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Reward processing dysfunction in ventral striatum and orbitofrontal cortex in Parkinson's disease

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ABSTRACT

Background: Parkinson's disease is a growing concern as the longevity of the world's population steadily increases. Both ageing and Parkinson's disease have an impact on dopamine neurotransmission. It is therefore important to investigate their relative impact on the fronto-striatal reward system. There has been little investigation of reward processing in terms of anticipation and reward outcome in Parkinson's disease. Abnormal responses during reward processing have previously been demonstrated in whole-brain analysis of Parkinson's patients with mild lateralized disease, but the exact impact in regions specific to reward processing is still unknown.
Objective: Here we aim to investigate the impact of Parkinson's disease on the orbitofrontal ventral striatal reward system in patients with moderate to severe clinical symptoms.
Methods: We utilized a monetary incentive delay (MID) task in 17 Parkinson's patients who were compared to two control groups stratified by age. The MID paradigm reliably activates the ventral striatum during reward anticipation and the orbitofrontal cortex during reward outcome processing.
Results: Relative to the two control groups, Parkinson's disease patients had abnormal task related activity during both reward anticipation in the ventral striatum and reward outcome in the orbitofrontal cortex. There were no effects of ageing.
Conclusion: These findings demonstrate abnormalities in anticipatory as well as reward outcome processing while treated primarily with levodopa. The orbitofrontal dysfunction during reward outcome processing may have specificity in Parkinson's disease, as it has been shown to be relatively unaffected by normal ageing.

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1. Introduction

To date the main risk factor for Parkinson's disease is increasing age [1]. Both ageing and Parkinson's disease are characterized by decreased dopaminergic availability in the brain, especially in the striatum [2]. The ventral striatal reward network is crucial in reward processing and is primarily regulated by dopamine [2]. It is now reasonably well understood that the reward network functions as an interplay between reward anticipation processing in the ventral striatum and reward outcome processing in the orbitofrontal cortex [2,3]. The functional relationship between outcome processing and reward anticipatory processing has been shown to be affected by ageing, and is thought to be associated with an age related decrease in normal dopaminergic activity in these regions [4]. Furthermore, it has been suggested that non-motor symptoms such as apathy [5] and impulsivity [6] are related to reward processing abnormalities in Parkinson's disease. It is, therefore, important to investigate reward processing in Parkinson's disease. However, there has been surprisingly little investigation of basic reward processing and its potential relationship with age related changes in Parkinson's disease.

Previous studies have demonstrated an interaction between reward anticipatory processing and cognitive control, related to dopamine cell loss in Parkinson's disease [7]. Only one study has investigated the potential impact of Parkinson's disease and its relationship with normal ageing on basic reward processing [8]. The authors reported uncorrected whole brain results in patients with mild disease without relevant disability, with the majority being treatment-naïve. Parkinson's patients were not distinguished in terms of reward anticipatory processing in the ventral striatum, but rather by prefrontal activity during reward outcome. A lack of such a difference in the ventral striatum is unexpected, and could be due to the inclusion of early stage Parkinson's disease patients. We aimed to investigate the impact of Parkinson's disease on the orbitofrontal ventral striatal reward system relative to age related changes in an age matched control group as well as a younger normal control group. To this end we utilized a monetary incentive delay (MID) task in 17 Parkinson's patients as compared to a control group stratified by age. This paradigm reliably activates the ventral striatum during reward anticipation and the orbitofrontal cortex during reward outcome processing [3,4]. As the effect of ageing on reward anticipatory processing has been documented [4], we hypothesized that there would be a relative decline in ventral striatal activity in both older age groups (Parkinson's and elderly controls), with Parkinson's patients exhibiting the greater decline. There are limited data investigating the association of Parkinson's disease with reward outcome processing especially in those with mild to moderate disease. We hypothesized such an effect would be present in the orbitofrontal cortex. Finally, we investigated the shift in the relationship between outcome processing and reward anticipatory processing in both the aforementioned regions in Parkinson's disease relative to our control groups [4].

2. Materials and methods

2.1. Participants

Participants are part of a larger cohort examining the genomic and environmental signatures that are common to Parkinson's Disease, Post Traumatic Stress Disorder, Schizophrenia and metabolic syndrome ("Shared Roots" study, MRC-RFA-UFSP-01-2013). The study has been approved by Health Research Ethics Committee (HREC N13/08/115) of Stellenbosch University, Tygerberg Hospital, Cape Town, South Africa.

All participants were recruited from the same geographical region and matched on socioeconomic status (lower to middle income status). A diagnosis of Parkinson's disease was clinically confirmed by a neurologist. An aged matched healthy older control group (OHC) was recruited. Controls were free of current significant psychopathology as well as other significant confounding medical conditions. To investigate for the potential effects of age, a younger healthy control group (YHC) was also recruited through the parent study.

2.2. Clinical assessments

All participants received a full clinical examination. They were screened for any confounding psychopathology using the Mini-International Neuropsychiatric Interview (MINI version 6.0.0). Parkinson's patients completed the Unified Parkinson's Rating Scale (UPDRS) (Version 3.0) [9]. Handedness was determined by the Edinburgh Handedness Inventory [10]. All participants were instructed to take their Parkinson's medication as normal, prior to scanning. All participants received a urine drug screen immediately before their MRI scan. Participants with severe head injury, confounding intra-cranial pathology, current severe psychopathology and/or drug abuse and other medical conditions that could confound behavioural as well as fMRI measures were excluded.

2.3. Monetary incentive delay fMRI paradigm

All participants performed a modified version of the MID task by Knutson et al. [11]. To enhance task comprehension, as well as keep the number of scan acquisitions to a minimum, only reward and neutral cues were used in this task. The task is described in detail elsewhere [4]. Briefly, during each scan trial participants were required to respond as rapidly as possible when a target cue was presented. A smiling face immediately preceded the target, to indicate a potentially rewarding trial, and a neutral face was presented prior to neutral trials. After seeing the face cue, a blue star was shown for a short pseudo random interval immediately followed by the target cue (i.e. reward anticipation). If a participant responded in time to the target cue, a screen with green lettering appeared indicating the total reward won (i.e. reward outcome). If a participant did not respond in time, red letters appeared. During reward trials, the monetary reward was incrementally increased (fixed increments of R10) (See Fig. 1).

The reward anticipation period as well as the inter-trial interval were "jittered" to reduce collinearity between reward anticipation and reward outcome (Mean duration 3286 ms, range 779–6729 ms; mean duration 3535ms, range 1029–6979ms respectively). The reward outcome period was 2000 ms per trial. The entire task therefore consisted of 60 trials, with a mean duration of 9571ms (range 4946–16107 ms), resulting in a total task duration of 9min 35s.

To ensure an equal number of rewarded and unrewarded trials, the duration of the target cue was adapted to the fastest response time of the participant during a training session. By matching task performance across subjects in this way, we controlled for differing levels of performance across the groups. The target score was set to approximately R150 (~10 USD) for each group.

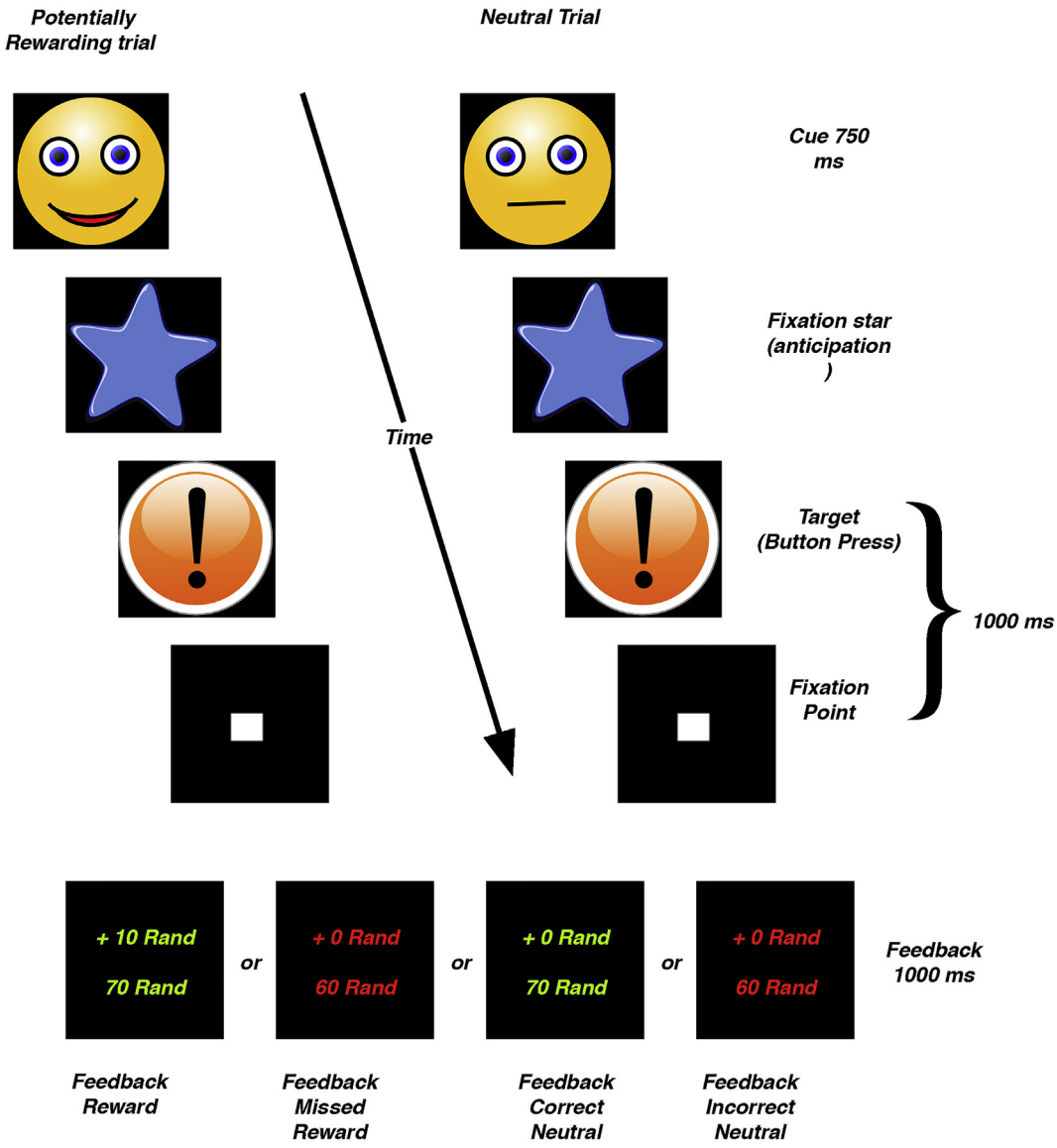

Fig. 1. Schematic representation of the Monetary Incentive Delay task.

2.4. Behavioural data analysis

Trial by trial response times were averaged for each individual for both neutral and potentially rewarding trials. Average response times were then compared between neutral trials and potentially rewarding trials across the three groups using a repeated measure analysis of variance (RMANOVA). Monetary award across the groups was compared with a standard ANOVA.

2.5. Image acquisition

Scans were acquired on a 3T Siemens Allegra at the Combined Universities Brain Imaging Centre (CUBIC). 622 whole-brain 2D-EPI images (TR = 1600 ms, TE = 23 ms, flip-angle: 72.5°, FOV: 256x256, 30 slices, 4 mm isotropic voxels) were acquired in about 16 mins. For image registration, a T1 ME-MPRAGE weighted structural scan was acquired (TR = 2530 ms; $TE_1 = 1.53$ ms $TE_2 = 3.21$, ms, $TE_3 = 4.89$ ms, $TE_4 = 6.57$ ms, flip-angle: 7°,FoV: 256 mm, 128 slices, 1 isotropic voxel size) [12].

2.5.1. Image preprocessing

Images were analyzed using SPM12 (http://www.fil.ion. ucl.ac.uk/spm/software/spm12/). Preprocessing and first-level statistical analysis was undertaken as previously described [13]. In brief, preprocessing involved correction for slice timing differences, realignment to correct for head motion, spatial normalization to the Montreal Neurological Institute template brain, and spatial smoothing to accommodate inter-individual differences in neuroanatomy. Head motion parameters were analysed to ensure that the maximum motion did not exceed a predefined threshold (scan-to-scan > 1.8 mm).

2.5.2. First level fMRI statistical analysis

The pre-processed time-series data for each participant was analysed using a general linear model (GLM) analysis. The model consisted of six factors of interest, representing haemodynamic changes time-locked to (1) anticipation during and after the presentation of the reward cue (reward anticipation), (2) anticipation during and after a neutral cue (neutral anticipation), (3) feedback reflecting a positive monetary reward outcome (reward outcome),

(4) feedback reflecting no reward, (5) feedback reflecting a correct response in a neutral trial (neutral correct outcome) and (6) feedback reflecting an incorrect response in a neutral trial (Fig. 1). The onset of the factors modelling anticipation (duration range 1529–7479 ms) was at the presentation of the cue, while the onset of the factors modelling feedback (duration: 2000ms) was at the presentation of the target, including the button press to the target and subsequent feedback (See Fig. 1). Motion parameters from the realignment procedure were included as factors of no interest. Low frequency drifts were removed from the signal by applying a high-pass filter with a cut-off frequency of 128 s.

2.5.3. Region of interest analyses

Primary analyses were performed in one region of interest (ROI): the combined bilateral ventral striatum for reward anticipation, and combined bilateral orbitofrontal cortex for reward outcome, based on previous findings by Knutson et al. [3]. These regions were defined using the AAL-atlas [14] and the Oxford-GSK-Imanova Striatal Connectivity Atlas for the ventral striatum [15]. For each participant, the mean activation level (expressed as percent signal change relative to the baseline signal) during the contrasts of interest specific to reward anticipation and reward outcome (reward anticipation, neutral anticipation, reward outcome and neutral correct outcome) was calculated over all the voxels of each ROI.

These values were used in a RMANOVA, testing for within-subject effects in activation levels between the neutral trials contrast *vs* the potentially rewarding trials contrast in the ventral striatum only (i.e. reward anticipation). Within-subject differences were assessed between the correct neutral trials contrast *vs* the positive reward outcome contrast in the orbito-frontal cortex (i.e. reward outcome) only. To investigate the activation shift between ventral striatum and orbito-frontal cortex previously found in ageing, we looked at reward anticipation (i.e. neutral trials *vs* potentially rewarding trials) vs reward outcome (i.e. correct neutral trials *vs* positive reward outcome) in both regions respectively. We also examined between group differences in the same analysis for both reward anticipation as well as reward outcome in the ventral striatum and orbitofrontal cortex respectively. All post hoc tests performed were corrected for multiple comparisons using the Tukey HSD correction. Only adjusted *p*-values are reported on. A p-value of $p < .05$ was considered significant for all analyses after correction for multiple comparisons.

2.6. Correlation analysis

To further explore potential clinical correlates, fMRI activity during reward outcome in the orbitofrontal cortex and reward anticipation in the ventral striatum were correlated using a Spearman rank-order correlation or Pearson *r*-correlation coefficient, where appropriate. To correct for multiple comparisons in our correlation analysis, we used the Bonferroni's correction for multiple comparisons.

3. Results

The final sample was comprised of 17 participants diagnosed with Parkinson's disease, 27 participants matched for age with the Parkinson's group (i.e. Older Healthy Controls, OHC) and 34 younger controls (i.e. Younger Healthy Controls, YHC) (See Table 1).

All three groups were matched for handedness, with most participants being right handed. Gender was not equally distributed across the three groups. In the control group as a whole, and supported by the literature [4,8], we did not find an effect of gender on reward anticipation ($F(1,36) = 0.72$, $P = .402$) in the ventral striatum nor on reward outcome in the orbitofrontal cortex ($F(1,36) = 0.00$, $P = .979$). We, therefore, chose not to correct for gender in the analysis.

3.1. Exclusions

The scan of one Parkinson's disease patient was excluded from the analysis due to excessive movement, leaving 17 usable Parkinson's datasets. No excessive motion was found for the remaining subjects, with no significant difference between groups. For more detailed motion assessment results, please see included supplementary material [16].

3.2. Behavioural results

All three groups displayed appropriate behavioural responses to the task. There was a main effect of response time when comparing all three groups indicating that all three groups responded more rapidly during potentially rewarding trials than neutral trials ($F(1,75) = 21.916, p < .001$). There was no significant group x reward interaction effect ($F(2,75) = 0.237, p = .789$) in terms of average response time from neutral to potentially rewarding trials among the three groups. This indicates a similar decrease in response time from neutral to reward cues among the three groups. There was a significant main effect of group for the average reaction time between the three groups ($F(2,75) = 4.706, p = .012$). As predicted, the Parkinson's disease group showed the slowest average responses compared to the healthy controls for both neutral and potentially rewarding cues. When comparing the different groups in pairs, post hoc tests revealed the Parkinson's patients to be significantly slower ($p = .008$), compared to YHC, but not the OHC ($p = .540$). To determine whether this difference was unique to Parkinson's disease, we pooled the healthy elderly and young control groups. We then compared all study controls to the Parkinson's disease group, controlling for age. This showed a significant group effect, with the Parkinson's group being significantly slower than both control groups combined ($F(1) = 4.054, p = .048$). This suggested that the Parkinson's disease group is responsible for the overall difference seen in the group wise comparison.

The task successfully controlled for varying performance levels of the three groups ensuring that all three groups won an equal amount of money when compared using a one-way ANOVA ($M_{Parkinson's} = R112.94$, $M_{OHC} = R128.15$ and $M_{YHC} = R124.12$, $F(2,75) = 1.774, p = .177$).

3.3. Reward anticipation in the ventral striatum

As expected, there was a main effect in terms of reward, with an increase in BOLD activity during reward anticipation in the ventral striatum in all three groups combined ($F(2,75) = 9.509, p = .003$). When comparing this increase from neutral to reward related activity in all three groups, we found a significant group x reward interaction effect ($F(2,75) = 3.303, p = .042$) as well as a significant group effect ($F(2,75) = 4.456, p = .015$). (See Fig. 2A). When comparing each individual group in terms of an increase between neutral and potentially rewarding cues, post hoc tests revealed a significant difference between Parkinson's patients and YHC ($p = .011$). There was no difference between the OHC and either of the comparison groups ($p = .292$ and $p = .260$ respectively). Similarly, to our behavioural analysis, we pooled both control groups. There was still a significant group x reward interaction effect ($F(1,75) = 4.267, p = .042$) as well as a significant main effect of group ($F(1,75) = 4.310, p = .041$) between the Parkinson's patients and the control groups.

Table 1
Demographic characteristics by group status.

	PD N = 17	SE	OHC N = 27	SE	YHC N = 34	SE	Test statistic	P
Age	62.59	2.447	61.96	1.01	34.74	1.60	T = 104.28	p < .001
Gender (M/F)	13/4		13/14		11/23		$X^2 = 8.86$	.012
Handedness (R/L)	15/2		27/0		33/1		$X^2 = 4.04$	.133
Years since diagnosis	5.78	3						
LED (mg/day)	618.76	83.19						
Hoehn & Yahr staging	2.5	0.16						
ADL (Best/Worst)	75.29/69.41	(2.29/2.01)						

LED = Levodopa equivalent dose; ADL = Activities of daily living.

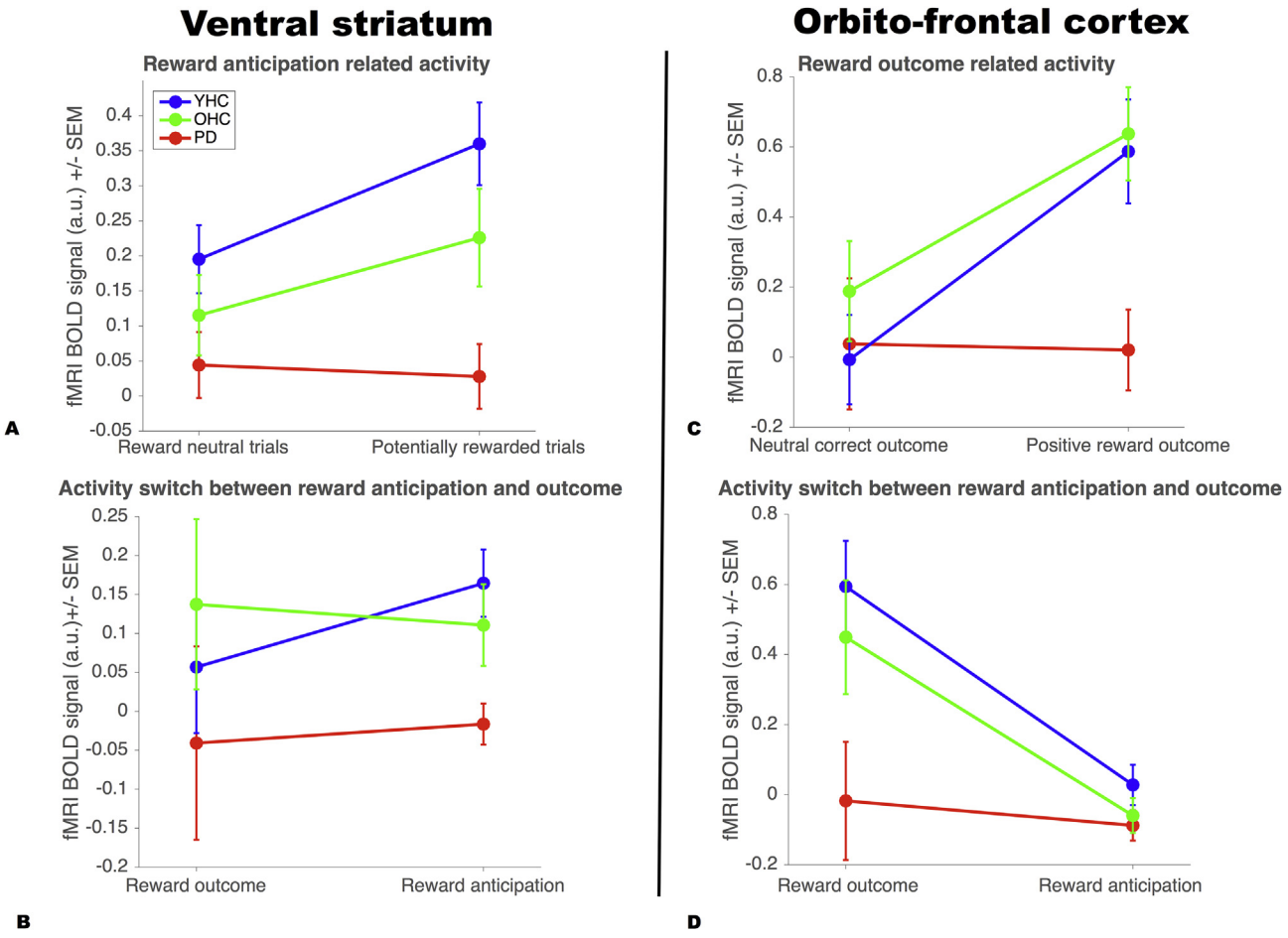

Fig. 2. Region of interest analysis of the Monetary Incentive Delay task. Graphs showing task related activity between the Monetary Incentive Delay task trials. A and B show activity in the ventral striatum. C and D show activity in the orbitofrontal cortex. YHC: Young Healthy Controls; OHC: Older Healthy Controls; PD: Parkinson's Disease; SEM: Standard Error of the Mean.

3.4. Reward outcome in the orbitofrontal cortex

There was a significant main effect for reward outcome in the orbitofrontal cortex ($F(2,75) = 4.155, p < .001$) when comparing all three groups. We found a significant group x reward interaction effect ($F(2,75) = 3.577$, $P = .033$) among the three groups (See Fig. 2C). We were unable to determine which group was driving this difference on post hoc testing, however, on pooling our control groups and controlling for age, there was still a significant group x reward interaction effect, showing abnormal activation in the Parkinson's group ($F(1,75) = 4.218, p = .044$). This suggests that the Parkinson's disease group is responsible for the overall difference seen in the group wise comparison.

3.5. Activation shift between reward outcome and reward anticipation in ventral striatum and orbitofrontal cortex

There was no main effect of activation levels when comparing outcome processing and reward anticipation processing in the ventral striatum amongst the three groups ($F(2,75) = 0.236, p = .629$), nor group x condition interaction effect ($F(2,75) = 0.371, p = .691$).

As expected, there was a main effect when contrasting reward anticipation related activity and reward outcome related activity in the orbitofrontal cortex across all three groups ($F(2,75) = 11.886, p = .001$). There was no significant group x condition interaction effect ($F(2,75) = 1.717, p = .18$). However, there

was a significant effect of group, with the Parkinson's disease group showing the lowest level of ventral striatal activity during anticipation and orbitofrontal activity during reward outcome processing ($F(2,74) = 6.11, p = .003$) (See Fig. 2D). This effect remained after pooling our control groups and controlling for age as per our previous analysis ($F(1,75) = 5.960, p = .017$).

3.6. Regression analysis

The results of our regression analysis are reported in Table 2. Although there was no significant relationship between mentation, behaviour and mood as measured by the UPDRS (Part 1), there was a trend for a positive relationship between reward anticipation related activity in the ventral striatum Levodopa Equivalent Dose ($r = 0.445$, $p = .073$) and self-reported depressive symptoms ($r = -0.426$, $p = .089$).

4. Discussion

We investigated the function of the fronto-striatal reward network in a group of medicated Parkinson's disease patients, healthy age matched controls, and a second group of young controls. Results show a significant difference in ventral striatal activity during reward anticipation for the three groups. Parkinson's patients had the most severe decline in both response speed and activity during reward anticipation in the ventral striatum of the three groups. We also found evidence for a blunted reward outcome response for Parkinson's patients in the orbitofrontal cortex. Furthermore, Parkinson's disease patients had impaired activation in both reward anticipation and outcome processing in the orbitofrontal cortex. There was no activation shift between anticipation and outcome processing in the ventral striatum. These results show changes in both cortical and subcortical reward processing present in treated Parkinson's disease.

We demonstrated a decline in ventral striatal activity in terms of reward anticipation in the Parkinson's disease group. These results support previous similar findings in a group of unmedicated Parkinson's disease patients [8]. The previous study reported a general decline in the ventral striatum in Parkinson's patients during reward anticipation, which was indistinguishable from normal ageing. In our present sample, we found no significant age-related difference. One may speculate that the differences we have observed are more pronounced since this study may reflect a more advanced stage of Parkinson's disease. As our sample did not include a medication free condition, it is not possible to parse out the influence of medication on our findings.

Even though we found no impact of age on ventral striatal reward activity, we cannot rule out an effect of age, given our small sample size and limited age range. The decline in dopamine neuron populations in both the ventral tegmental area and nigrostriatal pathway is known to lower the threshold for Parkinson's disease to manifest clinically [17]. Another explanation for our findings is that by affecting dopaminergic tone in the nigrostriatal pathway, Parkinson's medication may interfere with a relatively normal dopamine tone in the ventral tegmental area. Hypothetically, this may underlie abnormal activity in an otherwise normal functioning reward system [18]. As we did not measure the relative dopaminergic tone in our three groups, nor assess patients when they were medication free, we are not able to substantiate this hypothesis. It should be noted that only three were on dopamine agonists, so we expect this effect to be negligible.

Similarly, we found evidence for a blunted reward outcome response in the orbitofrontal cortex of Parkinson's patients. This supports abnormal prefrontal processing specific to Parkinson's disease as has been previously reported [8]. Here we extend these results by showing decreased activity in a frontal region well known to be involved in reward outcome processing [19]. Interestingly prefrontal activity related to reward outcome has not been reported to be related to ageing [4], which we confirm in our present sample. Orbitofrontal cortex dysfunction during reward outcome may represent a specific abnormality present in Parkinson's disease potentially related to either the disease process or to medication effects.

Although ventral striatal activity was decreased on average in our control sample relative to the younger control group, we failed to show a significant difference in ventral striatal activity during reward anticipation as well as an activation shift difference in our healthy elderly sample [4]. As our samples are of similar size, the reason for this is not clear. We speculate that this might be due to meaningful differences in sample demographics. For example, our control groups have a wider age range and we have included more female participants compared to our previous study [4].

Despite the limitations, our results have several important implications. Firstly, the decrease in both ventral striatal as well as orbitofrontal activity during reward processing in Parkinson's disease is present despite standard anti-parkinsonian drug treatment. Secondly, this change is likely a combination of disease factors and the normal ageing process. There is a clear need for additional prospective studies, combining direct investigation of dopamine metabolism with reward system function and evaluating the combined effects of increasing age, Parkinson's and dopaminergic medication.

Table 2
Clinical correlates of hypoactivation found on fMRI in Parkinson's disease.

	Reward anticipation in the VS		Reward Feedback in the OFC	
	r	P value	r	P value
Medication				
Levodopa Equivalent Dose	.445	.073*	-.036	.889
Section III UPDRS: Motor Examination				
Intellectual Impairment	-.110	.674	-.037	.886
Thought disorder	-.182	.501	-.089	.742
Depression	-.426	.089*	-.088	.738
Motivation/Initiative	-.159	.543	.070	.789

*: Trend $p < .10$.
VS: Ventral Striatum, OFC: Orbitofrontal Cortex.

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Potential conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2017.12.024.

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