Original Research Article

Influence of Mild Cognitive Impairment, Depression, and Anxiety on the Quality of Life of Patients with Parkinson Disease

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Abstract

Background: Neuropsychiatric symptoms (NPS) and mild cognitive impairment (MCI) are common in Parkinson disease (PD) and have a negative impact on the patient's quality of life (QoL). We aim to describe the effect of NPS and MCI on each other and on QoL. ***Methods:*** Sixteen MCI and 37 non-MCI PD patients completed different self-assessment questionnaires including the Parkinson's Disease Questionnaire (PDQ-39), the Beck Depression Inventory (BD), the Beck Anxiety Inventory (BAI), and the Self-Report Manic Inventory (SRMI). Linear regression with stepwise elimination was used to select the significant predictors of QoL and to control for confounding factors. ***Results:*** The significant linear regression model (R^2 = 0.68, $p \leq 0.01$) revealed significant effects of MCI ($p = 0.03$), BDI ($p \leq 0.01$), BAI ($p \leq 0.01$), age ($p = 0.03$), a trend of SRMI ($p = 0.06$), and disease duration ($p = 0.08$) on QoL. ***Conclusions:*** MCI, anxiety, depression, and age decrease QoL in patients with PD. NPS has the main influence in the prediction of QoL in patients with PD, whereas MCI is only of minor importance.

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Introduction

Parkinson disease (PD) is well known for its motor symptoms such as rigor, tremor, postural instability, and bradykinesia. However, there are also non-motor symptoms (NMS), which have a strong impact on quality of life (QoL), such as constipation, olfactory disturbances, and obsessional behavior [1–8]. The economic burden for society is comparable to that of strokes or heart failures [9, 10].

Furthermore, 10–50% of patients with PD are affected by depression and anxiety [11]. Depression and anxiety are described as neuropsychiatric symptoms (NPS) and, as such, from

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a subgroup of NMS [1]. Some NPS such as mania, obsessional behavior, and hallucinations are related to dopaminergic treatment [1, 12].

The core symptoms of mania are a decreased need for sleep, attention deficits, an increased urge of compulsive speech hyperactivity, and inappropriate behavior in any further situation [13].

Obsessive-compulsive disorder (OCD) is characterized by obsessive thoughts and compulsive acts. Such obsessive thoughts for instance refer to be consumed by an idea, an impulse, or an imagination without the ability to resist these [13].

Turning to depression, which is marked by a loss of interests, joylessness, low spirit, increased fatigability, and a reduced urge, cross-sectional studies show that around 40% of patients with PD suffer from depression [14–18]. Further, by affecting cognitive abilities and basic life skills of PD patients, depression may not only concern PD patients alone but also their relatives regarding the reduction of their QoL [13, 19–21].

Anxiety disorders including general anxiety disorders and panic attacks, which in other words may be defined as an inexplicable anxiety response to any situation or place [13], may affect up to 40% of PD patients [22, 23]. Notably, anxiety disorders and depression can predate the motor symptoms of PD [24, 25].

Mild cognitive impairment (MCI) is a common symptom even in newly diagnosed drug-naive PD patients [26–30] and is also associated with reduced QoL [31]. Therefore, the present study is focusing on specific changes of QoL in PD patients suffering from MCI. Former studies analyzed this relation but did not focus on the group of MCI patients, NPS, and their reduction in QoL. Whilst the connection between NPS and MCI remains debatable [32, 33], the effect of NMS in association with MCI on QoL in PD remains unexplored to this date. Further, in contrast to the study by Monastero et al. [32], which may seem similar to this study here, we examined depression, anxiety, and QoL separately and in more detail. Additionally, we did not split the MCI patients into different subgroups. Moreover, we examined the relative importance of the predictors to achieve a better understanding of the effects of MCI and NPS and their influence on QoL. Our hypothesis was that reduced cognition in PD patients may influence NPS and QoL.

For our study we used self-assessment questionnaires and cognitive tests to gather information about NPS, QoL, and cognition. Our aim was to examine the main effects of depression, anxiety, OCD, mania, MCI, and other confounding factors and their importance for QoL of PD patients.

Methods

Sample

We included 53 patients with PD fulfilling the criteria of the British Brain Bank [34]. The patients were participants of a cognitive training study of the University Hospital Basel (Department of Clinical Neurophysiology) [35]. Patients were recruited between May 2011 and March 2013 either via published advertisement or via the Movement Disorders Clinic of the University Hospital of Basel. Patients were excluded if (a) they had insufficient knowledge of the German language, (b) they had a Mini-Mental State Examination (MMSE) score ≤24, (c) they had an alcohol or drug dependency, (d) more than 2 questionnaires were not sufficiently fulfilled or missed, or (e) they suffered from other severe neurological conditions. We also excluded patients if they had more than 3 incomplete test criteria within the tests for the MCI classification.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the local ethics committee (Ethikkommission beider Basel, ref. No.: 135/11). All participants were fully informed of the nature of the study and gave their written informed consent.

Psychiatric and Psychological Assessment

Depression

We used the German version of the Beck Depression Inventory II (BDI) [36] to detect symptoms of depression. This self-assessment questionnaire consists of 21 questions with 4 possible answers ranging from 0 (e.g., "I don't have any thoughts of killing myself") to 3 (e.g., "I would kill myself if I had the chance") regarding the Likert scale. Total scores could range between 0 and 63. Please note that a higher point value may be an indication for more severe depression, respectively.

Anxiety

Symptoms of anxiety were measured with the German version of the self-assessment scale Beck Anxiety Inventory (BAI) [37]. This questionnaire consists of 21 questions, which are evaluated on a four-point Likert scale ranging from 0 (not at all) to 3 (severely – "it bothered me a lot"). The total score may range between 0 and 63. Please note that higher values indicate more severe anxiety, respectively.

Compulsion

We used the German version of the Obsessive-Compulsive Inventory-Revised (OCI-R) [38] to detect OCD. The scale consists of 18 items, which are valued on a five-point Likert scale, ranging from zero (not at all) to four (extremely). The total score may range between 0 and 72, increasing values refer to more severe anxiety.

Mania

To measure the symptoms of mania, we administered the German version of the Self-Report Manic Inventory (SRMI) consisting of 48 items. Each item is a statement such as (e.g., "I run into debt") and the patient replies whether it applies or not. The total score ranges from 0 to 48, whilst higher values indicate a more severe obsession, respectively [39, 40].

Quality of Life

We used the German version of the Parkinson's Disease Questionnaire (PDQ-39) [41, 42] to assess the patients' QoL. This self-assessment questionnaire consists of 39 items, which are evaluated on a five-point Likert scale, ranging from 0 (never) to 4 (always). Eight dimensions are used to describe the QoL.

For our analyses we used the PDQ-39 Summary Index (PDQ-39SI) [41, 43], where the 8 dimensions are summarized as 1 score. This score is between 0 and 100, giving an overview of the QoL in PD, whereas a higher score refers to a poorer QoL.

Criteria for MCI

MCI classification was made according to the level II criteria of the movement society task force [44].

Confounding Factors

Confounding factors include gender, levodopa dose per day (LEDD according to Tomlinson et al. [45]), age, disease duration, motor impairment, level of education in years, and the

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Table 1. Demographics of cognitively normal PD and PD-MCI patients

	PD (n = 37)	PD-MCI (n = 16)	Significance (Mann-Whitney)
Age, years	66±8.4	68±7.2	ns
Female	15 (40.54)	4 (25.00)	ns
Male	22 (59.46)	12 (75.00)	ns
Education, years	15±2.8	15±3.3	ns
MMSE, points	29±0.9	28±1.6	ns
Disease duration, years	8±4.9	8±5.4	ns
UPDRS III, points	16±11.4	14±11.1	ns
LEDD, mg/day	721±541	827±531.3	ns

Values are shown as n (%) or mean ± standard deviation. ns, not significant.

cognitive status. The severity of motor impairment was measured using the Unified Parkinson Disease Rating Scale (UPDRS III) [46] by trained neurologists. Cognitive status was compiled by using the MMSE [47].

Statistical Analyses

For statistical analysis we used RStudio Version 0.98.1103 for Macintosh [48]. A level of $p < 0.05$ was regarded as statistically significant.

We calculated Spearman's rank correlation to analyze the intercorrelation between all evaluated NPS, separately for patients with and without MCI. A Mann-Whitney U test was administered to examine differences between subgroups of the PDQ-39, PDQ-39-SI, the self-assessment questionnaires as well as the confounding factors in patients with and without MCI. To account for multiple testing, we used the Bonferroni correction. A linear regression model with Akaike Information Criterion (AIC) with backwards elimination [49] was applied to select the relevant predictors of QoL. The analyses were performed using age, gender, BDI, BAI, OCI-R, SRMI, disease duration, education, UPDRS III, LEDD, and cognitive status (MCI and non-MCI) as potential predictors for the QoL score. Stepwise backwards elimination was used to consecutively eliminate nonpredictive variables. The relative importance of the predictors was calculated with the package relaimpo [50] in R.

Results

Sample

According to our self-assessment questionnaires, in our sample, 32% of patients suffered from mild depression, 36% from mild anxiety, 13% from moderate anxiety, 4% from severe anxiety, 17% from OCD, and 6% from mania. Key numbers from the sample population are listed in Table 1, whilst Table 2 depicts a detailed register of the results and the cutoffs from the psychiatric and psychological assessments.

Correlations between the NPS and QoL

For patients with and without MCI each self-assessment questionnaire showed a significant correlation with QoL (Table 3). There were significant correlations between the different psychological self-assessment questionnaires.

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Table 2. Performance of cognitively normal PD and PD-MCI patients across tests

	PD (n =37)	PD-MCI (n = 16)	Significance (Mann-Whitney)
BDI II	7±4.1	7±3.9	ns
Minimal depression (0–9)	23 (62)	12 (75)	ns
Mild depression (10–18)	13 (35)	4 (25)	ns
Moderate depression (19–29)	0	0	–
Severe depression (30–63)	0	0	–
NA	1 (3)	0	–
BAI	10±8	8±6.3	ns
Minimal level of anxiety (0–7)	17 (46)	7 (44)	ns
Mild anxiety (8–15)	11 (30)	8 (50)	ns
Moderate anxiety (16–25)	7 (19)	0	–
Severe anxiety (26–63)	1 (3)	1 (6)	ns
NA	1 (3)	0	–
OCI-R	10±6.6	7±7.4	
Non-compulsivity (<18)	30 (81)	14 (87.5)	ns
Compulsivity (≥18)	7 (19)	2 (12.5)	ns
NA	0	0	–
SRMI	4±3.9	4±6.1	ns
Non-mania (<14)	34 (92)	15 (94)	ns
Mania (≥14)	2 (5)	1 (6)	ns
NA	1 (3)	0	–
PDQ-39SI	19±9.5	24±12.3	ns
Mobility	19±17.3	28±19.7	ns
Activities of daily living	22±18.7	26±16.6	ns
Emotional well–being	21±17.6	20 ±11.3	ns
Stigma	10±10.3	21±16.6	ns
Social support	5±9.3	9±14.6	ns
Cognitions	27±14.6	32±16.4	ns
Communication	17±18.5	24±23.3	ns
Bodily discomfort	38±18.5	31±19.2	ns
NA	1 (3)	0	–

Values are shown as mean ± standard deviation or n (%). ns, not significant; NA, no answer.

Table 3. Correlation between the self-assessment questionnaires stratified by cognitive status

Assessment	Cognitive status	BDI	BAI	OCI-R	SRMI
PDQ-39SI	MCI	0.53	0.72*	0.78*	0.56
	Non-MCI	0.61*	0.66*	0.53*	0.6*
SRMI	MCI	0.1	0.29	0.59	
	Non-MCI	0.43	0.59*	0.6*	
OCI-R	MCI	0.19	0.32		
	Non-MCI	0.22	0.51*		
BAI	MCI	0.6			
	Non-MCI	0.55*			

* $p \leq 0.01$.

Table 4. Correlations between the confounding factors and the psychological assessments, stratified by patients with and those without MCI

Assessment	Cognitive status	Gender (male)	Age	Education	Disease duration	UPDRS III	MMSE	LEDD
BDI	MCI	−0.25	0.16	−0.06	−0.30	−0.21	0.09	−0.17
	Non-MCI	−0.33	−0.02	0.05	0.25	0.29	−0.07	0.03
BAI	MCI	−0.09	0	0.03	0.12	0.33	0.19	0.10
	Non-MCI	−0.34	−0.12	−0.16	0.31	0.28	0.09	−0.01
OCI-R	MCI	0.14	0.38	−0.07	0.25	0.26	−0.20	−0.14
	Non-MCI	0.04	0.06	−0.03	−0.14	0.03	−0.20	0.11
SRMI	MCI	0.00	0	0.08	0.39	0.16	−0.11	0.48
	Non-MCI	−0.06	−0.24	−0.01	−0.04	−0.01	0.03	0.28
PDQ-39SI	MCI	−0.03	0.16	0.04	0.17	0.25	0.17	0.09
	Non-MCI	−0.23	−0.08	−0.09	0.40	−0.01	−0.20	0.33

Table 5. Multivariate regression analysis of the influence on quality of life

Influence factors	Estimate	Standard error	t value	p value
MCI (vs. non-MCI)	4.50	1.93	2.33	0.03*
BDI	0.87	0.25	3.46	≤0.01**
BAI	0.54	0.17	3.14	≤0.01**
SRMI	0.52	0.27	1.91	0.06
Age	0.28	0.12	2.24	0.03*
Disease duration	0.38	0.21	1.79	0.08
UPDRS III	−0.12	0.08	−1.44	0.16
LEDD	0.00	0.00	1.51	0.14

$R^2 = 0.68$. * $p \leq 0.5$; ** $p \leq 0.01$.

Confounding Factors and Their Correlations with NPS

Table 4 shows the correlations of the self-assessment questionnaires with the confounding factors. There are 2 significant positive correlations in the non-MCI cohort: between PDQ-39SI and disease duration and between BAI and gender. After correction for multiple testing, there were no significant correlations between the questionnaires and the confounding factors.

Difference in the Subscales of the PDQ-39 and the Summary Index Regarding the Cognitive Status

Figure 1 shows the differences between the patients with and without MCI in the PDQ-39-SI and the subscales. As the *p* values illustrate, there are no significant differences between patients with and those without MCI. Before correction for multiple testing, there was 1 significant correlation between stigma and cognitive status.

Regression Analysis

Table 5 shows the regression analysis with the influences on QoL. The significant model (adjusted $R^2 = 0.68$, $p \leq 0.01$) revealed significant influences of MCI ($p = 0.03$), BDI ($p \leq 0.01$), BAI ($p \leq 0.01$), age ($p = 0.03$), a trend of SRMI ($p = 0.06$), and disease duration ($p = 0.08$).
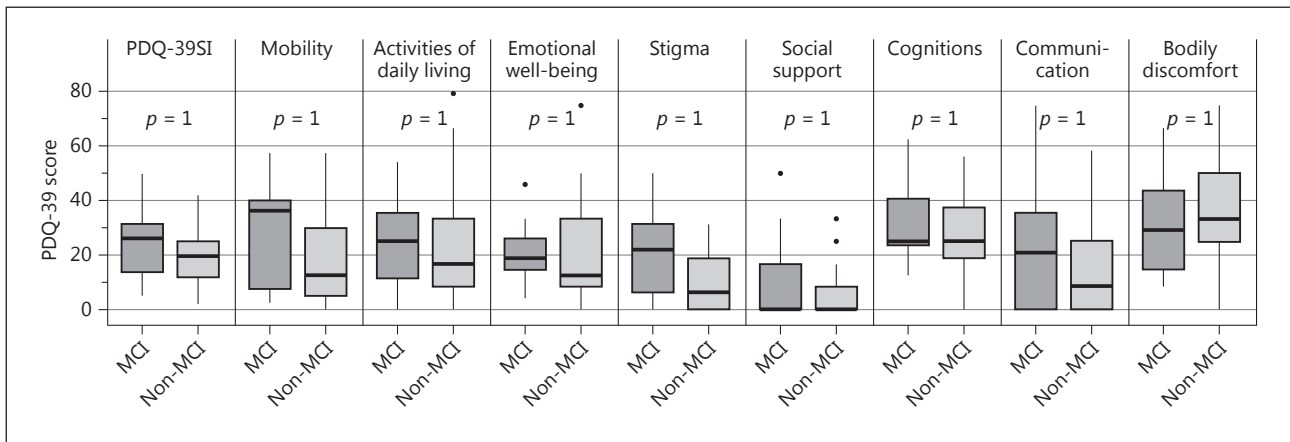
Fig. 1. Eight dimensions and summary index (SI) of the PDQ-39 with mean and SD.
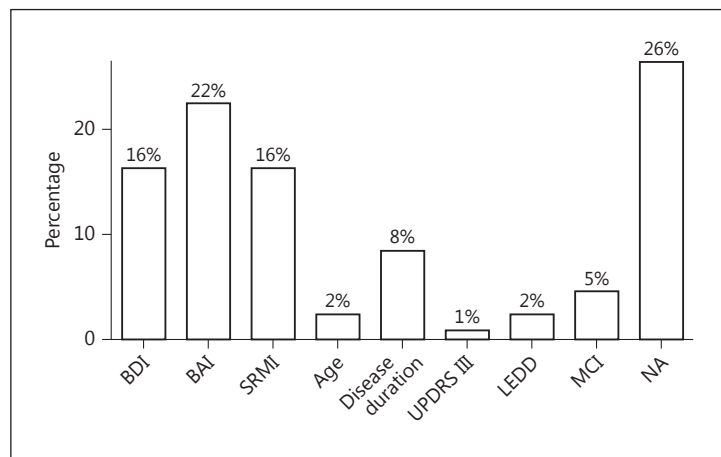

Fig. 2. Explained variance of quality of life.

Furthermore, UPDRS III and LEDD were not significant in the prediction of QoL but remained in the model according to AIC. The variables education, OCI-R, and gender dropped out from the linear regression model. Figure 2 displays the relative importance of the predictors: it shows that QoL in PD was mostly explained by NPS measurements, whereas sample- and disease-related factors were less important.

Discussion

In our study we showed that QoL in PD is influenced by anxiety, depression, MCI, and age. Our results confirm that NPS in association with MCI decrease QoL. QoL is mainly decreased by NPS, whereas the cognitive status is of minor importance. Mania and disease duration may further reduce QoL. Multiple studies show a relation between cognitive functions and QoL [51–54]. Depression and anxiety have been reported to be strong factors in terms of a decrease in QoL [55–62]. Thus, our results are in line with these findings, except for the influence of anxiety and depression on QoL. One study showed the reverse, in that depression may be the

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predominant factor for a low QoL compared to anxiety [57]. More interestingly, in our study, a significant effect of age on QoL has been found. Although other studies reported age to be no cause of a decrease in QoL [63–65], these studies have eliminated the factor age in their analysis due to having it as an exclusion criterion for their sample [66]. Thus, the true effect of age may have been overlooked in the first place. In contrast, our study contains a wide range of ages (i.e., ranging from 46 up to 84 years), which – in turn – may provide enough variance to calculate its true significance in the computed linear regression model. However, according to the relative importance in Figure 2, age does not seem to have a strong influence on QoL.

In this study, the disease duration was not significantly associated with a lower QoL. Yet, previously, disease duration has been understood as a predictor for a poorer QoL [63, 64, 67]; whereas in other studies disease duration was not significantly involved in their statistical analysis [65, 68]. In our study we had a higher disease duration within the sample compared to other studies [63, 64, 67] and lower than in the studies, which could not affirm a significant involvement of disease duration on the QoL [65, 68]. Possibly, disease duration loses its role as a predictor over time. Figure 2 shows that the relative importance of disease duration for QoL is low with about 8%.

OCI-R, education, and gender have been eliminated within the linear regression model. According to another study, OCD decreases QoL. However, in this study the authors explained that the self-assessment questionnaire they used did not allow an accurate differentiation between pathological and normal behaviors [69]. Further limitations are that QoL is a generic measurement, whereas the current living situation of OCD patients cannot be fully captured via normal QoL questionnaires [70]. The influence of education and gender on QoL remains debatable. First turning to gender, there is a study that showed a significant negative influence on QoL of female participants. However, the sample was not well balanced with a female to male gender ratio of 60 to 218 [61]. As a fact, other studies could not replicate this influence [56, 64, 65, 71]. In terms of education, the literature is yet to agree on its role in QoL [64, 65, 72]. However, unquestioned remains the fact that education has a protective effect on cognitive functions [72–74].

In regards to BDI, we have a representative sample of patients with mild depression and patients suffering from mild to more severe anxiety levels in comparison to other studies (i.e., depression studies [75–77]; anxiety studies [78–81]). The relationship between depression and anxiety has been examined in other studies [80–82]. However, most importantly, the BAI is not the most valuable tool for screening anxiety in PD. The literature suggests that a more suitable test for screening anxiety in PD is required [83, 84].

It could be shown that the result of the SRMI is not dependent on self-awareness [39]. This fact is very important for the adoption of a self-assessment questionnaire, since mania is often accompanied by anosognosia. The present study included 3 patients with mania (according to the SRMI) at the day of examination and mania still decreased the QoL, which is not common. In the presence of the typical symptoms, patients are more likely to be cheerful than in a bad mood. Thus, SRMI remained as a predictor variable in our model, due to the possible relationship between depression and mania in bipolar disorder and anxiety [85–87]. OCD also has a correlation with anxiety [88]. Yet, explaining the correlations between the different NPS measurements as in Table 3 is particularly difficult. At this point, it may be suggested that the correlation between depression and anxiety does not depend on the cognitive status. However, the cognitive status has an effect on the correlations between anxiety and OCD, anxiety and depression, anxiety and mania as well as OCI and mania. There were no significant correlations for the MCI patients. MCI may possibly override any relationships amongst other NPS.

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There was no correlation between LEDD and mania in our data in contrast to the findings of previous studies [89]. Furthermore, no significant involvement of LEDD in QoL was found in our model which is also not consistent with the literature [60, 61]. Maybe this finding is linked to the fact that the levodopa doses the patients received were fine-tuned, so they did not have Parkinson symptoms and also did not have much adverse reaction.

In our sample we had lower PDQ-39 scores as comparable studies [57, 65, 72, 90, 91], which may be attributable to a good medical care and good living standard.

Not all of the mentioned studies did use the questionnaires we did for this study. Some adopted the DSM-III or the DSM-IV criteria to diagnose depression, anxiety, OCD, and mania, whereas other studies used different self-reporting questionnaires like the Hospital Anxiety and Depression Scale (HADS) [92, 93] or the Hamilton Anxiety Rating Scale (HARS) [94, 95]. This might be a reason for the inconsistent findings between QoL and NPS over different studies.

However, self-assessment questionnaires are very practical, they give a comprehensive overview of the presence or absence of neuropsychiatric impairments. The advantage in this study is that we screened in an extended way for depression, anxiety, and mania and gathered the level of QoL in a more exact way. Moreover, we examined the influence from NPS in association with MCI on QoL.

Our results imply that NPS has a much greater effect on QoL in PD in comparison to cognitive status. According to Figure 2, the relative importance of MCI in QoL is only about 5%, whereas the influence of NPS is over 50%. Thus, this underlines the importance to screen for depression and anxiety in PD in order to adjust further therapy procedures. The 4 NPS (i.e., depression, anxiety, OCD, and mania) appear to be interconnected; however, the nature of the relationship is yet to be understood in full.

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Disclosure Statement

None of the authors have any conflicts of interest.

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