

The comparison of cognitive impairment between depression in Parkinson's disease and major depressive disorder

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ABSTRACT

Aim: Depression is not only a significant disorder that impacts the population, but it also manifests as a prevalent non-motor symptom associated with Parkinson's disease (PD). Despite considerable clinical and neuroimaging data regarding the pathophysiology of major depressive disorder (MDD), the neural mechanisms underlying depression in PD remain unresolved. This study aims to compare cognitive and demographic features in PD patients with depression and MDD patients.

Methods: Thirty-one Parkinson's patients with depression (PD-DEP) and 29 MDD individuals were recruited to the study. All participants underwent cognitive assessment with The Montreal Cognitive Assessment (MoCA) and The Mini-Mental State Examination (MMSE). Hamilton Depression Rating Scale (HDRS) was used to evaluate depression severity. Also, participants' demographic data was recorded.

Results: Compared with MDD, PD-DEP patients were older, less educated, and showed poorer MoCA/MMSE performance. A negative HDRS-MoCA correlation was found only in PD-DEP ($p=0.011$, $r=-0.464$). In binomial regression analyses age, Abstracting/Delayed Recall of MoCA subtests, education and, HDRS remained significant predictors for PD-DEP in the Backward Wald model.

Conclusion: Depression associated with PD is correlated with specifically impaired cognitive domains compared to MDD. These findings reinforce the hypothesis that depression related to PD constitutes a unique neuropsychiatric condition that needs more attention for the increased risk of cognitive deficit by clinicians.

Keywords: Parkinson's disease with depression, major depressive disorder, cognition, moca

INTRODUCTION

Parkinson's disease (PD) is traditionally diagnosed based on motor symptoms, including tremor, rigidity, and bradykinesia. However, clinical management must also address non-motor symptoms, which represent a significant aspect of the disease. These non-motor symptoms include neuropsychiatric disturbances such as depression, anxiety, sleep disorders, psychosis, behavioral changes, and cognitive impairments.^{1,2} Depression is one of the most prevalent and impactful non-motor symptoms, affecting 20% to 50% of PD patients,^{3,4} a rate much higher than that in the general population.⁵ Despite its prevalence, depression in PD is often underdiagnosed and undertreated in clinical practice.^{6,7} This can significantly worsen the progression and prognosis of the disease.⁸⁻¹¹ Although depression in PD may appear to represent a psychological reaction to coping with the chronic and debilitating effects of the disease, research suggests that it frequently predates the onset of motor symptoms. Studies

have found that individuals who later develop PD have an increased risk of depression even before diagnosis of PD.¹² This implies that PD itself serves as a biological risk factor for depression, independently of psychological reactions to the disease's motor symptoms. On the other hand, some studies have proposed the reverse, suggesting that depression may predispose individuals to develop PD later in life, as observed in other neurodegenerative diseases, such as Alzheimer's disease (AD).^{13,14}

Due to the intricate relationship between PD, depression, and cognitive impairment, including both neurobiological and psychological factors, it is crucially important to understand the shared pathophysiological mechanisms underlying these conditions,¹⁵ which could be essential for the development of effective therapeutic strategies, such as in other neurological diseases with a non-degenerative nature.¹⁶ In



that context, various pathophysiological theories have been proposed to explain depression in PD, including disrupted neurotransmitter function, brain metabolic abnormalities, and circuit dysfunction¹⁷⁻²³ as previously defined in Alzheimer's Disease²⁴⁻²⁶ Among them, there is strict evidence showing a decrease in frontal hypoperfusion and striatal dopamine transporter availability in PD-DEP compared to MDD patients.²⁷

These findings also align with neuroimaging studies in PD-DEP, which showed degree centrality abnormalities in the right middle prefrontal gyrus, anterior cingulate cortices, and supplementary motor cortices compared to PD without depression.²⁸ Also, a review based on SPECT analyses has found that several brain regions appear to be involved in depression, particularly the limbic system and the basal ganglia.²⁹ In addition, the serotonergic, dopaminergic, and noradrenergic systems also appear to be associated with depressive symptoms in PD.^{30,31} Despite this huge progress in understanding the underlying pathophysiological mechanism, a major limitation of clinical research into PD depression is that most studies rely on correlational analyses to examine depressive symptoms rather than directly comparing PD-DEP and MDD.³² Herein, a primary clinical approach to studying depressive symptoms and their influence on cognition in both groups may help determine whether depression should be considered an intrinsic feature of PD or a separate psychological reaction to it.

To the best of our knowledge, no research to date has directly compared patients with PD and depression and those with pure MDD in terms of cognitive changes.

METHODS

Ethics

The study was conducted with the permission of the Clinical Researches Ethics Committee of Alanya Alaaddin Keykubat University Faculty of Medicine (Date: 09/24/2025, Decision No: 13-14). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participants

Thirty-one PD-DEP and 29 individuals with MDD were recruited from the Alanya Research and Training Hospital, Department of Neurology. PD was diagnosed by an experienced neurologist based on the UK PD Society Brain Bank criteria. Selection criteria for the patients included a diagnosis of MDD in accordance with the DSM-5 as determined by experienced psychiatrists.

All patients were evaluated with the HDRS, the MoCA, and the MMSE. Depressive symptoms were assessed using the 17-item Hamilton Depression Rating Scale (HDRS-17), a clinician-administered instrument widely used to evaluate the severity of depressive symptoms. Total scores range from 0 to 52, with higher scores indicating greater symptom severity. MMSE and MoCA were applied to measure cognitive impairment, while the MMSE test was used to rule out dementia. The MMSE assesses orientation, memory, attention, language, and visuospatial abilities, with total scores ranging from 0 to 30, and lower scores indicating

greater impairment.³³ Cognitive performance was further assessed with MoCA, a brief screening instrument designed to detect mild cognitive impairment. The MoCA evaluates multiple cognitive domains, including visuospatial/executive, naming, attention, concentration and calculation, language, abstraction, delayed recall, orientation abilities, with total scores ranging from 0 to 30.³⁴

Exclusion criteria for all subjects were the following: a) MMSE score less than 22, b) history of head trauma, stroke, and substance abuse/dependence currently or in the past, c) clinical evidence of any other significant current or past psychiatric or neurological illnesses, and d) usage of antimentia medication. G*power (ver. 3.1.6.6) software was used to determine the sample size. This analysis indicated that a minimum sample size of 40 subjects would be required to achieve 90% power at $\alpha=0.05$.

Statistical Analysis

Data analysis was carried out using the commercial statistical package software for social sciences (SPSS version 25.0, IBM, USA). The Shapiro-Wilk test was used to check the normality of the variables. Continuous variables are presented as mean \pm standard deviation (mean \pm SD) or median (IQR), depending on the normality test of the variable. Normally distributed data were analyzed with Student's t-test, non-normally distributed data were analyzed with a Mann-Whitney U test, and binary variables were analyzed with Fisher's exact test. Categorical variables were presented as frequency (n) and percentage (%). Binomial logistic regression was used to assess the association between diagnosis (PD-DEP versus MDD) and MoCA subtests, adjusted by age, education, gender, and HDRS scores. Two-sided p-values and 95% CIs were used in SPSS software. Significance was determined at $p<0.05$.

RESULTS

PD patients with depression were older (68.42 \pm 8.57) and less educated (5.51 \pm 5.51) than depressive patients (age: 49.41 \pm 15.00, $p<0.001$; education years: 10.82 \pm 0.66, $p<0.001$). Also, cognitive tests scores were lower in PD-DEP (MoCA: 20.58 \pm 4.35, MMSE: 25.52 \pm 2.66) than MDD (MoCA: 24.17 \pm 2.48, $p<0.001$; MMSE: 27.24 \pm 1.72, $p=.004$). While male gender was more observed in the PD-DEP group, female patients were significantly dominant in MDD (Fisher's exact test, $p=0.036$, **Table 1**). Comparing the Z scores of MoCA subtests revealed that Visuospatial/Executive, Naming, Attention, Abstracting, and Orientation were more impaired in PD-DEP subjects compared to MDD subjects (**Table 1**).

We have also investigated the relationship between MoCA and HDRS with partial correlation by adjusting for age and education. While these two variables were negatively correlated with each other in the PD-DEP group ($r: -0.464$, $p: 0.011$), there was no correlation between them in the MDD group ($r: -0.123$, $p: 0.542$). Also, HDRS and MoCA were shown to have a negative correlation in the whole sample ($r: -0.446$, $p<0.001$, **Table 2**).

In univariate regression analyses, MoCA subtest Z scores were used for predicting diagnosis, adjusting for age, education, gender, and HDRS score (**Table 3**). However, no subtest

Table 1. The comparison of clinic and demographic data between depressive patients with Parkinson's disease and patients with major depressive disorder

	PD (n=31) mean±SD	MDD (n=29) mean±SD	p
Age	68.42±8.57	49.41±15.00	<0.001*
Education	5.51±5.51	10.82±0.66	<0.001*
Gender (male)	16 (52%)	7 (24%)	0.036*
HDRS	17.10±10.85	10.96±5.00	0.007*
MoCA	20.58±4.35	24.17±2.48	<0.001*
MMSE	25.52±2.66	27.24±1.72	0.004*
MoCA subtests			
Visuospatial/executive (z score)	-0.37±1.12	0.40±0.67	0.002*
Naming (z score)	-0.26±0.89	0.28±1.05	0.035*
Attention (z score)	-0.27±1.13	0.29±0.75	0.029*
Language (z score)	-0.14±1.17	0.15±0.76	0.249
Abstraction (z score)	-0.41±0.99	0.44±0.82	<0.001*
Delayed recall (z score)	-0.12±0.97	0.13±1.03	0.333
Orientation (z score)	-0.31±1.29	0.35±0.25	0.008*

PD: Parkinson's disease, MDD: Major depressive disorder, HDRS: Hamilton Depression Rating Scale, MoCA: Montreal Cognitive Assessment, MMSE: Mini-Mental State Examination, n: Number of patients, SD: Standard deviation. *p<0.05: Significance level

Table 2. The correlation between HDRS and MoCA score in PD, MDD, and the whole sample

Groups	r	p
PD	-0.464	0.011*
MDD	-0.123	0.542
Whole group	-0.446	<0.001*

HDRS: Hamilton Depression Rating Scale; MoCA: Montreal Cognitive Assessment; PD: Parkinson's disease, MDD: Major depressive disorder. *p: Significance level

significantly predicted the diagnosis. When all variables were involved in multivariable regression analyses, only age (p: 0.0231, odds ratio (OR): 1.17, CI [1.02-1.34]) and education (p: 0.026, OR: 0.70 [0.51-0.95]) were shown to be significant in the model. But, in forward analyses, HDRS (p=0.041, OR: 1.188 [1.01-1.4]), Abstracting (p=0.026, OR:0.27 [0.09-0.86]), and Delayed Recall (p=0.047, OR: 4.08 [1.02-16.30]) remained beside age and education for predicting PD-DEP in the Backward Wald method (Table 3).

Table 3. Binary logistic regression model for depression in patients with Parkinson's disease by variables

	Univariate OR (95% CI)	p	Multivariable OR (95% CI)	p	Multivariable (BW-WALD) OR (95% CI)	p
Age	1.14 (1.06-1.22)	< 0.001*	1.17 (1.02-1.34)	.023*	1.170 (1.05-0.31)	.006*
Education	0.75 (0.65-0.87)	< 0.001*	0.70 (0.51-0.95)	.026*	.749 (0.59-0.95)	.017*
HDRS	1.12 (1.01-1.23)	.019*	1.14 (0.94-1.39)	.164	1.188 (1.01-1.4)	.041*
Gender						
	Male (reference category)					
Female	0.29 (0.99-0.9)	.032*	0.79 (0.07-8.88)	.849		
MoCA subtests						
Visuospatial/executive	0.39 (0.20-0.75)	.005*	0.42 (0.10-1.71)	.228		
Naming	0.53 (0.29-0.98)	.043*	2.21 (0.49-9.84)	.295		
Attention	0.52 (0.28-0.96)	.038*	1.40 (0.33-5.78)	.641		
Language	0.73 (0.42-1.24)	.248	2.16 (0.61-7.58)	.228		
Abstracting	0.35 (0.18-0.68)	.002*	0.29 (0.07-1.18)	.086	0.27 (0.09-0.86)	.026*
Delayed recall	0.77 (0.46-1.29)	.327	5.13 (0.85-31.0)	.074	4.08 (1.02-16.30)	.047*
Orientation	0.19 (0.03-0.94)	0.042*	0.19 (0.01-3.69)	0.277		

CI: Confidence interval, OR: Odds ratio; HDRS: Hamilton Depression Rating Scale; MoCA: Montreal Cognitive Assessment, *p<0.05: Significance level, BW-WALD: Backward Wald

DISCUSSION

Despite the relatively large body of data concerning depression, its effect on cognition in PD patients with depression has rarely been explored in the literature.

Our sensitive logistic regression analysis supported previous literature, indicating specifically impaired cognition in PD-DEP patients. In the present study, one of our major findings was that cognition in PD was negatively affected by mood, which was not evident in the MDD group. In detailed regression analysis, PD was negatively affected by the severity of HDRS and certain MoCA subtests (Abstracting, Delayed Recall), consistent with previous literature on specific cognitive impairments in PD-DEP patients.³⁵⁻³⁷

From another point of view, this suggests the detrimental effect of mood on cognition in PD, which our study confirmed with a significant correlation observed between HDRS scores and cognition only in the PD-DEP group. Despite this, it is challenging to draw a concrete conclusion, as we have not included a pure PD group, a topic that warrants further study.

Here, it is worth mentioning that one possible explanation for the lack of significance between the groups could be the relatively small sample size, which may have compromised our ability to detect differences between the two PD subgroups. Nevertheless, the comparable mean values and minimal standard deviations indicate that sample size alone is unlikely to explain these findings fully. Furthermore, since this study concentrated on examining subclinical cognitive differences among the groups, we incorporated participants with MMSE scores of 22 points or higher. By excluding participants with cognitive impairment, we may have overlooked more pronounced group differences, since these were only identified in specific subtests, which were further affected by the small sample size.

Another important observation in this study is the slightly higher HDRS scores among PD-DEP patients compared to those with MDD. This difference may initially appear to derive from the additional effects of the degenerative nature of PD and its association with disease neurobiology.³⁸⁻⁴²

From the cognitive point of view, numerous studies have shown that individuals with PD encounter more significant specific cognitive symptoms (i.e., concentration difficulties) relative to those suffering from depression alone⁴³ although a recent novel study suggested that the comorbidity of MDD and PD is likely the result of certain shared pathological processes, rather than a direct mutual cause-and-effect relationship.^{40,44}

This observation is consistent with previous evidence that PD-DEP may constitute a unique clinical entity,⁴⁵ which poses diagnostic challenges, since specific symptoms may not entirely fulfil the criteria for MDD and dementia^{3,4} but lead to significant disability.^{46,47}

Limitations

Several limitations to this study should be noted. First, the participants were relatively healthy and older at the time of enrolment, with a narrow age range. The findings may not, therefore, be fully generalizable to the broader PD population with depression. Second, the sample size was relatively small, with a limited number of PD cases involving individuals with normal cognition, making it difficult to draw clear comparisons with the healthy control group. Our findings should therefore be regarded as exploratory and preliminary, requiring validation in larger, future studies with a similar design.

Despite these limitations, our research sheds valuable light on an underexplored area, specifically, whether cognitively and functionally healthy individuals with MDD exhibit differences in cognitive features compared to PD patients with depression.

CONCLUSION

As a conclusion, the results of this study suggest that clinical differences between PD-DEP and MDD are multifactorial, and the cognitive status of PD patients might be affected by the depressive state and characteristics of PD patients, emphasizing the significant role of brain circuits in depression associated with PD that should be evaluated in further studies.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Clinical Researches Ethics Committee of Alanya Alaaddin Keykubat University Faculty of Medicine (Date: 09/24/2025, Decision No: 13-14).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Concept: SC, GC, BY; Design: SC, GC; Supervision: BY; Data Collection and/or Processing: SC, GC; Analysis and/or Interpretation: SC, BY, HI; Literature Review: SC, GC; Manuscript Preparation: SC, GC, BY; Critical Review: All Authors

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