of DA transmission sensitization.

In general, our data did not exhibit significant differences between ON and OFF sessions in PD patients, though the rewarded switching task has repeatedly been shown to be strongly modulated by DA (Aarts *et al.*, 2010; Aarts *et al.*, in preparation). This could be a power issue, because the observed reward x switch interaction in both the PD OFF group and control group was driven by the first session and not by the second session (see Supplementary analyses), possibly due to habituation or learning effects. This leaves only a small number of PD patients in the first session (7 ON and 5 OFF medication, against 13 control subjects) exhibiting the strongest effects on our task. Consequently, since task-induced differences in behavioral data and brain activity between groups presumably are most explicit in the first session, the number of measurements taken in the second session does not strongly contribute to differences between ON and OFF sessions and may have even averaged out effects from the first session. Further data collection, which is still in progress, can hopefully solve this issue by adding more first session data of PD patients in both ON and OFF states, thereby increasing the power of statistical comparisons between these groups.

Due to the fact that data collection for this study is still in progress, the current PD patient and healthy control groups were not yet matched for age, premorbid IQ scores and depression scores. Both behavioral and brain activation results remained significant when age was entered as a covariate in statistical analyses, suggesting that the significant difference in age between the PD patient and control group did not explain our findings. Only when premorbid IQ scores and/or BDI scores were entered either separate from or together with age, the reported effects no longer held (see Supplementary analyses). It is likely that premorbid IQ scores and depression scores co-vary with disease severity, as has at least been demonstrated for the latter (Schrag, Jahanshahi & Quinn, 2001). We therefore did not use these covariates, because we would have possibly regressed out the group differences we were actually interested in. Note again that for the current experiment, data collection is still in progress and we will match our PD patient and control group on age, BDI scores and premorbid IQ scores with the inclusion of additional participants.

The findings from the current study could have important therapeutic implications. A well-documented literature exists on the use of external cues to overcome

motor akinesia in PD patients, a phenomenon known as kinesia paradoxa (Lewis, Byblow & Walt, 2000; Jiang & Norman, 2006). Hesitations and freezing have also been shown to be reduced in MPTP-lesioned monkeys due to motivational processes (with preferred food as rewards; Pessiglione *et al.*, 2004). Furthermore, the prominent placebo effect in PD has been found to be accompanied by endogenous DA release in the striatum and is suggested to be related to reward expectancy (de la Fuente-Fernández *et al*, 2001). We extend this literature on the use of external (reward) cues to reduce motor deficits in PD to the cognitive domain, showing that PD patients can use external cues to reduce switch deficits.

To conclude, we demonstrate that PD patients OFF medication can make use of monetary reward to reduce cognitive inflexibility in a rewarded task switching paradigm. In addition, we show that PD patients OFF their normal DA medication exhibit more switch-related activity in the dACC compared to healthy control on high relative to low reward, thereby revealing the underlying neural substrates of this compensatory process. Our results support the hypothesized mechanism that early PD patients OFF medication use the intact VM frontostriatal circuitry (involved in reward-processing) to compensate for the DA-depleted DL frontostriatal circuitry (involved in task-switching). The data also indicate that the dACC serves as an important nexus on the cortical level between these two separate circuits in early PD patients with already severely depleted DA levels in the dorsal striatum.

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FIGURES

Medications	
Levodopa (DA precursor)	6
Ropinirole (D3 agonist)	7
Pramipexole (D3 agonist)	3
*Mean L-DOPA equivalent dose**	*502 (546)*
Amantadine**	2
Tamsulosine (α1-blocker)	2
Omeprazol (H+/K+-ATP-ase inhibitor)	1
Simvastatine (A-(HMG-CoA-)reductase inhibitor)	2
Domperidone (peripheral DA-antagonist)	2
Cozaar (angiotensine-II-R-(AT1)-antagonist)	1
Pantoprazole (H+/K+-ATP-ase inhibitor)	1
Nexium (H+/ K+-ATP-ase inhibitor)	2
Suprimal (anti-histaminicum)	1
Citalopram (SSRI)	1

Table 1
*Medication taken by PD patients who participated in the study. Properties of the substance mentioned in brackets; number of PD patients taking the substance mentioned in the last column. * Mean L-DOPA equivalent dose (SD in brackets) calculated according to Wenzelburger et al. (2002). ** Amantadine is an anti-viral substance with an anti-Parkinson effect, of which the exact working mechanism in PD is unknown.*

Demographics			
	PD	control	*p*
Age	52.4 (10.0)	62.5 (5.4)	0.004
Disease duration	5.3 (3.4)	na	
Premorbid IQ	78.6 (13.0)	91.4 (7.1)	0.005
Education level	5.4 (0.8)	5.9 (0.9)	0.2
Depression score	8.7 (4.9)	3.6 (3.1)	0.005
Mental status	28.5 (1.2)	28.5 (1.1)	0.9
Impulsivity score	60.4 (6.5)	60.9 (6.9)	0.9

Table 2
Mean demographics and questionnaire scores for PD patients (PD) and healthy control subjects (control); SD in brackets. Premorbid IQ measured with Dutch Reading Test for Adults; Education level determined according to classification system of the Dutch Reading Test for Adults. Depression scores measured with Beck Depression Inventory. Mental status determined according to Mini Mental State examination. Impulsivity scores measured with the Barrat Impulsiveness Scale-11.

Symptoms and neuropsychology						
	ON	OFF	*p (ON vs OFF)*	Control average	*p(control vs ON)*	*p (control vs OFF)*
UPDRS	19.6 (7.9)	28.5 (9.6)	*0.001*	na	*na*	*na*
FAB	17.3 (1.2)	16.6 (1.4)	*0.1*	17.4 (0.6)	*0.8*	*0.1*
WM	6.0 (0.3)	5.8 (0.2)	*0.3*	6.2 (0.9)	*0.5*	*0.1*
Block	116.8 (6.3)	119.6 (9.1)	*0.6*	86.4 (28.2)	*0.006*	*0.011*
Digit	315.8 (16.3)	315.8 (14.6)	*1*	263.2 (55.0)	*0.028*	*0.021*
Digithit	202.2 (1.0)	200.4 (1.2)	*0.02*	200.6 (3.9)	*0.2*	*0.9*
	Least	Most	*p (Least vs Most)*			
TMTon	25.4 (5.5)	40.4 (31.8)	*0.1*			
TMToff	24.3 (5.8)	42.3 (25.7)	*0.015*			

Table 3

Mean symptoms and neuropsychological assessment scores for PD patients ON dopaminergic medication (ON), PD patients OFF dopaminergic medication (OFF), and healthy control subjects averaged over sessions (Control average). SD in brackets. UPDRS = Unified Parkinson's Disease Rating Scale scores (part III, motor examination); FAB = Frontal Assessment Battery; WM = working memory, assessed using digit span incorporated in the FAB; Block = time (s) to complete Block Completion task; Digit = time (s) to complete Digit Cancellation task; Digithit = number of correct hits on Digit Cancellation task. TMT = Timed Motor Test, with TMTon = time (s) for completion using either least or most impaired hand for PD patients ON medication, TMToff = time (s) for completion using either least or most impaired hand for PD patients OFF medication.

Reward effect				
Label	**Volume (mm3)**	**MNI coordinates**	**T**	**Z**
Right middle frontal gyrus	171	26 -6 46	7.07	5.05
		20 10 50	4.26	3.60
		28 8 56	4.12	3.51
Right precuneus	1525	12 -66 50	6.54	4.82
		10 -54 50	5.83	4.49
		-14 -66 56	5.18	4.14
Right middle frontal gyrus	480	32 54 24	6.12	4.63
		34 44 24	4.81	3.91
		32 44 14	4.78	3.91
Right calcarine gyrus	428	12 -70 16	5.88	4.51
		24 -60 8	5.02	4.05
		-8 -80 6	4.78	3.92
Left superior medial gyrus	468	0 18 42	5.43	4.28
		-4 12 46	5.40	4.27
		12 8 64	5.18	4.14
Left superior frontal gyrus	69	-26 -6 56	4.95	4.01
Left superior frontal gyrus	65	-24 -4 62	4.92	4.00
Left middle frontal gyrus	125	-34 58 14	4.69	3.86
		-36 46 26	4.38	3.68
		-32 48 14	3.98	3.42

Table 4

Signal change during high reward-cues relative to low reward-cues. Height threshold: $p < 0.001$, uncorrected for multiple comparisons. Extent threshold: 50 voxels. Frontal areas ($y > 1$) were employed in subsequent a priori determined region of interest analyses.

Switch effect				
Label	**Volume (mm3)**	**MNI coordinates**	**T**	**Z**
Left inferior parietal lobule	799	-36 -46 42	7.06	5.05
		-42 -40 40	6.40	4.76
		-28 -66 28	5.52	4.33
Right SMA	582	8 8 50	6.60	4.85
		-6 10 48	5.42	4.27
		-2 16 52	5.19	4.15
Right inferior frontal gyrus	301	42 22 10	6.18	4.65
		48 18 2	5.31	4.22
		30 24 -10	4.69	3.87
Left inferior frontal gyrus	530	-44 16 6	6.08	4.61
		-50 14 0	5.77	4.46
		-30 22 0	4.78	3.92
Left precentral gyrus	254	-50 0 42	5.07	4.09
		-38 -2 40	5.18	4.14
		-48 6 32	4.98	4.03
Left middle frontal gyrus	102	-30 6 52	4.97	4.03
		-38 2 52	4.24	3.58
		-22 6 62	3.79	3.29
Right superior frontal gyrus	52	26 -2 54	4.61	3.82

Table 5

Signal change during switch targets relative to repeat targets. Height threshold: $p < 0.001$, uncorrected for multiple comparisons. Extent threshold: 50 voxels. Frontal areas ($y > 1$) were employed in subsequent a priori determined region of interest analyses.

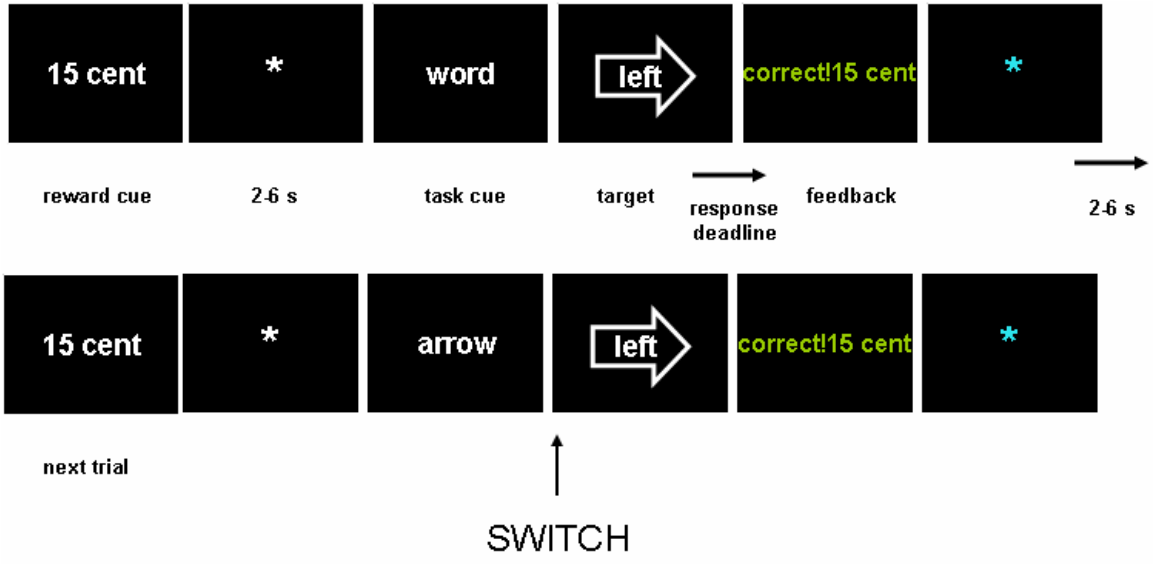


Figure 1

Example trials from the experimental paradigm. In both these trials the reward-cue indicated that the participant could earn 15 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, but to the arrow of the incongruent arrow-word Stroop-like target in the second trial. Hence, the second trial is an example of a switch of the task relative to the previous trial. There was a variable delay of 2-6 s between reward- and task-cues, and between trials, in which participants had to fixate on an asterisk in the middle of the screen.

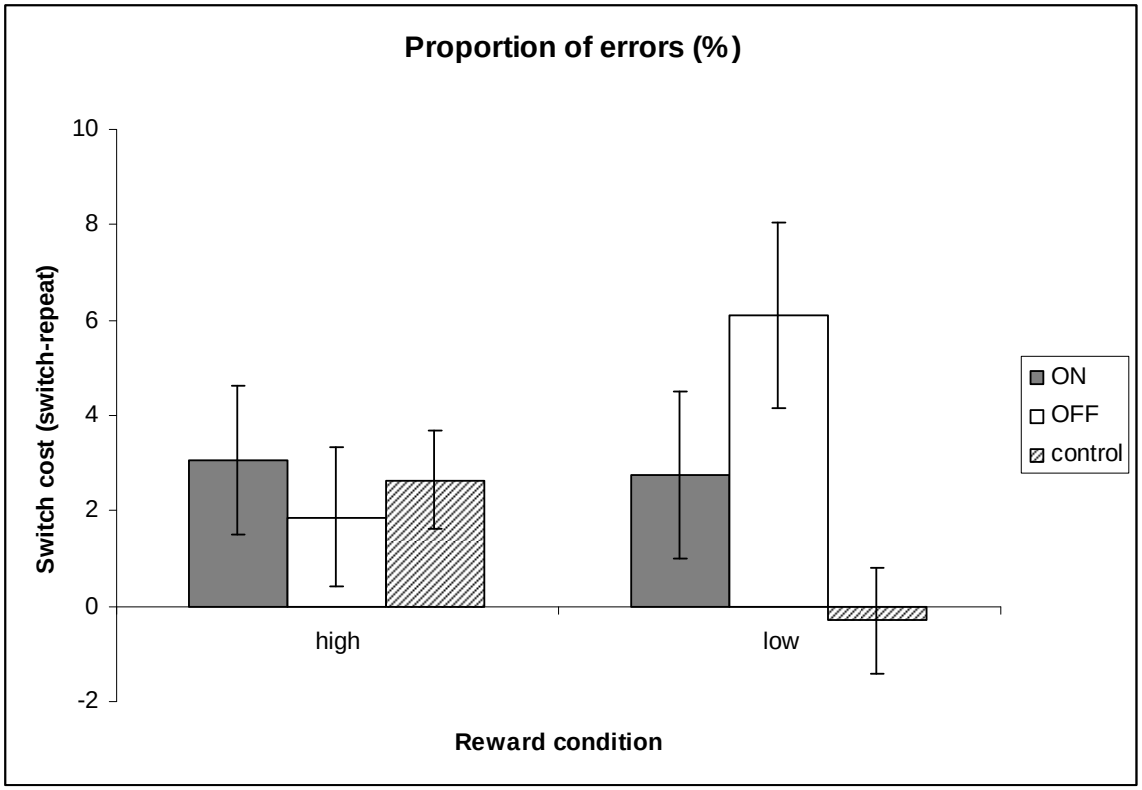


Figure 2a

Switch cost (switch – repeat trials) in the mean proportion of errors for the high and low reward condition. Error bars represent SE of the mean. ON = PD patients ON dopaminergic medication; OFF = PD patients OFF dopaminergic medication; control = healthy control subjects.

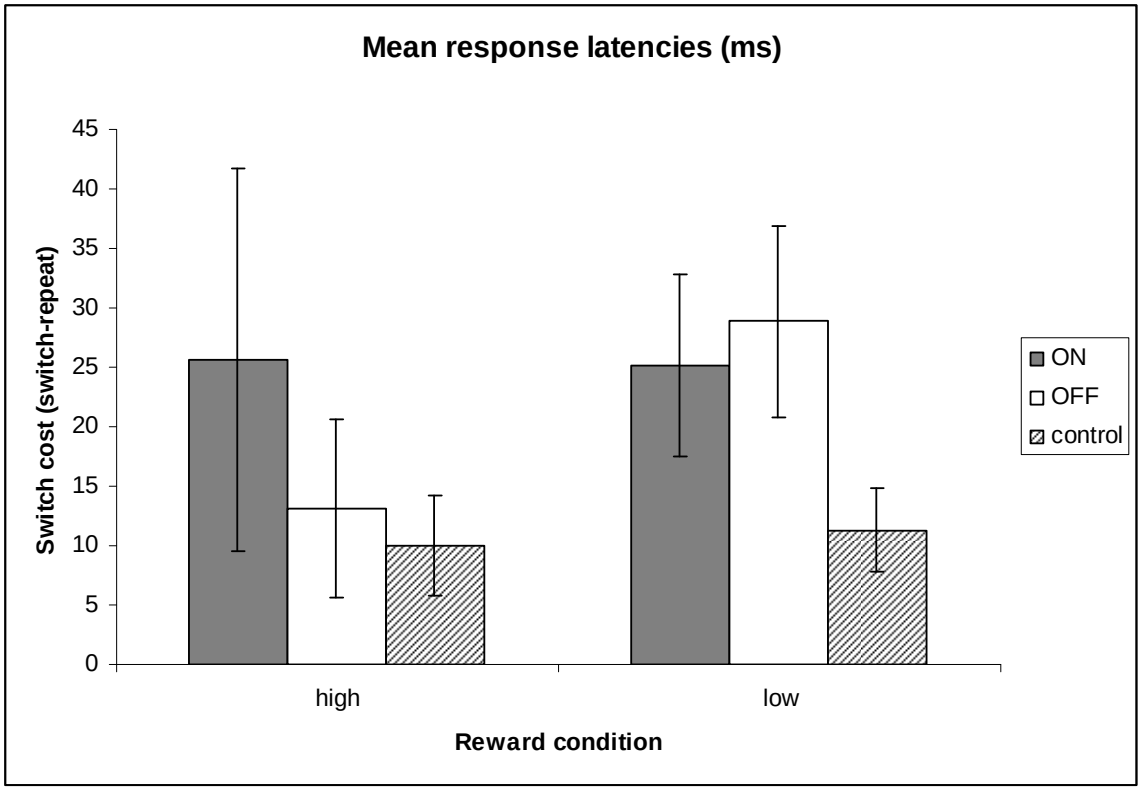
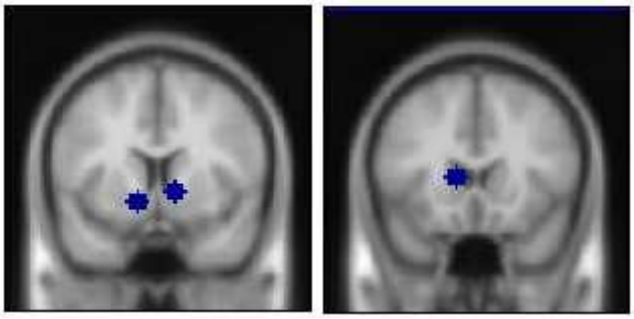


Figure 2b

Switch cost (switch – repeat trials) in the mean response latencies for the high and low reward condition. Error bars represent SE of the mean. ON = PD patients ON dopaminergic medication; OFF = PD patients OFF dopaminergic medication; control = healthy control subjects.



Figures 3a & 3b

Coronal sections showing 6 mm spheres constructed around peak coordinates of the bilateral nucleus accumbens (Fig. 3a; y = 8) and the left caudate nucleus (Fig. 3b; y = 18) from the study by Aarts et al. (2010). The bilateral neucleus accumbens region of interest was used in the current study to investigate the BOLD signal during reward anticipation in the ventral striatum. The left caudate nucleus region of interest was used to investigate the BOLD signal during the reward x switch interaction in the dorsomedial striatum.

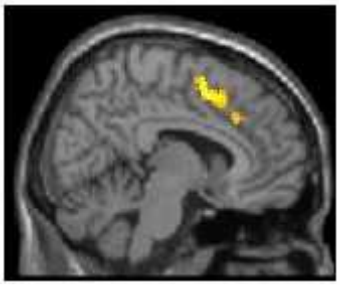


Figure 4a

Switch-related signal across groups (PD ON, PD OFF and healthy control subjects) in the dorsal anterior cingulate cortex (dACC; x = 8). The figure shows the BOLD activation pattern during switch relative to repeat targets, at $p < 0.001$, uncorrected for multiple comparisons. See Table 5 for all peaks that reached significance at this threshold.

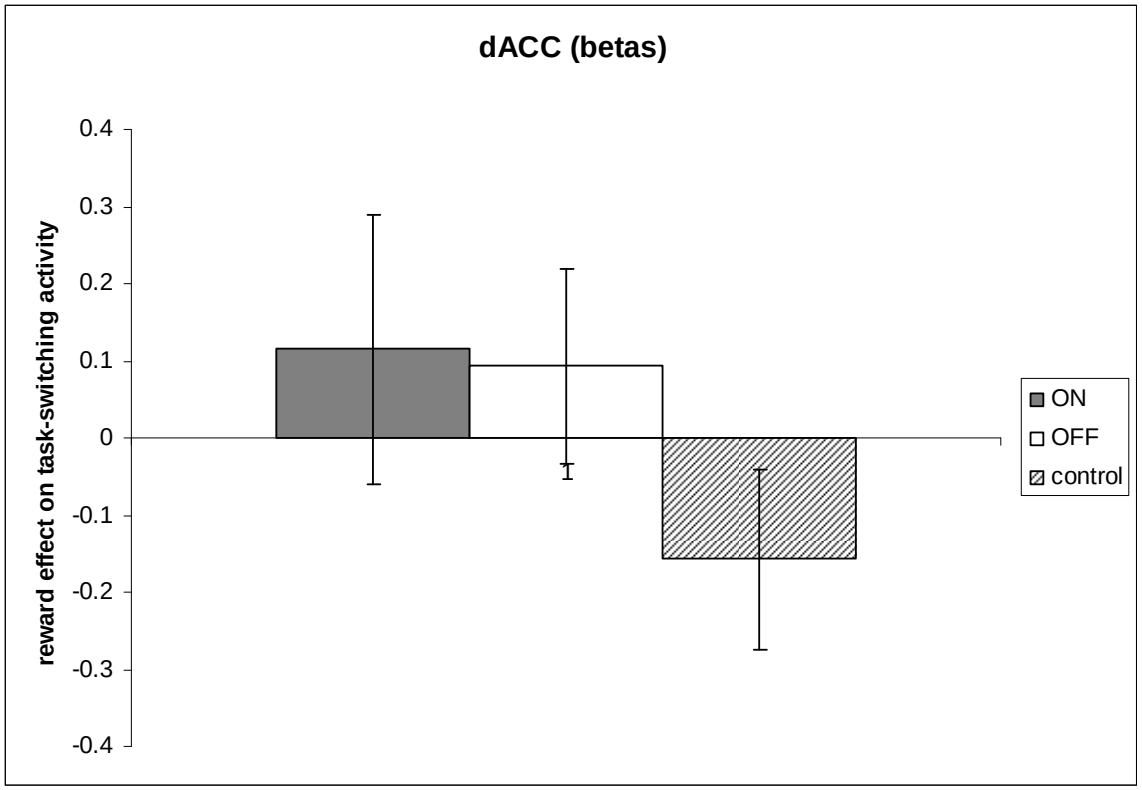


Figure 4b

Reward effect on task-switching activity. Figure shows the reward x switch interaction ((switch-repeat)high – (switch-repeat)low) for the mean beta weights extracted from the dACC region of interest as found in the switch-related activity contrast (Fig. 4a). Error bars represent SE of the mean. ON = PD patients ON dopaminergic medication; OFF = PD patients OFF dopaminergic medication; control = healthy control subjects.

dACC		
	High sw-rp	**Low sw-rp**
ON	0.641 (0.115)	0.526 (0.182)
OFF	0.324 (0.132)	0.231 (0.119)
control	0.105 (0.143)	0.263 (0.089)

Figure 4c

Mean beta weights extracted from the dACC region of interest (Fig. 4a) for switch relative to repeat targets for high and low reward trials. SE of the mean in brackets. ON = PD patients ON dopaminergic medication; OFF = PD patients OFF dopaminergic medication; control = healthy control subjects.

SUPPLEMENTARY ANALYSES

Session effects in healthy control subjects and PD patients

In the behavioral analyses of the error rates, we found a significant reward x switch x session effect when comparing the first and second session of healthy control subjects ($F_{(1,12)} = 5.9$; $p < 0.05$; Fig S1a) and PD patients ($F_{(1,10)} = 7.3$; $p < 0.05$; Fig S1b), with both healthy controls and PD patients showing the reward x switch effect in the first session ($F_{(1,12)} = 6.2$; $p < 0.05$ and $F_{(1,11)} = 7.3$; $p < 0.05$ respectively), but not in the second session ($F_{(1,12)} < 1$ and $F_{(1,11)} < 1$, respectively). This reward x switch interaction in the first session disappeared for PD patients when medication was entered as a covariate ($F_{(1,10)} = 1.1$; $p = .4$). As both the healthy control and PD patient group exhibited a reward x switch effect in the first session, we averaged the two separate sessions for the healthy controls in our analyses. We then continued to investigate the ON and OFF medication effects, which were also averaged over sessions and, therefore, could still explore reward x switch x group effects post-hoc.

When only using the error rates from the first session for statistical analyses, the results still replicated our findings found when using error rates from both sessions: The reward x switch interaction was only significant for the PD OFF versus control group comparison ($F_{(1,16)} = 7.5$; $p < 0.05$; Fig S1c), but not for the PD ON versus control group ($F_{(1,16)} = 2.4$; $p = 0.2$) or PD ON versus PD OFF comparison ($F_{(1,9)} < 1$). Simple effects revealed that switch cost was greater for PD patients OFF medication than for the control group in the low reward condition ($F_{(1,16)} = 5.9$; $p < 0.05$), as was the case in our analyses of the error rates for both sessions. Again, there was no significant difference in switch cost between these two groups in the high reward condition ($F_{(1,16)} < 1$).

Inclusion of the covariates BDI and premorbid IQ

Since patients had higher scores on the BDI and lower scores on our premorbid IQ measure compared with healthy controls (Table 2), we used each participant's BDI score and premorbid IQ score as covariates, together with the original covariate age, in the statistical analyses of behavioral data and the mean betas weights to see whether our

effects would still hold. The reward x switch effect in the error rates for the PD OFF versus control group comparison was no longer significant when including the BDI and premorbid IQ covariates, either separately or together, and either with or without the covariate age (Table S1a).

The reward x switch interaction in the dACC (Fig 5), which was selected from the main effect of switch, was no longer significant when including scores BDI and premorbid IQ scores as covariates, either separately or together, with or without the covariate age (Table S1b). Only when entering age and BDI score together in the repeated measures GLM, the reward x switch interaction remained significant ($F_{(1,21)} = 4.4$; $p < 0.05$).

Proportion of errors			
	df	F	*p*
Age	1,22	5.2	0.032
BDI	1,22	2.7	0.2
NLV	1,22	1.7	0.3
Age & BDI	1,21	2.5	0.2
Age & NLV	1,21	1.6	0.3
BDI & NLV	1,21	1.3	0.3
Age & BDI & NLV	1,20	1.3	0.3

Table S1a

Influence of the covariates age, BDI score and premorbid IQ score on the reward x switch interaction in the proportion of errors.

dACC			
	df	F	*p*
Age	1,22	4.4	0.047
BDI	1,22	1.2	0.3
NLV	1,22	< 1	0.8
Age & BDI	1,21	4.4	0.048
Age & NLV	1,21	1.9	0.2
BDI & NLV	1,21	< 1	0.6
Age & BDI & NLV	1,20	2.7	0.2

Table S1b

Influence of the covariates age, BDI score and premorbid IQ score on the reward x switch interaction in the mean beta weights extracted from the dACC region of interest (Fig. 4a).

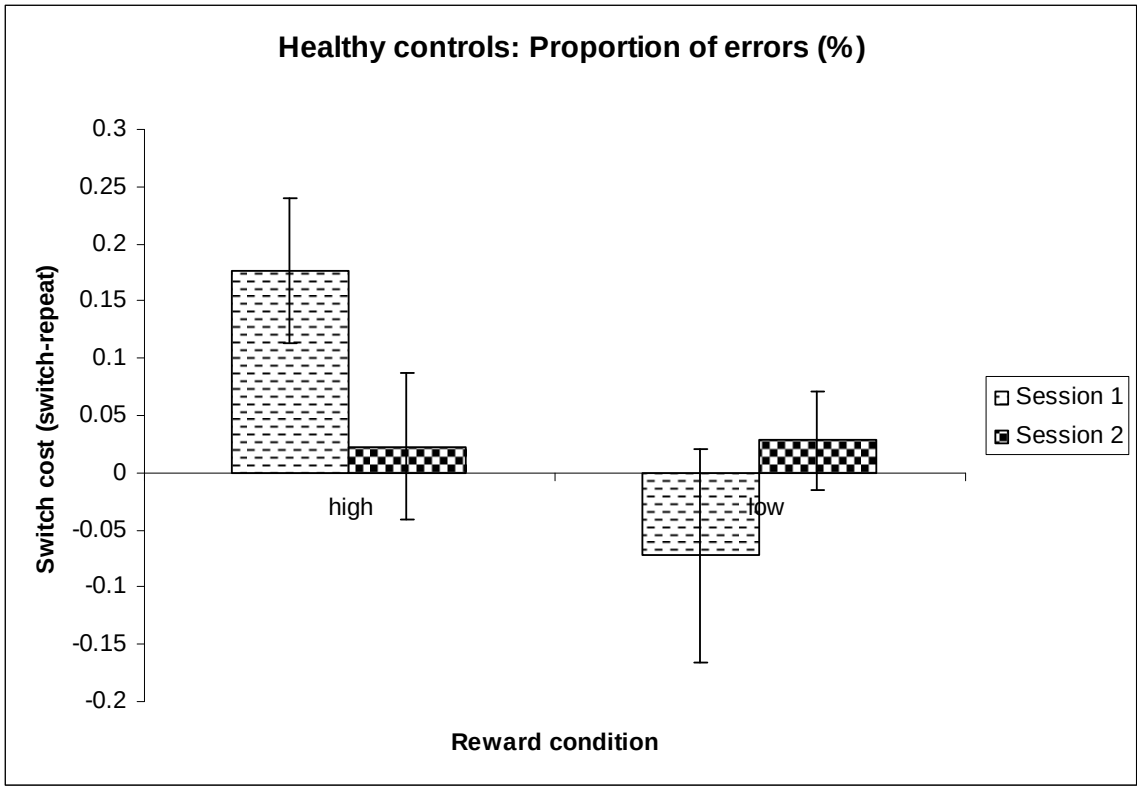


Figure S1a

Switch cost (switch – repeat trials) in the mean proportion of errors in the high and low reward condition plotted for the first and second session of the healthy control group. Error bars represent SE of the mean.

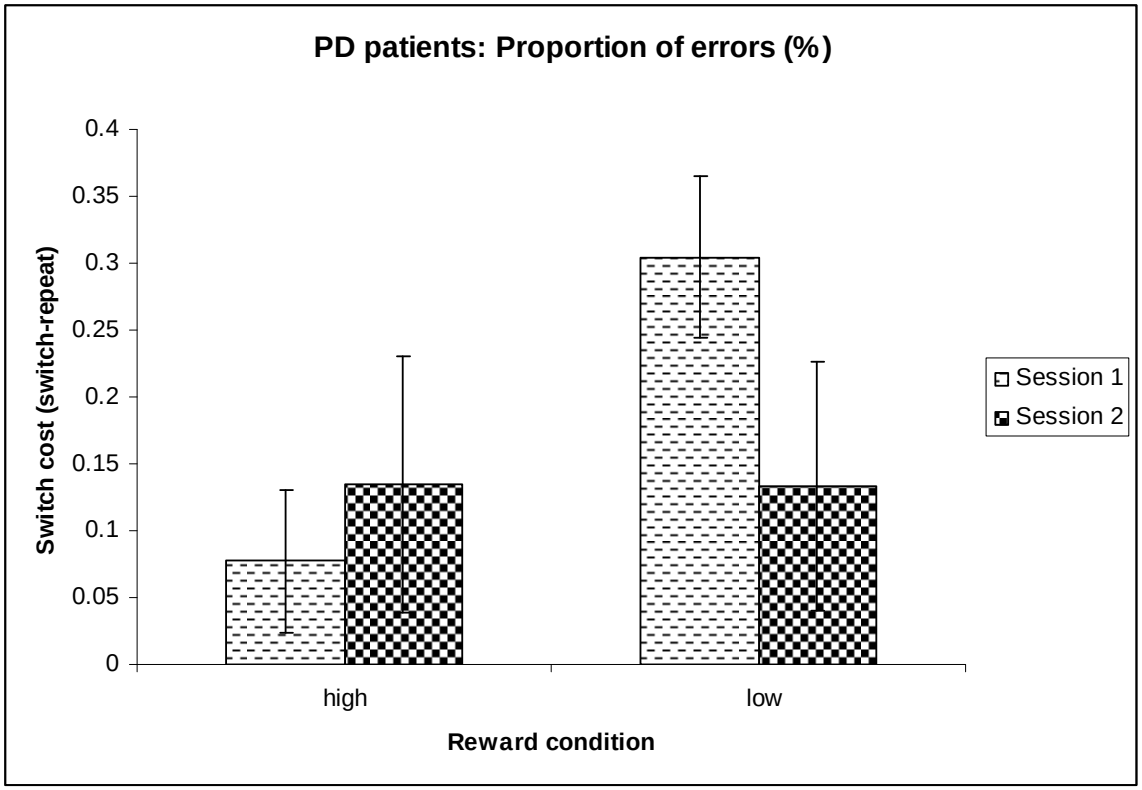


Figure S1b

Switch cost (switch – repeat trials) in the mean proportion of errors in the high and low reward condition plotted for the first and second session of the PD patient group. Error bars represent SE of the mean.

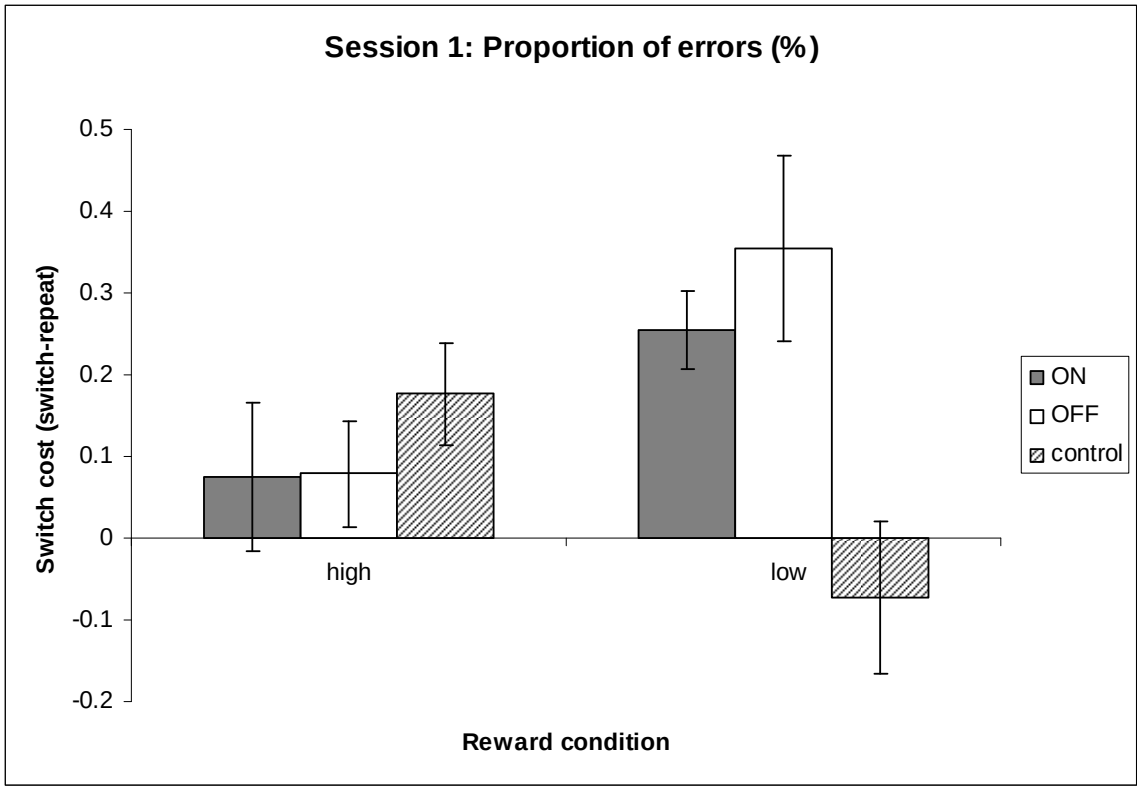


Figure S1c

Switch cost (switch – repeat trials) in the mean proportion of errors for the high and low reward condition plotted for the first session only. Error bars represent SE of the mean. ON = PD patients ON dopaminergic medication; OFF = PD patients OFF dopaminergic medication; control = healthy control subjects.

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