

Selective impairment of prediction error signaling in human dorsolateral but not ventral striatum in Parkinson's disease patients: evidence from a model-based fMRI study

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ABSTRACT

Animal studies have found that the phasic activity of dopamine neurons during reward-related learning resembles a “prediction error” (PE) signal derived from a class of computational models called reinforcement learning (RL). An apparently similar signal can be measured using fMRI in the human striatum, a primary dopaminergic target. However, the fMRI signal does not measure dopamine per se, and therefore further evidence is needed to determine if these signals are related to each other. Parkinson's disease (PD) involves the neurodegeneration of the dopamine system and is accompanied by deficits in reward-related decision-making tasks. In the current study we used a computational RL model to assess striatal error signals in PD patients performing an RL task during fMRI scanning. Results show that error signals were preserved in ventral striatum of PD patients, but impaired in dorsolateral striatum, relative to healthy controls, a pattern reflecting the known selective anatomical degeneration of dopamine nuclei in PD. These findings support the notion that PE signals measured in the human striatum by the BOLD signal may reflect phasic DA activity. These results also provide evidence for a deficiency in PE signaling in the dorsolateral striatum of PD patients that may offer an explanation for their deficits observed in other reward learning tasks.

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Introduction

Empirical and computational work implicates the midbrain dopamine (DA) system and its most prominent target, the striatum, in reward-based learning (Schultz, 1998, 2002). Notably, DA neurons in the animal midbrain respond phasically to primary rewards and stimuli that have come, via learning, to predict reward. The pattern of these phasic responses resembles a reward prediction error (PE) signal derived from formal reinforcement learning (RL) models (Rescorla and Wagner, 1972; Montague et al., 1996; Schultz et al., 1997; Sutton and Barto, 1998; Dayan and Abbott, 2001; Dayan and Balleine, 2002; Bayer and Glimcher, 2005; Daw and Doya, 2006; Morris et al., 2006). There is also a large body of human functional MRI studies (fMRI), showing reward- and specifically PE-related correlates in BOLD activity in both ventral and dorsal striatum (and also in the dopaminergic midbrain nuclei that innervate them) during learning tasks patterned after those used to elicit dopaminergic responses in animals (Delgado et al., 2000; Knutson et al., 2000; Pagnoni et al.,

2002; McClure et al., 2003; O'Doherty et al., 2003, 2004; Rodriguez et al., 2006; Schonberg et al., 2007; D'Ardenne et al., 2008; for review see O'Doherty, 2004).

Given the similarity in the responses, it is tempting to infer that the PE correlates in the striatum reflect its dopaminergic input. However, because BOLD is a general metabolic signal that does not measure dopamine release per se, providing direct evidence for such a link poses a considerable challenge. There is physiological evidence, from pharmacological MRI studies in animals, demonstrating that dopaminergic manipulations affect the BOLD signal in the striatum (for a review see Knutson and Gibbs, 2007). A recent fMRI study (Pessiglione et al., 2006) connected this effect directly to choice behavior in a reward learning task in humans, by demonstrating an effect of pharmacological manipulations of DA on responses to reward and punishment in the striatum. Here, we use a different approach to address this question by examining the effects of dopamine degeneration on BOLD correlates of PE as described by a detailed computational model of RL, in human subjects with a deficient dopaminergic system: patients with Parkinson's disease (PD).

Parkinson's disease involves degeneration of dopamine cells in the midbrain. A number of studies have demonstrated that PD patients show deficits in reward-related learning tasks (e.g. Frank et al., 2004;

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Table 1
Demographic and behavioral data.

| | Average (SD) healthy controls | Average (SD) Parkinson's disease |
|----------------------------|----------------------------------|-------------------------------------|
| Gender (female/male) | 13/4 | 5/2 |
| Age (years) | 60 (4.1) | 59 (3.7) |
| Education (years) | 17 (3.4) | 19 (5.2) |
| MMSE | 29 (1.6) | 28 (1.5) |
| RT Task Choice Trials (ms) | 900 (141) | 888 (192) |
| RT Task Force Trials (ms) | 681 (77) | 680 (97) |

In all the comparisons healthy controls $N=17$, PD patients $N=7$, except for MMSE scores for which healthy controls $N=15$. All independent t -test comparisons are nonsignificant ($p>0.3$ to $p>0.9$).

Cools et al. 2007; Dagher and Robbins, 2009). These behavioral impairments of PD patients in reward-related learning have been suggested to be caused by a deficit in the phasic prediction error signaling from dopamine neurons (Frank et al., 2004). As of yet, such a possibility has not been directly tested; thus, one aim of the present study was to test the hypothesis that PD patients exhibit an impairment in neural prediction error signaling. Further, the anatomical pattern of any such impairment would be informative as to whether PEs measured using human fMRI reflect dopaminergic activity. This is because the degeneration in PD is differential, with heavier cell loss in the nigrostriatal DA pathway (innervating the dorsal striatum) than in the mesolimbic pathway (innervating the ventral striatum) (Kish et al., 1988; Brooks, 2008; for a review on the DA system, see Joel and Weiner, 2000). Thus, we aimed to test whether the spatial pattern of impairments observed in neural prediction error signaling would match the pattern of selective dopaminergic degeneration in PD. An anatomically specific impairment reflecting the selective pattern of degeneration might also help to identify effects on the BOLD signal due to the underlying disease rather than medication used to treat it.

To address these aims, we used fMRI to scan medicated PD patients with early to moderate disease and healthy age-matched controls, while they performed a reward-based learning task. Given previous findings that PD patients are impaired in such tasks, relative to controls, it is important that any test for neural differences not be attributable simply to differences in the behavior (Price and Friston, 1999). Accordingly, we employed a simple reward learning task that patients could perform similarly to controls, allowing for an unconfounded test of the underlying neural signaling. The behavior and neuroimaging data were analyzed using a fully parametric model-based approach. We hypothesized that PE-related activity in patients would be impaired in the dorsal but not the ventral striatum, relative to activity in healthy controls. Given the prominent, though, importantly, not exclusive (e.g. Braak et al., 2003), effect of PD on the dopaminergic nigrostriatal projection, such a finding would provide evidence that BOLD PE signals reflect phasic DA activity.

Table 2
Clinical Characteristics of PD patients.

| Patient | Age | Gender | Disease duration since onset (years) | H and Y stage | Prominent disease side | Motor UPDRS | Education (years) | Medication |
|---------|------|--------|--------------------------------------|---------------|------------------------|-------------|-------------------|------------------------------------|
| 1 | 60 | Female | 2 | II | L | 9 | 16 | Amantadine, Selegiline |
| 2 | 59 | Male | 7 | III | L | 17 | 18 | L-Dopa, Ropinirole |
| 3 | 61 | Female | 9 | II | R | 16 | 16 | Amantadine, Rasagiline, Ropinirole |
| 4 | 58 | Female | 3 | I | L | 4 | 18 | Selegiline, Ropinirole |
| 5 | 52 | Female | 3.5 | II | R | 22 | 20 | |
| 6 | 64 | Female | 1.5 | I | R | 3 | 16 | Rasagiline |
| 7 | 57 | Male | 2 | II | R | 16 | 30 | Selegiline, Trihexyphenidyl |
| Average | 58.7 | | 4.0 | 1.9 | | 12.4 | 19.1 | |
| SD | 3.7 | | 2.9 | 0.7 | | 7.2 | 5.0 | |

H and Y—Hoehn and Yahr stage; UPDRS—Unified Parkinson's Disease Rating Scale.

Materials and methods

Subjects

Patients

Eleven right-handed PD patients participated in the study. Two patients failed to complete scanning (one due to rigidity and one due to claustrophobia) and two more datasets were excluded because the patients moved extensively (>10 mm and intra volume movements) during scanning and therefore were discarded from data analysis. Functional MRI data for seven patients (mean age, 58.7 (SD = 3.7); range, 52–64, 5 women) were therefore included in the analyses in this report. PD patients were diagnosed using Gelb et al.'s (1999) criteria. All patients were pre-assessed by a senior movement disorders neurologist (RI). The study was performed while patients were during the “on” phase of their regular medication regime. Response to anti-Parkinsonian medication was very good for all patients. Group demographic data are presented in Table 1. Individual demographic data for patients, including disease severity and medications are presented in Table 2.

Healthy controls

Seventeen right-handed controls participated in the study (mean age, 59.6; range, 52–67, 13 women). The healthy subjects were pre-assessed to exclude those with a prior history of neurological or psychiatric illness.

Ethics committee approval

All subjects gave informed consent, and the study was approved by the Ethics committees of the Tel Aviv Sourasky Medical Center, Hillel Yaffe Medical Center (Hadera), Meir Medical Center (Kfar-Saba) and the Department of Psychology of Tel Aviv University, Israel.

Imaging procedure

A GE 3.0T Excite scanner (General Electric Medical Systems, Milwaukee, WI) was used to acquire gradient echo T2* weighted echo-planar images (EPI) with BOLD (blood oxygenation level dependent) contrast. Each volume comprised of 40 axial slices of 3.0-mm thickness and 3.125mm in-plane resolution. All images were acquired using a standard quadrature head coil. The following parameters were used: TR/TE = 2500/30 ms, flip angle = 90°, 64 × 64 matrix with a FOV of 20 × 20 cm². The total number of volumes obtained ranged between 928 and 974 (39:50 to 41:45 min of total scanning), with the variation due to missed and wrong-key trials. (The scanning session for one of the subjects lasted for only 842 volumes and 35:55 min due to a software problem that shortened the inter-trial intervals by an average of 6 s). The volumes were obtained in 4 sessions per subject, each including intermixed task and control trials. This total time included scanning of additional volumes at the beginning of each session to allow magnetization stabilization.

For each subject, a series of clinical MRI sequences was also acquired, including high-resolution T1-weighted images (1 mm slice thickness, no gap, 0.9765 mm in-plane resolution), T2, and T2 FLAIR images. A senior neuroradiologist (YS) examined structural MRI scans of PD patients to exclude possible focal brain pathology that could contribute to the Parkinsonian signs. Healthy subjects' scans were also examined by the neuroradiologist to exclude pathological findings.

Task

The task was presented on a computer monitor using the software Presentation (Neurobehavioral systems, CA, USA), that was projected onto a screen visible via an angled mirror on top of the fMRI head coil. The reward task contained 2 slot machines, each with a pre-defined probability of winning a reward (a picture of a 20 NIS note, worth about \$5 US) of either 60%, or 30%. These slot machines were presented in two types of trials: free-choice ("Choice") trials, in which subjects had to choose one of the two slot machines by pressing the corresponding button (Fig. 1A), and forced-choice ("Forced") trials, in which only one of the slot machines was presented and subjects had to press the corresponding button.

Thirty-two Choice trials and 64 Forced trials (32 Forced trials for each of the two slot machines) were presented in a pseudo-randomly interleaved order. The order of rewarded trials for each of the slot

machines was pseudo-randomized to ensure that for the 60% slot machine there were no more than 3 consecutive rewarded trials, and for the 30% slot machine no more than two consecutive rewarded trials. Two instantiations of the pseudorandom trial orders and slot locations were used to minimize unnecessary between-subject variation.

Subjects were instructed to win as many points as possible, and were informed that the slots differ in their winning probabilities (they were not given their exact winning probabilities). They were also informed that only the color of the slot, and not its location, was the indication for its rewarding probability, and that the probability of winning remained stationary throughout the whole experiment. Subjects were not provided with a running total of winnings during the task and were only informed of the total points accumulated at the end of the experiment. Points won were not paid out in real money.

A control task was also included and its trials were interleaved with the reward-task trials. The control task was identical in structure, length and trial types to the reward task but differed in having two slot machines with different colors. These slot machines were associated with a non-rewarding control outcome (a scrambled 20 NIS note similar to Kim et al., 2006) with the same 30% and 60% probabilities as the reward task slot machines. Subjects were informed that the control trials were serving as a control to their behavior in the reward task, shown the colors of the control slot machines, and were instructed to

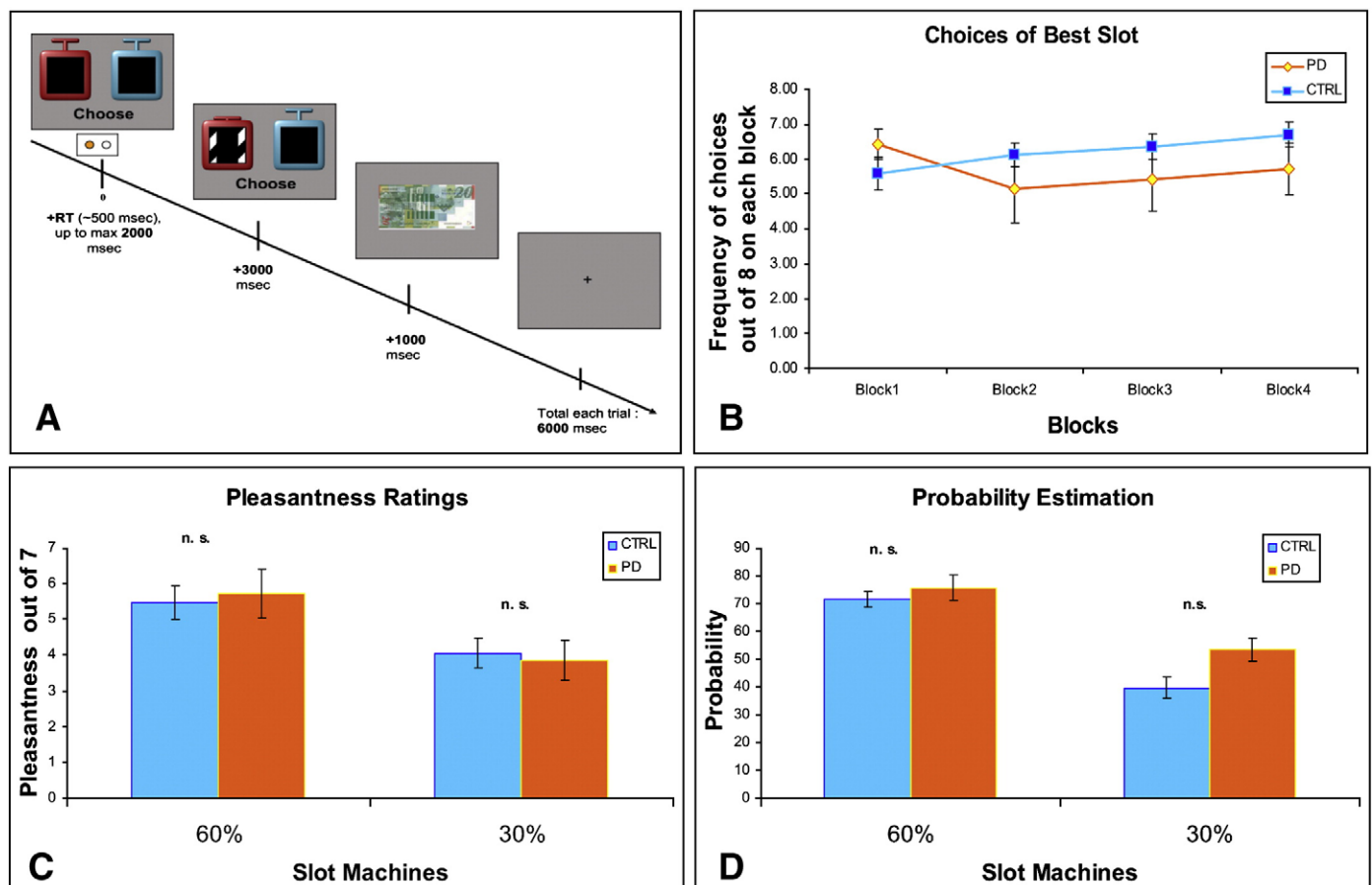


Fig. 1. (A) Trial structure: in each trial, whether Choice or Forced, subjects were prompted to choose a slot machine using a button press, within 2 s. If a slot machine was chosen in time, a lever on top of the chosen slot was depressed to indicate that a choice had been made and the inner part of the machine simulated a revolving display. Three seconds later, the machine(s) were removed from the screen and the outcome was presented for 1 s: either a picture of an outcome (money or scrambled money) or a blank gray screen. The last part of the trial was a small cross which remained on the screen until the total trial duration of 6 s was reached. On trials when subjects failed to respond within 2 s ("missed trials"), the message "You did not respond on time" (in Hebrew) appeared on the screen for 2 s. On forced-choice trials, if subjects pressed the button for the side where no machine was presented ("wrong-key trials"), the message "You pressed the wrong button" appeared on the screen for 2 s. Following missed or wrong-key trials, the erroneous trial was triggered again. Trials were separated by a 7- to 17-s inter-trial interval (mean 13 s), during which the cross was displayed. (B) Subjects' performance during fMRI scanning in choice trials of the task (\pm SEM) along 4 blocks of 8 choice trials in each. No difference was found between the groups in choice behavior. (C) Post experiment ratings (\pm SEM) show no differences between the PD and Control groups either in Pleasantness ratings (\pm SEM) or (D) in the Probability assessment of the two rewarded slot-machines.

try and choose a slot machine on time despite there being no possibility of winning points in these types of trials.

The colors of the slot machines were counterbalanced between subjects. The trials (192 in total) were evenly divided between the four scanning sessions.

Choice vs. Forced trials

The task included a majority of Forced trials in an effort to ensure that all subjects would be exposed to the reward contingencies of the slot machines and would consequently be able to perform similarly in the Choice trials.

Post-experiment ratings

After subjects were removed from the scanner, they were asked to report pleasantness ratings for each slot machine, using a scale ranging from 1 (least pleasant) to 7 (most pleasant). The subjects were also asked to provide an assessment of the assumed probability of winning of each slot machine, using a number from 0 to 100.

Psychological questionnaires and demographic data

Following the post-experiment ratings, subjects filled in several questionnaires, all in Hebrew: the Beck depression inventory (BDI; Beck, 1988; Beck et al., 1961); the obsessive–compulsive personality scale from the Wisconsin Personality Disorders Inventory (WISPI; Klein et al., 1993) and the obsessive compulsive inventory—revised version (OCI-R; Foa et al., 2002). The subjects responded to these questionnaires as part of a larger study protocol to enable future comparisons to subject populations with additional disorders. Subjects were also asked to report their age and years of education, and the experimenter administered the Mini Mental State Examination (MMSE) (Folstein et al., 1975).

Behavioral analysis

In order to test for group differences in choice behavior, we divided the 32 Choice trials into 4 blocks of 8 trials and assessed the number of choices of the 60% slot per-subject on each block.

Reinforcement learning model-based analysis

Subjects' decisions were modeled as a function of previous rewards using a standard temporal-difference learning algorithm (Sutton and Barto, 1998; the particular implementation was closest to that described in Schonberg et al., 2007). The model assigned a value for choosing each option based on previous rewards received from that option. The model's free parameters were chosen for each subject as those that best explain their choices given the rewards they received. (See [Supplementary Material](#) for equations and details.)

Having fit the model to choice behavior, we then used the values the model assigned to each option on each trial, as estimates of the subjects' value expectations in order to construct a trial-by-trial, parametric prediction error regressor for fMRI analysis. We modeled PE as occurring at two time points in each trial (e.g. O'Doherty et al., 2004; Daw et al., 2006; Schonberg et al., 2007): at the start, based on the expected value of the chosen option relative to the value of an average trial, and when the reward was delivered, based on the reward received relative to that expected. Full equations and details are described in [Supplementary Material](#).

Additional analyses of group differences

We conducted two additional whole-brain analyses using design matrices in which the PE regressor was subdivided. First, in order to

test whether differences between groups were present at both time points, the two temporal components of the PE (the beginning of the trial and the outcome) were modeled as two separate parametric regressors, each defined only at the appropriate event at each trial. Next, to test whether positive and negative PEs were differently affected by the disease, we separated the full PE regressor into two timeseries: one positively rectified and the other negatively rectified, and entered both as parametric regressors defined at both timepoints in each trial.

Finally, in order to test whether group differences were visible in a more traditional event-related analysis, we estimated a third model that contained no parametric regressors, and instead contained impulse events marking reward or non-reward trial outcomes.

Image analysis

Analysis of fMRI data was performed in SPM5 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK). To correct for subject motion, images were realigned to the first volume, then spatially normalized to a standard T2* template with a resampled voxel size of 3×3 mm. Images were then spatially smoothed by applying a Gaussian kernel with a full width at half maximum of 8 mm. High pass filtering with a cutoff period of 128 s was also applied to the data.

The structural T1 images of all subjects were normalized to a standard template. The normalized images were then used to create a normalized structural mean image upon which the t maps were overlaid to obtain anatomical localization. Each anatomical image of a PD patient was multiplied by 17/7 to equalize the weight of the PD subjects' brains while creating the mean anatomical brain.

Prediction error signals were generated for each subject as described above and then convolved with a canonical hemodynamic response function and regressed against each subject's fMRI data. The six scan-to-scan motion parameters produced during realignment were included to account for residual effects of scan-to-scan motion. Because PD involves uncontrolled tremor, we also included additional nuisance regressors to account for additional residual variance in trials in which we detected excessive movements, defined as larger than 1 mm in the x, y or z axes, or 1 degree in pitch, yaw or roll. These regressors contained impulse events for such trials. Contrast images were computed at the single-subject level by correlating PE signals during task and control trials as detailed above.

Group level analysis

The contrast images computed for each subject were taken to the group random effects level. We performed a whole-brain analysis, but given previous results and our hypothesis, we singled out dorsal and ventral striatum as areas of prior interest. Therefore we report striatal activations from the whole-brain analysis at an uncorrected threshold of $p < 0.001$, and additionally tested their significance small-volume corrected for FDR over striatal volumes. We used between-group contrasts to isolate areas showing enhanced correlations with PE signals in controls compared to PD. For these comparisons, the *t*-statistic maps were computed assuming unequal (rather than pooled) variances between groups.

Interaction analysis

We conducted an additional ROI analysis to investigate how between-group differences in PE signaling differed across the striatum. Specifically, we tested PE signaling for an interaction between the factors of group (PD vs. control) and striatal region (dorsal vs. ventral) using a two-way ANOVA. For this analysis, we extracted individual parameter estimates for each subject, for the effect of PE in Choice minus Forced trials (see Results) from one

voxel in each of left dorsal putamen and left ventral striatum. The voxels used for this analysis were selected in a manner that did not bias the subsequent interaction test. Specifically, we drew anatomical ROI's on the group mean anatomical image using MRICro (Chris Rorden, www.mricro.com) for left nucleus accumbens and left putamen (Supplementary Fig. 1). Putamen was demarcated with reference to a neuroanatomical atlas (Duvernoy, 1999); for nucleus accumbens, we followed the guidelines of Breiter et al. (1997; Ballmaier et al., 2004); notably, defining its superior border by a line connecting the most ventral point of the lateral ventricle to the most ventral point of the internal capsule at the level of the putamen. We then searched for maxima within each mask using the contrast of PE during Choice minus Forced trials in the control group only. The “ventral” voxel was defined as the peak voxel for this contrast within the accumbens mask; the global peak within the putamen mask was at the most ventral point of the putamen; thus we defined our “dorsal” voxel as the second peak found in the putamen mask, which was clearly in the dorsal portion of the structure. Note that although this procedure uses multiple comparisons over each area to select a voxel of maximal PE signaling (in the control group), since the selection procedure is identical in either region, it is unbiased with respect to the subsequent test of an interaction of region by group. Accordingly, it is unnecessary to correct the interaction test for multiple comparisons.

Results

Demographic data

Demographic data for the two subject groups are shown in Table 1. No significant differences were observed between the two groups concerning age ($p>0.6$) or education ($p>0.4$). No differences were seen in the MMSE ($p>0.4$), in which all subjects achieved a score higher than 25.

Psychological questionnaires

There were no significant differences between the two groups in any of the questionnaires filled out by subjects (data not shown, Student's t -test, all p values >0.2).

Behavioral results

In order to ensure that the PD patients performed in the task as well as controls, we tested for group differences in a large range of behavioral measures of performance in the task. As detailed below, we found no significant differences between the groups in any of our behavioral measures. This is a prerequisite for studying differences in neural signaling between patients and healthy control groups without these being confounded by a difference in performance (Price and Friston, 1999). No significant differences were seen between the two groups in choice behavior (Fig. 1B) when tested in a mixed ANOVA of Group (Healthy and PD) by Blocks of 8 choices (4 blocks) (main effect of Group: $F_{1,22} = 0.85$, $p>0.36$; Group \times Block interaction: $F_{3,66} = 1.93$, $p>0.13$). Because the PD group performed better on the first block of choices, and in order to test whether the two groups improved similarly in the task, we also tested the interaction between Group and a linear trend in choices across blocks. The results of this analysis were non-significant ($p>0.1$).

Similarly, in the fits of our reinforcement learning model to choice behavior, no significant differences were found between groups in the estimates of free parameters, nor in a measure of how well the model fit to each subject's choices (see Supplementary Material and Supplementary Table 1).

There were also no differences between the groups in reaction times in the Choice ($p>0.8$) and Forced trials ($p>0.9$), and on the

number of missed trials (higher number of this type of trials for the control group, $p>0.2$) and wrong-key trials ($p>0.5$).

There were no significant differences between the two groups in post-experiment ratings of pleasantness for the two slot machines (Fig. 1C, main effect of Group: $F_{(1,22)} = 0.0009$, $p>0.97$; Group \times Slot machine interaction: $F_{(1,22)} = 0.42$, $p>0.52$). Both groups overestimated the winning probabilities of both slot machines (which were 60% and 30%) and this overestimation tended to be higher for PD patients compared to control subjects (Fig. 1D, main effect of Group: $F_{(1,22)} = 4.07$, $p = 0.056$; Group \times Slot machine interaction: $F_{(1,22)} = 1.66$, $p>0.21$).

Neuroimaging results

Having established that patients behaved similarly to controls, and thus that any neural differences should be attributable to disease status rather than behavioral confounds, we sought differences in neural signaling between the groups.

Striatal prediction errors

We first sought to characterize PE-related activity in the striatum in the two groups separately. Consistent with prior reports of PE signaling during instrumental conditioning (O'Doherty et al., 2004; Schonberg et al., 2007), we found significant correlations between our model-derived PE signals during Choice trials and BOLD signals in both the ventral and dorsal striatum of healthy controls, significant at

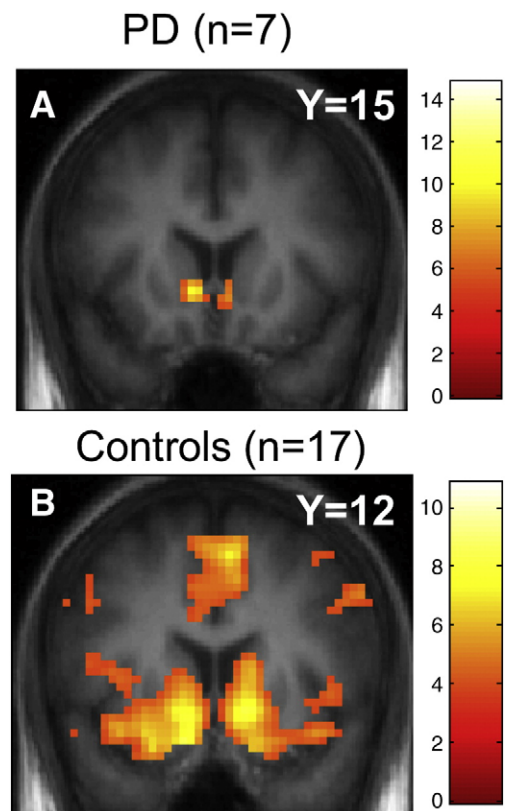


Fig. 2. Random effects analysis showing PE correlations in the ventral striatum during choice trials: (A) the PD subjects showed significant correlations with PE during choice trials bilaterally in the ventral striatum ($n = 7$) (shown at $p < 0.001$ uncorrected). (The Montreal Neurological Institute (MNI) coordinates for the group peaks of the PD group in the ventral striatum were: right ventral striatum: [6, 15, -6], Left ventral striatum: [-3, 9, -6].); (B) The healthy control group showed significant correlations with PE in choice trials in ventral and dorsal striatum ($n = 17$) (shown at $p < 0.001$, uncorrected) (MNI coordinates for the group peaks of the CTRL group in right ventral striatum were: [12, 9, -6], left ventral striatum: [-12, 6, -6]).

$p < 0.0001$ (uncorrected, Z -scores > 5 , Fig. 2B) bilaterally. In the PD group, the same analysis revealed significant PE activity ($p < 0.0005$ uncorrected, Z -scores > 3.4 , Fig. 2A) in a more localized region of the ventral striatum; no activations were noted in the dorsal striatum at $p < 0.001$ or even at $p < 0.01$ (both uncorrected whole brain analyses).

Unlike Choice trials, during Forced trials, BOLD activity did not correlate with modeled PE (at $p < 0.001$ uncorrected) anywhere in striatum in either group, suggesting that striatal prediction error signals to reward are strongly modulated by the degree to which subjects are faced with a choice between actions (Choice trials), compared to a situation where only a single action is available (Forced trials). This is consistent with previous findings that striatal PE signals are modulated by instrumental contingency (Zink et al., 2004). Furthermore, it is possible that these trials did not engage subjects enough to produce an observable PE signal.

Areas outside the striatum where BOLD activity correlated with PE during either Choice or Forced trials are shown in Supplementary Table 2.

Group differences

We next sought to characterize the differences between the two groups' PE signaling using a direct statistical comparison. This is because the apparent differences between separate group maps do not

in themselves demonstrate a difference between groups. For instance, results were likely significant over a wider area in the control group in part because it contains more subjects. The analyses presented below compare the two groups, in order to directly test for differences in their PE signaling, under the null hypothesis that it is the same. It should be emphasized that having more control subjects than patients does not compromise the validity of these tests; on the contrary, this improves our power for detecting any between-group difference by decreasing the standard error on the characterization of normal PE signaling.

We used the differential effect of PE in Choice minus Forced trials for each subject in each of the groups, and compared between the groups for differences in this effect. This approach exploits the lack of PE-related activity in Forced trials so as to better control for motor-related correlates that might confound PE particularly in the dorsolateral striatum (Note that Choice trials for the non-rewarded control outcome cannot be subtracted in this manner, since their onsets are predicted to engender a negative PE; see Supplementary Material). No difference was found between the groups in the ventral striatum at $p < 0.001$ uncorrected (whole brain analysis). In contrast, as shown in Fig. 3A, this analysis revealed a greater effect of PE in controls compared to PD in the left dorsolateral striatum (putamen; $p < 0.001$ uncorrected; a trend toward a difference between groups was also noted in the right putamen though above our uncorrected threshold at $p < 0.005$). Between-group differences in the dorsal

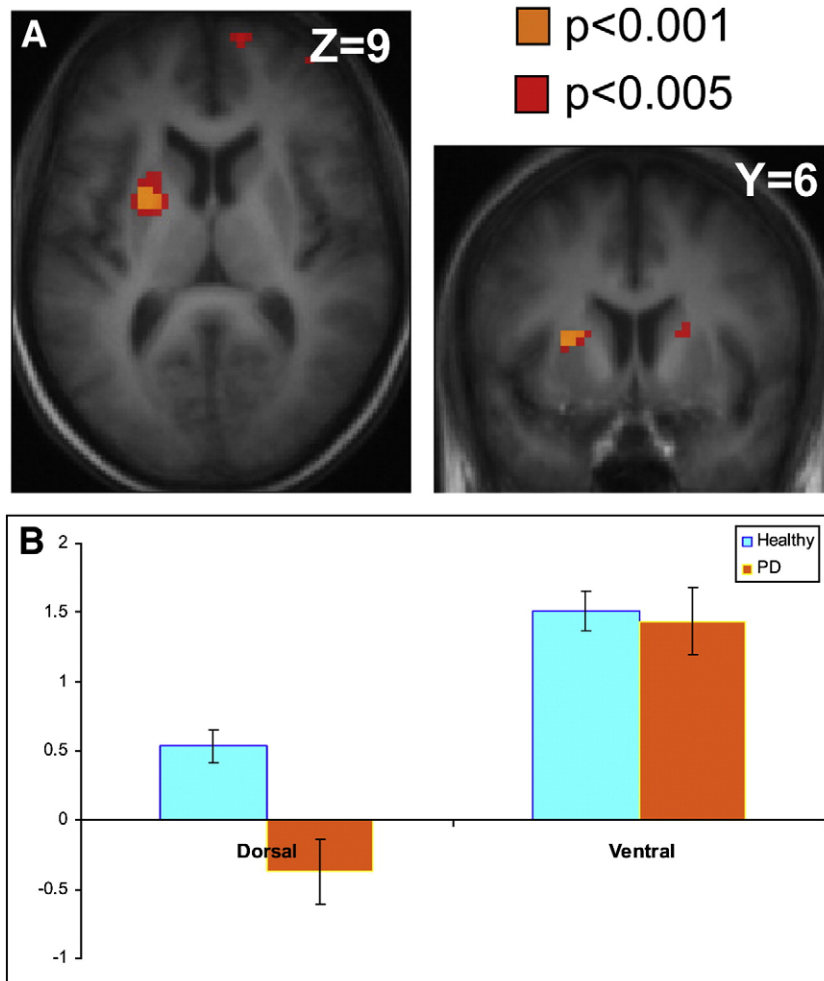


Fig. 3. Random effects analysis showing the PE-related activity in the dorsal striatum of controls but not of PD patients. (A) The difference between healthy subjects and PD patients in PE for Choice minus Forced trials was focused in the left dorsal putamen (shown at $p < 0.001$, uncorrected; MNI coordinates $[-27, 6, 9]$) and can be seen bilaterally at $p < 0.005$, uncorrected (right dorsal putamen at $[21, 6, 12]$); (B) average regression coefficients (\pm SEM) for PE during choice minus forced trials in the left striatum, collected from peaks in the NAcc and putamen identified using anatomically drawn masks of these structures. The interaction was significant at $p < 0.02$ due to increased PE signals in healthy controls compared to PD patients in the dorsal, but not ventral striatum.

striatum were significant ($p < 0.05$ FDR corrected) when small-volume corrected for the volume of our putamen mask. On the other hand, no differences were seen in PE between the two groups in the ventral striatum even at a threshold of $p < 0.01$ uncorrected (whole brain analysis). Other brain regions outside the striatum with effects at $p < 0.001$ uncorrected, were the left lateral OFC (MNI coordinate $[-27, 27, 21]$), and the right frontopolar cortex (MNI coordinates $[39, 57, 3]$). As we did not have prior hypotheses concerning these regions, and the activations did not survive whole brain correction ($p < 0.05$, FDR), we cannot draw strong conclusions about those additional extra-striatal activations.

The same result was also obtained when directly testing the effect of PE between groups in Choice trials alone, namely, differences were found in the same regions, albeit at a slightly less stringent significance level of $p < 0.005$ uncorrected in the left and $p < 0.01$ uncorrected in the right dorsolateral striatum.

Interaction analysis

Finally, we tested whether the effect of PD on PE signaling differed between different striatal regions. Although the between-group comparisons discussed above suggest such a difference, they do not directly demonstrate it, since the finding of a positive effect in one region, but no positive finding in another, does not statistically confirm that there is a difference between the regions. Therefore, we tested for an *interaction* between Region (dorsal or ventral striatum) and Group (PD or control). We isolated the voxel of peak PE signaling in each region (see Materials and methods), and collected individual parameter estimates for the PE effect in Choice minus Forced trials in each subject there. The interaction of Group \times Region (Fig. 3B) was significant at $p < 0.02$ ($F_{1,22} = 6.48$; note that because these voxels were selected separately in a manner unbiased for the interaction test, this test does not require correction for multiple comparisons: see Materials and methods). A Tukey *post hoc* test revealed that the difference between controls and PD patients in PE-related BOLD was significantly ($p < 0.005$) higher in dorsal than ventral striatum, consistent with the spatial pattern of results reported above.

Further analyses of group differences

The analyses reported above examined BOLD correlates of a parametric PE signal derived from a computational model of the phasic dopaminergic response. These were aimed to identify the portion of the striatal signal hypothesized to differ between patients and controls. This approach, we reasoned, would maximize power in detecting any between-group differences. However, the PE signal is a complex construct that could be decomposed into a number of different parts whose BOLD correlates might have potentially dissociable neural causes. Thus, we conducted several additional analyses using decomposed or simplified versions of the PE regressor in order to investigate whether the group differences we detected might preferentially be associated with particular portions of the full PE signal. Because of the hypothetically reduced power due to the need to estimate more parameters (and as presented below the actually weaker results) of these analyses, we report group differences at a relaxed whole-brain threshold of $p < 0.005$ uncorrected. It should also be noted that these additional investigations are *post-hoc* in the sense that the regressors here are derived from and not statistically independent from the ones used previously. Future studies will be required to specifically and independently test any specificity of Parkinson's disease effects on subcomponents of PE.

PE at the time of choice vs. time of outcome

The full PE signal contains components at two time-points: the first is an anticipatory component at the beginning of the trial; the

second is the component when the outcome is revealed. We repeated our analyses with these events, and their associated PE modulators, entered separately. The comparison between groups of the strength of PE BOLD correlations on Choice minus Forced trials at the beginning of the trial (Supplementary Fig. 2A) did not reveal any differences in striatum even at $p < 0.01$, uncorrected. However the analogous analysis at the time of outcome (Supplementary Fig. 2B) revealed greater PE-related activity in healthy controls compared to PD patients in an area of left dorsal striatum (at $p < 0.005$, uncorrected, $Z > 2.5$). No other between-group differences were found at this threshold anywhere else in striatum. These results suggest that the difference in PE correlates between groups may be preferentially attributable to PE signaling at outcome time.

Positive and negative PE

An ongoing question is whether the brain processes positive and negative events using common or distinct mechanisms (Daw et al. 2002; Pessiglione et al., 2006; Seymour et al., 2007; Tom et al. 2007). We conducted an additional analysis in which separate parametric regressors were defined for positive and negative PE (at both choice and outcome time-points). The comparison between groups (in Choice minus Forced PE) revealed greater PE-related activity in healthy controls compared to PD patients bilaterally (at $p < 0.005$ uncorrected, $Z > 2.87, 2.66$) in dorsolateral striatum for positive PE (Supplementary Fig. 3A), but not for negative PE (even at $p < 0.05$ uncorrected) (Supplementary Fig. 3B). The lack of a significant difference was apparently not simply due to an overall lack of negative PE signaling, as there was activity associated with negative PE in bilateral ventral striatum in healthy controls ($p < 0.001$ uncorrected) and also less significant negative PE correlates in the PD group (at $p < 0.005$ uncorrected.) These results suggest that the difference between groups may be preferentially associated with positive PE (see also Daw et al. 2002; Pessiglione et al., 2006; Seymour et al., 2007).

Reward vs. non-reward

Finally, we considered a traditional event-related contrast analysis of Reward vs. non-Reward without any computational modeling. For this, we simply generated regressors with Reward and non-Reward outcome events, rather than the graded parametric PE signal at these times, and then tested the contrast between them. The between-group difference (in the contrast of Reward minus non-Reward, in Choice minus Forced trials), emerged in left dorsolateral striatum ($p < 0.005$ uncorrected, $Z > 2.6$, Supplementary Fig. 4). This result suggests that the between-group difference in striatal signaling is not strongly dependent on the particular assumptions made in our computational model.

Discussion

We used a reward-based learning task in PD patients to investigate the relationship between reward learning, DA, and BOLD signals at DA target areas in the human striatum. We searched for BOLD correlates of a trial-by-trial PE signal, derived from a computational RL model of the phasic dopaminergic response (McClure et al., 2003; O'Doherty et al., 2003, 2004; for review see Niv and Schoenbaum, 2008). We hypothesized that if these BOLD effects reflect dopaminergic activity, then patients would show a pattern of impairments in the expression of this signal mirroring the differential pattern of degeneration of midbrain dopamine nuclei in mild to moderate PD. Consistent with our hypothesis, PD patients exhibited significantly impaired PE signaling compared to healthy controls in the dorsal putamen, which receives dopaminergic input from the more seriously affected substantia nigra pars compacta. In contrast, the PE effect in the ventral

striatum, innervated by fibers from the less affected ventral tegmental area, was indistinguishable from healthy controls. Note that although BOLD correlates of PE have most often been reported in ventral striatum, they have also previously been observed in dorsal putamen (McClure et al., 2003). An interaction analysis confirmed the spatial pattern of the impairment, which parallels PET and SPECT studies (for review, see Brooks 2008) indicating that in early PD, the putamen (i.e., dorsolateral striatum) is the most heavily affected area, with dopaminergic terminals functioning at less than 50% of normal levels. In comparison, the caudate nucleus (i.e., dorsomedial striatum) and ventral striatum display nearly intact DA function. Thus, although PD impacts additional neurotransmitter systems (e.g., Braak et al., 2003), and although differences between the groups in our study may also relate to chronic or acute effects of the anti-Parkinsonian medication, the anatomical pattern of the impairment and the fact that the effects are seen on phasic PE signaling appear most parsimoniously explained as reflecting the dopaminergic degeneration. Together, then, these results add to the body of data supporting the presumption, previously hypothesized to interpret many imaging studies (e.g. McClure et al., 2003; O'Doherty et al., 2003, 2004, D'Ardenne et al., 2008), that the PE effect in striatal BOLD reflects the effects of phasic dopaminergic activity.

Pessiglione et al. (2006) have also provided important evidence for the contribution of DA to BOLD activity in the striatum of healthy humans. Using pharmacological manipulations which included dopaminergic stimulation by L-Dopa and blockade by haloperidol, they induced changes both in BOLD and in choice behavior, and performed a computational learning model analysis to identify areas correlating with PE in the striatum. However, in that study, the effects of DA drugs were tested solely on averaged outcome-related time-courses of activity in these areas, and not on the full computational parametric PE signal. Our current study therefore demonstrates how an altered dopaminergic state, as manifested in PD, affects the specific, trial-to-trial parametric BOLD PE signal. This computational analysis also distinguishes our work from previous fMRI studies that have studied the effect of PD on reward-related BOLD signals (Kunig et al., 2000; Cools et al., 2007; Schott et al., 2007), none of which, to our knowledge, have studied PE signaling parametrically using a specific RL model. The additional statistical power likely afforded by an analysis that captures trial-to-trial parametric variation in PE signaling (insofar as this may capture additional variability in the signal left un-modeled in simple contrasts) may be one reason why we were able to detect differences in dorsolateral striatal signaling between PD patients and controls, which was not seen in another recent study on reward prediction in PD (Schott et al., 2007). In this respect, it is interesting, though not statistically conclusive, that our analysis using a reward vs. non-reward contrast (Supplementary Fig. 3) produced results that were significant only at a slightly lower threshold of $p < 0.005$.

Another feature of the present study is that we aimed to test our neural hypotheses—that is, that changes in dopamine signaling produce differences in BOLD activity—under circumstances where these differences could not be attributable to differences in behavior (Price and Friston, 1999). In addition to the Pessiglione et al. (2006) study, where the dopaminergic manipulations affected choice behavior together with BOLD signaling, studies of PD patients have repeatedly found behavioral impairments in reward-related tasks (see e.g. Frank et al., 2004; Cools et al., 2007). Accordingly, we here designed a relatively simple task, including only two rewarding stimuli and a majority of Forced-choice trials that we hoped would aid the PD patients in learning the correct responses. It is thus possible that PD patients used a compensatory mechanism to achieve normal performance in the task, despite their PE impairments. For instance, the inclusion of Forced-choice trials might have engaged the “observational” form of learning that Shohamy et al. (2004) found to be unaffected by PD, and attributed to MTL structures rather than

striatum (Poldrack et al., 2001; Aron et al., 2004). The present study did not focus on locating any compensatory mechanisms, but rather on detecting differences in striatal PE signaling using a specific model for its activity.

Although, by design, we studied neural differences during intact learning behavior, our study nevertheless helps to integrate a number of results supporting the broader picture of dopaminergic involvement in instrumental learning from reward (e.g. McClure et al., 2004, though see Berridge, 2007). For instance in a similar, albeit more difficult task, the degree of PE correlation in striatal BOLD was found to predict performance of healthy subjects (Schonberg et al., 2007). The present study supports our suggestion of a dopaminergic basis for that effect.

Another example is the interpretation of a number of human studies, already mentioned, which have shown that PD, and anti-Parkinsonian dopaminergic medications, affect reward learning in a variety of tasks (e.g., Cools et al. 2001; Frank et al., 2004; Shohamy et al., 2005; Swainson et al., 2006; Schmidt et al., 2008; Kobayakawa et al., 2008; Bódi et al., 2009; Dagher and Robbins, 2009). It has been hypothesized that these deficits relate to putatively impaired phasic PE signaling (e.g. Frank et al., 2004; Guthrie et al., 2009), though such an impairment has not been previously demonstrated in PD patients. Indeed the dopamine system signals on both tonic and phasic time scales (Grace, 1991; Goto et al., 2007), and a reduction in tonic rather than phasic signaling is typically presumed to underlie the prominent motor symptoms associated with PD (e.g., Schultz, 1998). In contrast, our results provide indirect support for the hypothesis that deficits in reward learning tasks may have arisen instead due to deficient phasic PE signaling. One interesting question in this respect is how to reconcile our finding that the PE deficit in our study tended toward significance only for positive, rather than negative, PEs (Supplementary Fig. 1) with demonstrations (Bódi et al., 2009, see also Frank et al., 2004) that patients on medication (as ours were) have behavioral deficits related to learning from punishment. One potentially important difference is that in our study, negative PE arose due to omitted reward rather than punishment. In any case, one hypothesis (Frank et al., 2004) is that deficits in punishment result from tonic effects of medication, which block the post-synaptic detection of phasic DA pauses signaling negative PE. If our analysis preferentially detected pre-synaptic phasic activity, it might have been blind to this effect. In general, the interaction between the signaling in these two time scales, its relation to PD and anti-Parkinsonian treatments, and how it affects reward-related behavior are all subjects of active research (e.g. Guthrie et al., 2009).

Two limitations of our study concern the small number of patients successfully studied, and their being tested while on dopaminergic medication. Imaging studies with PD patients tend to have small sample sizes due to subject attrition (e.g. Mattay et al., 2002; Cools et al., 2007); in our case, only 7 of 9 PD subjects who completed the full scanning session yielded usable data (two more patients were unable to complete the full scanning session). Nevertheless, we believe that the results of this study are robust despite the small sample size of the patient population. In particular, we partly compensated for the small number of patients by using a larger number of controls: this is a (more economical) way to increase power for detecting differences between groups. We stress that our key findings are not only based on a negative result such as the failure to detect an effect in PD patients while detecting one in controls (which would raise a question whether there was sufficient power to detect the effect in the PD group by itself), but rather on a direct between-group comparison and on a group-by-region interaction. In both tests the power to detect differences is improved by having a larger group size of control subjects. Also, the result is a positive one, i.e. a rejection of the null hypothesis that the effect of PD on PE signaling is the same across both sub-regions of the striatum.

Second, our subjects were tested on heterogeneous medications and at different doses, and without comparing them to patients off

medication or to drug-naïve patients we cannot definitively rule out the possibility that the differences we found between groups are due, in whole or part, to medication rather than disease. Nevertheless, some features of our results appear more consistent with dopaminergic degeneration. Most importantly, the spatial pattern of impairment we observed matches that of the underlying selective neurodegeneration, not that of medication (which is systemic). It is difficult to see how systemic medication could, by itself, explain the differential pattern of impairment across striatum. In fact, it has been suggested (Robbins, 2000) that since dosages are calibrated to motor symptoms (which reflect dopaminergic dysfunction in the dorsal striatum) the net effect of medication combined with spared dopaminergic function (in the ventral striatum) may be the opposite of the pattern we report here: that is, an “overdose” of dopaminergic function in other areas and restored DA function in the dorsal striatum. Accordingly, Cools et al. (2007) directly investigated the effect of dopaminergic medication by comparing PD patients on and off medication (rather than medicated PD patients to healthy controls, as reported here). In that study, dopaminergic medication impaired BOLD activity in the ventral but not dorsal striatum. The effects reported herein have the opposite spatial pattern compared to what would be expected from medication on the basis of Cools et al.'s (2007) result, supporting our suggestion that the effect we found is primarily driven by disease rather than by medication. All these raise the question why this would be the case here, when effects of medication on striatal BOLD are well documented in previous studies (e.g. Mattay et al., 2002; Pessiglione et al. 2006; Cools et al., 2007). One possibility, again, is the nature of our statistical analysis: by seeking differences in the part of the BOLD activity that correlates with a model of the phasic spiking of dopamine neurons, we may improve the specificity of our analysis for BOLD signals related to the response of dopamine neurons rather than other, tonic or postsynaptic, pharmacological effects.

Two further interpretational issues relate to attentional and motor differences. The fact that choice behavior in the task, as well as the reaction times, was similar in both groups helps to alleviate doubts that the neural differences we report are the result of differences in attention or concentration that might have been altered due to medication or disease effect. Finally, as we report between-group differences in BOLD PE, which appears to be particularly driven by differences in striatal response during outcome receipt (Supplementary Fig. 1), we do not believe that these differences are related to hypothetical subtle differences in the motor parameters of subjects' button pressing.

To conclude, in the present study we have shown for the first time that prediction error activity in the human striatum of PD patients was differentially affected by disease and was detectably abnormal only in the dorsal putamen, which is innervated by the depleted nigrostriatal pathway. These findings suggest that PE signals measured in the human striatum by the BOLD signal likely reflect midbrain phasic DA activity. Furthermore these findings fill in a missing link in the puzzle of the role of PE signals in reward-related learning and thus provide additional support to the RL hypothesis of dopamine.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2009.08.011.

References

- Aron, A.R., Shohamy, D., Clark, J., Myers, C., Gluck, M.A., Poldrack, R.A., 2004. Human midbrain sensitivity to cognitive feedback and uncertainty during classification learning. *J. Neurophysiol.* 92, 1144–1152.
- Ballmaier, M., Toga, A.W., Siddarth, P., Blanton, R.E., Levitt, J.G., Lee, M., Caplan, R., 2004. Thought disorder and nucleus accumbens in childhood: a structural MRI study. *Psychiatry Res.* 130, 43–55.
- Bayer, H.M., Glimcher, P.W., 2005. Midbrain dopamine neurons encode a quantitative reward prediction error signal. *Neuron* 47, 129–141.
- Beck, A., 1988. Beck Depression Inventory. The Psychological Corporation, London.
- Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. *Arch. Gen. Psychiatry* 4, 561–571.
- Berridge, K.C., 2007. The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology (Berl)* 191, 391–431.
- Bódi, N., Kéri, S., Nagy, H., Moustafa, A., Myers, C.E., Daw, N., Dibó, G., Takács, A., Bereczki, D., Gluck, M.A., 2009. Reward-learning and the novelty-seeking personality: a between- and within-subjects study of the effects of dopamine agonists on young Parkinson's patients. *Brain*, Electronic Publication ahead of print, 2009.
- Braak, H., Del Tredici, K., Rub, U., de Vos, R.A., Jansen Steur, E.N., Braak, E., 2003. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol. Aging* 24, 197–211.
- Breiter, H.C., Gollub, R.L., Weisskoff, R.M., Kennedy, D.N., Makris, N., Berke, J.D., Goodman, J.M., Kantor, H.L., Gastfriend, D.R., Riorden, J.P., Mathew, R.T., Rosen, B.R., Hyman, S.E., 1997. Acute effects of cocaine on human brain activity and emotion. *Neuron* 19, 591–611.
- Brooks, D.J., 2008. Technology insight: imaging neurodegeneration in Parkinson's disease. *Nat. Clin. Pract. Neurol.* 4, 267–277.
- Cools, R., Barker, R.A., Sahakian, B.J., Robbins, T.W., 2001. Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cereb. Cortex* 11, 1136–1143.
- Cools, R., Lewis, S.J., Clark, L., Barker, R.A., Robbins, T.W., 2007. L-DOPA disrupts activity in the nucleus accumbens during reversal learning in Parkinson's disease. *Neuropsychopharmacology* 32, 180–189.
- Dagher, A., Robbins, T.W., 2009. Personality, addiction, dopamine: insights from Parkinson's disease. *Neuron* 61, 502–510.
- D'Ardenne, K., McClure, S.M., Nystrom, L.E., Cohen, J.D., 2008. BOLD responses reflecting dopaminergic signals in the human ventral tegmental area. *Science* 319, 1264–1267.
- Daw, N.D., Doya, K., 2006. The computational neurobiology of learning and reward. *Curr. Opin. Neurobiol.* 16, 199–204.
- Daw, N.D., Kakade, S., Dayan, P., 2002. Opponent interactions between serotonin and dopamine. *Neural Netw.* 15, 603–616.
- Daw, N.D., O'Doherty, J.P., Dayan, P., Seymour, B., Dolan, R.J., 2006. Cortical substrates for exploratory decisions in humans. *Nature* 441, 876–879.
- Dayan, P., Abbott, L.F., 2001. *Theoretical neuroscience: computational and mathematical modeling of neural systems*. Massachusetts Institute of Technology Press, Cambridge, Massachusetts.
- Dayan, P., Balleine, B.W., 2002. Reward, motivation, and reinforcement learning. *Neuron* 36, 285–298.
- Delgado, M.R., Nystrom, L.E., Fissell, C., Noll, D.C., Fiez, J.A., 2000. Tracking the hemodynamic responses to reward and punishment in the striatum. *J. Neurophysiol.* 84, 3072–3077.
- Duvernoy, H.M., 1999. *The Human Brain*. Springer-Verlag, Vienna.
- Foa, E.B., Huppert, J.D., Leiberg, S., Langner, R., Kichic, R., Hajcak, G., Salkovskis, P.M., 2002. The obsessive–compulsive inventory: development and validation of a short version. *Psychol. Assess* 14, 485–496.
- Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. “Mini-mental state.” A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198.
- Frank, M.J., Seeberger, L.C., O'Reilly, R.C., 2004. By carrot or by stick: cognitive reinforcement learning in parkinsonism. *Science* 306, 1940–1943.
- Gelb, D.J., Oliver, E., Gilman, S., 1999. Diagnostic criteria for Parkinson disease. *Arch. Neurol.* 56, 33–39.
- Goto, Y., Otani, S., Grace, A.A., 2007. The Yin and Yang of dopamine release: a new perspective. *Neuropharmacology* 53, 583–587.
- Grace, A.A., 1991. Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. *Neuroscience* 41, 1–24.
- Guthrie, M., Myers, C.E., Gluck, M.A., 2009. A neurocomputational model of tonic and phasic dopamine in action selection: a comparison with cognitive deficits in Parkinson's disease. *Behav. Brain Res* 200, 48–59.
- Joel, D., Weiner, I., 2000. The connections of the dopaminergic system with the striatum in rats and primates: an analysis with respect to the functional and compartmental organization of the striatum. *Neuroscience* 96, 451–474.
- Kim, H., Shimojo, S., O'Doherty, J.P., 2006. Is avoiding an aversive outcome rewarding? Neural substrates of avoidance learning in the human brain. *PLoS Biol.* e233, 4.

- Kish, S.J., Shannak, K., Hornykiewicz, O., 1988. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. *N. Engl. J. Med.* 318, 876–880.
- Klein, M.H., Benjamin, L.S., Rosenfeld, R., Treece, C., Husted, J., Greist, J.H., 1993. The Wisconsin Personality Disorders Inventory: development, reliability and validity. *J. Pers. Disord.* 285–303.
- Knutson, B., Gibbs, S.E., 2007. Linking nucleus accumbens dopamine and blood oxygenation. *Psychopharmacology (Berl)* 191, 813–822.
- Knutson, B., Westdorp, A., Kaiser, E., Hommer, D., 2000. fMRI visualization of brain activity during a monetary incentive delay task. *Neuroimage* 12, 20–27.
- Kobayakawa, M., Koyama, S., Mimura, M., Kawamura, M., 2008. Decision making in Parkinson's disease: analysis of behavioral and physiological patterns in the Iowa gambling task. *Mov. Disord.* 23, 547–552.
- Kunig, G., Leenders, K.L., Martin-Solch, C., Missimer, J., Magyar, S., Schultz, W., 2000. Reduced reward processing in the brains of Parkinsonian patients. *Neuroreport* 11, 3681–3687.
- Mattay, V.S., Tessitore, A., Callicott, J.H., Bertolino, A., Goldberg, T.E., Chase, T.N., Hyde, T.M., Weinberger, D.R., 2002. Dopaminergic modulation of cortical function in patients with Parkinson's disease. *Ann. Neurol.* 51, 156–164.
- McClure, S.M., Berns, G.S., Montague, P.R., 2003. Temporal prediction errors in a passive learning task activate human striatum. *Neuron* 38, 339–346.
- McClure, S.M., York, M.K., Montague, P.R., 2004. The neural substrates of reward processing in humans: the modern role of fMRI. *Neuroscientist* 10, 260–268.
- Montague, P.R., Dayan, P., Sejnowski, T.J., 1996. A framework for mesencephalic dopamine systems based on predictive Hebbian learning. *J. Neurosci.* 16, 1936–1947.
- Morris, G., Nevet, A., Arkadir, D., Vaadia, E., Bergman, H., 2006. Midbrain dopamine neurons encode decisions for future action. *Nat. Neurosci.* 9, 1057–1063.
- Niv, Y., Schoenbaum, G., 2008. Dialogues on prediction errors. *Trends Cogn. Sci.* 12, 265–272.
- O'Doherty, J.P., 2004. Reward representations and reward-related learning in the human brain: insights from neuroimaging. *Curr. Opin. Neurobiol.* 14, 769–776.
- O'Doherty, J.P., Dayan, P., Friston, K., Critchley, H., Dolan, R.J., 2003. Temporal difference models and reward-related learning in the human brain. *Neuron* 38, 329–337.
- O'Doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K., Dolan, R.J., 2004. Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science* 304, 452–454.
- Pagnoni, G., Zink, C.F., Montague, P.R., Berns, G.S., 2002. Activity in human ventral striatum locked to errors of reward prediction. *Nat. Neurosci.* 5, 97–98.
- Pessiglione, M., Seymour, B., Flandin, G., Dolan, R.J., Frith, C.D., 2006. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature* 442, 1042–1045.
- Poldrack, R.A., Clark, J., Pare-Blagoev, E.J., Shohamy, D., Creso Moyano, J., Myers, C., Gluck, M.A., 2001. Interactive memory systems in the human brain. *Nature* 414, 546–550.
- Price, C.J., Friston, K.J., 1999. Scanning patients with tasks they can perform. *Hum. Brain Mapp.* 8, 102–108.
- Rescorla, R.A., Wagner, A.R., 1972. A theory of Pavlovian conditioning: The effectiveness of reinforcement and non-reinforcement. In: Black, A.H., Prokasy, W.F. (Eds.), *Classical Conditioning, 2: Current Research and Theory*. Appleton Century-Crofts, New York, pp. 64–69.
- Robbins, T.W., 2000. Chemical neuromodulation of frontal-executive functions in humans and other animals. *Exp. Brain Res.* 133, 130–138.
- Rodriguez, P.F., Aron, A.R., Poldrack, R.A., 2006. Ventral-striatal/nucleus-accumbens sensitivity to prediction errors during classification learning. *Hum. Brain Mapp.* 27, 306–313.
- Schmidt, L., d'Arc, B.F., Lafargue, G., Galanaud, D., Czernecki, V., Grabli, D., Schupbach, M., Hartmann, A., Levy, R., Dubois, B., Pessiglione, M., 2008. Disconnecting force from money: effects of basal ganglia damage on incentive motivation. *Brain* 131, 1303–1310.
- Schonberg, T., Daw, N.D., Joel, D., O'Doherty, J.P., 2007. Reinforcement learning signals in the human striatum distinguish learners from nonlearners during reward-based decision making. *J. Neurosci.* 27, 12860–12867.
- Schott, B.H., Niehaus, L., Wittmann, B.C., Schutze, H., Seidenbecher, C.I., Heinze, H.J., Duzel, E., 2007. Ageing and early-stage Parkinson's disease affect separable neural mechanisms of mesolimbic reward processing. *Brain* 130, 2412–2424.
- Schultz, W., 1998. Predictive reward signal of dopamine neurons. *J. Neurophysiol.* 80, 1–27.
- Schultz, W., 2002. Getting formal with dopamine and reward. *Neuron* 36, 241–263.
- Schultz, W., Dayan, P., Montague, P.R., 1997. A neural substrate of prediction and reward. *Science* 275, 1593–1599.
- Seymour, B., Daw, N., Dayan, P., Singer, T., Dolan, R., 2007. Differential encoding of losses and gains in the human striatum. *J. Neurosci.* 27, 4826–4831.
- Shohamy, D., Myers, C.E., Grossman, S., Sage, J., Gluck, M.A., Poldrack, R.A., 2004. Cortico-striatal contributions to feedback-based learning: converging data from neuroimaging and neuropsychology. *Brain* 127, 851–859.
- Shohamy, D., Myers, C.E., Grossman, S., Sage, J., Gluck, M.A., 2005. The role of dopamine in cognitive sequence learning: evidence from Parkinson's disease. *Behav. Brain Res.* 156, 191–199.
- Sutton, R.S., Barto, A.G., 1998. *Reinforcement Learning*. MIT, Cambridge, MA.
- Swainson, R., SenGupta, D., Shetty, T., Watkins, L.H., Summers, B.A., Sahakian, B.J., Polkey, C.E., Barker, R.A., Robbins, T.W., 2006. Impaired dimensional selection but intact use of reward feedback during visual discrimination learning in Parkinson's disease. *Neuropsychologia* 44, 1290–1304.
- Tom, S.M., Fox, C.R., Trepel, C., Poldrack, R.A., 2007. The neural basis of loss aversion in decision-making under risk. *Science* 315, 515–518.
- Zink, C.F., Pagnoni, G., Martin-Skurski, M.E., Chappelw, J.C., Berns, G.S., 2004. Human striatal responses to monetary reward depend on saliency. *Neuron* 42, 509–517.