Impact of Parkinson medication on neuropsychiatric and neurocognitive symptoms in patients with advanced Parkinson disease prior to deep brain stimulation

Jan Häckert, Astrid Roeh, Susanne Karch, Thomas Koeglsperger, Alkomiet Hasan, Irina Papazova

Angaben zur Veröffentlichung / Publication details:

Häckert, Jan, Astrid Roeh, Susanne Karch, Thomas Koeglsperger, Alkomiet Hasan, and Irina Papazova. 2025. "Impact of Parkinson medication on neuropsychiatric and neurocognitive symptoms in patients with advanced Parkinson disease prior to deep brain stimulation." Pharmacopsychiatry 58 (1): 5–13. https://doi.org/10.1055/a-2446-6877.

Impact of Parkinson Medication on Neuropsychiatric and Neurocognitive Symptoms in Patients with Advanced Parkinson Disease Prior to Deep Brain Stimulation

Authors
Jan Haeckert[1], Astrid Roeh[1], Susanne Karch[2], Thomas Koeglsperger[3, 4], Alkomiet Hasan[1, 5], Irina Papazova[1]

Affiliations
1 Department of Psychiatry, Psychotherapy and Psychosomatics, Medical Faculty, University of Augsburg, Augsburg, Germany
2 Department of Psychiatry and Psychotherapy, University Hospital Munich, LMU Munich, München, Germany
3 Department of Neurology, LMU University Hospital, LMU Munich, Munich, Germany
4 Department of Translational Brain Research, German Center for Neurodegenerative Diseases (DZNE), Munich, Germany
5 DZPG (German Center for Mental Health), partner site Munich/Augsburg, Germany

Keywords
advanced Parkinson disease, Parkinson medication, dopamine agonists, neurocognitive deficits, impulsivity

Correspondence
Jan Haeckert, MD
Department of Psychiatry, Psychotherapy and Psychosomatics
Medical Faculty
University of Augsburg Geschwister-Schoenert-Straße 1
86156 Augsburg
Germany
Jan.Haeckert@med.uni-augsburg.de

Supplementary Material is available at
https://doi.org/10.1055/a-2197-0882

ABSTRACT

Introduction This study evaluates the impact of Parkinson disease (PD) medication in advanced PD on neuropsychological performance, psychiatric symptoms, impulsivity and the quality of life. In the 4-year period 27 patients with advanced PD, scheduled for deep brain stimulation (DBS) surgery (N = 27, mean age: 58.9 ± 7.1, disease duration: 10.0 years ± 4.2) were examined preoperatively. We hypothesized that a high dosage of PD medication or current use of dopamine agonists affect cognitive functioning and psychiatric wellbeing.

Methods We performed two subgroup analyses with low versus high levodopa-equivalent Dosage (LED) medication and without versus with dopaminagonistic medication.

Results The neuropsychological testing revealed significant differences in the verbal learn- and memory-test (VLMT) during the learning passage (U = 36.500, Z = − 2.475, p = 0.012) and in the subtest of the semantic fluency of Regensburg verbal fluency test (RWT) (t(25) = − 2.066, p = 0.049) with better results for patients without dopaminagonistic medication. Pearson correlation analyses of LED in correlation with the clinical and cognitive dependent variables showed a significant higher PANSS total score in patients with higher LED medication (r = 0.491, p = 0.009). In addition, lower LED treatment was associated with significant higher scores in the impulsivity perseverance subtest (r = − 0.509, p = 0.008).

Discussion In conclusion, we found lower LEDs to be correlated with a better perseverance in the impulsivity test and additional treatment with a dopamine agonist influenced some verbal learning tasks and the PANSS total score in patients with advanced PD. This should be considered prior to DBS surgery.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder of older people, affecting 2–3 % of the population > 65 years [1]. It is primarily characterized by bradykinesia and additional symptoms such as muscular rigidity or a 4–6 Hz resttremor or postural instability, as well as non-motor signs and symptoms [2]. The socioeconomic burden of this progressive neurodegenerative disease and the personal impairment due to the continuing deterioration is high [3, 4]. Especially for patients who experience drug effect fluctuations in their disease course, it has been shown that deep brain stimulation (DBS) at a relatively early disease stage is beneficial for their further clinical course and their further participation in normal social and working life [4]. Cognitive dysfunction and psychiatric symptoms affect almost all PD patients sooner or later in the disease course and tend to be more severe as the illness progresses [5]. Compared to healthy agematched people, patients with PD exhibit a more rapid cognitive decline in a number of cognitive domains – in particular, executive, attentional, and visuospatial domains, as well as memory [6]. Even at diagnosis, a substantial one-third of patients exhibit significant cognitive impairments. This prevalence doubles within a span of 4 years, and in the early stages, dementia may be as prevalent as 10 % [7, 8]. It is assumed that the dopaminergic medication shows a U-shaped relationship between dopamine levels and the integrity of cognitive domains affected in PD patients [9]. As DBS is considered for patients who experience motor fluctuations, it is critical to evaluate the extent of cognitive impairment and behavioral issues that might not allow a safe surgery outcome [10–12]. Threshold values of recognized measuring instruments (e. g., MoCA, MMSE) have been postulated in the past, but are not covered by data [13]. While manifest dementia was already defined as an absolute contraindication for DBS surgery, there are currently no clear recommendations regarding mild cognitive impairment [11]. In addition to the defining dopamine-related motor and non-motor symptoms, PD has been increasingly recognized as a heterogeneous multisystem disorder involving other neurotransmitter systems such as the serotonergic, noradrenergic, and cholinergic circuits [6], leading to the clinical symptomatology of affective disorders, mainly depressive episodes, but also psychotic episodes, frequently provoked by the PD related medication in the course of the disease. Depression is considered the most common psychiatric comorbidity [14] and occurs with a prevalence of 30–35 % in PD patients [15]. Early recognition of depressive episodes and consequent treatment are crucial, particularly concerning the evaluation of potential DBS as a treatment option for PD. Especially severe depression and suicidal tendencies are considered exclusion criteria for DBS [13]. This is explained by the fact that an insufficiently stabilized postoperative depression possesses a significant risk factor associated with the attempt or completion of suicide following DBS [16]. In relation to this, it was stipulated that, with respect to psychiatric disturbances, surgery should be deferred in patients with unstable psychiatric conditions until the symptoms have been managed adequately [11]. Furthermore, there is evidence that the target of DBS may influence affective outcomes, although the published data on this is insufficient [15, 17]. Psychotic symptoms are also common phenomena in PD, especially in the progressed course of the disease when dopaminergic medication has to be stepwise adjusted. Risk factors for developing Parkinson's disease psychosis (PDP) are disease duration and severity, as well as treatment involving dopamine agonists and catechol-O-methyltransferase (COMT) inhibitors [18, 19]. Furthermore, PD patients are at increased risk of PDP with concomitant cognitive impairment, depression, and treatment with anticholinergics [18].

However, comprehensive evaluation of several psychiatric dimensions and their relationship to the treatment of motor symptoms in patients with advanced PD prior to DBS are sparse. Thus, we aimed to evaluate neuropsychiatric deficits, psychiatric symptoms, impulsivity, and the quality of life in PD patients with the neurological indication for DBS. We hypothesized that patients with a high dosage of dopaminergic medication or current use of dopaminagonistic medication show higher deficits in neurocognitive testing, more severe psychotic symptomatology or a higher impulsivity than patients with lower dopaminergic medication or without dopaminagonistic medication.

Materials and Methods

Subjects

Twenty-seven patients with advanced PD (N = 27) participated in this study between February 2016 and July 2020, after providing written informed consent. The purpose of the psychiatric consultation, as part of the preoperative routine, was the assessment of a comprehensive psychiatric and neuropsychologic baseline assessment prior to the planned DBS operation. The study protocol was designed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of medical faculty at the Ludwig-Maximilians University (LMU) Munich (Reference Number: 110–16).

Setting

After neurological assessment and the indication for deep brain stimulation due to their advanced PD, patients were scheduled for an appointment at the psychiatric department of the Ludwig-Maximilians University Hospital, Munich. The assessment started with a detailed neuropsychological evaluation that lasted about 1 hour, a personality, impulsivity, and quality of life test, and psychosis and depression interviews as detailed below. Finally, the patients were examined and evaluated by a board-certified psychiatrist (AH) for manifest psychiatric illness. In total, the patients spent 4 to 6 hours to complete this evaluation protocol.

Outcome parameters

Patients received a standardized clinical, neurologic and psychiatric evaluation, a standardized neuropsychological (NP) protocol consisting of: (a) the multiple choice vocabulary test (MCVT) form B according to Lehrl [20] evaluating the age- and degradation-stable language-related intelligence, (b) the repeatable battery for the assessment of neuropsychological status (RBANS) according to Randolf [21] evaluating immediate memory, visuospatial/constructional, language, attention and delayed memory, (c) the letter-number span (LNS) according to Gold [22] measuring the working memory capacity, (d) the verbal learn- and memory-test (VLMT)

according to Helmstaedter [23] testing verbal learning and memory skills, (e) the Regensburg verbal fluency test (RWT) according to Aschenbrenner [24] testing cognitive flexibility and the recall of information from memory and (f) the planning test according to Kohler & Beck [25] which measures the ability to plan and implement goals with the intention to achieving them. Furthermore, we applied a personality disorder assessment with a structured clinical interview for DSM-IV (SKID) [26], evaluated the patients quality of life using the PD questionnaire-39 (PDQ-39) [27], the positive and negative syndrome scale (PANSS) evaluating psychotic experiences [28], the depression inventory with Hamilton [29] and Becks depression scale (BDI-II) [30], the geriatric depression scale (GDS) [31] testing depressive symptoms and an impulsivity rating with the impulsive behavior scale-8 (I-8) [32]. Finally, we performed a physical assessment of PD using the unified PD rating scale (MDS-UPDRS) by a board-certified neurologist (JH) [33].

Statistical analysis

All analyses were carried out using SPSS 28 (IBM, Armonk, NY, USA), with a significance level of $\alpha = 0.05$. Descriptive statistics were employed to assess baseline demographic data. The neuropsychological test results, PANSS results, depression tests, impulsivity test, PDQ-39 questionnaire, and UPDRS ratings were tested with the Shapiro-Wilk test for normal distribution (**Supplement Table S1** and **S2**). Descriptive data were presented with mean ± standard deviation, minimum, maximum, and standard error of the mean (SEM). Following baseline evaluation (▶ **Table 1**), we applied a median split to categorize our sample into 1) patients with low Levo-Dopa Equivalent Dosage (LED [34, 35]) (≤ 1232 mg) and high LED Dosage (> 1232 mg) (14 vs. 13 patients) and 2) patients with and without current dopamine-agonistic medication (17 vs. 10 patients). In cases where normal distribution was confirmed, further testing was conducted using independent t-tests (see **Supplement Table S3** and **S4**); where normal distribution was violated, we performed Mann-Whitney-UTests (**Supplement Table S5** and **S6**). Furthermore, we performed Pearson correlation analyses of LED with the other clinical and cognitive dependent variables (▶ **Table 2**). Due to the exploratory nature of the study, results were not corrected for multiple comparisons.

Results

Baseline Characteristics

Twenty-seven patients with advanced PD (4 female, mean age: 58.9 ± 7.1, disease duration: 10.0 years ± 4.2, mean LED: 1220 mg ± 367.6 mg, median LED: 1232 mg) participated in this study from February 2016 and July 2020 after giving informed consent (▶ **Table 1**).

Neuropsychological Testing

The majority of patients reached average or even good results (▶ **Table 1**) in NP testing. In the MCVT (mean: 34.07 ± 3.882, normal range: 20–35), the VLMT (learning) (mean: 12.30 ± 2.569, normal Range: 8–12), the VLMT (recall after interference) (mean: 10.30 ± 3.473, normal range: 6–10), the VLMT (delayed recall) (mean: 11.04 ± 3.777, normal range: 6–10), the Planning Test (moves) (mean: 41.48 ± 5.648, normal range: 33–40), and the Planning Test (errors) (mean: 0.50 ± 0.722), the average performance was at the upper border of the normal range. For the RBANS (recall story) (mean: 8.37 ± 2.950, normal range: 6–11), the RWT (k-words) (mean: 16.89 ± 7.255, normal range: 10–20), the RWT (gr-words) (mean: 16.81 ± 6.282, normal range: 10–20), the RWT (food products) (mean: 28.93 ± 9.770, normal range: 20–40), and the RWT (clothes/flowers) (mean: 15.00 ± 6.051, normal range: 10–20), the average performance was average. The performance of patients in the RBANS (learning the story) (mean: 14.41 ± 5.056, normal range: 12–20), the LNS (mean: 13.19 ± 3.578, normal range: 12–20), and the planning test (solved tasks) (mean: 4.00 ± 0.659, normal range: 4–6), was at the lower border of the normal range.

In the subgroup analysis of patients comparing high versus low LED-treated patients, there were no differences in the neuropsychological test results (**Supplement Table S3** and **Table S5**). However, the comparison of patients with versus without a dopaminagonistic medication revealed significant differences in the VLMT during the learning passage with higher scores and, thus, a better performance in the subgroup without dopaminagonistic medication ($U = 36.500$, $Z = -2.475$, $p = 0.012$) (**Supplement Table S6**). Also, in the subtest of the food products of RWT, we found a significant difference ($t_{(25)} = -2.066$, $p = 0.049$) with better results for patients without dopaminagonistic medication as compared to those with a dopaminagonistic medication (**Supplement Table S4**). All other neuropsychological results did not differ significantly between groups (all $p > 0.151$).

Structured clinical interview for DSM-IV (SKID-II)

The structured clinical interview for DSM-IV, part II revealed a trend towards an obsessive personality in 14 patients (52 %) and in 2 patients a trend towards a dependent personality. Nevertheless, the criteria for a manifest personality disorder were not fulfilled.

Quality of Life (PDQ-39)

The PDQ-39 Quality of Life revealed impairments in the subtests of mobility (33.61 ± 21.15), activities of daily living (30.71 ± 20.68), emotional wellbeing (27.01 ± 19.83), and bodily discomfort (35.49 ± 22.83). These results were within the normal range of patients with advanced PD [36]. The PDQ-39 total score in this cohort was 24.89 (± 13.14) (▶ **Table 1**). The subgroup analyses revealed no differences, either in the low vs. high LED (all $p > 0.104$) or in the without vs. with dopaminagonistic medication group (all $p > 0.19$) (**Supplement Table S3** and **S4**).

Positive and Negative Syndrome Scale (PANSS)

The PANSS results were in a normal range of the tested symptomatology (▶ **Table 1**) with a mean total score of 42.63 (± 7.00). In the subgroup analysis of high versus low LED patients, the PANSS total score with higher scores differed significantly in the group with higher LED medication ($t_{(25)} = -2.093$, $p = 0.047$) (**Supplement Table S3**). Analyses comparing patients with and without dopaminagonistic medication showed a trend towards higher PANSS-positive subscores in patients with dopaminagonistic medication ($p = 0.074$; no significant results) (**Supplement Table S4**).

▶ **Table 1** Baseline characteristics.

	Minimum	Maximum	Mean	SEM	SD	Normal Range
Baseline Characteristic						
Age	45	71	58.85	1.362	7.075	
Duration of illness (years)	4	20	10.00	0.801	4.160	
LED (mg)	700	2000	1220.15	70.747	367.613	
Neuropsychological Testing						
MCVT (Patient)	22	40	34.07	0.747	3.882	20–35
RBANS (Learning the story)	3	21	14.41	0.973	5.056	12–20
RBANS (Recall story)	2	12	8.37	0.568	2.950	6–11
LNS	7	22	13.19	0.702	3.578	12–20
VLMT (Learning)	6	15	12.30	0.494	2.569	8–12
VLMT (Recall after interference)	2	15	10.30	0.668	3.473	6–10
VLMT (delayed Recall)	1	15	11.04	0.727	3.777	6–10
VLMT (delayed recognising)	− 1	15	11.00	0.790	4.030	10–14
RWT (k-words)	7	32	16.89	1.396	7.255	10–20
RWT (gr-words)	3	27	16.81	1.209	6.282	10–20
RWT (food products)	12	52	28.93	1.880	9.770	20–40
RWT (clothes / flowers)	5	26	15.00	1.165	6.051	10–20
Planning Test (moves)	33	55	41.48	1.178	5.648	33–40
Planning Test (solved tasks)	3	6	4.00	0.135	0.659	4–6
Planning Test (errors)	0	2	0.50	0.147	0.722	0
Positive and Negative Scale (PANSS)						
PANSS positive	7	14	9.67	0.374	1.941	
PANSS negative	7	18	10.44	0.535	2.778	
PANSS general	16	32	22.89	0.937	4.870	
PANSS total	30	56	42.63	1.346	6.995	
Depression Scales						
BDI	0	21	7.00	1.145	5.838	
HAMD	1	23	9.04	1.171	6.086	
GDS	0	11	3.52	0.607	3.155	
Impulsivity Test						
Urgency	1.0	4.0	1.981	0.1531	0.7808	
Intention	2.0	5.0	3.769	0.1365	0.6961	
Perseverance	2.5	5.0	3.827	0.1107	0.5647	
Risk taking	1.5	5.0	2.962	0.2183	1.1129	
Quality of Life (PDQ-39)						
Mobility	0	75.0	33.611	4.0701	21.1489	
Daily Activities	4.17	75.00	30.7100	3.97950	20.67808	
Emotional Well-being	0	66.67	27.0063	3.81573	19.82710	
Stigma	0	62.50	16.6667	3.74465	19.45779	
Social support	0	50.00	13.8870	3.04916	15.84393	
Cognition	0	68.75	21.7593	3.50472	18.21103	
Communication	0	41.67	19.7541	2.48238	12.89880	
Physical discomfort	0	83.30	35.4926	4.39367	22.83020	
PDQ-39SI	5.42	61.09	24.8893	2.52922	13.14222	
Unified Parkinson Disease Rating Scale (UPDRS)						
Total section 1	1	30	10.07	1.239	6.439	
Total section 2	2	29	14.37	1.198	6.227	
Total section 3	1	51	20.22	2.356	12.242	
Total section 4	0	17	8.89	0.940	4.886	

LED: Levo-Dopa Equivalent Dosage; MCVT: multiple choice vocabulary test; RBANS: repeatable battery for the assessment of neuropsychological status; LNS: letter-number span; VLMT: verbal learn- and memory-test; RWT: Regensburg verbal fluency test; BDI: Becks depression scale; HAMD: Hamilton-Depression scale; GDS: Geriatric Depression Scale; PDQ-39: PD questionnaire-39.

▶ **Table 2** Pearson correlation of LED in correlation with all other clinical parameters. Significant results are indicated with *.

	Correlation to LED mg (Pearson-correlation)	p-value
Neuropsychological Testing		
MCVT (Patient)	0.084	0.679
RBANS (Learning the story)	− 0.271	0.171
RBANS (Recall story)	− 0.168	0.402
LNS	0.157	0.445
VLMT (Learning)	0.204	0.308
VLMT (Recall after interference)	0.228	0.253
VLMT (delayed Recall)	0.086	0.670
VLMT (delayed recognising)	0.012	0.953
RWT (k-words)	0.042	0.836
RWT (gr-words)	− 0.011	0.956
RWT (food products)	0.078	0.698
RWT (clothes / flowers)	− 0.179	0.372
Planning Test (moves)	− 0.072	0.744
Planning Test (solved tasks)	0.082	0.704
Planning Test (errors)	0.102	0.636
Positive and Negative Scale (PANSS)		
PANSS positive	0.298	0.131
PANSS negative	0.267	0.178
PANSS general	0.369	0.058
PANSS total	0.491	**0.009***
Depression Scales		
BDI	0.336	0.093
HAMD	0.330	0.093
GDS	0.280	0.158
Impulsivity Test		
Urgency	0.151	0.462
Intention	− 0.190	0.353
Perseverance	− 0.509	**0.008***
Risk taking	− 0.279	0.167
Quality of Life (PDQ-39)		
Mobility	0.210	0.294
Daily Activities	0.309	0.116
Emotional Well-being	0.334	0.088
Stigma	0.159	0.427
Social support	0.362	0.064
Cognition	0.272	0.170
Communication	0.145	0.469
Physical discomfort	0.098	0.627
PDQ-39SI	0.277	0.162

LED: Levo-Dopa Equivalent Dosage; MCVT: multiple choice vocabulary test; RBANS: repeatable battery for the assessment of neuropsychological status; LNS: letter-number span; VLMT: verbal learn- and memory-test; RWT: Regensburg verbal fluency test; PANSS: positive and negative syndrome scale; BDI: Becks depression scale; HAMD: Hamilton-Depression scale; GDS: Geriatric Depression Scale; PDQ-39: PD questionnaire-39.

Depression Scales

With regard to depressive symptoms, five patients achieved scores on the self-ratings scales for mild depressive symptoms in the Geriatric Depression Scale (GDS; defined as GDS ≥ 5), six patients in the BDI-II (defined as BDI ≥ 14), and ten patients in the Hamilton-Depression scale (defined as HAMD ≥ 9). However, none of the patients fulfilled the criteria for a clinically relevant depressive episode according to the consultant psychiatrist assessment (▶ **Table 1**). Subgroup analyses comparing patients with lower versus high LED as well as with and without dopaminagonistic medication did not establish significant differences (all $p > 0.085$) (**Supplement Table S3, S4, S5** and **S6**).

Impulsivity Test

The impulsivity behavior scale-8 (I-8) showed average results in the four subtests of urgency, intention, perseverance, and risk-taking (▶ **Table 1**). In the subgroup-analysis of low versus high LED, lower LED treatment was associated with higher scores in the perseverance subtest $t_{(24)} = 2.816$, $p = 0.010$ (**Supplement Table S3**). The subgroup-analysis of patients with versus without dopaminagonistic medication revealed no differences between groups (all $p > 0.288$) (**Supplement Table S4** and **S6**).

Unified Parkinson Disease Rating Scale (UPDRS)

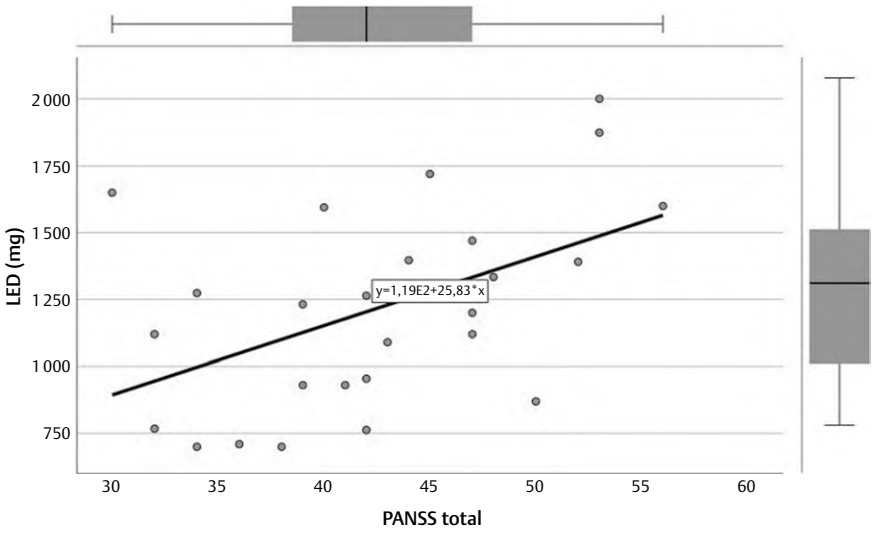
The UPDRS testing showed mild to moderate impairment with the given medication according to the categorization proposed by Martinez-Martin [37] in the four total scores (total section 1: 10.07 ± 6.44, total section 2: 14.37 ± 6.23, total section 3: 20.22 ± 12.24, total section 4: 8.89 ± 4.89) which reflects a good medicinal adjustment of the patients with not yet pronounced fluctuations of the clinical symptomatology (▶ **Table 1**). Subgroup analyses revealed no differences neither in the low vs. high LED nor in the without vs. with dopaminagonistic medication group (**Supplement Table S3, S4, S5** and **S6**).

Correlation analysis of LED with the clinical and cognitive dependent variables

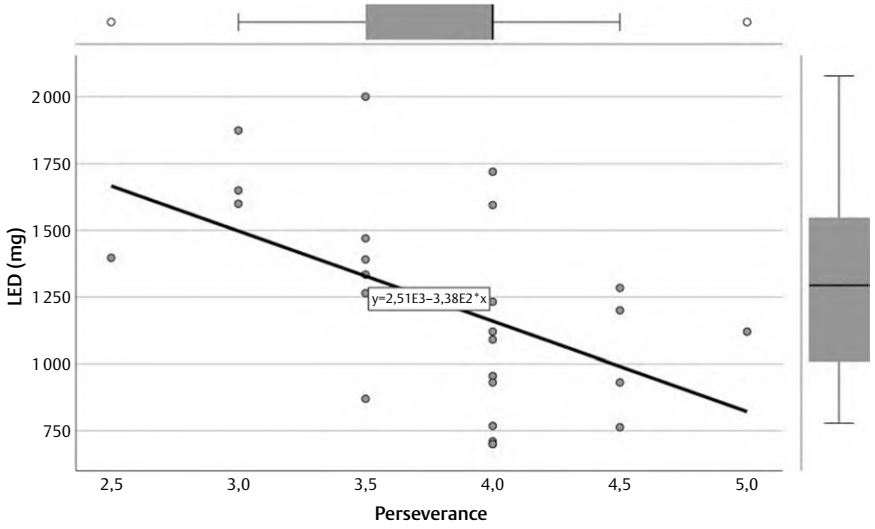
Pearson correlation analyses of LED with the clinical and cognitive dependent variables revealed a trend for the PANSS general score $r = 0.369$, $p = 0.058$ and a significant result for the PANSS total score $r = 0.491$, $p = 0.009$ (▶ **Table 2** and ▶ **Fig. 1**) with higher PANSS results in patients with higher LED medication. Regarding the impulsivity test the correlation showed a significant result $r = -0.509$, $p = 0.008$ (▶ **Table 2** and ▶ **Fig. 2**) in the perseverance subtest with higher perseverance results in patients with lower LED medication.

Discussion

In this study, we evaluated cognitive performance and a range of neuropsychiatric symptoms in relation to the PD medication in a well-characterized group of patients with PD prior to undergoing DBS. We demonstrate that patients receiving additional dopaminergic medication exhibited poorer performance in the VLMT during the learning phase and in the RWT subtest focusing on semantic fluency (food products). Furthermore, we found a significant difference in the PANSS total score with higher scores in the group with higher LED medication. This observation was further support-



▶ **Fig. 1** Pearson correlation of LED in correlation with the PANSS total score. LED – Levo-Dopa Equivalent Dosage, PANSS – positive and negative syndrome scale.



▶ **Fig. 2** Pearson correlation of LED in correlation with perserverance. LED – Levo-Dopa Equivalent Dosage.

ed by Pearson correlation analysis. The depression scales showed no differences between the medication subgroups, while our impulsivity test revealed better results in the perseverance subtest for patients with lower LED medication. Interestingly, more than 50 % of our sample showed signs of an obsessive personality according to the structural interview testing. Overall, our comprehensive examination of the patients did not reveal any pathological findings that would contraindicate the planned DBS operation.

Considering the neuropsychological test results, our findings indicate that levodopa medication does not exhibit a dosage-dependent influence. However, the presence of additional dopaminergic medication has been shown to negatively impact performance in the VLMT learning phase and the RWT semantic fluency subtest (**Supplementary Tables S4** & **S6**). Although the results may also be caused by the already advanced PD itself, previous studies have shown that dopamine depletion due to the disease and a negative impact of the fronto-striatal network, can impair the lexico-semantic system [38]. However, in that study, a negative effect of the lexico-semantic system was provoked in patients in depletion of the levodopa medication and in those in the Parkin-

son's off-state, whereas these deficits diminished when patients were in the on-state [38]. Other publications have indicated that the verbal fluency performance in patients with PD did not differ irrespective of whether they were treated with levodopa or a dopamine agonist [39]. Our findings are in principle in accordance with those previously published studies.

The personality assessment of our cohort revealed an elevated frequency of obsessive-compulsive behavior and dependent behavior; however, the criteria for a diagnosable personality disorder were not met. The fact that the SKID-2 test is not standardized for patients with a neurodegenerative disease, but is designed for the diagnosis of young, healthy people, certainly limits the interpretation of the results. Personality changes have long been considered pre-motor features of patients with PD. Most of the studies that have explored the clinical correlates of personality in PD found no significant association between personality traits and clinical parameters such as disease duration, Hoehn & Yahr stage or UPDRS [40]. Only a few studies have investigated the association between PD drugs and personality traits. For example, one study showed no differences in the personality traits of patients who received dopamine agonistic therapy compared to the patients who did not receive dopamine agonists [41]. However, when medication was converted to LED, a significant effect on extraversion and openness to experience was observed with lower personality scores associated with higher LED levels [41]. Another study demonstrated that in young, drug-naive patients with PD, after the introduction of anti-Parkinsonian drugs, only dopamine agonists induced a significant increase in seeking novelty and reward processing [42]. Furthermore, in a large cohort study of the Swedish twin registry, an increased percentage of neuroticism and introversion in patients with PD has been established [43].

In the impulsivity testing, we found higher scores in the perseverance subtest in the patient group with lower LED scores, whereas the subgroup analysis of patients without versus with dopaminagonistic treatment revealed no significant difference. In the impulsivity behavior scale-8, the perseverance subitems reflect the abilities of the patients to complete their upcoming tasks and organize their time accordingly to be able to complete requirements on time. It is not surprising that patients with low LED manage their time accordingly to accomplish tasks, as they always have to reckon with off-phases or hypokinesia as the disease progresses. In contrast to our findings, there exists a well-established association between impulsive behavior and the administration of high doses of dopamine [44–47]. The fact that our test results do not confirm the results of the previous literature may arise from the limitations of our test procedure; specifically, the use of the impulsive behavior scale-8 does not sufficiently capture and differentiate the symptoms of the patients.

With regard to psychotic symptoms in advanced PD, it has already been shown that these symptoms are common side effects of the PD medication [18], which means that the results of our study are consistent with those in the literature. The prevalence of complex visual hallucinations among patients with PD ranges from 22 % [48] to 38 %, with minor psychotic symptoms present in up to 72 % of patients with PD [49]. In our cohort, a mean positive PANSS score of 9.67 was in the low normal range (minimum: 7, maximum: 49) compared to positive PANSS scores in PD patients with psychotic symptoms (mean positive score: 15–17) [50]. Common risk factors for experiencing psychotic symptoms in PD patients are dopaminergic drugs, especially a therapy with dopamine agonists and catechol-O-methyltransferase (COMT) inhibitors [18, 51, 52]; however other factors are also important, such as dementia and visuospatial impairment, as well as general factors such as old age and more advanced disease stage [52]. Our findings in patients with advanced PD prior to DBS are important, as psychotic experiences or major psychiatric symptoms are considered exclusion criteria for DBS. Our findings in this specific cohort underscore that psychotic experiences can be identified even in the absence of a clinical profile indicative of PDP, and these experiences are associated with pharmacological treatment. Concerning depressive symptoms and episodes among PD patients, ten individuals in our cohort scored above the lower limit on the self-rating HAMD, indicating values in the range of mild depressive symptoms. However, clinical evaluation did not reveal significant symptomatology indicative of a major depressive episode. A relatively high incidence of depressive episodes in patients with PD has been well-established in the literature, with episodes even preceding the diagnosis of PD [1, 15, 53]. The underlying mechanism for this is assumed to be the imbalance and changes in dopamine, serotonin, and noradrenergic transmitters [54]. Using dopamine agonists as a primary treatment for depression in patients with PD has led to mixed results [54]. A systematic review of ten non-RCT studies led to inconclusive results and insufficient evidence for the use of dopamine agonists in the treatment of depressive episodes in patients with PD [55]. Considering all our findings, one could conclude that cognitive symptoms and psychotic experiences are more relevant than depressive symptoms in patients with advanced PD prior to DBS.

One limitation of our study is that one should be aware that dichotomizing continuous variables using a median split may result in the loss of information, especially regarding individual differences. Thus, our analyses should be interpreted with caution [56]. Furthermore, we did not correct our results for multiple comparisons. Apart from that, our cohort might be too small to show significant differences in the subgroup analyses of the impulsivity test we used. A clear strength of the study is the comprehensive neurocognitive and psychiatric work-up of PD patients with advanced disease duration prior to DBS.

In summary, we present the findings of a comprehensive cognitive and psychiatric assessment of patients with advanced PD prior to DBS. We were able to establish a link between PD medication and cognitive functioning and psychotic experiences, as well as the presence of relevant obsessive-compulsive traits and impulsivity. Our findings highlight the need for comprehensive cognitive and psychiatric assessments prior to DBS as some of the presented findings can be modified through the adaption of PD medication or psychiatric treatment. Future trials should evaluate the impact of the longitudinal course of our findings prior to and post-DBS.

Declarations

Informed consent was obtained from all individual participants included in the study. The study protocol was designed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of medical faculty at the Ludwig-Maximilians University (LMU) Munich (Reference Number: 110–16).

Conflict of Interest

A. Hasan was a member of the advisory boards of Boehringer-Ingelheim, Lundbeck, Janssen, Otsuka, Rovi, and Recordati and received paid speakership by these companies as well as by AbbVie and Advanz. He is editor of the German schizophrenia guideline. T. Koeglsperger has been granted research funding and has received compensation for speaking engagements from Abbott, AbbVie, and Medtronic. All other authors report no conflicts of interest. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

[1] Poewe W, Seppi K, Tanner CM et al. Parkinson disease. Nat Rev Dis Primer 2017; 3: 17013. DOI: 10.1038/nrdp.2017.13

[2] Hughes AJ, Daniel SE, Kilford L et al. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992; 55: 181–184. DOI: 10.1136/jnnp.55.3.181

[3] Yang W, Hamilton JL, Kopil C et al. Current and projected future economic burden of Parkinson's disease in the U.S. Npj Park Dis. 2020; 6: 15. DOI: 10.1038/s41531-020-0117-1

[4] Schuepbach WMM, Rau J, Knudsen K et al. Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med 2013; 368: 610–622. DOI: 10.1056/NEJMoa1205158

[5] Broeders M, de Bie RMA, Velseboer DC et al. Evolution of mild cognitive impairment in Parkinson disease. Neurology 2013; 81: 346–352. DOI: 10.1212/WNL.0b013e31829c5c86

[6] Aarsland D, Creese B, Politis M et al. Cognitive decline in Parkinson disease. Nat Rev Neurol 2017; 13: 217–231. DOI: 10.1038/nrneurol.2017.27

[7] Foltynie T, Brayne CEG, Robbins TW et al. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain 2004; 127: 550–560. DOI: 10.1093/brain/awh067

[8] Williams-Gray CH, Foltynie T, Brayne CEG et al. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain 2007; 130: 1787–1798. DOI: 10.1093/brain/awm111

[9] Cools R. Dopaminergic modulation of cognitive function-implications for l-DOPA treatment in Parkinson's disease. Neurosci Biobehav Rev 2006; 30: 1–23. DOI: 10.1016/j.neubiorev.2005.03.024

[10] Voon V, Kubu C, Krack P et al. Deep brain stimulation: Neuropsychological and neuropsychiatric issues. Mov Disord 2006; 21: S305–S327. DOI: 10.1002/mds.20963

[11] Munhoz RP, Picillo M, Fox SH et al. Eligibility criteria for deep brain stimulation in Parkinson's disease, tremor, and dystonia. Can J Neurol Sci J Can Sci Neurol 2016; 43: 462–471. DOI: 10.1017/cjn.2016.35

[12] Massano J, Garrett C. Deep brain stimulation and cognitive decline in Parkinson's disease: A clinical review. Front Neurol 2012; 3. DOI: 10.3389/fneur.2012.00066

[13] Höglinger G, Trenkwalder C et al. Parkinson-Krankheit, S2k-Leitlinie, in: Deutsche Gesellschaft für Neurologie (Hrsg.), Leitlinien für Diagnostik und Therapie in der Neurologie. 2023

[14] Nilsson FM, Kessing LV, Sørensen TM et al. Major depressive disorder in Parkinson's disease: A register-based study. Acta Psychiatr Scand 2002; 106: 202–211

[15] Aarsland D, Påhlhagen S, Ballard CG et al. Depression in Parkinson disease – epidemiology, mechanisms and management. Nat Rev Neurol 2012; 8: 35–47. DOI: 10.1038/nrneurol.2011.189

[16] Voon V, Krack P, Lang AE et al. A multicentre study on suicide outcomes following subthalamic stimulation for Parkinson's disease. Brain 2008; 131: 2720–2728

[17] Follett KA, Weaver FM, Stern M et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N Engl J Med 2010; 362: 2077–2091

[18] Samudra N, Patel N, Womack KB et al. Psychosis in Parkinson disease: A review of etiology, phenomenology, and management. Drugs Aging 2016; 33: 855–863

[19] Schaeffer E, Berg D. Dopaminergic therapies for non-motor symptoms in Parkinson's disease. CNS Drugs 2017; 31: 551–570. DOI: 10.1007/s40263-017-0450-z

[20] Lehrl S. Mehrfach-Wortschatz-Intelligenztest: MWT-B 5. Aufl., Balingen: Spitta. 2005

[21] Randolph C. Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Psychological Corporation San Antonio, TX; 1998

[22] Gold JM, Carpenter C, Randolph C et al. Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. Arch Gen Psychiatry 1997; 54: 159–165

[23] Helmstaedter C, Lendt M, Lux S. Veerbaler Lern- und Merkfähigkeitstest: VLMT. Göttingen: Beltz Test; 2001

[24] Aschenbrenner S, Tucha O, Lange KW. Regensburger Wortflüssigkeits-Test: RWT. Göttingen; Bern; Toronto; Seattle: Hogrefe, Verl. Für Psychologie. 2000

[25] Kohler J, Beck U, Hohnecker B. Neuropsychological assessment of basic planning competence. Journal of the International Neuropsychological Society 2003; 9: 519

[26] Wittchen H-U, Zaudig M, Fydrich T. Strukturiertes klinisches Interview für DSM-IV: SKID; eine deutschsprachige, erweiterte Bearbeitung der amerikanischen Originalversion des SCID. Göttingen [u.a.]: Hogrefe, 1997

[27] Jenkinson C, Fitzpatrick R, Peto V et al. The Parkinson's Disease Questionnaire (PDQ-39): Development and validation of a Parkinson's disease summary index score. Age Ageing 1997; 26: 353–357

[28] Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13: 261–276

[29] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23: 56

[30] Beck AT, Steer RA, Brown GK. Manual for The Beck Depression Inventory Second Edition (BDI-II). San Antonio: Psychological Corporation; 1996a

[31] Yesavage JA. Geriatric depression scale. Psychopharmacol Bull 1988; 24: 709–711

[32] Whiteside SP, Lynam DR. The five factor model and impulsivity: Using a structural model of personality to understand impulsivity. Personal Individ Differ 2001; 30: 669–689

[33] Goetz CG, Tilley BC, Shaftman SR et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. Mov Disord 2008; 23: 2129–2170. DOI: 10.1002/mds.22340

[34] Schade S, Mollenhauer B, Trenkwalder C. Levodopa equivalent dose conversion factors: An updated proposal including opicapone and safinamide. Mov Disord Clin Pract 2020; 7: 343–345. DOI: 10.1002/mdc3.12921

[35] Tomlinson CL, Stowe R, Patel S et al. Systematic review of levodopa dose equivalency reporting in Parkinson's disease: Systematic review of LED reporting in PD. Mov Disord 2010; 25: 2649–2653. DOI: 10.1002/mds.23429

[36] Hagell P, Nygren C. The 39 item Parkinson's disease questionnaire (PDQ-39) revisited: Implications for evidence based medicine. J Neurol Neurosurg Amp Psychiatry 2007; 78: 1191–1198. DOI: 10.1136/jnnp.2006.111161

[37] Martínez-Martín P, Rodríguez-Blázquez C, Mario Alvarez et al. Parkinson's disease severity levels and MDS-Unified Parkinson's Disease Rating Scale. Parkinsonism Relat Disord 2015; 21: 50–54. DOI: 10.1016/j.parkreldis.2014.10.026

[38] Herrera E, Cuetos F, Ribacoba R. Verbal fluency in Parkinson's disease patients on/off dopamine medication. Neuropsychologia 2012; 50: 3636–3640. DOI: 10.1016/j.neuropsychologia.2012.09.016

[39] Brusa L, Pavino V, Massimetti MC et al. The effect of dopamine agonists on cognitive functions in non-demented early-mild Parkinson's disease patients. Funct Neurol 2013; 28: 13–17

[40] Santangelo G, Piscopo F, Barone P et al. Personality in Parkinson's disease: Clinical, behavioural and cognitive correlates. J Neurol Sci 2017; 374: 17–25. DOI: 10.1016/j.jns.2017.01.013

[41] Volpato C, Signorini M, Meneghello F et al. Cognitive and personality features in Parkinson disease: 2 sides of the same coin? Cogn Behav Neurol 2009; 22: 258–263. DOI: 10.1097/WNN.0b013e3181c12c63

[42] Bodi N, Keri S, Nagy H et al. Reward-learning and the novelty-seeking personality: A between- and within-subjects study of the effects of dopamine agonists on young Parkinson's patients. Brain 2009; 132: 2385–2395. DOI: 10.1093/brain/awp094

[43] Sieurin J, Gustavsson P, Weibull CE et al. Personality traits and the risk for Parkinson disease: A prospective study. Eur J Epidemiol 2016; 31: 169–175. DOI: 10.1007/s10654-015-0062-1

[44] Evans AH, Lawrence AD, Potts J et al. Factors influencing susceptibility to compulsive dopaminergic drug use in Parkinson disease. Neurology 2005; 65: 1570–1574. DOI: 10.1212/01.wnl.0000184487.72289.f0

[45] Voon V, Fernagut P-O, Wickens J et al. Chronic dopaminergic stimulation in Parkinson's disease: From dyskinesias to impulse control disorders. Lancet Neurol 2009; 8: 1140–1149. DOI: 10.1016/S1474-4422(09)70287-X

[46] Weintraub D. Impulse control disorders in Parkinson's disease: Prevalence and possible risk factors. Parkinsonism Relat Disord 2009; 15: S110–S113. DOI: 10.1016/S1353-8020(09)70794-1

[47] Antonelli F, Ko JH, Miyasaki J et al. Dopamine-agonists and impulsivity in Parkinson's disease: Impulsive choices vs. impulsive actions. Hum Brain Mapp 2014; 35: 2499–2506. DOI: 10.1002/hbm.22344

[48] Fénelon G, Alves G. Epidemiology of psychosis in Parkinson's disease. J Neurol Sci 2010; 289: 12–17. DOI: 10.1016/j.jns.2009.08.014

[49] Williams DR, Warren JD, Lees AJ. Using the presence of visual hallucinations to differentiate Parkinson's disease from atypical parkinsonism. J Neurol Neurosurg Psychiatry 2007; 79: 652–655. DOI: 10.1136/jnnp.2007.124677

[50] Pollak P. Clozapine in drug induced psychosis in Parkinson's disease: A randomised, placebo controlled study with open follow up. J Neurol Neurosurg Psychiatry 2004; 75: 689–695. DOI: 10.1136/jnnp.2003.029868

[51] Munhoz RP, Teive HA, Eleftherohorinou H et al. Demographic and motor features associated with the occurrence of neuropsychiatric and sleep complications of Parkinson's disease. J Neurol Neurosurg Psychiatry 2013; 84: 883–887. DOI: 10.1136/jnnp-2012-304440

[52] Aarsland D, Marsh L, Schrag A. Neuropsychiatric symptoms in Parkinson's disease. Mov Disord 2009; 24: 2175–2186. DOI: 10.1002/mds.22589

[53] Ishihara L, Brayne C. A systematic review of depression and mental illness preceding Parkinson's disease. Acta Neurol Scand 2006; 113: 211–220. DOI: 10.1111/j.1600-0404.2006.00579.x

[54] Laux G. Parkinson and depression: Review and outlook. J Neural Transm 2022; 129: 601–608. DOI: 10.1007/s00702-021-02456-3

[55] Leentjens AF. The role of dopamine agonists in the treatment of depression in patients with Parkinson's disease: A systematic review. Drugs 2011; 71: 273–286

[56] MacCallum RC, Zhang S, Preacher KJ et al. On the practice of dichotomization of quantitative variables. Psychol Methods 2002; 7: 19–40. DOI: 10.1037/1082-989X.7.1.19