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RESEARCH

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Impact of Parkinsonism comorbid depression on cognitive functions

Ghaydaa A. Shehata[1], Hassan M. Farweez[1], Anwar M. Ali[1], Huda S. Hassan[2], Amal M. Tohamy[1], Mohamed Mostafa[1], Mostafa A. Ibrahim[1], Khaled Tarek[3], Asmaa Ahmed Elrashedy[4], Ramy Abdelnaby[5], Mohamed Elsayed[6] and Dina Elsayed Gaber[7*]

Abstract

Background Parkinson's disease (PD) is a chronic progressive neurodegenerative disabling disease and involves about 1–3% of the worldwide population over the age of 60. A significant prevalence of psychopathological symptoms has been recorded as most patients with PD developed over their disease course neuropsychiatric symptoms such as depression, anxiety, sleep disorders, psychosis, and cognitive and behavioral abnormalities. These non-motor symptoms, which could appear decades before motor ones, become disturbing symptoms during the later phases of the disease. Hence, the current research aims to study depressive symptoms in Parkinson's disease patients. Thirty-six patients with Parkinson's disease aged from 40 to 65 years (20 males and 16 females) and 36 age and sex-matched controls (19 males and 17 females) were included in the study. Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr scale, Schwab and England's scale, Mini-Mental State Examination, Cognitive Ability Screening Instrument, and Hamilton Depression Rating Scale were applied to assess depression in both groups.

Results Patients were 20 males and 16 females (mean age 52.44 ± 7.45), mean duration of Parkinsonism was 3.88 years. The mean value for Hoehn and Yahr scale was 1.97 ± 1.42, for UPDRS T was 42.41 ± 20.91 and Schwab England's scale was 74.77 ± 17.78. Concerning cognition, MMSE was significantly lower among patients 25.33 ± 3.63, than in the control group and CAS total was significantly lower in patients (16 ± 71.35) than in the control group 9.81 ± 84.62.

Conclusion Depressive symptoms are widespread in Parkinson's disease. Depression should be strictly determined and addressed, particularly in patients with more advanced cognitive impairment who are at a higher risk of developing or worsening depression.

Keywords Parkinson's disease, Depressive symptoms, Non-motor symptoms, MMSE, CAS, Cognition

*Correspondence:
Dina Elsayed Gaber
dina.gaber@alexmed.edu.eg
[1] Department of Neurology and Psychiatry, Assiut University Hospitals, Assiut, Egypt
[2] Psychology, Faculty of Art, Assiut University, Assiut, Egypt
[3] Medical Student, Faculty of Medicine, Cairo University, Cairo, Egypt
[4] Faculty of Medicine, Kafr-El-Shaikh University, kafr-el shaik, Egypt
[5] Department of Neurology, RWTH Aachen University, Pauwels Street 30, 52074 Aachen, Germany
[6] Department of Psychiatry and Psychotherapy III, C, Leimgrubenweg 12-14, 89075 Ulm, Germany
[7] Department of Neurology, Faculty of Medicine, Alexandria University, Alexandria, Egypt

Background

Parkinson's disease (PD) is a chronic progressive neurodegenerative disabling disease [1] and involves about 1–3% of the worldwide population over the age of 60 [2, 3]. After Alzheimer's disease, PD has been the second most frequent neurodegenerative condition [4, 5].

Early substantial loss of dopamine-producing neurons in the substantia nigra pars compacta (SNpc), and an extensive accumulation of the neuronal protein called alpha-synuclein (aSyn) protein are hallmarks of PD [6]. Typical Parkinsonian motor symptoms include

bradykinesia, tremor, stiffness, and subsequently postural imbalance due to dopamine insufficiency in the basal ganglia [6, 7]. Although PD is generally thought of as a motor condition, individuals with the disease experience a broad range of non-motor symptoms [8, 9]. A significant prevalence of psychopathological symptoms has been recorded as the majority of patients with PD developed over their disease course neuropsychiatric symptoms such as depression, anxiety, sleep disorders, psychosis, and cognitive and behavioral abnormalities [7]. These non-motor symptoms, which could appear decades before motor ones, become disturbing symptoms during the later phases of the disease [6].

The prevalence of depressive disorders in people with Parkinson's disease (PD) varies greatly between studies, from 2.7 to over 90%, among non-motor symptoms, depression is most frequently encountered among people with Parkinson's disease; in fact, one in two of these patients have been shown to have depression [10]. As a result, depression is among the most observed neuropsychiatric disorders in PD [8]. However, the estimated prevalence varies depending on the criteria of "case-ness", the population selected, the depressive categories or distinctive mood disturbances studied, and the manifestation and course heterogeneity [11]. Even though depression was commonly observed in Parkinson's disease patients, only 1% of them acknowledged they experienced depression, according to the Global Parkinson's Disease Survey Steering Committee (2002) [12]. Also, considering that depression is frequently ignored in PD due to the high degree of overlap in symptoms, the accuracy of these findings is difficult to judge [13, 14].

The mechanisms involved in depression in PD are unidentified. Although psychological aspects are valuable, social influences and disabilities are not the primary drivers of depressive disorders in people with PD [15]. Instead, neurological considerations linked with the underlying degenerative condition and its somatic therapies provide a setting for an increased prevalence of depressive symptoms in individuals with PD compared with individuals with other chronic debilitating disorders accompanied by disability [11].

However, the degeneration of dopaminergic neurons and intraneuronal Lewy bodies in the SNpc are the cornerstone neuropathological abnormalities of PD; it is widely understood that neurological pathology in PD expands beyond the midbrain and includes distinct degeneration of noradrenergic and serotonergic neurons. Together, these neural components are connected to mood and reward system modulation and mood abnormalities in Patients with PD and the overall population [8].

Depression in PD is regarded as a direct outcome of the neurodegenerative pathway rather than a consequence of the chronic condition [16, 17]. In addition, it is among the most significant aspects of PD patients' low quality of life, corresponding to or even more potent than the intensity of their motor deficits [14] as it is also correlated to worsened motor deficits and accelerated disease progression [13]. Despite these findings, depressive symptoms in people with PD are underdiagnosed and undertreated [18].

The etiology of depression may include mTOR expression in the infralimbic cortex, as Garro-Martínez and colleagues study highlighted [19].

One naturally occurring tryptophan (Trp) metabolite that has been shown to have neuroprotective qualities also known as kynurenic acid (KYNA). Neurodegeneration, neuroinflammation, and nociception are all significantly impacted by KYNA. Patients with neurodegenerative illnesses like Parkinson's and Alzheimer's disease or psychiatric disorders like depression are shown to have reduced levels of KYNA [20].

Regarding imaging, Coa and colleagues in 2021 performed a study on tensor-regression-based platform for structurally differentiating among nondepressed, depressed parkinsonism patients and healthy controls with a good prediction accuracy. Simultaneously, neurological distinctions between individuals with depressed parkinsonism and those without it were observed in the corpus callosum, cerebellum, and right superior temporal gyrus, as well as in the bilateral fronto-occipital lobe, left temporal lobe, bilateral basal ganglia, and thalamus. Tensor-regression-based platform crucial part in the statistical processing of complicated, high-dimensional MRI imaging data to help the radiological diagnosis of depression and Parkinson's disease comorbidity [21].

In a study by Gustafsson and colleagues in nation-wide cohort study it concluded that There was a clear correlation between depression and eventual Parkinson's disease (PD), as evidenced by the time-dependent impact, dose–response pattern for recurrent depression, and absence of evidence for coaggregation among siblings. With a follow-up time of almost two decades, the connection was strong, suggesting that depression might be a causative risk factor or an extremely early prodromal symptom of Parkinson's disease [22].

Hence, our research seeks to study depressive symptoms in PD patients, which is crucial for providing high-quality care for such patients and outlining the real disease burden of Parkinsonism.

Methods

The current study was a case–control study patients fulfilling the criteria included total was 36 patients with Parkinson disease aged from 40 to 65 years (20 males and 16

females) and 36 age and sex-matched controls (19 males and 17 females) were included in the study.

Patients with Parkinson's plus or with risk factors like hypertension, diabetes mellitus, infections, cerebrovascular insult, and drug intake of antipsychotics were excluded from the study.

All patients and control group were subjected to detailed history taking and examination. Scales were applied to all patients and the control group. Unified Parkinson Disease Rating Scale (UPDRS) [23] which is composed of 4 parts to assess the degree of mentation, behavior and mood, activity of daily living, motor assessment, and complications of therapy was applied and documented. Also Hoehn and Yahr scale for staging of the disease as well as Schwab and England's scale for daily living activity were assessed. Mini-Mental State Examination [24] and Cognitive Ability Screening Instrument (CASI) [25] were used to assess the cognitive function. Hamilton Depression Rating Scale (HDRS) was applied to assess depression in both groups.

The study was approved by Alexandria University hospitals ethical committee. All patients or their relatives wrote written consent.

Statistical analysis was through IBM SPSS v25 software was used for the data analysis. Data normality was checked visually by examining histograms and *Q*–*Q* plots and statistically using Shapiro–Wilk's test. The majority of the data was non-normally distributed. Student's *T*-test or Mann–Whitney *U* test was conducted to compare means of continuous variables. Chi-square test was used for comparison of categorical variables. ROC curve analysis was conducted to test the diagnostic accuracy of trans-cranial Doppler indices in differentiating between cases and controls. The optimum sensitivity and specificity were obtained according to Youden index. The area under the curve (AUC) was obtained. *P*-values less than 0.05 were considered statistically significant.

Results

This study was carried out on 36 Parkinson disease patients, (M/F ratio, 20/16) with mean age of 52.44 ± 7.45 years. The mean duration of the disease was 3.88 years. The control group consisted of also 36 age- and gender-matched healthy persons (M*F* ratio, 19/17) with mean age of 49.94 ± 6.26 years with non-significant difference than the patients group ($p = 0.813$). The social scale was 12.5 ± 1.15 in the patients and 12.47 ± 1.32 in the control with a non-significant difference also ($p = 0.917$) as shown in Table 1.

The mean scores that measure the severity of Parkinson disease in the patients under the study are mentioned in Table 2.

Table 1 Demographic data of the patients and control groups

	Patients	Control	*p*-value
Number	36	36	–
M/F ratio	20/16	19/17	–
Age	52.44 ± 7.45	49.94 ± 6.26	0.813
Social scale	12.5 ± 1.15	12.47 ± 1.32	0.917
Mean duration of the disease	3.88 years	–	

M: male, F: female

Table 2 Scores measuring severity of Parkinson's disease group

Variables	Patients ($n = 36$)
UPDRS I (mentation, behavior, mood)	3.58 ± 2.25
UPDRS II (activities of daily living)	15.27 ± 7.71
UPDRS III (motor activities assessment)	19.69 ± 4.05
UPDRS IV (complications)	4.13 ± 4.05
UPDRS T	42.41 ± 20.91
Hoehn and Yahr	1.97 ± 1.42
Schwab England	74.77 ± 17.78

UPDRS Unified Parkinson's Disease Rating Scale

Mini-Mental State Examination (MMSE) score was significantly lower in Parkinson's disease patients (25.33 ± 3.63) than in control group (28.25 ± 1.98, $p < 0.001$). In contrast to the MMSE, an increase of the Hamilton Depression Rating Scale (HDRS) score was recorded for the patients group (11.08 ± 8.15) than the controls (0.166 ± 1.73, $p < 0.001$).

For cognitive ability screening instrument score, was significantly lower in the patient group (7.53 ± 2.51) compared to the control group (8.28 ± 1.86, $p < 0.001$) with regard to long-term memory (LTM). Also for short-term memory (STM), the same was observed where the patients group had a significantly lower score (8.46 ± 2.88) than the control score (11.68 ± 1.07, $p < 0.001$). For attention and mental manipulation, the patients group showed also significantly lower scores than the control as mentioned in Table 3.

For drawing, abstract thinking and total score of CASI scale, the patient group recorded significantly lower scores than the control ($p = 0.011$, 0.001 and 0.001), respectively.

Regarding Hamilton depression score among the studied sample, in the Parkinson's patients, ($n = 14$, 38.89%) were normal while 61.1% $n = 22$ patients suffered from depression and their distribution was ($n = 15$, 41.67%) showed mild depressive symptoms, ($n = 5$, 13.89%) showed moderate symptoms, and ($n = 2$, 5.56%) severe depressive symptoms. Compared to healthy controls, all of them ($n = 36$, 100%) were normal (Fig. 1).

Table 3 Cognition and depression data in the patients and control groups

Variables	Patients ($n=36$)	Controls ($n=36$)	*P* Value
MMSE	25.33 ± 3.63	28.25 ± 1.98	0.001
HDRS	11.08 ± 8.15	0.166 ± 1.73	0.001
CASI-LTM	7.53 ± 2.51	8.28 ± 1.86	0.248
CASI-STM	8.46 ± 2.88	11.68 ± 1.07	0.001
CASI-Att	7.58 ± 0.937	8.56 ± 0.843	0.001
CASI-MM	4.80 ± 2.84	7.63 ± 1.17	0.001
CASI-Orient	12.11 ± 3.70	13.14 ± 396	0.388
CASI-Draw	7.06 ± 2.50	8.31 ± 2.93	0.011
CASI-Abst	8.17 ± 2.55	11.58 ± 0.874	0.001
CASI-Fluen	8.47 ± 2.02	8.11 ± 1.76	0.230
CASI-Lang	7.17 ± 1.81	7.33 ± 1.91	0.739
CASI-Tot	71.35 ± 16	84.62 ± 9.81	0.001

MMSE Mini-Mental State Examination, *HDRS* Hamilton Depression Rating Scale, *CASI* Cognitive Ability Screening Instrument, *LTM* long-term memory, *STM* short-term memory, *ATT* attention, *MM* mental manipulation, *Orient* orientation, *Draw* Drawing, *Abst* abstraction, *Flu* fluency, *Lang* languages, *Total* total score

Regarding the Mini-Mental State Examination revealed that of the Parkinson's patients, ($n=27$, 75%) showed no cognitive impairment, ($n=5$, 13.89%) had mild impairment, ($n=4$, 11.11%) were moderate, and none were severely impaired. This is in contrast to controls where only ($n=3$, 8.33%) had mild cognitive impairment and the rest were normal (Fig. 2).

Parkinson's disease severity as indicated by UPDRS total score showed significant positive correlation with age, Hoehn and Yahr scale and HDRS in Parkinson's patients. Conversely, a negative association was found with daily living activities as indicated by Schwab and England score and Cognitive Ability Screening Instrument total score, as shown in Table 4.

Discussion

Despite being preliminary and non-randomized, the study results strongly suggest that people with PD are more likely to develop depressive symptoms and cognitive impairment as we studied 36 Parkinsonism patients and 36 age and sex-matched controls.

Concerning the cognitive function, the current study showed that it was significantly lower than the control group; this was in concordance with another study by Vásquez and colleagues in 2019, which was conducted on 40 Parkinson's patients and stated lowered mini-mental state exam using MOCA score even in absence of a cognitive complaint [26]. Data on the prevalence rate of Parkinson's disease's mild cognitive impairment were

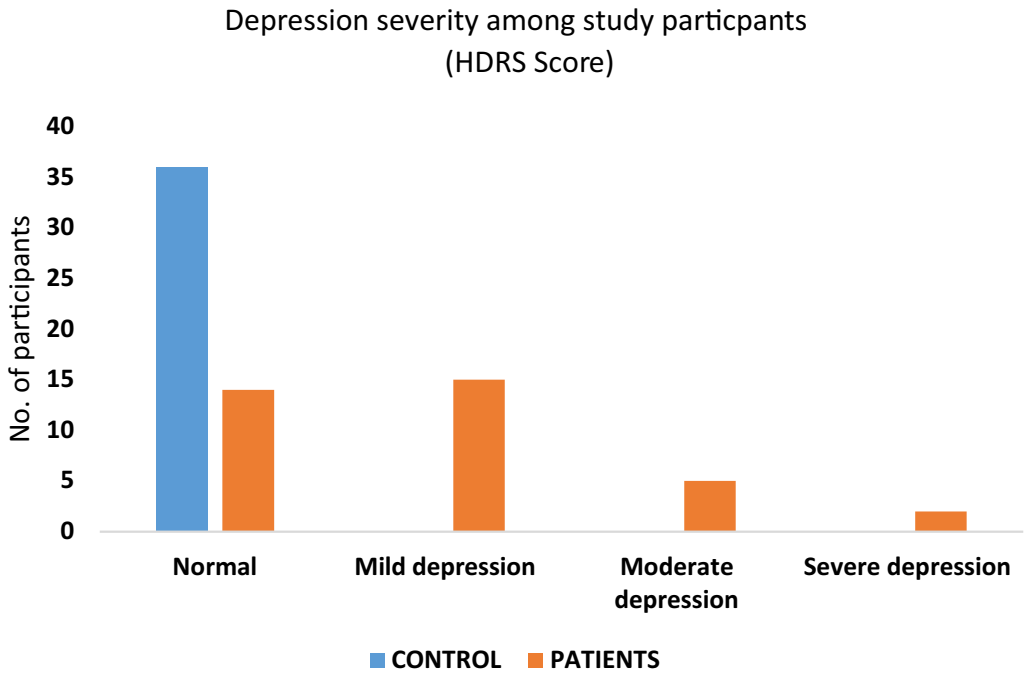

Fig. 1 Depression severity according to HDRS scores among study participants. Regarding Hamilton depression score among the studied sample, in the Parkinson's patients, ($n=14$, 38.89%) were normal while 61.1% $n=22$ patients suffered from depression and their distribution was, ($n=15$, 41.67%) showed mild depressive symptoms, ($n=5$, 13.89%) showed moderate symptoms and ($n=2$, 5.56%) severe depressive symptoms. Compared to healthy controls, all of them ($n=36$, 100%) were normal

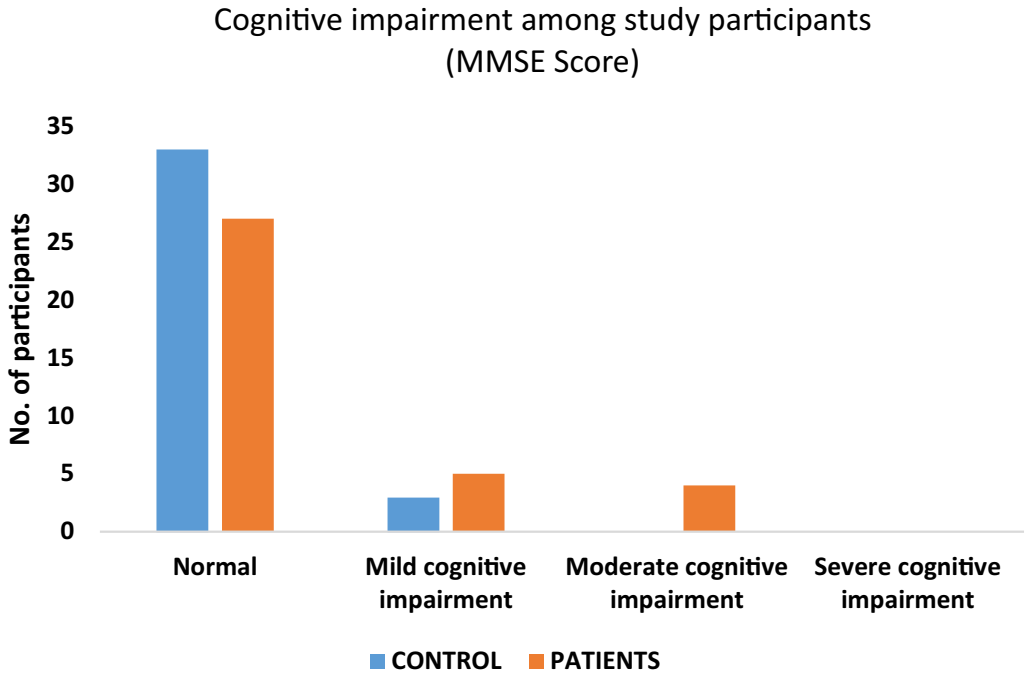

Fig. 2 level of cognitive impairment according to MMSE among study participants. Regarding the Mini-Mental State Examination revealed that of the Parkinson's patients ($n=27$, 75%) showed no cognitive impairment, ($n=5$, 13.89%) had mild impairment, ($n=4$, 11.11%) were moderate, and none were severely impaired. This is in contrast to controls where only ($n=3$, 8.33%) had mild cognitive impairment and the rest were normal

Table 4 Correlation of Parkinson's severity (UPDRS total score) and population characteristic

Parameter	Spearman's r	*P* value
Age	**0.384**	**0.021**
Hoehn and Yahr	**0.760**	**< 0.001**
Schwab and England	**– 0.781**	**< 0.001**
Social scale	– 0.262	0.123
HDRS	**0.694**	**< 0.001**
CASI Total	**– 0.403**	**0.015**

BOLD variables showed significant correlation and a statistically significant difference

UPDRS Unified Parkinson's Disease Rating Scale, *HDRS* Hamilton Depression Rating Scale, *CASI* Cognitive Ability Screening Instrument

mixed from a number of prospective and cross-sectional researches, ranging roughly from 20 to 70% [27].

In a study by costa and colleagues in 2018, they showed a strong correlation between Parkinson's disease and melancholy, apathy, and anxiety and Parkinson's disease induced mild cognitive impairment [28].

According to the literature, depressive syndromes with PD have a wide range of prevalence estimates, ranging from 2.7 to over 90%. The characteristics of the population investigated, how the patient is diagnosed, the subtypes of depressive disorder evaluated, and the statistical approaches adopted could be factors in this variability [10, 29]. Depression affects 20–35% of persons with PD, with an 18% 1-year incidence of minor depression as its prevalence and incidence differ based on the diagnostic criteria [10, 30]. Apathy, anhedonia, psychosomatic, and neurovegetative symptoms, such as exhaustion, attention difficulties, and insomnia, are prominent in PD patients; consequently, diagnosing depression in patients with PD can be complicated [31].

According to a systematic review, major depressive disorder affected 17% of PD patients, whereas minor depression affected 22% [10]. These findings were similar to ours as PD severity, as indicated by UPDRS total score, showed a significant positive correlation with age, Hoehn and Yahr scale, and depression symptoms in PD patients. Conversely, a negative association was found with daily living activities, as indicated by Schwab and England score and Cognitive Ability Screening Instrument total score.

Some researchers believe that difficulty in daily activities is more closely linked to depression than motor disability [32, 33]. Irritability and dysphoria are more common in PD depression than in non-PD severe depression, whereas guilt, self-blame, and suicide attempts are less common [34]. Suicidal thoughts affect about 17–30% of people with PD, and this percentage is

twofold more than the overall population The suicidal attempts rate was between 0.7 and 4.3% [35].

In a study by Kotgal and colleagues. in 2018 it showed that Serotoninergic innervation correlates negatively with cortical beta amyloid load in Parkinson's disease. Serotoninergic drugs may change the metabolism of beta amyloid and hence lower the risk of cognitive declined due to Parkinson disease [36]. Hence its very important to study the impact of Parkinson disease on depression and cognitive decline.

In a study by Petkus and colleagues in 2019, they demonstrated that after following 362 Parkinson patient not suffering from dementia for a year, worse cognitive functioning across all cognitive domains was linked to a rise in anxiety and depressive symptoms [37].

There has been researching into the gender differences in PD depression as some findings have demonstrated a link between sex and depressed mood in PD patients, whereas others have not [9] like our findings ($p=0.813$). Also, the social scale was 12.5 ± 1.15 in the patients and 12.47 ± 1.32 in the control, with no significant difference ($p=0.917$). The reason for divergences between studies may be that the effect of sex is not very strong, and a large sample is needed to demonstrate it [9].

A previous study reported that cognitive decline (MMSE < 24) is a predictor of depression in PD patients [5]. Other research has shown that depression can cause and exacerbate cognitive impairment in PD patients [38]. These findings were in line with our study regarding the cognition and depression data in the patients and controls; the MMSE score showed a significant decrease in the patients than in the control group ($P<0.001$). In contrast to the MMSE, an increase in the HDRS score was recorded for the PD group than the control group ($P<0.001$).

With or without dementia, cognitive impairment is becoming a more widely recognized non-motor consequence of PD with major therapeutic implications [39]. Care home admission, mortality, and higher caregiver burden have all been attributed to cognitive impairment in PD. Cognitive impairment is also prevalent at the time of PD diagnosis [40]; according to Aarsland and colleagues [41], 19% of their untreated Patients with PD had cognitive impairment at the initial diagnosis. Thus, cognitive impairment is a concern from the beginning of PD and contributes considerably to the disease morbidities and death [39].

Memory is not a single entity, but various memory systems are supplied by many brain structures, including implicit memory and explicit (or declarative) memory. Explicit memory is gained by top-down approaches in which multiple brain areas assist in the learning experience. On the other hand, implicit memory is acquired by bottom-up approaches, in which the memory is primarily determined by the knowledge to be learned. The information-gathering into short-term memory and information extraction from long-term storage are most likely influenced by impaired attention and frontal-executive skills, which are frequent in PD. As a result, memory testing in PD patients has mainly concentrated on explicit and implicit memory [39].

Several studies show that in PD patients without dementia, both verbal and non-verbal explicit memory can be affected. Numerous investigations have indicated that early PD can affect both rapid and prolonged wordless learning, although the consequences on identification are less clear [39–41]. In our study, for cognitive ability screening instrument score, there was a significant decline in the patient group (7.53 ± 2.51) compared to the control group ($8.28 + 1.86$, $p<0.001$) as regards long-term memory. Also, for short-term memory, the same was observed where the PD group had a significantly lower score (8.46 ± 2.88) than the control group (11.68 ± 1.07, $p<0.001$). The PD group also showed significantly lower scores than the control group for attention and mental manipulation. The PD group recorded significantly lower scores than the control for drawing, abstract thinking, and total score on the CASI scale ($p=0.011$, 0.001, and 0.001, respectively).

Randomized clinical trials would be necessary to fully evaluate the long-term influence of depressive symptoms on PD patients' life quality and cognition.

Conclusion

The current study highlights the correlation between reduced cognitive and daily living activities and a higher Hamilton depression score and a higher UPDRS in Parkinson's disease. Patients suffering from Parkinson's disease typically experience extensive and enduring depressive symptoms. Depression should thus be properly diagnosed and treated, especially in people with more severe cognitive impairment who are more likely to experience depression or aggravate existing depression.

Abbreviations

UPDRS	Unified Parkinson's Disease Rating Scale
MMSE	Mini-Mental State Examination
PD	Parkinson's disease
SNpc	Substantia nigra pars compacta
aSyn	Alpha-synuclein
KYN	Kynurenine
CASI	Cognitive Ability Screening Instrument
HDRS	Hamilton Depression Rating Scale
IBM SPSS	Software platform offers advanced statistical analysis
AUC	Area under the curve

STM	Short-term memory
MOCA	Montreal Cognitive Assessment

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Author contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by (GAS, HMF, AMA, HSH, AMTm MM, MAI, KT). The first draft of the manuscript was written by (AAE, RA, MEGE, DEG) and all authors commented on previous versions of the manuscript. D.E.G: revision of the results and the manuscript and the corresponding author. All authors have read and approved the manuscript.

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Availability of data and materials
The research data supporting the results reported in the article are totally available upon request from the corresponding author.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the Ethics Committee (EC) of Faculty of Medicine which is constituted and operates according to the International Conference on Harmonisation-Good Clinical Practice ICH GCP guidelines (Food and Drug Administration guideline) and applicable local and institutional regulations and guidelines which govern EC operation. The approval was obtained by the monthly meeting of EC on 11th November 2022. And hence this research was registered in Alexandria faculty of medicine by number 0305852. A written informed consent was obtained from all subjects prior to recruitment to the study. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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