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Chapter 5

Prefrontal cortex and striatal activation by feedback in

Parkinson's Disease

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5.1 Abstract

Positive feedbacks reinforce goal-directed behavior and evoke pleasure. In Parkinson's disease (PD) the striatal dysfunction impairs motor performance, but also may lead to decreased positive feedback (reward) processing.

This study investigates two types of positive feedback processing (monetary feedback and positive informative feedback), both compared to meaningless feedback, in PD patients and elderly healthy controls, using fMRI. In addition, positive informative feedback will be compared to monetary feedback to determine whether positive informative feedback is just as salient as monetary feedback.

Healthy controls showed increased activation in the left putamen during the monetary feedback condition compared to both the positive informative and meaningless feedback condition, without an effect in the medial Prefrontal Cortex (mPFC). In contrast, PD patients showed increased activation in the left putamen during the meaningless feedback condition compared to both positive feedback conditions. In addition, PD patients showed increased activation of the mPFC during both positive feedback conditions. This suggests that when confronted with positive feedback, the mPFC compensates for the striatal deficit.

In conclusion, striatal activation was seen in healthy controls specifically during the monetary feedback condition. PD patients did not differentiate between both types of positive feedback. If PD patients are provided with positive feedback, the mPFC compensates for the striatal dysfunction. If however, PD patients are provided with meaningless feedback, the mPFC is less stimulated and the striatum becomes prominent. This study thus demonstrates striatal involvement in positive feedback processing and altered positive feedback processing in PD.

5.2 Introduction

In everyday life positive feedbacks in response to human action are an obvious phenomenon. These feedbacks may differ both in style and intensity, e.g. receiving money will be evaluated differently than a positive verbal remark. Positive feedbacks (also designated as “rewards”) reinforce goal-directed behavior and evoke positive feelings (Schultz, 1997). Various brain areas may be associated with positive feedback processing (reward processing) in humans, in dependence of the behavioral task used during neuroimaging. However, certain brain areas are consistently associated with reward processing in healthy humans: striatum (nucleus accumbens, nucleus caudatus, putamen), orbitofrontal cortex, anterior cingulate gyrus and other parts of the prefrontal cortex (McClure et al., 2004).

Parkinson’s disease (PD) is characterized by a dysfunctional striatum, due to a progressive degeneration of dopaminergic neurons in the substantia nigra. Motor symptoms are the clinical hallmark, however depression, cognitive dysfunction and other signs and symptoms are often present (Lauterbach, 2004). The striatum is extensively connected with the prefrontal cortex through the so-called fronto-striatal circuits. Due to the dysfunction of the striatum these circuits are functionally impaired as well in PD (Alexander et al., 1986).

Neuroimaging studies investigated reward processing in PD using various tasks and methods. Using a pattern recognition task during $H_2^{15}O$ Positron Emission Tomography (PET), Kunig et al. (2000) showed a lack of striatal activation in response to reward in PD patients. Furthermore, they reported that the dorsolateral prefrontal cortex and the anterior cingulate gyrus, did show activation in PD patients in response to reward, suggesting a compensatory strategy reflected by a shift from striatal to prefrontal regions for reward processing. Schott et al. (2007) also reported such increased cortical activation. They used a reward-prediction paradigm during functional Magnetic Resonance Imaging (fMRI) and showed increased activation during reward feedback in the medial prefrontal cortex and anterior cingulate gyrus in PD patients. Goerendt et al. (2004) examined the processing of rewards of different magnitudes in PD patients and healthy controls using $H_2^{15}O$ PET. They showed that task completion time improved with increasing reward magnitude. In healthy controls this was associated with increased prefrontal and rhinal cortex activity. In contrast, PD patients showed a cerebellar vermis overactivation, also suggesting a compensatory strategy which in that study was reflected by a shift from prefrontal regions to the cerebellum. These studies thus provide arguments that reward processing is altered in PD.

Rewards or feedback also play an important role in learning. It has been reported that PD patients specifically show impairments when learning is based upon feedback compared to learning without receiving feedback (Shohamy et al., 2004). Furthermore, PD patients “on”

levodopa learn better when learning is based upon receiving positive feedback, while PD patients “off” levodopa learn better when learning is based upon receiving negative feedback (Frank et al., 2004). Learning is thus influenced by the use of levodopa.

The present study uses fMRI to investigate the consequences of dysfunctional fronto-striatal circuits for the processing of positive feedback, using PD as a model disease. In this context not many studies have been performed. The current study aims to extend previous findings by investigating two types of positive feedback (“monetary feedback” and “positive informative feedback”) rather than rewards of different magnitudes. Both types are compared to a “meaningless feedback” condition. All three types are embedded in a working memory task.

Since PD is characterized by a dysfunction of the fronto-striatal circuits, we specifically focused on the brain activation patterns in the basal ganglia and frontal regions.

In addition, we have addressed the question whether positive informative feedback is just as salient as monetary feedback by comparing the activation in the striatum and prefrontal cortex during the positive informative feedback condition to the activation within these areas during the monetary feedback and meaningless feedback conditions. This was investigated in PD patients “on” levodopa compared to elderly healthy controls. We hypothesized that PD patients show an altered feedback processing. Specifically, it was expected that PD patients show a decreased striatal activation during both types of positive feedback conditions compared to the meaningless feedback condition, while showing increased prefrontal activation during both types of positive feedback conditions compared to the meaningless feedback condition.

5.3 Experimental paradigm

Subjects

Twenty-three subjects were included in this study: eleven PD patients (nine males (82%) and two females (18%)) and twelve healthy controls (ten males (83%) and two females (17%)). PD patients were on average 58.7 (SD=7.6) years old and showed a mean score of 5.9 (SD=0.8) on a Dutch education scale ranging from 1 (Elementary school not finished) to 7 (University degree). Demographic and illness characteristics of all patients are described in table 5.1. Healthy controls were on average 58.8 (SD=6.1) years old and showed a mean score of 6.0 (SD=0.9) on a Dutch education scale. Both groups showed on average a high education level. Groups were matched for age, gender and level of education. All patients were diagnosed with idiopathic PD according to the criteria of the

UK Parkinson's Disease Society Brain Bank and were assessed in regular on-state. Unified Parkinson's Disease Rating Scale (UPDRS), part III (Fahn et al., 1987) scores were obtained from all patients and a Levodopa Equivalent Daily Dose (LEDD) was calculated according to the following formula: levodopa dose (100 mg) x 1 (added with 0.2 x levodopa dose if using entacapone with each dose) + (slow release levodopa x 0.7) + bromocriptine x 10 + ropinirole x 20 + pergolide x 100 + pramipexole x 100 (Esselink et al., 2004). Exclusion criteria were neurological disorders other than PD and depression (Montgomery-Åsberg Depression Rating Scale score < 15 (Leentjens et al., 2000).

All participants gave their written informed consent prior to study inclusion. The study was approved by the Medical Ethical Committee of the University Medical Center Groningen, the Netherlands.

Table 5.1 Demographic and illness characteristics of patients (n=11)

Patient	Sex	Age	Education	Disease duration	UPDRS	LEDD
1	Male	65	5	1	18	188
2	Male	61	7	8	21	750
3	Female	61	6	5	18	300
4	Male	60	6	14	8	920
5	Male	63	6	2	26	150
6	Male	65	7	2	10	600
7	Male	47	6	11	20	795
8	Male	47	6	1	11	450
9	Male	70	4	4	25	50
10	Male	55	6	4	17	300
11	Female	52	6	4	16	450
Mean		58.7	5.9	5.1	17.3	450.2
SD		7.6	0.8	4.2	5.8	285.7

Procedure

In order to investigate differences between PD patients and elderly healthy controls with regard to the distribution of cerebral activations related to positive feedback conditions compared to a meaningless feedback condition, Blood Oxygen Level Dependent (BOLD) responses were measured during performance of a working memory task with delayed response as described earlier (Kunig et al., 2000; Martin-Soelch et al., 2001). This task was learned before scanning during which participants were informed that the meaningless feedback condition did not have a negative meaning and represented a condition during which they did not receive any information about their performance.

One task sequence, presented with Psychtoolbox (© 2000 by David Brainard & Denis Pelli) under Matlab 5.3 (The MathWorks, Natick, Massachusetts, USA), comprised the following components (see also Figure 5.1):

- During one second an image with three regular rectangular *instruction* patterns was presented on the screen.
- A blank screen was then presented for 2.5 ± 0.5 seconds (uniformly distributed).
- A single *cue* pattern was presented at one of the three previous locations for two seconds. The subjects had to decide whether or not this pattern was presented at the same position as in the *instruction* pattern. If so, they were instructed to press the right button with their right middle finger; if not, they were instructed to press the left button with their right index finger.
- A blank screen followed this pattern during 3.5 ± 1.5 seconds (uniformly distributed). Feedback was given during one second followed by a blank screen during 3.0 ± 1.0 seconds (uniformly distributed) that completed one trial.

The visual stimuli were presented on a computer screen, approximately 1.5 m from the eyes, which was viewed through a mirror mounted on the head coil of the scanner.

Three types of feedback were given in blocks of approximately four minutes, each constituting twenty trials. In the monetary feedback block, money was earned for each correct response indicated by displaying "EUR 1.50" (ca. USD 2.25) on the screen. During the positive informative feedback block "OK" was depicted on the screen after each correct response. During these positive feedback conditions, the total amount of money earned or the total number of "OK" was given in the lower half of the screen. In these conditions, an incorrect response led to the feedback "XY" and the total score remained unchanged. During the meaningless feedback block, "XY" was depicted on the screen after both correct and incorrect responses. During this condition, the lower half of the screen always displayed "Total XY". All three feedback conditions were thus identical except for the type of feedback that was received.

Each subject performed three sessions, each session containing all three different feedback blocks (approximately 4 minutes = 1 block). These blocks were presented in a balanced randomized order. Between two sessions, two minutes of rest were given. The maximum amount of money which could be earned was EUR 90 (ca. USD 135).

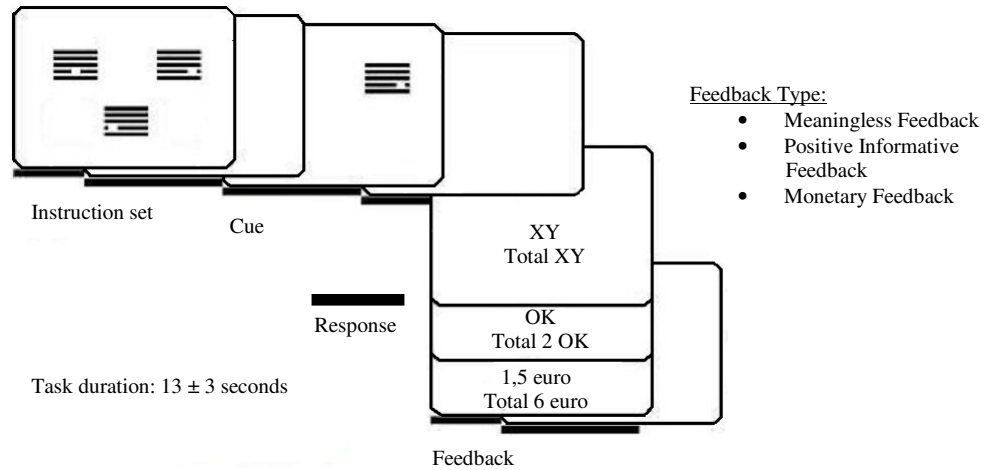


Figure 5.1: Pattern Recognition Task with Delayed Response, adapted from Kunig et al. (2000). During one second an image with three regular rectangular *instruction* patterns was presented on the screen. A blank screen was then presented for 2.5 ± 0.5 seconds. A single *cue* pattern was then presented at one of the three previous locations for two seconds. The subjects had to decide whether or not this pattern was presented at the same position as in the *instruction* presentation. If so, they were instructed to press the right button with their right middle finger; if not, they were instructed to press the left button with their right index finger. A blank screen followed this pattern during 3.5 ± 1.5 seconds. Feedback was given during one second followed by a blank screen during 3.0 ± 1.0 seconds that completed one trial. Three types of feedback were given in blocks of three minutes, each containing twenty trials. In the monetary feedback condition, money was earned for each correct response indicated by displaying "EUR 1.5" (ca. USD 2.25) on the screen. During a positive informative feedback condition "OK" was depicted on the screen after a correct response. During these two conditions, the total amount of money earned or the total number of "OK" was given in the lower half of the screen. In these conditions, an incorrect response led to the feedback "XY" and the total score remained unchanged. During the meaningless feedback condition, "XY" was depicted on the screen after both correct and incorrect responses. During this condition, the lower half of the screen always displayed "Total XY".

Data acquisition

A 3 Tesla whole body scanner (Philips type Intera, Eindhoven, Netherlands) and the 6-channel SENSE head coil were used to obtain 264, 261 and 263 scans for run 1, 2 and 3, respectively. Each scan consisted of 46 axial slices using the Echo Planar Imaging (EPI) technique. The repetition time was 3 sec. The slices were acquired interleaved in an ascending order. Voxel dimensions were 3.5 mm isotropically.

Reaction times and hit rates (i.e. the percentage of correct responses) of all participants were measured to assess performance rates during the three feedback conditions.

Data analyses

Preprocessing and analyses were applied with SPM2 (Wellcome Department of Cognitive Neurology, London, UK). Preprocessing consisted of the following steps: slice time correction (reference slice=1), realignment, normalization (using a standard EPI-template) and smoothing (three dimensional Gaussian filter, FWHM=10 mm). Also jittering was applied.

All models used the canonical hemodynamic response function. A two-level approach including random-effects was applied for statistical analysis, using box-car regression to compare the three feedback conditions. It was assumed that the monetary feedback was more salient than positive informative feedback. Therefore the following block design was used: First the monetary feedback condition was contrasted with the meaningless feedback condition for each subject. These contrast images were used as input for the second level analysis. Comparison between groups of subjects was performed with a second-level two-sample t-test. Within-group analyses were performed with a second-level one-sample t-test. This contrast (monetary feedback condition versus meaningless feedback condition) was used as input for the region of interest (ROI) analysis.

The ROI analysis (using MARSBAR; Brett et al. (2002)) was performed for two ROIs. The first ROI was defined by the voxels (located in the striatum) for which the contrast monetary feedback versus meaningless feedback showed a significantly stronger activation in healthy controls compared to PD patients ($p < 0.001$, uncorrected). The other ROI was defined by the cluster of voxels (located in the prefrontal cortex) for which the contrast monetary feedback versus meaningless feedback resulted in a significant activation within the PD group ($p < 0.001$, uncorrected). The activation of these two ROIs was further explored by evaluating the effect of positive informative feedback, in contrast to both other feedback conditions.

Although the original design of this study was focused on separating cue, retrieval and feedback processing, this appeared impossible in practice. However, all three feedback conditions were identical, except for the type of feedback received. We therefore assume that the contrasts resulted in the identification of BOLD responses that were mainly associated with feedback processing, instead of cue or retrieval processing.

STATISTICA (V5.5, Statsoft, Tulsa, OK, USA) was used to perform additional statistical analyses. Normality of data was analyzed using Q-Q plots and the Shapiro-Wilk Test. All variables were normally distributed. A repeated measures ANOVA, with a Newman-Keuls post hoc analysis, was performed to determine differences in fMRI signals during the three feedback conditions. This was performed for both ROIs, within both groups. A repeated

measures ANOVA was performed to determine differences in reaction times and hit rates between the three feedback conditions, between and within both groups. In addition, Pearson correlations were calculated within both groups between hit rates, reaction times and activation in both ROIs. For the correlations with hit rates and reaction times two new variables were calculated by subtracting the hit rates/reaction times during the meaningless feedback condition from the hit rates/reaction times during the monetary feedback condition for all participants. The variable reflected the performance during the monetary feedback condition relative to the meaningless feedback condition, just as the mPFC and putamen activation reflects activation during monetary feedback relative to the meaningless feedback condition. Within the PD patients group Pearson correlations were also calculated between UPDRS-III score, LEDD and the mPFC and left putamen activation.

5.4 Results

Functional MRI data

Voxel-based analysis

In this section differences are shown that resulted from both within and between group analyses, contrasting the monetary feedback condition to the meaningless feedback condition, which was used as input for the ROI analysis. This enabled the identification of the prefrontal and striatal foci of maximal intensity.

Within the elderly healthy controls, the monetary feedback condition versus meaningless feedback condition contrast, yielded significant bilateral high parietal and dorsal midbrain and pons activations (see figure 5.2). Since we specifically focused on the brain activation patterns in the basal ganglia and frontal regions, these results will not be discussed below.

Within the PD group, the monetary feedback condition versus the meaningless feedback condition contrast yielded significant activations of the right occipital and some parietal cortex regions as well as prefrontal areas. The latter comprised bilateral presupplementary motor area and medial prefrontal cortex, cingulate gyrus and right superior frontal gyrus (Brodmann areas: 6, 8, 24 and 32), and will further be indicated as mPFC region (see figure 5.3).

The contrast monetary feedback condition versus meaningless feedback condition in the elderly healthy control group compared to the same contrast in the PD group resulted in a strong positive effect in the left putamen (see figure 5.4). In other words, the cerebral activation induced by the monetary feedback condition was larger in the left putamen of

elderly healthy controls than in that of the PD patients. The opposite contrast did not yield significant differences.

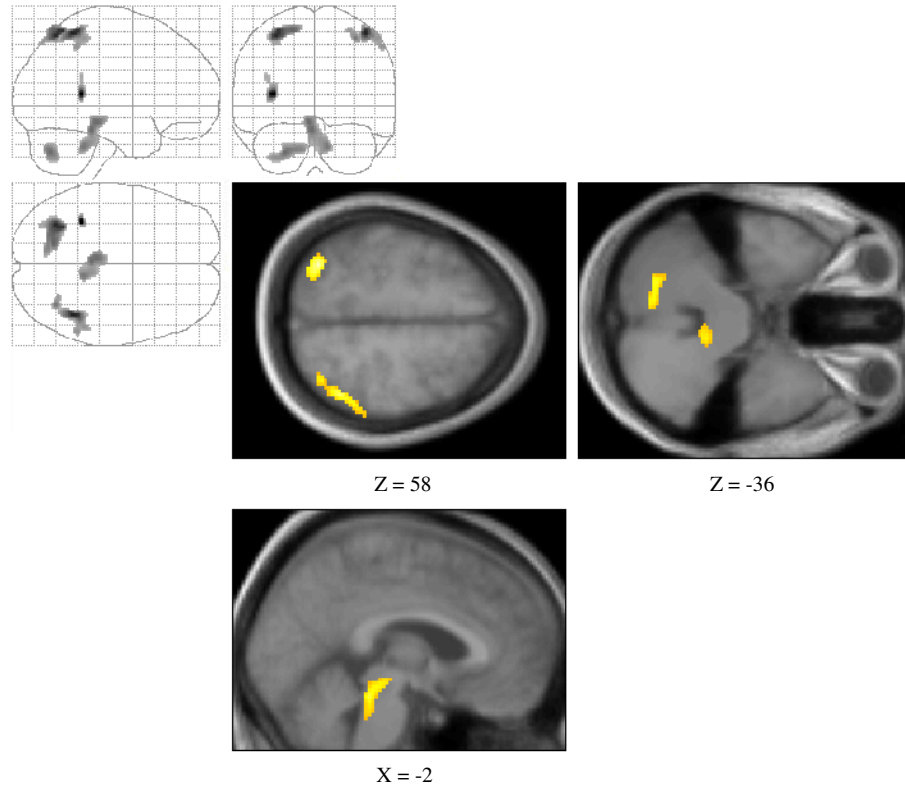


Figure 5.2: Effect of the monetary feedback condition compared to meaningless feedback condition in the pons/midbrain region (MNI coordinates: -2, -34, -20 and 10, -40, -34), left cerebellum (MNI coordinate: -16, -70, -36) and parietal cortex (MNI coordinates: left -32, -64, 58 and right 42, -50, 60) which was present in healthy controls, while no such activation pattern was found in PD patients (block design). Horizontal and sagittal slices on mean T1 image of the contrast (uncorrected, $p < .001$).

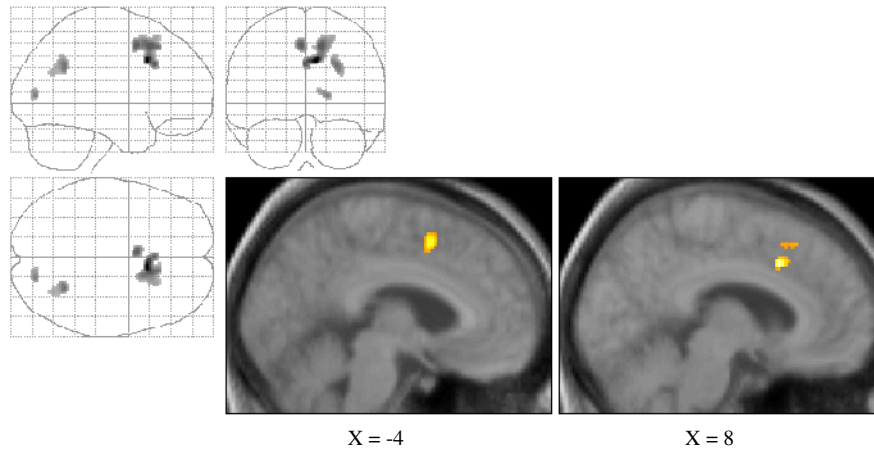


Figure 5.3: Effect of the monetary feedback condition compared to meaningless feedback condition in mPFC (MNI coordinate: 8, 16, 36), which was present in D patients while no such activation pattern was found in elderly healthy controls (block design). Sagittal slices on a mean T1-image of the contrast (uncorrected, $p < .001$).

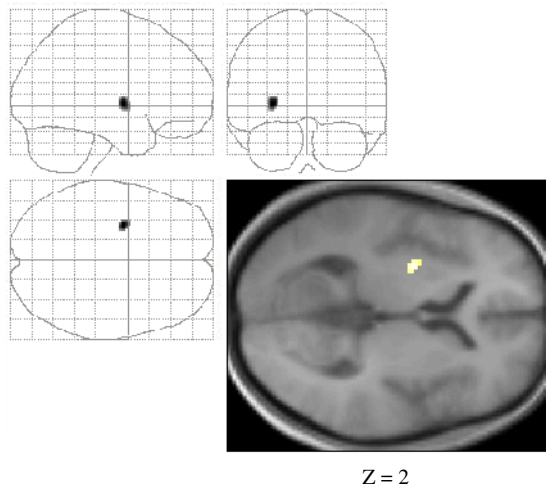


Figure 5.4: Effect of the monetary feedback condition compared to the meaningless feedback condition in the left putamen (MNI coordinate: -30, -4, 2), which was significantly larger in healthy controls than in PD patients (block design). Horizontal slice on mean T1 image of the contrast (uncorrected, $p < .001$).

ROI-based analysis

The responses in mPFC and left putamen were further explored by evaluating the effect of positive informative feedback. The fMRI signal (expressed in mean effect size) in these

regions was plotted for all three feedback conditions, for both groups (see bar graphs in figure 5.5). This revealed that the effects in the left putamen during monetary feedback condition compared to that during meaningless feedback condition showed an opposite profile in the two groups: Relative to the meaningless feedback condition, a positive effect of the monetary feedback condition was present in the left putamen of healthy controls, while this effect was negative in the PD group (see figure 5.5).

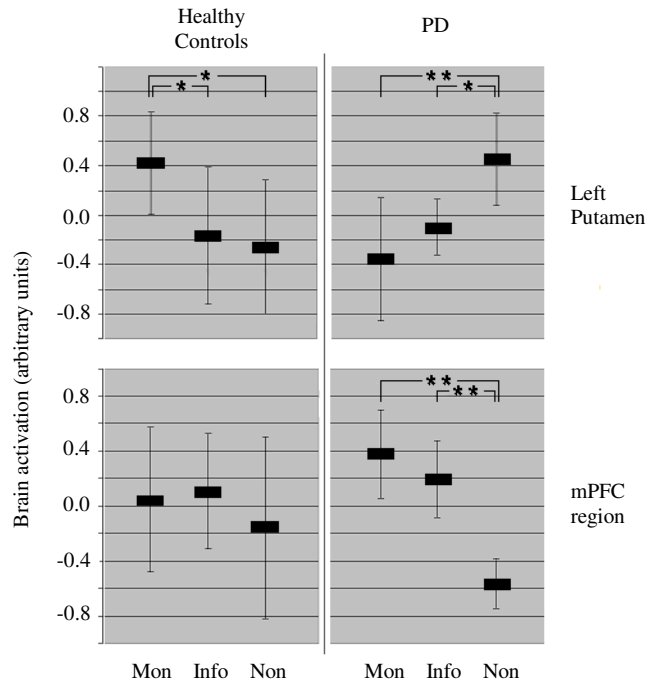


Figure 5.5: Brain activation (mean effect size) in left putamen and mPFC in healthy controls and PD patients during the three separate feedback conditions (Monetary feedback (Mon), Positive informative feedback (Info) and Meaningless feedback (Non)). Brain activation is depicted in arbitrary units and corrected to zero mean. Values of one condition (Mon, Info or Non) are relative to the other two conditions in the same population and region. Absolute effect sizes between two groups therefore cannot be directly compared. Significant differences between brain activations are indicated with a * and ** ($p < 0.05$ and $p < 0.01$ respectively, using an ANOVA repeated measures, with a Newman-Keuls post hoc analysis).

Referring to figure 5.5, the effect in the left putamen of healthy controls during the positive informative feedback condition differed significantly from that of the monetary feedback condition and was not significantly different from the effect in the left putamen during the meaningless feedback condition. In contrast, in the PD group the effect in the left putamen

during the positive informative feedback condition did not differ significantly from that during the monetary feedback condition, while it did differ significantly from the meaningless feedback condition.

The effects in the mPFC during the monetary feedback condition, positive informative feedback condition and meaningless feedback condition did not differ from each other in the healthy control group. In PD patients, however, the effect in the mPFC during the monetary feedback condition was significantly larger than during the meaningless feedback condition. Moreover, the effect of positive informative feedback condition in the mPFC region did not differ significantly of that during the monetary feedback condition, which implied that it significantly differed from the effect of the meaningless feedback condition (see figure 5.5).

Behavioral data

PD patients showed lower hit rates than healthy controls ($F=6.31$, $p=0.02$). Within both groups the hit rates did, however, not differ between the three feedback conditions ($F=1.44$, $p=0.25$; see table 5.2). Furthermore, a trend was found toward slower reaction times of PD patients compared to healthy controls ($F=3.40$, $p=0.08$; see table 5.2). Within both groups, responses were significantly faster during the monetary feedback condition than during the positive informative feedback condition ($p=0.04$) and meaningless feedback condition ($p=0.02$).

Table 5.2 Hit rates (in percentage) and reaction times (in seconds) during monetary feedback (Mon), positive informative feedback (Info) and meaningless feedback (Non) of PD patients ($n=11$) and healthy controls ($n=12$)

	PD patients			Healthy controls		
	Mon	Info	Non	Mon	Info	Non
Hit rates:						
M	82.88	79.85	78.18	90.28	91.11	90.97
SD	11.11	14.33	13.95	7.71	7.43	6.57
Reaction times:						
M	1.4	1.5	1.5	1.3	1.4	1.4
SD	0.1	0.1	0.1	0.1	0.2	0.2

In addition, significant associations were found between the LEDD score and the activation in the mPFC region and the left putamen (see table 5.3). No correlations were found between UPDRS, part III and the left putamen and mPFC region (see table 5.3). Furthermore, in both PD patients and healthy controls no associations were found between

hit rates and the activation in the mPFC and putamen. However, a trend toward a significant association was found between reaction times and mPFC activation within PD patients. No associations were found between reaction times and putamen activation within PD patients and between reaction times and mPFC and putamen activation within healthy controls (see table 5.3).

Table 5.3 Associations (one-tailed) between UPDRS, LEDD, hit rates and reaction times and the difference in fMRI signal between monetary reward and meaningless feedback of the mPFC and left putamen in PD patients (n=11) and healthy controls (HC; n=12)

	Left putamen		mPFC	
	PD r (p)	HC r (p)	PD r (p)	HC r (p)
Reaction times	-0.01 (0.48)	-0.27 (0.20)	0.47 (0.07)	0.12 (0.35)
Hit rates	-0.20 (0.28)	-0.03 (0.46)	-0.21 (0.27)	-0.12 (0.35)
UPDRS	-0.15 (0.33)	-0.36 (0.14)		
LEDD	-0.45 (0.08)	0.60 (0.03)		

5.5 Discussion

The aim of this study was to investigate the consequences of dysfunctional fronto-striatal circuits for the processing of two different types of positive feedback conditions (monetary feedback and positive informative feedback) both compared to a meaningless feedback condition. This was investigated in PD patients “on” levodopa compared to elderly healthy controls. In addition, positive informative feedback was compared to monetary feedback to determine whether positive informative feedback was just as salient as monetary feedback.

In healthy controls, relative to PD patients, the left putamen showed an increased activation during the monetary feedback condition compared to the positive informative and meaningless feedback conditions. The latter two feedback conditions did not differ. No activation was observed on the right side. Most likely the left putamen showed significant activation since participants had to push the button with the fingers of their right hand during the task, which is consistent with de la Fuente-Fernandez et al. (2000) who showed that right hand preference was associated with left putamen activation. The activation in the left putamen during the monetary feedback condition provides an argument for the striatal involvement in positive feedback processing in healthy elderly controls and is consistent with previous neuroimaging studies focused on reward processing, which can also be designated as positive feedback (Knutson et al., 2000; McClure et al., 2004; Thut et al.,

1997; Zald et al., 2004). Moreover, this documents that in elderly healthy controls monetary feedback results in more salient activation patterns than positive informative feedback and suggests that in healthy controls the left putamen was mainly activated in response to the rewarding aspects of the task.

In PD patients, relative to healthy controls, the left putamen did not show an increased activation during the monetary feedback condition compared to the meaningless feedback condition. Instead, the left putamen showed higher activation during the meaningless feedback condition, relative to both the monetary feedback and positive informative feedback conditions. The latter two did not differ. This suggests that in PD patients monetary feedback is thus not more salient than positive informative feedback. Moreover, the activation pattern of the left putamen in PD patients is opposite to the same activation pattern shown in healthy controls. This suggests that PD patients not only fail to activate their putamen during both positive feedback conditions but on the contrary show an increased activation when provided with meaningless feedback. Although this may appear contra intuitive at first sight, we propose the following explanation: During the meaningless feedback condition PD patients are not provided with any external information about their performance. They thus have to generate *internal* responses to perform the task. This is reflected by relative increased left putamen activation in PD patients. Previously the generation of internal responses was associated with increased prefrontal activation in PD patients “off” medication (Jahanshahi et al., 1995). However in our study PD patients were assessed “on” levodopa. This might facilitate the relative increased activation of the left putamen, which can be inferred from the negative correlation between the activation of the left putamen and levodopa use, i.e. PD patients who use more levodopa show an increased activation of the left putamen during meaningless feedback condition relative to the monetary feedback condition. Thus, the use of levodopa might enhance the activation of the left putamen during the meaningless feedback condition, which we suggest to reflect involvement in the generation of internal responses in PD patients. In line with these suggestions are the findings that an internally modulated response associated with reward uncertainty also induces striatal dopamine release in PD (de la Fuente-Fernandez et al., 2001; de la Fuente-Fernandez et al., 2004).

PD patients showed relatively increased activation in the mPFC during both the monetary feedback and positive informative feedback conditions, compared to the meaningless feedback condition. This activation pattern was not found in healthy controls. These results suggest that the activation pattern of the mPFC in PD patients is not specific for the monetary feedback condition but occurs during both types of positive feedback. This

indicates that these activation patterns may be the result of the positive feedback and external nature of both conditions, compared to the internal nature of the meaningless feedback condition (see above). Indeed, in PD performance improvement by specified external cueing is a well-known clinical phenomenon (Georgiou et al., 1994; Rubinstein et al., 2002). The activation pattern of the mPFC is also facilitated by levodopa use, i.e. the mPFC activation showed a positive association with levodopa use. This suggests that PD patients who use more levodopa showed an increased activation of the mPFC during positive feedback conditions. Levodopa thus also improves the generation of actions due to positive, external feedback conditions.

In addition, the relatively *decreased* activation of the left putamen during the monetary feedback condition compared to the meaningless feedback condition in PD patients and the relatively *increased* activation of the mPFC resulting from the same contrast, may suggest a compensatory mechanism, i.e. a shift from striatal to the mPFC for positive feedback processing. This is consistent with previous studies on reward processing (Kunig et al., 2000) and cognition in PD patients (Bruck et al., 2005; Monchi et al., 2006), which also suggested cortical compensatory mechanisms in PD. Functional coherence between mPFC and striatum is inferred from interconnection between the two (Alexander et al., 1986; Taylor et al., 1990), and previous studies confirm the role of the mPFC in reward processing (Kunig et al., 2000; Ridderinkhof et al., 2004). Furthermore, the activation of the left putamen and the mPFC were negatively associated (data not shown), i.e. the more mPFC activation (or compensation), the less left putamen activation (or internal processing). This suggests that the mPFC down-regulates the activity of the putamen.

The involvement of the mPFC in the compensatory mechanism is consistent with the prescribed role of the mPFC in performance monitoring, i.e. the mPFC is thought to be activated when performance adjustment is needed, e.g. when anticipated rewards need to be obtained (Ridderinkhof et al., 2004; Van der Graaf et al., 2006). The mPFC is thus in an optimal position to compensate for the striatal dysfunction in PD, when confronted with positive (both monetary and positive informative) feedback and implies that PD patients perform the feedback task more controlled instead of automatic.

Considering compensation in PD one might expect that PD patients ideally would regain the ability to perform at a behavioral level as well as healthy controls. However, although the mPFC activation was associated with reaction times within PD patients, they showed a trend toward slower reaction times than healthy controls, being the slowest during the meaningless feedback condition and made more errors during all feedback conditions, compared to healthy controls. Thus even though the compensatory mechanism appears to

support reaction times, it apparently did not enable PD patients to perform as well as healthy controls. On the other hand, one might speculate that without the compensatory mechanism, PD patients would have performed even worse.

Since mainly males were included, our results may have been influenced by gender. However, within both groups the ratio between males and females was similar. Therefore the influence of previously reported gender differences in activation of the mesocorticolimbic reward circuitry (Adinoff et al., 2003; Hoefft et al., 2008), is probably limited.

In conclusion, this study demonstrates striatal involvement in positive feedback processing and altered positive feedback processing in PD. A striatal activation specifically during the monetary feedback condition was seen in healthy controls, but not in PD. PD patients did not differentiate between both types of positive feedback. If PD patients “on” levodopa are provided with positive, external, feedback the mPFC dominates response behavior, while the striatum plays a rather irrelevant role. If however, PD patients “on” levodopa are provided with meaningless feedback, the mPFC is less stimulated and internally driven responses, mediated by the striatum, become prominent. The shift from striatal to prefrontal activation in PD patients is thus related to both types of positive feedback processing, while the generation of internal responses is less mediated by a compensatory mechanism.

