Chapter 6

Positive feedback processing associated with novelty seeking in Parkinson's disease

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Submitted

6.1 Abstract

Novelty seeking (NS) is thought to be associated with positive feedback (also designated as reward) processing. Parkinson's disease (PD) is characterized by dysfunctional fronto-striatal circuits, which might result in low NS. The aim of this study was to investigate the consequences of dysfunctional fronto-striatal circuits in PD for NS. In addition, it was investigated to what extent NS was associated with an altered positive feedback processing in PD, using a positive feedback task during fMRI.

NS was assessed in 23 PD patients and 23 age and gender-matched healthy controls. A subgroup of 11 PD patients and 12 healthy controls performed a positive feedback task during fMRI.

PD patients and healthy controls scored equal on NS. In healthy controls higher NS scores were associated with increased left putamen activity during the monetary feedback condition, relative to the meaningless feedback condition. In contrast, in PD patients higher NS scores were associated with decreased left putamen activity during monetary feedback condition relative to meaningless feedback condition. In addition, higher NS scores in PD patients were associated with increased mPFC region activation during the monetary feedback condition, relative to the meaningless feedback condition.

In conclusion, NS is associated with positive feedback processing, which in healthy controls is reflected by increased striatal activation. In PD a shift from striatal to prefrontal regions for positive feedback processing and hence NS is observed. The fronto-striatal dysfunction in PD thus does not seem to result in low NS. Instead, reduced putamen activity is compensated by increased mPFC region activity, which may partly mediate NS.

6.2 Introduction

Positive feedbacks can elicit approach behavior and have motivational value (Martin-Soelch et al., 2001). Several studies (Martin-Soelch et al., 2001; McClure et al., 2004; Zald et al., 2004) suggest that the striatum and prefrontal cortex are associated with positive feedback processing (also designated as rewards) in healthy individuals. Furthermore, Haruno & Kawato (2006) suggested that the putamen is mainly involved in evaluating actions in terms of rewards, whereas the caudate nucleus and ventral striatum are mainly engaged in the learning process, by comparing actual and predicted rewards.

Parkinson's Disease (PD) is characterized by a dysfunctional striatum, due to a degeneration of dopaminergic neurons in the substantia nigra. The striatum is extensively connected with the prefrontal cortex through the so-called fronto-striatal circuits, which are dysfunctional too in PD. This not only leads to motor symptoms but also to an altered positive feedback (or reward) processing (Kunig et al., 2000). It has been reported that PD patients show a decreased striatal activation during reward processing and instead show increased prefrontal activation (Kunig et al., 2000; Schott et al., 2007).

A decreased positive feedback processing in PD is thought to be associated with a behavioral trait called low novelty seeking (NS; Menza et al. (1993a)). NS is 'a heritable tendency toward intense exhilaration or excitement in response to novel stimuli, cues for potential rewards or potential relief of punishment, which leads to frequent exploratory activity in pursuit of potential rewards as well as active avoidance of monotony and potential punishment' (Cloninger, 1987). Individuals who score low on NS questionnaires can be characterized as 'slowly engaged in new interests, often becoming preoccupied with narrowly focused details, and requiring considerable thought before making decisions' (Cloninger, 1987). These individuals thus appear to be less sensitive to positive feedbacks. Several studies focused on NS in PD and although some reported low NS in PD (Kaasinen et al., 2001; Menza et al., 1993a; Tomer & Aharon-Peretz, 2004), others did not (Jacobs et al., 2001). Furthermore, it was hypothesized that when people approach novel stimuli they experience pleasure, which reflected by an increase in dopamine. Therefore, FDOPA Positron Emission Tomography (PET) was used to investigate the associations between NS and the striatal dopaminergic functioning. Menza et al. (1995) found a relation between NS in PD and dopamine uptake of the left caudate nucleus. However, Kaasinen et al. (2001) did not find associations between NS and striatal dopaminergic uptake.

Thus, it remains unclear if PD patients are indeed low novelty seekers. The aim of this study was to investigate the consequences of dysfunctional fronto-striatal circuits in PD for

NS. In addition, it was investigated to what extent NS was associated with an altered positive feedback processing in PD, using a positive feedback task during fMRI.

6.3 Methods

Subjects

NS was assessed in twenty-three PD patients and twenty-three age, gender and for education matched healthy controls. A subgroup of eleven PD patients and twelve age, gender and for education matched healthy controls were assessed with fMRI. All patients were diagnosed with idiopathic PD according to the criteria of the UK Parkinson's Disease Society Brain Bank. The motor severity of all PD patients was rated with the Unified Parkinson's Disease Rating Scale, part III (Fahn et al. (1987); UPDRS; M=17.0; SD=6.0). On a Dutch education scale, which ranges from 1 (elementary school not finished) to 7 (university degree), the median score of both groups was 6, which is higher than average (Table 6.1 describes demographic and illness characteristics). Exclusion criteria were other neurological disorders and other significant comorbidity. All participants signed an informed consent. The Medical Ethical Committee at the University Medical Center Groningen, the Netherlands, approved this study.

Table 6.1 Demographic and illness characteristics of all PD patients (n=23), PD patients who were assessed with fMRI (n=11), all healthy controls (n=23) and healthy controls (HC) who were assessed with fMRI (n=12)

	Patients (All)		Patients (fMRI)		HC (All)		HC (fMRI)	
	M (SD)	Range	M (SD)	Range	M (SD)	Range	M(SD)	Range
Age	61.0 (8.3)	47-78	58.7 (7.6)	47-70	62.0 (8.5)	47-82	58.8 (6.2)	47-69
Education	5.7 (0.9)	4-7	5.9 (0.8)	4-7	6.0 (1.0)	4-7	6.0 (0.9)	5-7
Disease duration	5.3 (4.5)	0.3-16	5.1 (4.2)	1-14				
UPDRS part III	17.0 (6.0)	8-33	17.3 (5.8)	8-26				

Procedure and material

NS was assessed with a shortened version of the Temperament and Character Inventory (TCI-125). The TCI-125 is a true/false questionnaire which is based on the Psychobiological Model of Temperament and Character of Cloninger et al. (1993). Seven behavioral traits are measured, including NS.

A subgroup of eleven PD patients and twelve age and gender matched healthy controls were assessed with fMRI during which they were presented with a positive feedback task that was learned before scanning. This task is a pattern recognition task with delayed response and contains three different feedback conditions: a meaningless feedback condition during which participants received "XY" on a screen for each response, a positive informative feedback condition during which participants received "OK" on a screen for each correct response and a monetary feedback condition during which participants received 1.50 Euro (ca.USD 2.25) for each correct response (Kunig et al., 2000; Thut et al., 1997). See chapter 5 for a detailed description of the task.

Data analyses

A two-level-random-effects approach and a Region of Interest (ROI) analysis was performed. 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 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). For a detailed of fMRI data acquisition and fMRI data analysis see chapter 5.

Further statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS 14.0). Normality of data was analyzed with Q-Q plots and the Shapiro-Wilk test. All variables were normally distributed.

An independent samples t-test (one-tailed) was used to compare PD patients and healthy controls on the mean NS scores. In addition, Pearson correlations were calculated to determine the associations between the activation in the left putamen, mPFC region (which resulted from the contrasts described above) and NS within both groups.

6.4 Results

Functional MRI data

Within the PD group, the monetary feedback condition versus the meaningless feedback condition contrast yielded significant activations in the prefrontal cortex. This area comprised bilateral presupplementary motor area, the medial prefrontal cortex, anterior cingulate gyrus and right superior frontal gyrus (Brodmann areas: 6, 8, 24 and 32). This area 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.

Further analyses were also focused on the effect of positive informative feedback compared to both other feedback conditions. The results of this analyses are beyond the scope of this chapter and are described in chapter 5.

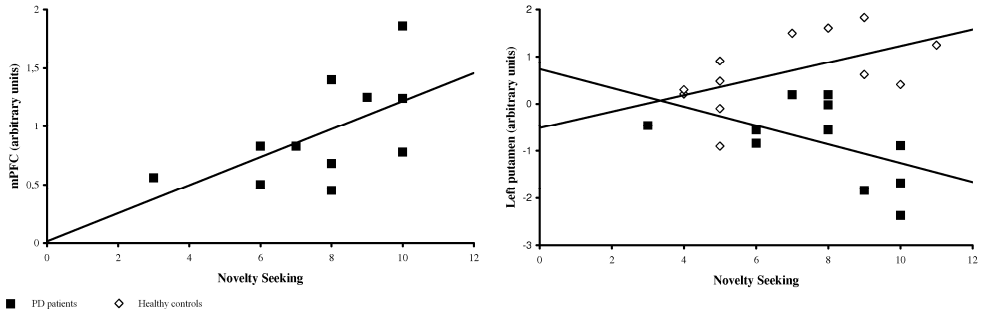
PD patients (M=6.9; SD=2.5) and healthy controls (M=7.7; SD=2.9) scored equally on NS (t=-1.09; p=0.14).

Associations between NS and the activation of the left putamen and mPFC region were determined in the PD group as well as in the healthy control group. In the PD group a negative trend was found between NS and the activation of the left putamen, while in the control group a positive association was found between NS and the activation of the left putamen. These correlations differed significantly according to Fisher's z (z=-2.42, p=.01). Furthermore, NS was in the PD group significantly related to the activation of the mPFC region. In the healthy control group, no association was found between NS and the activation of the mPFC region. (See table 6.2 for correlations in both groups and figures 6.1 and 6.2 for scatters of significant associations and trends). In addition, a partial correlation between the activation of the left putamen and NS, controlled for the effect size of the mPFC region, was calculated in the PD group (r=-.28, p=.22; one-tailed).

Table 6.2 Associations between novelty seeking and the effect sizes of the left putamen and medial prefrontal cortex in PD group (n=11) and control group (n=12; one-tailed)

	PD patients		Healthy controls	
	r	p	r	p
Left putamen	-0.51	0.06	0.55	0.03
mPFC	0.59	0.03	0.23	0.21

Figure 6.1 Scatterplots of associations between novelty seeking and the activation of mPFC region in PD group (n=11) and the activation of the left putamen in Control group (n=12) and PD group (n=11).



6.5 Discussion

The aim of this study was to investigate the consequences of dysfunctional fronto-striatal circuits in PD for NS. In addition, it was investigated to what extent NS was associated with an altered positive feedback processing in PD, using a positive feedback task during fMRI.

The fMRI analyses showed that healthy controls showed increased activation in the left putamen during the monetary feedback condition compared to both the meaningless feedback condition, without an effect in the mPFC. In contrast, PD patients showed increased activation in the left putamen during the meaningless feedback condition compared to the monetary feedback condition. In addition, PD patients showed increased activation of the mPFC during both positive feedback conditions. The direct implications are discussed of these fMRI results are discussed in chapter 5. The remaining part of this discussion is focused on NS and the associations between NS and these activation patterns.

PD patients and healthy controls obtained equal scores on NS. Jacobs et al. (2001) previously reported this, however low NS in PD was also found (Kaasinen et al., 2001; Menza et al., 1993a; Tomer & Aharon-Peretz, 2004).

Interestingly, contrasting associations between NS and the activation of the left putamen were found in both groups. In the healthy control group a positive association was found between NS and the activation of the left putamen, indicating that healthy controls who score higher on NS show an increased activation in the left putamen during monetary feedback condition, relative to the meaningless feedback condition. Kaasinen et al. (2001) and Menza et al. (1995) previously investigated the association between NS and the striatal dopaminergic functioning. Since the putamen is mainly innervated by dopamine our finding is inconsistent with the former, while it is consistent with the latter. Furthermore, it confirms the hypothesis of Menza et al. (1993a) that NS is associated with positive feedback processing.

In contrast to the relation in the healthy control group, a negative association between NS and the activation of the left putamen was found in the PD group. This indicates that PD patients who score higher on NS show a decreased activation during the monetary feedback condition relative to the meaningless feedback condition (and consequently and increased activation in the left putamen during the meaningless feedback condition, relative to the monetary feedback condition). This relation seems contradictory with the expectation that high NS is associated with an increased striatal activation in response to positive feedback. However, a positive association was found between NS and the activation of the mPFC region. This means that PD patients who score higher on NS show a relatively increased activation in the mPFC region during the monetary feedback condition, relative to the meaningless feedback condition.

Thus, in our group of PD patients higher scores on NS were associated with a relatively decreased activation in the left putamen and a relatively increased activation in the mPFC region during the monetary feedback condition, relative to the meaningless feedback condition. These findings suggest a compensatory mechanism, i.e. a shift from striatal to prefrontal regions for positive feedback processing and hence NS. This was previously suggested by studies focused on positive feedback (in those studies designated as rewards) processing (Kunig et al., 2000; Schott et al., 2007) and cognition in PD (Bruck et al., 2005; Monchi et al., 2006; Schott et al., 2007). Moreover it is consistent with the prescribed role of the mPFC region which is thought to be involved in performance monitoring and is activated when performance adjustment is needed, for example when anticipated rewards need to be obtained (Ridderinkhof et al., 2004). This indicates that PD patients are able to respond to novel stimuli due to the mPFC region, which signals that a positive needs to be

obtained. In addition, the found association between the activation of the left putamen and NS does no longer exist when controlled for the reward related activation of the mPFC region. Thus, NS appears to be mediated by the mPFC in contrast to healthy controls in whom NS is mediated by the left putamen.

In conclusion, our findings suggest that NS is associated with striatal positive feedback processing in healthy controls. The dysfunction of the fronto-striatal circuits in PD does, however, not result in low NS in PD patients. Instead, NS is (partly) mediated by the mPFC region in PD, which provides a compensatory mechanism for positive feedback processing in PD. This suggests that the fronto-striatal dysfunction in PD does not necessarily has to lead to behavioral changes, at least in the early stages of the disease when cortical pathology is supposed not to be that severe yet. Interesting future research should be focused on the development and maintenance of compensatory mechanisms in PD.