Attenuated neural response to gamble outcomes in drug-naive patients with Parkinson’s disease

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Parkinson’s disease results from the degeneration of dopaminergic neurons in the substantia nigra, manifesting as a spectrum of motor, cognitive and affective deficits. Parkinson’s disease also affects reward processing, but disease-related deficits in reinforcement learning are thought to emerge at a slower pace than motor symptoms as the degeneration progresses from dorsal to ventral striatum. Dysfunctions in reward processing are difficult to study in Parkinson’s disease as most patients have been treated with dopaminergic drugs, which sensitize reward responses in the ventral striatum, commonly resulting in impulse control disorders. To circumvent this treatment confound, we assayed the neural basis of reward processing in a group of newly diagnosed patients with Parkinson’s disease that had never been treated with dopaminergic drugs. Thirteen drug-naive patients with Parkinson’s disease and 12 healthy age-matched control subjects underwent whole-brain functional magnetic resonance imaging while they performed a simple two-choice gambling task resulting in stochastic and parametrically variable monetary gains and losses. In patients with Parkinson’s disease, the neural response to reward outcome (as reflected by the blood oxygen level-dependent signal) was attenuated in a large group of mesolimbic and mesocortical regions, comprising the ventral putamen, ventral tegmental area, thalamus and hippocampus. Although these regions showed a linear response to reward outcome in healthy individuals, this response was either markedly reduced or undetectable in drug-naive patients with Parkinson’s disease. The results show that the core regions of the meso-cortico-limbic dopaminergic system, including the ventral tegmental area, ventral striatum, and medial orbitofrontal cortex, are already significantly compromised in the early stages of the disease and that these deficits cannot be attributed to the contaminating effect of dopaminergic treatment.

Keywords: fMRI; reward; mesolimbic system; Parkinson’s disease; drug-naive
Introduction

Although Parkinson’s disease is primarily characterized as a movement disorder, there has been growing attention towards the non-motor disturbances in sensory, affective and cognitive domains (Lyons and Pahwa, 2011; Chen et al., 2012). The clinical spectrum of Parkinson’s disease comprises a wide range of non-motor symptoms such as autonomic dysfunction, hyposmia and psychiatric and sleep disorders (Langston, 2006; Gallagher et al., 2010). These non-motor symptoms are increasingly recognized as important factors affecting the patient’s quality of life (Langston, 2006; Soh et al., 2011). Several recent studies have shown that many non-motor symptoms, in particular depression, anxiety, rapid eye movement sleep disorder and hyposmia may precede the onset of motor symptoms in Parkinson’s disease (Alonso et al., 2009; Jacob et al., 2010; Kano et al., 2011; Lyons and Pahwa, 2011; Wu et al., 2012; Yu et al., 2012). Along similar lines, personality changes such as increasing introversion and decreased novelty seeking have been identified as possible preclinical signs (Kano et al., 2011), and have been hypothesized to result from a relatively early degeneration of the mesolimbic dopaminergic pathways that extend beyond classical nigrostriatal motor circuits (Ross et al., 2000; Braak et al., 2003, 2004; Kano et al., 2011). Such deficits in novelty seeking and approach behaviour are congruent with the emerging consensus that dopamine is a transmitter involved in the computation of short-term reward prediction errors (phasic dopamine) and the long-term reward expectations (tonic dopamine) (Dayan and Balleine, 2002; Montague et al., 2004; Berridge, 2007; Glimcher, 2011).

Some non-motor symptoms that are associated with Parkinson’s disease reflect deficits in motivational drive and reward processing. Many patients suffer from depression and apathy, defined as a loss of motivation and interest and a reduction in effortful behaviour (Aarsland et al., 2012; Gallagher and Schrag, 2012). For instance, in a prospective study on 80 patients with Parkinson’s disease, ~50% showed signs of apathy, and 30% of these did not express co-morbidity with depression (Kirsch-Darrow et al., 2006).

Another major motivational dysfunction, encountered in up to 13.6% of patients receiving dopamine replacement therapy, is the inability to appropriately control impulses to engage in rewarding behaviours. The clinical spectrum is broad and includes hypersexuality, compulsive shopping, pathological gambling, punting, compulsive eating, as well as compulsive use of dopaminergic medication (Weintraub et al., 2010; Ambermoon et al., 2011; Voon et al., 2011; Vilas et al., 2012). These impulse control disorders often have major adverse consequences on the quality of life of the patient and their caregivers (Wolters et al., 2008). Multiple intrinsic and extrinsic factors are thought to contribute to impulse control disorders in Parkinson’s disease. Male gender, early disease onset, depression, pre-existing recreational drug or alcohol use, and novelty seeking personality traits are associated with a higher prevalence of impulse control disorders. However, dopamine replacement therapy, in particular the treatment with dopamine agonists, constitutes the main risk factor for developing impulsive behaviours (Weintraub et al., 2010; Ambermoon et al., 2011; Cilia and van Eimeren, 2011). The relevance of dopamine treatment for the manifestation of impulse control disorders is further supported by the fact that untreated patients with Parkinson’s disease do not differ in impulse control disorder frequency from healthy control subjects (Antonini et al., 2011; Cilia et al., 2011). Because the mesolimbic dopaminergic system is relatively less affected by the neurodegenerative process than the mesostriatal dopaminergic system, the occurrence of impulse control disorders has been attributed to a relative overstimulation of the mesolimbic system by dopamine treatment (Morris et al., 1996; Booij et al., 1999; Cools et al., 2003; Braak et al., 2004). Complementary to the ‘overdose hypothesis’, it has been hypothesized that a pre-existing dysfunction of the mesocortico-limbic pathway may predispose to impulse control disorders in patients with Parkinson’s disease (Balarajah and Cavanna, 2012).

The high prevalence of motivational deficits such as depression or apathy, which often precede the onset of motor symptoms, as well as the risk of inducing impulse control deficits when starting dopamine treatment suggest that the meso-cortico-limbic circuits are already dysfunctional early in the disease before the administration of dopamine medication. However, this hypothesis remains to be explicitly addressed, since reward function in Parkinson’s disease has almost exclusively been probed in patients who had ongoing or prior dopamine therapies. Such studies reveal that patients with Parkinson’s disease tend to make suboptimal choices (relative to healthy control subjects) in gambling tasks, and appear to be hypersensitive to rewards and hyposensitive to punishment (Robinson and Berridge, 1993; Czernyceki et al., 2002; Thiel et al., 2003; Perretta et al., 2005; Abou-Sleiman et al., 2006; Mimura et al., 2006; Berridge et al., 2007; Schott et al., 2007; Kobayakawa et al., 2008, 2010; van Eimeren et al., 2009; Frosini et al., 2010; Housden et al., 2010; Schonberg et al., 2010; Voon et al., 2010). A hypersensitivity to rewarding cues appears to be particularly associated with impulse control disorders. In two 11C-raclopride PET studies, patients with impulse control disorders showed a greater endogenous dopamine release during gambling (Steeves et al., 2009) and in the context of reward-related cues (O’Sullivan et al., 2011) relative to patients without an impulse control disorder. While most of this evidence is congruent with a hyper-dopaminergic dysfunction, it remains to be shown whether this reflects a primary dysfunction or is driven by the confounding effects of dopamine treatment.

Using functional MRI, this study was designed to characterize the function of meso-cortico-limbic circuits in de novo patients who have been newly diagnosed with Parkinson’s disease. Given that the disease process is most likely related to a hyper-dopaminergic state (Schott et al., 2007; Bodi et al., 2009), our central hypothesis was that in the absence of ongoing or prior dopamine treatment, the reward responsivity of the mesocortical-limbic system would already be attenuated in the early motor stage of Parkinson’s disease. Additionally, we hypothesized that this impaired reward responsivity would correlate with clinical measures of disease severity as reflected by the Movement Disorder Society Unified Parkinson’s Disease Rating Scale score (Goetz et al., 2007). We tested these hypotheses by probing functional responses of the mesolimbic and mesocortical systems while...
recently diagnosed drug-naive patients with Parkinson’s disease engaged in a simple probabilistic gambling task.

Materials and methods

Subjects

Thirteen de novo patients with Parkinson’s disease (eight males, mean age: 58 ± 10 years) who were naïve to dopamine medication and 12 healthy control subjects (five males, mean age: 60 ± 7 years) without a history of impulse control disorders or other psychiatric or neurological symptoms participated in the study (Table 1). Written consent was obtained from all participants according to the Declaration of Helsinki, and the study was approved by the local research ethics committee. Newly diagnosed patients with Parkinson’s disease were prospectively recruited from the outpatient clinic for movement disorders at the Department of Neurology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany. Diagnosis of Parkinson’s disease had been made within a 2-week period before testing by a movement disorder specialist (C.B.) in accordance with the UK Parkinson’s Disease Society Brain Bank clinical diagnostic criteria. The inclusion criterion was that patients had not previously been treated with dopamine drugs. Additionally, patients should not have undergone a diagnostic levodopa test in the 12 months before the study. Three patients had a low dose acute levodopa test in the past (>2 years ago), but had not used any dopamine medication since then. The reported onset of motor symptoms ranged from ~0.5 to ~5 years (median symptom duration: 3 years).

Prior to scanning, all subjects were examined using the Movement Disorder Society Unified Parkinson’s Disease Rating Scale (Goetz et al., 2007) motor rating scale (part III) and classified according to the Hoehn and Yahr (Hoehn and Yahr, 1967; Goetz et al., 2004) and Schwab and England scales (Schwab, 1968). Global cognitive function was assessed using the Mini-Mental State Examination (Folstein et al., 1975). Presence of depression was measured using Beck Depression Inventory II (Psychological Corporation). To rule out increased risk-taking behaviour or the presence of problematic gambling, we used the Barratt Impulsiveness Scale (Patton et al., 1995) and the Gambling Addiction Questionnaire of the Berlin Gamblers Advisory Committee. Through a clinical interview with the patients and if available through their spouses, we ascertained that none of the patients had explicit recall of any impulse control disorder-like behaviours or reported typical symptoms associated with impulse control disorders such as pathological gambling, compulsive sexual behaviour, compulsive shopping, compulsive/binge eating or punding.

Gambling task

During each functional MRI acquisition session (60 trials), participants engaged in a simple gambling task (Fig. 1) that has been shown to reliably elicit reward-related responses in the basal ganglia (Yacubian et al., 2006). A similar version of the gambling task has been used in a previous study that revealed abnormalities in reward responsivity in ventral striatum in pathological gamblers (Reuter et al., 2005). At the onset of each trial, two playing cards were presented alongside iconic representations of the money (low-stake = 2 €, or high-stake = 5 €) which could be lost or won. Subjects were required to decide within 3 s which card to gamble on. Subjects indicated their decision by a button press (right index for left, or middle for right) and after a jittered resting period (1–7 s, flat probability distribution) the outcome was revealed. Between trials there was also a jittered resting period (1–7 s, flat probability distribution). Outcome contingencies were set and explicitly instructed to the participants, so that red cards resulted in winning the stake, black cards in losing. A running total amount of cumulative gains and losses was displayed above the card at all times during the trial.

Each subject was randomly assigned to one of five preset pseudo-randomized sequences of gambling trials. In macaque monkeys, phasic dopaminergic responses have been shown to be maximally responsive to unpredictable outcomes, and at the single cell level within the ventral tegmental area and substantia nigra, firing rates are commonly maximal for reward probabilities of 0.5 (Schultz et al., 2008). Therefore, gamble probabilities were set to 0.5 for winning versus losing. Stimuli were presented by back-projection, viewed using a head-coil mirror. Task presentation and recording of behavioural responses were performed using the software Presentation (Neurobehavioral Systems, Inc.). Before scanning, subjects received a standardized verbal description of the task, in which they were instructed not to press the same button constantly, and truthfully informed of the outcome probabilities and that the cumulative total would be realized in physical currency at the end of the experiment after 60 gambles. To ensure task competence, subjects were trained on the task outside the scanner (10–15 trials).

Functional magnetic resonance imaging data acquisition and analysis

Functional MRI scanning was performed on a 3T MRI Scanner (Siemens Trio, Siemens) with a 12-channel head coil. Thirty-eight transversal slices (slice thickness 3 mm) were acquired in each volume (repetition time: 2.5 s; echo time 34 ms; flip angle: 90°; field of view 216 mm) using gradient echo T2*-weighted echo planar imaging. The first three volumes of each participant were discarded to eliminate T1 saturation effects. High-resolution (1 mm3 voxel size) T1-weighted images were acquired for each subject, using a MP-RAGE sequence.

Our regions of interest in the basal ganglia are vulnerable to accumulation of iron in Parkinson’s disease (Bartzokis et al., 1994; Pfefferbaum et al., 2010). We therefore compared the individual signal strength in the basal ganglia (defined according to WFU Pickatlas; Maldjian et al., 2003) between groups to rule out whether

| Table 1 Demographics, test scores and task performance of unmedicated de novo patients with Parkinson’s disease and control subjects |
|-----------------|-----------------|
| **Patients**    | **Controls**    |
| Number (males)  | 13 (8 males)    | 12 (5 males)    |
| Age (years)     | 58 ± 10         | 60 ± 7          |
| Disease duration (years) | 3.0          | Not applicable |
| UPDRS motor score (SD) | 25.6 ± 8.7 | 0.1 ± 0.3       |
| MMSE (SD)       | 29.7 ± 0.7      | 29.6 ± 0.8      |
| BIS             | 66.0 ± 5.6      | 65.3 ± 5.8      |
| GAQ             | 0.3 ± 1.1       | 0.25 ± 0.62     |
| Mean response time (s) | 1.06 ± 0.19 | 1.08 ± 0.23     |
| Missed card choices % (range) | 3.3 (0–11.7) | 0.8 (0–11.7)   |

BIS = Barratt Impulsiveness Scale; GAQ = Gambling Addiction Questionnaire; MMSE = Mini-Mental State Examination; UPDRS = Unified Parkinson’s Disease Rating Scale.
blood oxygen level-dependent signal changes in the basal ganglia were due to structural or morphological confounds.

Data preprocessing and analysis were performed using statistical parametric mapping 8 (SPM8, Wellcome Department of Imaging Neuroscience, London, UK). Data preprocessing consisted of realignment (rigid body motion correction), segmentation of the high-resolution T1 image, to which the functional images then were co-registered. All images were spatially normalized to Montreal Neurological Institute (MNI) space using the normalization parameters obtained from the segmentation procedure and subsequently smoothed with a Gaussian kernel of 8 mm full-width at half maximum.

First level data analysis was performed on each subject using the general linear model in which events of interest were modelled as stick functions convolved with a canonical haemodynamic response function, as implemented in SPM8. To model the choice phase, we constructed two regressors time-locked to the onset of the choice to independently model high and low stake trials. Note that the choice phase included both the button-press and a period of outcome anticipation, which could not be separated in this design due to their complete co-linearity. To model the outcome phase we constructed four regressors (time-locked to onset of the outcome) for all factorial combinations of outcome (win versus loss), and value (high versus low). Twenty-four movement regressors were extracted to model residual effects of movement after rigid body realignment (Friston et al., 1996). Modelling of residual effects of movement after rigid body realignment was handled by adding a Volterra expansion of the movement parameters as nuisance regressors in the general linear model. This filter contains the six motion parameters estimated from the rigid body realignment procedure as well as the parameters from the previous volume to take care of spin history effects. Also the filter is expanded to second order (movement parameters squared) giving a total of 24 additional free parameters in the estimation of the general linear model.

After model estimation the planned contrasts for each event type were computed using one sample t-tests (unless otherwise specified). The contrast images from each subject were entered in a group-level random effects analysis. We computed one-way ANOVAs separately for all choice and outcome events. To compare motor activity at the time of button press in the choice phase, we created a first order contrast for (Choice) between groups on the second level. We created a first-order parametric linear t-contrast for (wins versus losses) for the groups separately and between groups.

All statistical inferences applied a significance threshold of \( P < 0.05 \) after correction for multiple comparisons. Correction was performed using the family-wise error (FWE) at the cluster level using the family-wise error correction method as implemented in SPM. We used an uncorrected threshold of \( P < 0.001 \) to define the extent of each cluster.

The mesolimbic and mesocortical regions defined as regions of interest, included the ventral tegmental area, ventral striatum, putamen, caudate nucleus, thalamus, hippocampus and medial orbitofrontal cortex. Where region of interest analysis was performed, correction for number of regions of interest was performed, unless otherwise stated. For each region of interest we used the anatomical region as defined in the WFU Pickatlas (Maldjian et al., 2003). For activations outside the predefined regions of interest, FWE correction considered all voxels in the brain. Note that all statistical parametric maps shown were thresholded at an uncorrected \( P < 0.001 \) for display purposes. Relative blood oxygen level-dependent signal changes were computed using the rfxplot toolbox (Glascher, 2009), and \( x, y, z \) in figures refer to the coordinates of the peak voxel in MNI stereotactic space. Unified Parkinson’s Disease Rating Scale motor scores and Barratt Impulsiveness Scale scores were taken to the random effects level as covariates of interest, where age was treated as a nuisance covariate. Reaction times and other behavioural data were statistically analysed using SPSS (SPSS Inc.). For behavioural data analyses, significance level was set at \( P < 0.05 \) and group data are given as mean ± standard deviation (SD).

## Results

### Behavioural data and motor scores

The clinical data as well as the group data for each test are listed in Table 1. Thirteen dopamine-naive patients with Parkinson’s disease and 12 healthy control subjects completed the experiment (additionally one patient with Parkinson’s disease and six control subjects were excluded due to non-compliance and technical problems). Mean Unified Parkinson’s Disease Rating Scale motor score of the 13 drug-naive patients was 25.6 (± 8.7 SD). At the time of study, clinical tests and a detailed clinical interview yielded no evidence of depressive disorder (Beck Depression Inventory II mean 5.8 ± 4.6 SD, maximal Beck Depression Inventory II score: 63), dementia (Mini-Mental State Examination 29.7 ± 0.7 SD, cut-off point: 25), increased risk-taking behaviour (Barratt Impulsiveness Scale 66 ± 5.6 SD, maximal Barratt Impulsiveness Scale score: 120), or pathological gambling (Gambling Addiction Questionnaire 0.3 ± 1.1 SD, maximal Gambling Addiction Questionnaire score: 20).

Response times for gamble performance did not differ between groups [patients with Parkinson’s disease: 1.06 ± 0.19 s versus healthy control subjects: 1.08 ± 0.23 s; two-sample t-test:...
Increases in regional activity with reward outcome value

The main aim of our analysis was to identify brain regions where regional activity showed a linear increase with reward outcome. Therefore, analysis focused on the gamble outcome phase. Because our statistical model included separate regressors for each outcome value (from high losses to high wins), we were able to compute weighted contrasts that test for the positive linear effect of outcome value on regional activity. As expected, this contrast showed a widespread distribution of functional activation for healthy control subjects (Fig. 2). Activations included many of the core hedonic and affective regions of interest within the meso-cortical-limbic system, which are expected to be critically involved in processing of reward outcome value. Linear increases in activity with reward outcome were found in the ventral striatum, ventral tegmental area, caudate nucleus, thalamus, hippocampus and medial orbitofrontal cortex (Table 2). Region of interest analysis revealed that positive linear responses in the hippocampus and ventral tegmental area were significant. For ventral striatum, caudate nucleus, thalamus, and medial orbitofrontal cortex, the linear increases were significant even after correction for multiple comparisons across the whole brain.

In contrast, patients showed no significant activations in any of the predefined regions of interest or elsewhere in the brain, even at an exploratory threshold ($P < 0.001$ uncorrected). Only when we applied a very liberal threshold ($P < 0.01$ uncorrected), the ventral putamen (bilateral), orbitofrontal cortex (right) and the occipital lobe (bilateral) displayed weak statistical trends towards a linear increase in activity with reward outcome value (Fig. 2). Equivalent contrasts testing the negative linear effect of outcome value did not show any significant effects for either group, even at trend level.

Between-group differences in reward related activity

Within the predefined regions of interest, patients with Parkinson’s disease showed a significantly reduced neural response to increasing reward outcome values compared with healthy control subjects. The positive linear relationship between reward outcome and outcome-related activity was attenuated in the ventral and dorsal putamen, ventral tegmental area, thalamus, the caudate nucleus, hippocampus, medial frontal gyrus, inferior frontal gyrus and occipital visual areas ($P < 0.05$ FWE, Table 2). The results show that core regions of the meso-cortico-limbic dopaminergic system, including the ventral tegmental area, ventral striatum, and medial orbitofrontal cortex, are already significantly compromised in the early stages of the disease. Additionally, the insula, cerebellum, premotor and superior frontal area showed a similar trend towards a reduced responsiveness to reward outcome value at a more liberal exploratory threshold ($P < 0.001$ uncorrected), but these decreases did not survive whole-brain correction (Fig. 3). The same group comparison for the negative linear effect of outcome value did not show any significant effect, even at trend level.

Attenuation in the patients’ linear response to reward outcome could be due to a deficit in the magnitude of responses to either losses, gains or to both. To distinguish these possibilities we performed the same contrast independently for wins and losses. Testing for the between group difference (healthy control subjects > patients with Parkinson’s disease) in the positive linear responses to value for wins, patients showed significantly attenuated responses in the dorsal putamen, caudate nucleus, thalamus, ventral tegmental area, posterior parietal cortex, inferior and medial frontal gyrus and the left motor cortex and right cerebellum (Fig. 4A). Isolating the high magnitude wins from the low showed this effect was mainly produced by the high magnitude outcomes. The converse contrast, testing the negative linear effect for wins, did not show any significant effect.

Testing for group differences (healthy control subjects > patients with Parkinson’s disease) in the positive linear response to losses, we found no significant effect. The converse contrast testing the negative linear response to losses, showed significantly less deactivation in patients with Parkinson’s disease compared with control subjects in the ventral putamen, parahippocampal gyrus and hippocampus, thalamus and medial and superior frontal gyrus (Fig. 4B). Separating high losses and low losses shows this effect was mainly carried by high losses. Statistical conjunction of
linear effects and a more liberal inclusive mask contrast for both wins and losses showed no significant regions.

**Increases in reward related activity with Unified Parkinson’s Disease Rating Scale or Barratt Impulsiveness Scale scores**

In the patient group, we regressed the individual Unified Parkinson’s Disease Rating Scale score against the outcome value-based parameter estimates to identify brain regions where neural responses to reward outcome showed a linear relation with clinical impairment. Outcome-related activity in the bilateral ventral premotor region (left > right) centred on the junction between inferior frontal sulcus and precentral sulcus—also referred to as the inferior frontal junction region—and the right inferior frontal gyrus showed a trend towards a positive linear increase with outcome value ($P < 0.001$ uncorrected). This statistical trend suggests increased responsivity to reward outcome values with severity of motor symptoms. The converse contrast for negative linear reward responses showed no significant activations. As with the analysis above, we computed the Unified Parkinson’s Disease Rating Scale regression independently for wins and losses. Surprisingly, for wins-only we did not find any region

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**Figure 2** Linear effect of outcome value. The effect of outcome value on outcome-related neural activity tested by computing the weighted contrasts of the separate regressors set for each outcome value (from high losses to high wins). (A) Statistical parametric maps showing widespread increases in activity with reward outcome value, including many of the hedonic and affective regions of interest within the basal ganglia and mesocortical dopamine system. The statistical maps are thresholded at $P < 0.001$ (uncorrected). The bar gives the colour coding of $T$-values for each voxel. P = posterior; A = anterior; L = left; R = right. (B) The corresponding statistical parametric maps in patients with Parkinson’s disease showed only trend activations in ventral putamen, right orbitofrontal cortex and occipital visual areas bilaterally, when applying a more liberal threshold [$P < 0.01$ (uncorrected)]. (C) Activation profile of outcome-related activity for regional peak activation in right ventral striatum. Healthy controls (left) show a stronger increase in outcome-related activity with outcome value than drug-naive de novo patients with Parkinson’s disease (right, $Z = 2.94$). PD = Parkinson’s disease.
that correlated (positively or negatively) with Unified Parkinson's Disease Rating Scale. The loss-specific contrast showed the same profile of regions as the full value (wins and losses) regression indicating that it is the loss-specific response that was carrying this effect.

To identify brain regions where the reward response covaried with risk-taking propensities (across subjects) we regressed the individual Barratt Impulsiveness Scale scores onto the subject-specific linear effect of outcome value. In right dorsal putamen, left thalamus, left insula and right inferior frontal gyrus, the linear increase in neural response with outcome value correlated positively with individual Barratt Impulsiveness Scale scores (cluster level, P < 0.05 FWE, Fig. 5). Neither the converse contrast for negative linear reward responses, nor the independent analyses for wins or losses showed a significant linear relationship with individual Barratt Impulsiveness Scale scores.

**Discussion**

This is the first functional neuroimaging study to investigate the neural basis of reward sensitivity in a group of recently diagnosed, drug-naïve patients with Parkinson's disease. By including only untreated patients with Parkinson's disease, we avoided any confounding effects of anti-parkinsonian medication that would modify dopaminergic transmission. We found that early Parkinson's disease is associated with a marked and widespread attenuation of the neural response to gamble outcomes across a broad distribution of the mesocortical and mesolimbic systems, extending into classical motor areas (Fig. 2). Compared with healthy control subjects, DOPA-naïve patients with Parkinson's disease showed either a substantially attenuated or undetectable linear representation of rewards and punishments in the ventral putamen, ventral tegmental area, thalamus and subthalamic nucleus, the caudate nucleus, hippocampus, insula, medial frontal, inferior frontal and superior frontal areas (Fig. 3). Additionally, deficits were evident in motor cortices, the ventral premotor cortex and cerebellum (anterior lobe) and even in the visual cortical areas of the occipital lobe. The finding that patients with Parkinson's disease expressed significantly attenuated neurometric reward response functions was further corroborated by the absence of a linear main effect of outcome value in any of the mesocortical or mesolimbic networks of interest. The lack of discernable signals is particularly remarkable given that monetary losses or gains have consistently been shown to induce strong and reproducible effects on blood oxygen level-dependent responses in these regions (Knutson et al., 2000, 2001; Yacubian et al., 2006; Schott et al., 2008; Urban et al., 2012).

**Table 2 Functional MRI results of reward outcome**

<table>
<thead>
<tr>
<th>Anatomical area</th>
<th>x, y, z</th>
<th>t-stat</th>
<th>Cluster size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group: linear increase in regional activity with reward outcome value (P &lt; 0.05, FWE corrected for whole brain)</td>
<td></td>
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<td></td>
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<tr>
<td>Right anterior putamen</td>
<td>15, 8, −2</td>
<td>8.72</td>
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<tr>
<td>Left anterior putamen</td>
<td>−15, 11, 1</td>
<td>9.30</td>
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<tr>
<td>Right thalamus</td>
<td>9, −16, 1</td>
<td>7.03</td>
<td>297</td>
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<td>Left thalamus</td>
<td>−9, −16, 1</td>
<td>8.83</td>
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</tr>
<tr>
<td>Right occipital cortex</td>
<td>36, −88, 7</td>
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</tr>
<tr>
<td>Left occipital cortex</td>
<td>−27, −94, 10</td>
<td>9.57</td>
<td>2134</td>
</tr>
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<td>Medial orbitofrontal gyrus</td>
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<td>Left inferior frontal gyrus</td>
<td>−39, 50, 4</td>
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<td>Right caudate nucleus</td>
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<td>Left caudate nucleus</td>
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<td>7</td>
</tr>
<tr>
<td>Left ventral tegmental area</td>
<td>−3, −19, −14</td>
<td>5.24</td>
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</table>

Stronger increase in reward–outcome related activity in the control group relative to the patient group (P < 0.05, FWE after region of interest analyses corrected for number of regions of interest)

<table>
<thead>
<tr>
<th>Anatomical area</th>
<th>x, y, z</th>
<th>t-stat</th>
<th>Cluster size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right putamen</td>
<td>18, 8, −2</td>
<td>4.74</td>
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<tr>
<td>Left putamen</td>
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<td>Right thalamus</td>
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<td>Medial orbitofrontal gyrus</td>
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<tr>
<td>Left inferior frontal gyrus</td>
<td>−42, 53, 4</td>
<td>4.60</td>
<td>49</td>
</tr>
<tr>
<td>Right caudate nucleus</td>
<td>15, 8, −2</td>
<td>4.53</td>
<td>13</td>
</tr>
<tr>
<td>Left caudate nucleus</td>
<td>−15, 11, 1</td>
<td>4.80</td>
<td>13</td>
</tr>
<tr>
<td>Right hippocampus</td>
<td>30, −16, −14</td>
<td>4.80</td>
<td>37</td>
</tr>
<tr>
<td>Left ventral tegmental area</td>
<td>−3, −19, −11</td>
<td>3.98</td>
<td>4</td>
</tr>
<tr>
<td>Right occipital cortex</td>
<td>36, −76, 28</td>
<td>4.83</td>
<td>12</td>
</tr>
</tbody>
</table>

Anatomical areas with their (x, y, z) coordinates and statistical values indicated.
Figure 3 Differences in the linear responses to reward outcome value between healthy control subjects and patients with Parkinson’s disease. (A) Axial statistical parametric maps displaying regions showing a stronger increase in activity with reward outcome value for control subjects than for patients. Significant value related differences for healthy control subjects versus patients with Parkinson’s disease are present in the ventral and dorsal putamen, ventral tegmental area, thalamus and subthalamic nucleus, the caudate nucleus, hippocampus, insula, cerebellum, medial frontal, inferior frontal and superior frontal areas, premotor and occipital visual areas. The statistical maps are thresholded at $P < 0.001$ (uncorrected), extent threshold 50 voxels. The bar gives the colour coding of $T$-values for each voxel. $P =$ posterior; $A =$ anterior; $L =$ left; $R =$ right. (B–D) Parameter estimates for outcome-related activity for regional peak activation in left putamen (B), left ventral tegmental area (C) and right hippocampus (D). All areas show a flattened or undetectable linear increase in neural response with outcome value in patients with Parkinson’s disease, whereas healthy control subjects show a clear linear reward value related activity in these key regions of the mesolimbic system. PD = Parkinson’s disease.
In all of the aforementioned regions, attenuation in the patient’s linear response to outcome values was present for both gains and losses. In mesolimbic structures, the caudate nucleus and ventral tegmental area showed a marked attenuation of neural responses to gain magnitude, whereas the ventral putamen showed a significantly reduced responsiveness to loss magnitude (Fig. 4) and no region expressed a statistical conjunction of attenuation effects for both wins and losses. This shows that early in the presentation of Parkinson’s disease, specific subregions of the mesolimbic system become more insensitive to losses whereas others selectively lose their sensitivity to gains (Fig. 4). One possible underlying cause of the diminished linear response would be that the neurodegenerative process in Parkinson’s disease induced substantial non-linearity in the neurometric response function to outcome value. Although our paradigm only elicited two magnitudes of gains/losses and therefore does not allow for non-linear inference, our parameterization of the response function does allow independent estimation of the response to each magnitude. The four independent main effects for each outcome value show substantially the same result as discussed above, mainly carried by high wins and high losses, and thus the between group difference cannot be due to suboptimal parameterization of the response function.

**Figure 4** Differences in the linear responses to reward outcome value between healthy control subjects and patients with Parkinson’s disease for wins and losses, respectively. (A) Axial statistical parametric map showing significantly higher win related activation for healthy control subjects versus patients with Parkinson’s disease, in the dorsal putamen, caudate nucleus, thalamus, ventral tegmental area, posterior parietal cortex, inferior and medial frontal gyrus and the left motor cortex and right cerebellum. (B) Axial statistical parametric map showing significantly less loss-related deactivation in patients with Parkinson’s disease compared with healthy control subjects in the ventral putamen, parahippocampal gyrus and hippocampus, thalamus and medial and superior frontal gyrus. The statistical maps are thresholded at $P < 0.001$ (uncorrected). The bar reflects the colour coding of $T$-values for each voxel. P = posterior; A = anterior; L = left; R = right.

**Figure 5** Interindividual differences in risk-taking behaviour as reflected by the Barratt Impulsiveness Scale score are associated with increased reward-value related activity in the right putamen and left thalamus in the patient group. (A) Axial parametric map showing a cluster in the right putamen (peak $t$-score = 7.97 at $x = 24, y = -10, z = 7$, cluster extent = 46 voxels) and left thalamus (peak $t$-score = 7.34 at $x = -18, y = -16, z = 7$, cluster extent = 46 voxels), where reward-related activity showed a positive linear relationship with the individual Barratt Impulsiveness Scale score. The statistical maps are thresholded at $P < 0.001$ (uncorrected). The bar reflects the colour coding of $T$-values for each voxel. P = posterior; A = anterior; L = left; R = right. (B) The scatter plot illustrates the positive linear increase in the estimated reward related blood oxygen level-dependent response with the Barratt Impulsiveness Scale score for the peak voxel of the right putamen, indicating higher sensitivity to reward outcome value with increased risk-taking behaviour. BOLD = blood oxygen level-dependent.
To test whether intersubject variability in clinical severity correlated with neural response to gamble outcomes, we tested for a linear relationship between the individual Unified Parkinson’s Disease Rating Scale III score and regional response profile to reward value (to both gains and losses). Activity in the right inferior frontal gyrus and inferior frontal junction region only showed a trend towards increased responsiveness to reward outcome values with severity of motor symptoms. Intersubject variability in risk-taking behaviour correlated with neural responses to gamble outcomes in patients. The individual Barratt Impulsiveness Scale scores showed a positive linear relationship with reward outcome value responses in the right dorsal putamen, left thalamus, left insula and right inferior frontal gyrus. This relation indicates higher reward responsiveness in the right dorsal putamen and left thalamus in patients with stronger risk-taking behaviour (Fig. 5). This finding shows that the pre-existing risk-taking trait enhances the responsiveness of cortical and subcortical brain regions to rewarding outcomes. We speculate that such enhanced responsiveness might influence the individual susceptibility to impulse control disorders in response to dopamine therapy. Since the present study was not designed to address potential links between pre-existing impulsivity and dopamine-triggered impulse control disorders, this interesting question needs to be addressed in larger prospective functional MRI studies.

Taken together, the evidence presented here suggests that the encoding of reward and punishment outcomes is already significantly impoverished in newly diagnosed patients with Parkinson’s disease before the initiation of dopamine replacement pharmacotherapy. It shows that the remaining reward sensitivity may be curtailed down from large swathes of mesolimbic, mesocortical, motor and occipital regions down to a few islands within orbitofrontal cortex, ventral putamen and occipital cortex. It is of interest that even for these remaining regions, there is a significant reduction in the response magnitude compared with healthy control subjects (Fig. 2). Thus, the results indicate that this attenuated responsiveness to reward outcome value is widespread and involves the majority of regions within the reach of dopaminergic transmission. This includes classical reward structures of the basal ganglia and medial orbitofrontal cortex, but also extending into classical motor structures.

Our findings are of importance for current pathophysiological concepts of Parkinson’s disease for a number of reasons. As pointed out above, it has been postulated that the mesolimbic system is only marginally affected at the early stages of Parkinson’s disease due to a later involvement of the ventral striatum relative to dorsal striatum (Fearnley and Lees, 1991; Morrish et al., 1996; Cools et al., 2001; Braak et al., 2004). Our results challenge the concept of relatively intact limbic circuits in the earliest phases by showing that the reward responses of the mesolimbic and mesocortical system are already significantly impaired. This has implications for the dopamine ‘overdose theory’, which predicts that dopamine medication causes aberrant reinforcement behaviour by excessive stimulation of a relatively intact reward processing in the mesolimbic system. Our data suggest that in early stages of Parkinson’s disease there is a significantly reduced reward responsibility in the ventral striatum before dopamine replacement therapy has started. This could be analogous to the findings in pathological gamblers (without Parkinson’s disease), who show decreased reward activity in the mesolimbic system (Reuter et al., 2005; van Holst et al., 2010; Cilia and van Eimeren, 2011; Miedl et al., 2012). The enhanced level of dopamine induced by the dopamine medication leading to pathological gambling in patients with Parkinson’s disease could consequently be analogous to the heightening of dopamine release in the mesolimbic system in pathological gamblers caused by gambling. This aberrant increase in dopamine transmission could trigger erroneous expectancy coding and beliefs regarding the probability of winning and thus contribute to continuation of gambling despite heavy losses (Schultz, 2007; Clark et al., 2009; van Eimeren et al., 2010), as has been suggested before (van Eimeren et al., 2010; O’Sullivan et al., 2011). This, in combination with higher loss sensitivity correlated with Unified Parkinson’s Disease Rating Scale, could explain why patients with Parkinson’s disease without dopamine medication tend to learn better from punishment and show loss avoidant behaviour (i.e. ‘learning by stick’). This would then convert to increased risk-seeking behaviour and learning from positive rewards after the initiation of dopamine medication (i.e. ‘learning by carrot’), in accordance with what was also recently shown in a behavioural study in mainly drug naïve patients with Parkinson’s disease (Frank et al., 2004, 2007; Schott et al., 2007; Bodi et al., 2009), which still supports the basic tenet of the ‘overdose theory’.

The behavioural correlates of this early neuronal deficit remain to be fully tested, and will be the target of future investigation. Of particular clinical importance will be assessing the degree to which these functional responses are clinically useful as an endophenotypic predictor of the response to dopamine treatment and its side effects, as well as predicting pathological and behavioural trajectories. Neurobiological insight into the drug-naïve state thus provides an essential window into the nascence of Parkinson’s disease and its future remedy.

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**References**


