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### Parkinson's disease

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**Chapter 2**

**Striatal activity (FDOPA-PET) associated with cognitive items of  
depression rating scale (MADRS) in Parkinson's disease**

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## 2.1 Abstract

Motor symptoms form the hallmark of Parkinson's disease (PD), although other features like depression are often present. Currently used depression rating scales measure affective and somatic symptoms. These somatic symptoms of depression can also be core PD symptoms, suggesting an overlap of symptoms between depression and PD. Using in vivo radiotracer methods striatal dopaminergic dysfunction is found in both PD and depression.

This study investigates to what extent the overlapping symptoms of depression and PD are associated with the striatal dopaminergic dysfunction typical for PD.

Symptoms of depression were assessed in 23 PD patients who did not have major depression according to the Montgomery-Åsberg Depression Rating Scale (MADRS; cut-off <18) and according to a trained psychologist who interviewed all patients. The striatal dopaminergic activity of patients was assessed with FDOPA-PET.

Dopaminergic activity of the putamen and caudate nucleus was associated with MADRS total score and specifically with the symptom "Concentration difficulties".

These results suggest that the typical striatal dopaminergic dysfunction of PD can cause symptoms that can also be categorized as symptoms of depression. Especially cognitive symptoms measured by a depression rating scale may be based on the dopaminergic dysfunction of the striatum in PD patients.

## 2.2 Introduction

Depression has a prevalence of approximately 40% in Parkinson's disease (PD; Cummings & Masterman, 1999) and is perhaps the most common co-morbid disorder. Depression rating scales, such as the Montgomery-Åsberg Depression Rating Scale (Montgomery & Åsberg, 1979; MADRS), are often used in research and clinical practice. These scales contain items measuring affective symptoms (e.g. reported sadness) as well as items measuring somatic symptoms of depression (e.g. reduced sleep). These somatic symptoms can also be core PD symptoms, suggesting an overlap of symptoms between depression and PD. Examples of these overlapping symptoms are cognitive dysfunction, psychomotor retardation, flat affect, masked face, anergia, anxiety and sleep disorders.

At a neurochemical level we also find overlap: dopaminergic dysfunction is found in both depression and PD. In PD the degree of striatal dopaminergic deficiency significantly contributes to the severity of motor symptoms and cognitive impairment (Van Beilen et al., 2008). Furthermore, Weintraub et al. (2005b) found that depression in PD was associated with decreased dopamine transporter availability in the left putamen measured by a radiolabeled tropane that selectively binds to dopamine transporter sites using Single Photon Emission Computed Tomography. Also, Remy et al. (2005) showed a relative reduction of [<sup>11</sup>C]RTI-32, an in vivo marker of both dopamine and noradrenaline transporter sites measured with Positron Emission Tomography (PET), in the left ventral striatum of depressed PD patients. In contrast, Broussolle et al. (1999) used PET to measure dopa-decarboxylase activity (FDOPA) and did not find associations between mood and striatal FDOPA uptake in PD.

The dopaminergic system is also involved in the pathophysiology of non-PD depression. FDOPA-PET was used to show decreased presynaptic dopamine function in the left caudate nucleus of depressed patients with affective flattening and psychomotor retardation (Martinot et al., 2001). Also, decreased dopamine transporter binding potential, was found in both the bilateral caudate nucleus and putamen of depressed patients, by means of [<sup>11</sup>C]RTI-32 PET (Meyer et al., 2001).

The neurochemical overlap of PD and depression might partially explain the symptom overlap. The aim of this study was therefore to investigate whether overlapping symptoms of depression and PD are associated with the striatal dopaminergic dysfunction typical for PD. The striatal dopaminergic activity was measured by FDOPA-PET and the symptoms of depression were assessed with the MADRS.

PD patients included in this study were non-depressed according to the MADRS (cut-off <18) and according to a trained psychologist who interviewed all patients and who was

blind to neuroimaging data and motor scores of patients. Depressed PD patients were excluded. In that population it was not possible to answer our research question, whether overlapping symptoms of depression and PD are associated with the striatal dopaminergic dysfunction *typical for PD*, because due to the neurochemical overlap of depression and PD the striatal dopaminergic dysfunction in depressed PD patients could not be completely ascribed to PD.

While previous neuroimaging studies on depression in PD involved mild and moderately advanced or heterogeneous (mild, moderate and severely advanced) samples of patients, our study included only moderately to severely advanced PD patients.

## 2.3 Methods

### *Subjects*

23 idiopathic PD patients, in accordance with the criteria of the UK Parkinson's Disease Society Brain Bank, participated in this study. The Unified Parkinson's Disease Rating Scale (UPDRS; Fahn et al., 1987) was used to assess the motor severity of patients (M=46.7; SD=12.0). The patient group consisted of 12 men (52%) and 11 women (48%; Table 2.1 describes demographic and illness characteristics of patients). Exclusion criteria were dementia (Mattis Dementia Rating Scale, score > 130), depression (MADRS total <18 and according to the opinion of the trained psychologist) and other neurological disorders. The Medical Ethical Committee of the University Medical Center Groningen (UMCG) approved the study. All participants gave their informed consent according to the declaration of Helsinki.

Table 2.1 Demographic and illness characteristics of PD patients (n=23)

	Mean (SD)	Range
Age	60.1 (8.1)	47-71
Education (7 levels)	4.0 (1.4)	1-6
Disease duration (years)	11.6 (4.9)	3-20
UPDRS part III	46.7 (12.0)	26-74
FDOPA uptake putamen*	0.68 (0.17)	0.35-0.98
FDOPA uptake caudate*	0.86 (0.25)	0.46-1.41

\* Uptake ratio: unitless (see Methods)

### ***PET data acquisition and analysis***

All PET measurements were performed at the UMCG PET Center on a Siemens ECAT Exact HR<sup>+</sup> (n=12) or ECAT 951 (n=11) scanner. Subjects were positioned supine in a resting state with their eyes closed and ears unplugged. After pretreatment with 2 mg/kg carbidopa to block peripheral dopa-decarboxylase activity,  $180 \pm 33$  MBq of FDOPA was intravenously injected over 1 minute with an infusion pump. All subjects were measured following a static or dynamic protocol with identical time range for data analysis. The static protocol consisted of 1 single scan from 90-120 minutes post-injection, while the dynamic protocol consisted of 21 time frames with increasing duration over 120 minutes: subsequently the last 2 frames (2 x 900 sec.) were averaged to create an equivalent volume to the static scan.

Statistical Parametric Mapping 99 (SPM99) was used with linear spatial normalization (affine only; Friston, 1995) to align the measured volume data to a regional Cerebral Blood Flow (rCBF) template fixed in Talairach coordinate space (Talairach & Tournoux, 1988). The sum of the early frames (1-10) was used for normalization of FDOPA parameters to the SPM CBF template. Region of interest (ROI) analysis was based on a standardized template fixed in Talairach coordinate space. This template, consisting of 6 ROIs (putamen, caudate and occipital lobe on both sides), was used to sample the volume data and compute mean ROI activity concentration.

Specific FDOPA uptake was expressed as a striato-occipital ratio (SOR) index (Dhawan et al., 2002; unitless) following the equation:  $SOR\ index = (C_{ROI} - C_{REF}) / C_{REF}$  ( $C_{ROI}$  = average (left and right) ROI activity,  $C_{REF}$  = average occipital activity in the occipital reference region).

### ***Statistical analyses***

Since patients were scanned on two different scanners, t-tests for all variables were performed to exclude differences between types of scanner used. No significant differences were found.

Normality of data was analyzed. All data were normally distributed except some of the MADRS items. The mean score of PD patients on the MADRS total was determined.

Since direction of the correlations was predictable based on previous literature (Remy et al., 2005; Weintraub et al., 2005b), one-tailed correlations were calculated. Pearson correlations were calculated between the MADRS total and the mean FDOPA uptake values of the combined left and right putamen and combined left and right caudate nucleus. Because motor symptoms and the dopaminergic activity of the putamen are associated in

general it was possible that a relation between MADRS total and the dopaminergic activity of the putamen was determined by the association between motor severity of PD patients and the putaminal dopaminergic activity. Therefore a partial correlation between depression MADRS total and the dopaminergic activity of the putamen, controlled for the motor severity (UPDRS) was calculated.

Additionally, Spearman correlations were determined between all individual MADRS items and FDOPA uptake values of the putamen and caudate nucleus. Bonferroni corrections (Holm, 1979) were used to correct for 20 (2 FDOPA uptake values x 10 MADRS items) comparisons.

## 2.4 Results

The mean score of patients on the MADRS total was 9.4 (SD=3.5; range 3-15). Striatal FDOPA uptake values of the studied PD group were comparable to those found in a previous study (Hilker et al., 2005).

MADRS total was related to the mean dopaminergic activity of the putamen ( $r=-.44$ ;  $p=.02$ ) and caudate nucleus ( $r=-.50$ ;  $p=.01$ ). The association between MADRS total and the putamen remained significant when controlling for the influence of motor severity of PD patients ( $r=-.44$ ,  $p=.02$ ).

**Table 2.2** One-tailed Spearman correlations between the items of the MADRS and FDOPA uptake of the bilateral caudate nucleus and putamen (n=23)

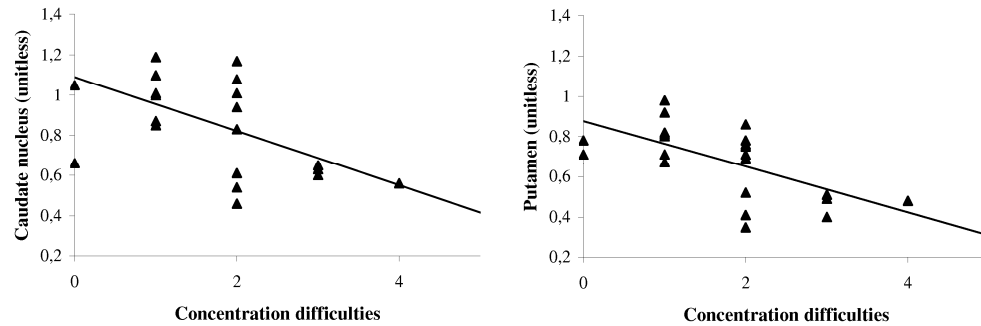
	Caudate Nucleus		Putamen	
	r	p	r	p
1 – Observed Sadness	-0.32	0.06	-0.29	0.09
2 – Reported Sadness	0.01	0.48	-0.02	0.46
3 – Inner Tension	-0.12	0.30	0.00	0.50
4 – Reduced Sleep	0.05	0.40	0.17	0.21
5 – Reduced appetite	0.09	0.35	0.09	0.35
6 – Concentration difficulties	-0.58*	0.00	-0.62*	0.00
7 – Lassitude	-0.41	0.03	-0.21	0.17
8 – Inability to feel	-0.47	0.01	-0.27	0.10
9 – Pessimistic thoughts	-0.04	0.41	0.04	0.42
10 – Suicidal thoughts	-0.15	0.25	-0.17	0.22

\* Correlation is significant after Bonferroni correction

The dopaminergic activity of the putamen and caudate nucleus were, after Bonferroni correction, associated with the MADRS item Concentration difficulties (table 2.2 and figure 2.1). All other MADRS items were not related to the dopaminergic activity of the putamen and caudate nucleus (table 2.2), however without the Bonferroni correction the dopaminergic activity of the caudate nucleus was associated with Lassitude and Inability to feel.

All scatter plots of the associations between the dopaminergic activity of the putamen and caudate nucleus and MADRS items were checked. None of these scatter plots showed associations that were determined by outliers.

Figure 2.1 Scatterplots of associations between Concentration difficulties and the FDOPA uptake of the bilateral caudate nucleus and putamen (n=23)



## 2.5 Discussion

PD patients who participated in this study had a moderately to severely advanced disease status and were not depressed according to the MADRS and according to the opinion of a trained psychologist who interviewed all patients and who was blind to neuroimaging data and motor scores of PD patients. It was investigated to what extent the overlapping symptoms of depression and PD were associated with the striatal dopaminergic dysfunction, typical for PD, measured by FDOPA-PET.

Interesting negative associations were found between the MADRS total and the dopaminergic activity of the bilateral caudate nucleus and putamen. The association between the MADRS total and the dopaminergic activity of the putamen remained significant when controlling for the influence of motor symptoms which could have mediated this association.



These findings are consistent with previous findings of Mayberg et al. (1990) who used fluorodeoxyglucose PET and associated depression in PD with bilateral caudate nucleus. Weintraub et al. (2005b) also showed associations between depression in PD and the left anterior putamen using Single Photon Emission Computed Tomography and a radiolabeled tropane that selectively binds to the dopamine transporter site. By means of [<sup>11</sup>C]RTI-32 PET Remy et al. (2005) showed that depression in PD was associated with the left ventral striatum, however these results can be ascribed to the dopaminergic as well as to the noradrenergic neurotransmitter system. Also, investigations that were focused on the dopaminergic neurotransmitter system in depressed patients without PD are consistent with the results found in this study and reported a decreased dopaminergic functioning of the bilateral caudate nucleus and putamen (Meyer et al., 2001) and left caudate nucleus (Martinot et al., 2001).

Our results thus suggest that the striatal dopaminergic dysfunction, typical for PD, can cause symptoms which can also be categorized as symptoms of depression. Clinically this implicates that when assessing depression in PD one should be aware of a confounding influence of PD symptoms.

The MADRS item Concentration difficulties was in particular associated with the dopaminergic activity of the bilateral caudate nucleus and putamen. Concentration is an aspect of cognition and according to the MADRS Concentration difficulties represents a difficulty in collecting one's thoughts mounting to incapacitating lack of concentration (Montgomery & Asberg, 1979). The association between Concentration difficulties and the caudate nucleus is in accordance with the model of parallel fronto-striato-thalamic loops (Alexander et al., 1986). According to this model the disruption of the dorsolateral prefrontal loop at the level of the caudate nucleus might cause cognitive deficits in PD. This is confirmed by several studies in which associations between the caudate nucleus and cognition were found (Bruck et al., 2001; Dubois & Pillon, 1997; Muller et al., 2000; Van Beilen et al., 2008).

The original model of fronto-striato-thalamic loops suggested that the putamen is involved in the motor loop (Alexander et al., 1986; see figure 1.1). This is however not in accordance with the relation between the putamen and Concentration difficulties which was found in this study. But, associations between the putamen and cognition in PD have recently been reported by several authors (Lozza et al., 2004; Muller et al., 2000; Van Beilen et al., 2008). A possible explanation for the association between cognition and the putamen is offered by Monchi et al. (2006) who found that the putamen was specifically active during the execution of non-routine actions. Non-routine actions are actions that require attention and

concentration and can not be performed automatically. The study of Monchi et al. (2006) therefore also offers an explanation for the association between Concentration difficulties and the dopaminergic functioning of the putamen which was found in this study.

Taking into account that the PD patients who participated in this study were not depressed, these results suggest that Concentration difficulties in PD may be based on the typical dopaminergic dysfunction of the striatum in PD. Therefore Concentration difficulties does not seem to belong to the core symptoms of depression in PD. This is confirmed by Ehrt et al. (2006) who reported that depressed PD patients had more concentration difficulties than depressed patients without PD.

Also, in previous research it was found that depression can worsen cognitive performance of PD patients (Troster et al., 1995; Uekermann et al., 2003). However, based on the results of our study it can be suggested that since depression rating scales contain cognitive items, cognitive performance can also worsen depression rating scale scores. Thus, when assessing depression in PD one should be aware of a confounding influence of the cognitive symptoms of PD.

All other MADRS items were not associated with the dopaminergic activity of the striatum. However, without the Bonferroni correction, the MADRS items Lassitude and Inability to feel were related to the dopaminergic functioning of the bilateral caudate nucleus.

According to the MADRS (Montgomery & Asberg, 1979), Lassitude represents a difficulty getting started or slowness initiating and performing everyday activities. Since a difficulty getting started or slowness initiating activities are typical motor and cognitive symptoms of PD it is not surprising that Lassitude was related to the striatal dopaminergic functioning. This is confirmed by a previous study of our research group in which an association was found between Lassitude and the motor symptoms of PD (Koerts et al., 2008).

The item Inability to feel was also related to the striatal dopaminergic functioning without the Bonferroni correction. This item represents the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. Inability to feel is often called anhedonia which has been associated with the dopaminergic reward processing of the striatum in major depression (Tremblay et al., 2005). Also, in PD a decreased dopaminergic reward processing has been reported (Kunig et al., 2000).

Thus, besides cognitive symptoms also the symptoms Lassitude and Inability to feel may be based on the dopaminergic dysfunction of the striatum in PD.

Two previous studies are not in accordance with the associations found in this study. Weintraub et al. (2005b) did not find associations between depression in PD and the caudate nucleus and right putamen and Broussolle et al. (1999) used FDOPA-PET and also did not find associations between depression in PD and the dopaminergic activity of the striatum. Two possible explanations can be given for the discrepancy between Weintraub et al. (2005b), Broussolle et al. (1999) and the results found in this study. A first possible explanation could be that while moderately to severely advanced patients were included in this study, Broussolle et al. (1999) and Weintraub et al. (2005b) included more heterogeneous samples of PD patients. Due to the fact that the symptoms and signs of moderately to severely advanced PD patients are more severe it is possible that there are more overlapping symptoms in that category than in mildly advanced PD patients. Moreover in mildly advanced PD patients the dopaminergic dysfunction of especially the caudate nucleus is less pronounced. A second explanation for the discrepancy between our study and Weintraub et al. (2005b) and Broussolle et al. (1999) might be that Weintraub et al. (2005b) and Broussolle et al. (1999) did not necessarily exclude PD patients with major depression whereas this study did.

Summarizing, our results suggest that the typical striatal dopaminergic dysfunction of PD can cause symptoms that can also be categorized as symptoms of depression. Especially, cognitive symptoms measured by a depression rating scale may be based on the dopaminergic dysfunction of the striatum in PD patients. Also, the motor and reward related aspects of depression might be based on the dopaminergic dysfunction in PD. Clinically these results implicate that when assessing depression in PD one should be aware of a confounding influence of the symptoms of PD.