Chapter 8

Cognition and depression in Parkinson's disease

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To be submitted

8.1 Abstract

This study investigates the influence of depression on cognition in PD. Non-motor symptoms, such as cognitive deficits and depression, are often present in PD. In patients with major depression without PD cognitive deficits have also been observed. Depression in PD might therefore exacerbate cognitive deficits.

Forty-seven PD patients participated in this study. Ten were depressed, thirty-seven were not depressed. All patients were assessed with an extensive neuropsychological battery, including tests for memory and executive functions and a questionnaire assessing dysexecutive problems in daily life.

Depressed PD patients did not show a significantly decreased performance on all neuropsychological tests, compared to non-depressed PD patients. However, depressed PD patients reported significantly more dysexecutive problems in daily life.

8.2 Introduction

Parkinson's disease (PD) is a neurodegenerative movement disorder that is characterized by motor symptoms, such as tremor, rigidity, bradykinesia and akinesia. However, non-motor symptoms are often present. Two frequently observed non-motor symptoms in PD are cognitive impairments and depression. Cognitive impairments have been described in the early stages of the disease and in PD patients without dementia (Dubois & Pillon, 1997; Muslimovic et al., 2005). Impairments in executive functions and memory are the cognitive impairments that are most often present (Muslimovic et al., 2005; Verleden et al., 2007). Depression has a prevalence of approximately 40% in PD and is thought to be the result of a combination of a psychological reaction to having PD and the neurochemical changes inherent to the disease.

In patients with major unipolar depression without PD impairments in executive functions and memory have also been reported (Baudic et al., 2004). Depression can therefore be a factor that exacerbates cognitive impairments in PD. Several studies were focused on the influence of depression on cognition in PD (Boller et al., 1998; Costa et al., 2006; Cubo et al., 2000; Kuzis et al., 1997; Norman et al., 2002; Silberman et al., 2007; Starkstein et al., 1990a; Troster et al., 1995; Uekermann et al., 2003). However, only a few of these studies used an extensive neuropsychological battery and much controversy remains. One study reported that depressed PD patients showed more impairments in memory and language compared to non-depressed PD patients (Troster et al., 1995), while another reported that depressed PD patients showed impairments in concept formation and set-switching relative to non-depressed PD patients (Kuzis et al., 1997). Also, it has been suggested that mild depressive symptoms exacerbate cognitive impairments in PD (Uekermann et al., 2003), while others reported that minor depression does not significantly affect cognitive functions in PD (Costa et al., 2006).

The aim of this study was therefore to investigate the influence of depression on cognition in PD focusing specifically on the impairments in executive functions and memory, which are most often present. Standard neuropsychological tests were used in addition to a rating scale focused on assessing dysexecutive problems in daily life. Comparisons will be made between depressed and non-depressed PD patients. In addition, performance of non-depressed and depressed PD patients on all neuropsychological tests will be compared to published normative data to obtain an assessment that is clinically more meaningful.

8.3 Methods

Patients

47 PD patients participated in this study. All were diagnosed with idiopathic PD according to the criteria of the Parkinson's Disease Society Brain Bank. The presence of depression was determined using the Montgomery-Åsberg Depression Rating Scale (MADRS; cut-off 14/15 (Leentjens et al., 2000)). Ten (21%) PD patients were depressed. The demographic and clinical characteristics of non-depressed and depressed PD patients are described in table 8.1. The level of education was rated using a Dutch education scale ranging from 1 (elementary school not finished) until 7 (university degree). An estimated premorbid-IQ score was determined for all patients using the Dutch version of the National Adult Reading Test (Nelson, 1991). The activities of daily living and motor severity of all patients were assessed using respectively the Unified Parkinson's Disease Rating Scale part II and III (Fahn et al., 1987). A Levodopa Equivalent Daily Dose (LEDD) score was calculated for each patient 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). The groups of non-depressed and depressed PD patients did not differ in age (t=0.11; p=0.91), gender (Chi-square=1.21; p=0.27), level of education (t=0.13; p=0.90), estimated IQ (t=-0.51; p=0.62), LEDD score (t=-0.89; p=0.38), UPDRS activities of daily living score (t=-0.56; p=0.58) and UPDRS motor score (t=0.27; p=0.79).

Exclusion criteria were dementia (Mini Mental Examination Score < 24) and other significant co morbidity. This study was approved by the Medical Ethical Committee of the University Medical Center Groningen, the Netherlands. All patients signed an informed consent prior to study inclusion.

Stimulus material and procedure

All patients were assessed in regular on state and were presented with neuropsychological tests for the following cognitive functions:

Verbal memory: A Dutch modification of the Rey Auditory Verbal Learning Test, the 15-Words Test (Saan & Deelman, 1986), was used to assess verbal memory. Fifteen words were presented 5 times. After each time patients were required to name the words they remembered. A Learning score was calculated representing the total number of words patients remembered over these 5 trials. After 20 minutes patients were unexpectedly asked

which words they still remembered, which resulted in a Recall score. Subsequently, the 15 words of the test, mixed with 15 new words, were read out loud to patients who had to determine which words they heard before. This resulted in a Recognition score defined as the number of words that were correctly recognized.

Table 8.1 Demographic and illness characteristics of non-depressed PD patients (n=37) and depressed PD patients (n=10)

	Non-depressed		Depressed	
	M (SD)	range	M (SD)	range
Age	63.4 (8.4)	47-77	63.1 (9.2)	50-77
Gender				
- Male	22 (60%)		4 (40%)	
- Female	15 (41%)		6 (60%)	
Education	5.4 (1.1)	3-7	5.3 (1,1)	4-7
IQ estimation	104.4 (14.0)	72-130	106.9 (13.7)	89-130
MMSE	27.4 (1.4)	24-29	27.5 (1.6)	25-29
MADRS	6.1 (4.0)	0-14	21.4 (3.5)	15-26
LEDD	529.7 (416.6)	0-1512.5	670.7 (549.4)	0-1725
Disease duration	6.7 (4.6)	0-17	4.4 (2.9)	0-10
UPDRS – II	9.3 (4.4)	2-19	10.3 (4.4)	4-18
UPDRS – III	25.0 (8.6)	11-53	24.2 (6.2)	15-38

Executive functions:

- Inhibition: The Stroop Color Word Test (Stroop, 1935) was used to assess inhibition. The target measure was the Color-Word subtask. This task requires patients to suppress the automatic tendency to read, while naming the color of words that are themselves color names. The performance was corrected for psychomotor speed.
- Cognitive flexibility: Cognitive flexibility was assessed with the Trailmaking Test (Reitan, 1958), Odd Man Out (Flowers & Robertson, 1985) and Alternating Fluency. The Trailmaking Test consists of two parts. Part A requires patients to draw a line, as fast as possible, between numbers (1-25) in ascending order. In part B numbers and letters are used and patients need two switch attention between both concepts: they have to draw a line between both types of stimuli in ascending order, alternating between numbers and letters and also as fast as possible. The target measure was the performance on part B corrected for psychomotor speed, the so-called B/A index.

The Odd Man Out requires patients to indicate which shape, of a set of four shapes, is different. Three selection rules are possible. Two sets of twelve cards are used. For each set patients have to specify a different rule. Subsequently, both sets of cards are alternated four times and the total number of incorrect responses are rated.

During the Alternating Fluency task patients are asked to produce as many words in two minutes, alternating between the categories articles of clothing and town names. The target measure was the total number of generated words minus errors (naming the same word twice).

- Planning: The Zoo-map of the Behavioral Assessment of the Dysexecutive Syndrome (Wilson et al., 1996) was used to assess planning. Patients need to plan a route through a zoo visiting previously specified attractions and following a set of rules. The test consists of two parts. The first part is presented as an unstructured situation, patients are not provided with information that could help them plan a route and only the attractions that need to be visited and the rules are presented. In contrast, part two is structured. An action plan which needs to be followed is provided in addition to the same set of rules as in part one. Both parts are rated by calculating the total number of correctly visited attractions minus errors (e.g. visiting attractions that were not previously specified, not obeying the rules).
- Working memory: The digit span of the Wechsler Adult Intelligence Scale (Stinissen et al., 1970) was used to assess working memory. Patients had to repeat a string of digits of increasing length. The test contains a forward and a backward condition. The total number of strings that was repeated correctly was rated.
- Fluency:
    - Semantic fluency: Patients were required to name Animals and Professions, as many as possible in one minute, without naming the same animal or profession twice. The total number of correctly named Animals and Professions was rated.
    - Letter fluency: Patients were required to name as many words as possible in one minute beginning with the letters D, A and T (equivalent to F, A, and S in English; Schmand et al. (2008)). The naming of the same word twice and of names (of persons and towns) was not allowed. The total number of correctly named words beginning with a D, A or T was rated, which were combined into one Letter fluency score.

- Questionnaire for the dysexecutive syndrome (DEX): the DEX questionnaire is specifically focused on assessing dysexecutive problems in daily life. It contains 20 questions such as "I find it difficult to focus my attention and am easily distracted" and "I act without thinking and do the first thing that comes to mind" which can be scored on a 5-point scale ranging from 0 (never) to 4 (very often). Two versions of the DEX are available, a self-rating and a rating by an independent observer who has insight in the daily life of the patient (spouse, child or close friend). The total score on the DEX, which can be calculated for the self-rating and the independent rating, is the sum of all the items. The items of the DEX can be clustered into the following factors (Burgess et al., 1998):
    - Inhibition: this factor includes those items that are related to the ability to suppress a habitual response, including impulsivity and disinhibition.
    - Intentionality: this factor includes those items that are related to planning and maintenance of goal-directed behavior.
    - Executive memory: this factor includes those items that are related to confabulation and the inability to recall the correct order of events.
    - Positive affect: this factor includes those items that are related to variable motivation, aggression and euphoria.
    - Negative affect: this factor includes those items that are related to shallow affect and apathy.

Statistical analyses

The statistical analyses consisted of two parts. The first part of the analyses comprised a comparison of non-depressed PD patients and depressed PD patients. Normality of data was analyzed using the Shapiro-Wilk test and QQ-plots. Not all variables were normally distributed in both groups. Therefore, non-parametric tests were used to verify the results of the parametric tests. The results of the non-parametric tests supported our parametric findings, therefore only the results of the parametric tests are described.

Independent samples t-tests were used to compare non-depressed PD patients and depressed PD patients on the performance on the tests for verbal memory and executive functions and DEX questionnaire. In addition, both groups were compared on the subscales of the DEX, using t-tests. A related samples t-test was used to compare the self-rating of patients on the DEX to the rating of an independent observer, in both the non-depressed and depressed group.

The second set of analyses was equivalent to the procedures used in clinical practice. Using normative samples of healthy subjects, which have been determined for several neuropsychological tests (15 Words Test (Schmand, 2005), Stroop (Schmand et al., 2003), Trailmaking test (Schmand et al., 2003), Odd Mann Out (Pomati et al., 1996), Digit span (Stinissen et al., 1970), Semantic Fluency (Van der Elst et al., 2006) and Phonemic fluency (Schmand et al., 2008)), standard, percentile, scores were derived for each patient. All normative data sets included a correction for age (except for Letter fluency which is not influenced by age (Schmand et al., 2008)) and when relevant a correction for gender and level of education. Cognitive impairment on tests was defined as a performance equivalent to the performance of the worst 10% of the normative sample, i.e. 90% of healthy subjects (of the same age and when relevant of the same gender and level of education) performed better on the cognitive test. When standard scores could not be derived, cognitive impairment on a test was defined as performing 1.5 standard deviations below the mean score (equivalent to the 8^{th} percentile or lower) of a population healthy elderly subjects (Zoo map (Wilson et al., 1996), DEX questionnaire (Burgess et al., 1998)).

In addition, for each patient the total number of tests and questionnaires on which they showed an impairment was rated. The percentage of non-depressed and depressed patients that showed an impairment on 0, 1, 2 or 3 or more tests was calculated. Cognitive impairments were thought to be present when performance on at least 3 tests and questionnaires was impaired (Muslimovic et al., 2005).

8.4 Results

The first set of analyses showed that depressed PD patients did not differ from non-depressed PD patients on verbal memory and on all tests for executive functions (see table 8.2). However, depressed PD patients did rate the dysexecutive problems they experience in daily life as significantly worse than non-depressed PD patients. Also, the independent observers rated the dysexecutive problems experienced in daily life of depressed PD patients as significantly worse than those of non-depressed PD patients (see table 8.2). Within both the depressed and non-depressed groups of PD patients, the self-rating on the DEX did not differ from the rating of the independent observer (depressed PD patients: $t=0.67$, $p=0.51$; non-depressed PD patients: $t=1.48$, $p=0.19$). Therefore the self-rating and independent-observer rating of the DEX were combined for further calculations. Depressed PD patients scored significantly higher on all the subscales of the DEX than non-depressed PD patients (see table 8.3).

Table 8.2 Comparison of non-depressed PD patients (n=37) and depressed PD patients (n=10) on verbal memory and executive functioning (one-tailed)

	Non-depressed		Depressed			
	M (SD)	range	M (SD)	range	t	p
Verbal memory:						
- Learning	32.53 (9.77)	17-59	31.60 (5.56)	23-41	0.29	0.39
- Recall	5.46 (2.72)	0-11	5.60 (3.06)	0-10	-0.14	0.44
- Recognition	25.94 (3.69)	14-30	24.78 (4.63)	16-30	0.91	0.18
Executive functions:						
Inhibition	1.71 (0.35)	1.00-2.53	1.80 (0.49)	1.33-2.88	-0.70	0.24
Cognitive flexibility						
- Trailmaking B/A	2.31 (0.66)	1.34-4.78	2.66 (1.11)	1.68-5.37	-1.25	0.11
- OMO	4.54 (4.90)	0-19	3.20 (2.86)	0-8	0.82	0.21
- Alternating fluency	26.03 (6.47)	10-39	24.80 (5.59)	18-29	0.54	0.30
Planning						
- Profile score	2.31 (1.13)	0-4	2.30 (1.06)	1-4	0.04	0.49
- Unstructured	2.25 (4.13)	-7-8	2.40 (3.72)	-3-8	-0.10	0.46
- Structured	7.66 (1.06)	3-8	7.90 (0.32)	7-8	-0.71	0.24
Working memory	12.51 (4.19)	5-24	13.10 (3.96)	7-18	-0.39	0.35
Fluency						
- Animals	21.66 (5.38)	8-33	21.56 (5.43)	14-31	0.05	0.48
- Professions	14.86 (4.02)	8-22	16.78 (2.77)	12-21	-1.35	0.09
- Letter	37.42(14.68)	11-71	44.89 (14.44)	26-68	-1.36	0.09
DEX						
- Self rating	15.72 (8.78)	1-37	33.71 (12.67)	19-54	-4.46	0.00
- Independent rater	14.45(11.82)	0-46	28.00 (9.26)	17-43	-2.82	0.00

Table 8.3 Comparison of non-depressed (n=37) and depressed (n=10) PD patients on DEX subscales (one-tailed)

	Non-depressed	Depressed		
	M (SD)	M (SD)	t	p
Inhibition	0.80 (0.53)	1.41 (0.61)	-2.72	0.01
Intentionality	0.84 (0.56)	1.94 (0.56)	-4.86	0.00
Executive memory	0.43 (0.38)	0.95 (0.47)	-3.11	0.00
Positive affect	0.64 (0.54)	1.42 (0.82)	-3.15	0.01
Negative affect	0.97 (0.57)	2.14 (0.83)	-4.46	0.00

The second set of analyses used a more clinical approach and determined the clinical significance of the cognitive impairments in depressed and non-depressed PD patients by comparing their performance to published normative samples. In both depressed and non-depressed PD patients the highest frequency of impairment was observed in the verbal memory domain, mainly on the learning score of the 15-Words test (see table 8.4). In the

domain of executive functions the highest frequency of impairment was observed in the depressed PD patients group on the self-rating (30%) of the DEX. In the depressed PD group this was followed by independent rating of the DEX and Trailmaking B/A (both 20%), Fluency animals (11%) and Inhibition (10%). On the OMO, Zoo map, Digit span and Fluency professions and Letter fluency none of the depressed PD patients obtained a score that was clinically significant. Within the non-depressed PD patients group the highest frequency of cognitive impairment was found on Fluency professions (20%). This was followed by Letter fluency (18%), Fluency animals (9%), independent rating on the DEX (8%), Trailmaking B/A and Inhibition (both 6%), Zoo map (5%), self rating on the DEX and Digit span (both 3%). On the OMO none of the non-depressed PD patients obtained a score that was clinically significant (see table 8.4). Considering the number of tests on which an impairment was found, 20% of depressed PD patients showed impairments on three or more tests or questionnaires compared to 14% of non-depressed PD patients (see table 8.5). Thus in general, depressed PD patients showed a slightly higher frequency of cognitive impairment than non-depressed PD patients. This was reflected by higher frequencies of cognitive impairment on several tests and questionnaires of verbal memory and executive functions in depressed PD patients.

Table 8.4 Percentage of impaired non-depressed PD patients (n=37) and depressed PD patients (n=10) on verbal memory and executive functioning

	Non-depressed % impaired patients	Depressed % impaired patients
Verbal memory:		
• Learning	33	60
• Recall	20	20
Executive functions:		
Inhibition	6	10
Cognitive flexibility		
• Trailmaking B/A	6	20
• OMO	0	0
Planning		
• Profile score	5	0
Working memory	3	0
Fluency		
• Animals	9	11
• Professions	20	0
• Letter	18	0
Dysexecutive questionnaire		
• Self rating	3	30
• Independent observer	8	20

Table 8.5 Percentage of depressed and non-depressed PD patients showing impairments on a number of tests or questionnaires

Number of impaired tests	Non-depressed, %	Depressed, %
0	31	30
1	36	30
2	19	20
≥ 3	14	20

8.5 Discussion

The aim of this study was to investigate the influence of depression on cognition in PD. Comparisons were made between depressed and non-depressed PD patients. In addition, performance of non-depressed and depressed PD patients was compared to published normative data to obtain an assessment that was equivalent to procedures used in clinical practice.

The frequency of cognitive impairment was slightly higher in depressed than in non-depressed PD patients: depressed PD patients showed a higher frequency of impairment on 3 or more tests and they showed the highest frequency of impairments on several of the separate tests. Depressed PD patients specifically showed higher frequencies of impairment on verbal memory, cognitive flexibility and inhibition. Previously, impairments in verbal memory (Costa et al., 2006; Troster et al., 1995) and cognitive flexibility (Costa et al., 2006; Kuzis et al., 1997) were reported in PD with depression. Furthermore, these results are consistent with studies using cognitive rating scales, such as the Mini Mental State Examination and Mattis Dementia Rating Scale, showing decreased performance of depressed PD patients compared to non-depressed PD patients (Cubo et al., 2000; Norman et al., 2002; Starkstein et al., 1990a).

Depressed PD patients did however not show higher frequencies of impairment on all cognitive functions. In fact, on planning and working memory non-depressed PD patients showed a higher frequency of impairment, compared to depressed PD patients. Furthermore, although depressed PD patients showed a slightly higher frequency of impairment on the animal fluency task, none of the depressed PD patients showed an impairment on the profession fluency task and letter fluency task, while respectively 20% and 18% of the non-depressed PD patients were impaired on these tasks. The decreased performance of non-depressed PD patients on these cognitive functions compared to depressed PD patients is not consistent with previous literature, showing fluency and

working memory impairments in PD patients with depression (Kuzis et al., 1997; Uekermann et al., 2003). The relatively small group of depressed PD patients currently included in this study and the fact that probably no PD patients with major depression were included most likely influenced the results (Costa et al., 2006).

The slightly higher frequency of impairment of depressed PD patients was not reflected by a significantly decreased performance of depressed PD patients, compared to non-depressed PD patients, on the neuropsychological tests that were used. The relatively low number of depressed PD patients and the probability that no PD patients with major depression were currently included in this study, probably influenced these findings as well. However, depressed PD patients did report significantly more dysexecutive problems in daily life than non-depressed PD patients. This same pattern was also indicated by independent raters. Furthermore, the self-rating of dysexecutive problems in daily life did not differ from the independent rating, suggesting that the higher scores of depressed PD patients on this questionnaire are not related to a lack of insight in the disease, which may accompany the dysexecutive syndrome (Burgess et al., 1998). Also, activities in daily life related to motor symptoms of PD (UPDRS-II), could not have influenced these results, since depressed and non-depressed PD patients did not differ in their level of activities in daily life. These findings thus suggest that depressed PD patients *experience* dysexecutive problems to a more severe extent than non-depressed PD patients. This is in line with reports of associations between a decreased quality of life and an increased severity of depression (Schrag et al., 2000). Moreover, this same pattern of an increased experience of cognitive problems with no decreased performance on neuropsychological tests was previously observed in elderly patients with major depression without PD, compared to elderly healthy controls (Fischer et al., 2008).

Depressed PD patients specifically experienced Inhibition, Intentionality, Executive Memory, Positive Affect and Negative Affect problems in daily life to a more severe extent than non-depressed PD patients. It can be suggested that the Positive and Negative Affect complaints (variable motivation, aggression, euphoria, shallow affect and apathy) can be attributed to the depression. However, apathy and variable motivation have also been observed in PD patients without depression (Kirsch-Darrow et al., 2006). Furthermore, the largest differences between depressed and non-depressed PD patients on the DEX were observed for the Negative affect and Intentionality (assesses planning and maintenance of goal-directed behavior in daily life) subscales. In both of these subscales apathy plays a large role, especially when apathy is considered to be a concept that includes emotional/affective aspects (i.e. an inability to associate affective and emotional signals

with ongoing and forthcoming behaviors) and cognitive aspects (reductions in self-generated voluntary and purposeful behavior caused by impairments in cognitive functions needed to elaborate the plan of actions; Levy & Dubois (2006). Based on these finding it can be suggested that the problems of the dysexecutive syndrome experienced by depressed PD patients in daily life are to a large extent represented by apathy, both the emotional/affective and cognitive type.

An interesting observation that is worth discussing was that depressed PD patients had a shorter disease duration and used more antiparkinsonian medication than non-depressed PD patients (even though this difference was not significant), while depressed and non-depressed PD patients were similar in the severity of motor symptoms and the level of activities in daily life (see table 8.1). This could suggest that depressed PD patients show a faster disease progression and use earlier and more antiparkinsonian medication. Previously it was suggested that depression can be a prognostic factor for the disability of PD patients, even though this evidence was limited (Post et al., 2007). Future research should therefore be focused on the progression of the disease of depressed PD patients compared to non-depressed PD patients.

In our experience depressed PD patients lack the interest and energy and are difficult to motivate to volunteer for research projects. This difficulty most likely caused that only a relatively small group of depressed PD patients and no PD patients with major depression were included in this study.

At this point it can be concluded that even though depressed PD patients did not show a significantly decreased performance on the neuropsychological tests compared to non-depressed PD patients, and only showed a slightly higher frequency of impairment, they reported more dysexecutive problems in daily life. Depression thus appears to influence cognition in PD negatively, mainly in the experience of depressed PD patients.

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