Objective: The aim of this research was to elucidate the effect of deep brain stimulation on apathy, and cognitive functions in the pre and post-operative period. Materials Methods: This study was conducted in Adana City Training Research Hospital, Parkinson and Movement Disorders Center between January to December 2022. Individuals were evaluated by a multidisciplinary commission consisting of neurology, neurosurgery and psychiatrists. Thirty six, aged between 18–70 years who underwent Deep Brain Stimulation at the neurosurgery clinic were included in the study. Hamiltonanxiety and depression, apathy assessment, standard mini-mental test and Montreal Cognitive Assessment scales are applied to the patients. Results: The mean Apathy Score at the pre-op was 47.77±15.83 in patients who had undergone DBS operation while it was 30.83±13.59 in the post–op. This decrease was statistically significant ($p<0.003$) and indicated clinical improvement. The average Hamilton Anxiety scale scores at the pre–op was 11.50±5.14, and s 10.22±5.57 at the post-op with no clinical significance ($p=0.28$). The UPDRS-ON value was determined as 22.55±7.53 in the pre–op and 14.50±6.99 in the post–op significantly ($p<0.001$). UPDRS-OFF was found to be significant with pre–op 37.44±9.85, compared to post–op 23.44±7.86 ($p<0.001$). Conclusion: Regarding the results of this study, it was found that sub – thalamic stimulation led to stabilization of both motor and non-motor complications. Additionally DBS ameliorated apathy and Parkinson's Disease symptoms of patients significantly. Future studies with larger sample size that focus on both pharmacological and non-pharmacological treatments might provide better clinical aspects.

APATHY & COGNITIVE SYMTOMS IN DEEP BRAIN STIMULATIONSTIMULATIONSTIMULATIONSTIMULATIONSTIMULATIONSTIMULATIONSTIMULATIONSTIMULATIONSTIMULATIONSTIMULATIONSTIMULATIONS'

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Abstract

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both motor and non-motor non-motor non-motor non-motor non-motor complications. Additionally DBS DBS DBS DBS DBS ameliorated apathy and Parkinson's Parkinson's Parkinson's Parkinson's Parkinson's Disease symptoms of patients significantly. significantly. significantly. significantly. significantly. Future studies with larger larger larger larger larger sample size that focus on both pharmacological and non-pharmacological and non-pharmacological and non-pharmacological and non-pharmacological and non-pharmacological treatments might provide better clinical aspects.

Introduction

Idiopathic Parkinson's disease *(IPD)* is the second most common neurodegenerative disease after Alzheimer's disease and affects approximately 1.8% of the population over 60 years of age *(1)*. The main clinical symptoms are resting tremor, bradykinesia, rigidity and postural reflex disorder. Although it is considered a movement disorder and recognized by cardinal motor signs and symptoms, these are just the tip of the iceberg *(2, 3)*.

Parkinson's disease*(PD)* is classified as a neuropsychiatric disorder because of the non-motor symptoms *(NMS)* including cognitive, mood, autonomic and sleep disorders, as well as the motor symptoms that complicate the patients' lives, both in the pre-motor stage and throughout the entire course of the disease as it directly affects the quality of life and independence of the person *(4)*. Regarding this fact, the analogy of the perfect storm, which means a situation in which many bad things happen at the same time, consists of a combination of motor and non-motor symptoms.

Non-motor symptoms such as mood, impulse control disorders and cognitive dysfunctions are associated not only with dopaminergic defects in the basal ganglia but also with abnormalities in other neurotransmitter systems (5,6).

Non-motor symptoms have common etiopathogenesis with the motor symptoms of Parkinson's disease, and emerge as adverse effecys of the treatment in Parkinson's disease. It has been suggested that psychiatric symptoms arise as a result of the chaotic interaction and change of neurotransmitters such as dopamine, serotonin, nor-adrenaline and acetylcholine, beyond trying to understand the basis of a single one *(7)*. In previous literature it was reported that certain psychiatric diseases such as depression anxiety disorder schizophrenia are risk factors for Parkinson's disease. In this context, Parkinson's disease is a very complex and chronic disease *(8)*. Cognitive dysfunction is a common symptom in Parkinson's disease patients. It manifests itself in a wide spectrum ranging from insidious onset, slow progression, mild intellectual impairment that can affect some areas of cognitive functions, especially executive functions, to severe dementia *(9)*.

Awareness of the importance of neuropsychiatric and cognitive symptoms, including apathy, in the management of patients with Parkinson's disease has increased over the last decade. Apathy, a common neuropsychiatric disorder that can precede the onset of the first motor symptoms of Parkinson's disease, is the unique combination of a lack of purposeful action, often self-initiated, and a diminished responsiveness to stimuli, giving the person the appearance of apathy, affect flattening, or mind blankness. The prevalence of apathy in PD is between 16.5% and 40% and may occur early in the disease. In neurologic diseases, apathy is associated with atrophy in some brain regions such as the anterior cingulate, dorsolateral prefrontal cortex and orbitofrontal cortex or dysfunction in the basal ganglia *(10)*.

Parkinson's disease treatment can be divided into two as medical and surgical. In order to achieve a better levodopa response in Parkinson's disease, surgical treatment as deep brain stimulation treatment of subthalamic nucleus *(STN)* and globus pallidus internus *(GPi)* is applied *(Evidence Level – 1)*. According to UK National Institute of Clinical Excellence *(NICE)* guidelines, individuals must be resistant to medical therapy, have side effects depending on the medication, and be medically and psychologically fit with prolonged 'off' periods *(11)*.

Deep Brain Stimulation *(DBS)* is the most commonly used surgical method for the motor symptoms of Parkinson's disease. In this procedure, microelectrodes are placed in one of the two regions of the brain *(subthalamic nucleus or globus pallidus region)* in order to give high-frequency electrical stimulation *(12).* This stimulation regulates the signal that is missing in Parkinson's patients. DBS surgery is the most preferred surgery as it is safe, effective, fully reversible and adaptable to the patient. This treatment is applied to patients who are resistant to drugs or have side effects *(13).*

The subthalamic nucleus, medial globus pallidus and ventral middle nucleus of the thalamus are the most poignant target areas for deep brain stimulation. Among these, the subthalamic nucleus, which has been the most studied and experienced region in recent years, seems to be the most suitable area for Parkinson's patients. Although many mechanisms have been proposed about how deep brain stimulation affects the brain, its effect is not fully understood, but it is thought to improve brain function by neutralizing abnormal brain activity. Anatomically, the STN consists of three subunits: dorsolateral motor area, ventromedial cognitive area and medial limbic area, with a central location in the limbic region thalamocortical connection and basal ganglia. The effects of STN DBS on motor and non-motor symptoms may be influenced not only by electrical stimulation but also by the location of the stimulating electrode within the STN. For example, stimulation in the ventromedial part will cause symptoms related to limbic connected circuits, e.g. hypomania/mania-like state can be eliminated by stimulating the dorsal part *(10).*

Although some of the study results suggest that STN DBS causes cognitive deterioration,*(9)* ome suggest that there is no significant cognitive impairment in long-term follow-up,*(14)* and some suggest that the long-term cognitive impairment is due to the progression of the disease rather than stimulation, the predominant studies suggest that STN DBS worsens verbal fluency, memory and executive functions*(15).*

The Montreal Cognitive Assessment (MoCA) and Standardized Mini Mental Test (SMMT), which we used in our study, are short, easy-to-administer scales for detecting cognitive impairment. MoCA has high sensitivity and specificity especially in mild stages of cognitive impairment. In more advanced stages, the SMMT is still widely used because it can be administered to the untrained population for screening purposes. However, due to their inability to define detailed cognitive areas, they do not allow us to make additional comments except that there was no cognitive deterioration in our patients in the early period*(16).*

In this research, we aimed to elucidate the effect of deep brain stimulation on apathy and cognitive functions in the pre and post-operative period. We believe that the outcomes of this study will to improve the clinical applications and provide better clinical usage.

Materials & Method

A total of 18 patients aged between 18 – 70 years, who were diagnosed with Parkinson's disease and followed up in the neurology clinic of our institution have been enrolled within the scope of this research. The patients were evaluated by a commission of specialists consisting of neurologist, neurosurgeon, and psychiatrist in a multidisciplinary approach. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation *(institutional and national)* and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution at *10/05/2022* with protocol number *1928* and informed consent has been obtained from all participants.

Inclusion Criteria

Patients between the ages of 18-70 who were diagnosed with Parkinson's disease between 28/01/2022 and 31/12/2022, followed up in the neurology clinic of our institution and underwent DBS in neurosurgery were included in the study. Individuals were required to be literate, volunteer to participate in the study and not have a psychiatric history that would interfere with the operation (affective disorder, severe anxiety,

psychotic history, suicidal history, major depression, manic episode, bipolar affective disorder, personality disorder). Each patient was evaluated by a psychiatrist and a psychologist for apathy levels before and after DBS.

Exclusion Criteria

Patients with severe disease symptoms or hearing/speech disabilities preventing them to cooperate during clinical or laboratory evaluations, serious or uncontrolled medical conditions *(hepatic, renal, gastroenterological, respiratory, cardiovascular, neurological, or oncological)* were excluded.

All patients included in the study were evaluated at preoperative month 0 and postoperative month 6 and each patient was administered the Sociodemographic Data Form, Structured Clinical Interview for DSM-5 Disorders - Clinician Version, Ham-A and Ham-D scales, Apathy Rating Scale, MoCA and standardized mini mental tests. The evaluation was made in this way because the expected motor (dyskinesia, etc.) and non-motor (apathy, depression, hallucinations, etc.) complications were observed in the early postoperative period and effective stimulation parameters were reached at the 6th month.

Τηερε ις νο ςονσενσυς ον τηε τιμε το σταρτ δεεπ βραιν στιμυλατιον αφτερ ελεστροδε πλαςεμεντ ιν τηε συβτηαλαμις νυςλευς, βυτ διφφερεντ αππλιςατιονς αρε σεεν. Αππροπριατε προγραμμινγ οφ στιμυλατιον παραμετερς ιν τηε ποστοπερατιε περιοδ ις ονε οφ τηε μοστ ιμπορταντ παραμετερς αφφεστινγ τηε συςςεσς οφ τρεατμεντ. Εμπιριςαλλψ, μανψ στιμυλατιον παραμετερς ηαε βεεν τριεδ το οβταιν τηε βεστ ςλινιςαλ ρεσπονσε. Ιν ορδερ το σεε ωηιςη στιμυλατιον παραμετερ ΔΒΣ ρεσπονδς βεττερ, τηε μοστ ςομμον ςλινιςαλ ρεσπονσε ωας βασεδ ον τηε δισαππεαρανςε οφ ριγιδιτψ, ανδ ιν τηε αβσενςε οφ ριγιδιτψ, τηε ςλινιςαλ ρεσπονσε το βραδψκινεσια ανδ ρεστινγ τρεμορ. Στυδιες ινεστιγατινγ τηε σπεςιφις εφφεστ οφ αμπλιτυδε, πυλσε ωιδτη ανδ φρεχυενςψ ηαε φουνδ τηατ αμπλιτυδε ηας α μορε σιγνιφιςαντ εφφεστ ον ιμπροινγ μοτορ σψμπτομς ιν Παρκινσον′ς πατιεντς. Ιμπλαντατιον οφ ελεστροδες ανδ ελεστριςαλ στιμυλατιον ηαε α σψνεργιστις εφφεστ το ιμπροε τηε μοτορ σψμπτομς οφ Παρκινσον′ς δισεασε. Δυρινγ τηις περιοδ, τηε δοσες οφ αντι-παρκινσονιαν δρυγς αρε γραδυαλλψ ρεδυςεδ το αοιδ δψσκινεσιας. Ανοτηερ ιμπορταντ ποιντ ις το ωαιτ φορ α ωηιλε βεφορε σταρτινγ ελεστριςαλ στιμυλατιον δυε το πλαςεβο ανδ νοσεβο εφφεστς σεεν αφτερ ελεστροδε ιμπλαντατιον. . Τηε προςεδυρε ωας περφορμεδ υνδερ λοςαλ ανεστηεσια. Σπεςιαλ ανδ περμανεντ ελεστροδες αρε ιμπλαντεδ ιν τηε ταργετ ποιντς οφ τηε βραιν. Ιν τηε λαστ παρτ οφ τηε συργερψ, α ηιγη-τεση βαττερψ ωας πλαςεδ υνδερ τηε σκιν ιν τηε ςηεστ αρεα ανδ ςοννεςτεδ το τηε ελεστροδες πλαςεδ ιν τηε βραιν. . Τηε προςεδυρε ωας περφορμεδ υνδερ λοςαλ ανεστηεσια. Σπεςιαλ ανδ περμανεντ ελεστροδες ωερε πλαςεδ ιν τηε ταργετ ποιντς οφ τηε βραιν. Ιν τηε λαστ παρτ οφ τηε οπερατιον, α ηιγη-τεση βαττερψ ωας πλαςεδ υνδερ τηε σκιν ιν τηε ςηεστ αρεα ανδ ςοννεςτεδ το τηε ελεστροδες πλαςεδ ιν τηε βραιν. Ιν τηε 3ρδ ποστοπερατιε ωεεκ, βαττερψ δεπλοψμεντς ωερε σταρτεδ ας 60 μς πυλσε ωιδτη, 130 Ηζ φρεχυενςψ, 1 μ, ανδ τηε λεαδοπα εχυιαλεντ δοσες υσεδ βψ τηε πατιεντς ωερε δεςρεασεδ ανδ εφφεστιε στιμυλατιον παραμετερς ωερε ρεασηεδ ιν τηε 6τη μοντη ανδ πλαννινγ ωας μαδε το βε ιν τηε ρανγε οφ 50-70 μς πυλσε ωιδτη, 130-150 Ηζ φρεχυενςψ, 2-4 μ.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences 25.0 (SPSS). Descriptive statistics are given as mean ± standard deviation or median-quartile range according to the distribution of continuous variables. Categorical variables are summarized as numbers and percentages. In the main group, participants were divided into those with and without preoperative diagnosis. Cut off values in the scales applied were interpreted as those with and without a diagnosis. Normal distribution parameters were analyzed with Student's t-test for intergroup comparison. Normality was analyzed by Shapiro Wilks test. If the distribution was not normal, the Mann-Whitney U test was used to compare two independent groups. Dependent variables are ordinal and continuous. Comparison of dependent variables was done with Paired-Samples T test. Chi-square test was used to analyze categorical variables. A P value of 0.05 was considered statistically significant.

Results

Distributions of baseline demographic, age of onset of Parkinson's disease and duration of disease were denoted in *Table 1*. The mean age of the individuals was 55.22±8.68 years. Gender distirbution was as follows: 44.40% *(n=8)* were female and 55.6% *(n=10)* were male. When the marital status was investigated, 100% of the 18 patients were married. Only 22.20% of the patients had a job. The mean age at onset of Parkinson's disease was 40.39±13.78 years, and the duration of the disease was 14.72±9.39 years. Comorbid diseases was; diabetes in 4 *(22.20%)* and hypertension in 4 *(22.20%)* patients. None of the patients included in the study was diagnosed with juvenile Parkinson's disease.

Ten subjects (55.57%) had Parkinson's disease and 2 patients (11.08%) had a history of psychiatric illness in their family. Five individuals (27.80%) used psychiatric medication and 9 patients (50%) had depressive symptoms It was observed that 9 of the patients included in the study had a history of depressive disorder and none of the depressive symptoms had psychotic features. The depressive symptoms were mostly slowing of movements caused by Parkinson's disease, inability to perform activities of daily living as a result of dyskinesia and dystonia caused by drug use, somatic symptoms such as pain and contraction in the extremities, vegetative symptoms such as sleep and appetite problems, and none of the patients had depressed mood symptoms such as self-harm (Table 2).

While the mean value of Apathy Score at the pre – operative 0^{th} month was 47.77±15.83 in patients who had undergone DBS operation, it was 30.83±13.59 in the post – operative 6^{th} month. This decrease was statistically significant *(p=0.003)* and indicated clinical improvement. In 7 of the 18 patients included in the study, the Hamilton depression (HAM-D) score before DBS was greater than 14, and a significant decrease was found in HAM-D scores after DBS except for 1 patient.

Hamilton anxiety (HAM-A) score was found to be greater than 15 in 5 of the patients and a significant decrease was recorded in HAM-A scores after DBS except for 3 patients. The average of Hamilton Anxiety scale scores at the pre – operative 0^{th} month was 11.50±5.14, and determined as 10.22±5.57 at the post – operative 6^{th} month with no clinical significance *(p=0.280)*. The Unified Parkinson's disease rating scale (UPDRS), UPDRS ON value was determined as 22.55±7.53 in the pre – operative 0^{th} month and 14.50±6.99 in the post – operative 6^{th} month significantly *(p<0.001)*. UPDRS OFF was found to be significant with pre – operative 0^{th} month 37.44±9.85, compared to post – operative 6 month 23.44±7.86 *(p<0.001)*. UPDRS motor scores of the patients were recorded in the off period in addition to the best on period. Statistically significant regression was observed at 6 months in both periods. (p<0.001)

The effective dose of levadopa was 1416.38±341.72 mg in pre operative 0^{th} month and 977.77±317.60 post – operative 6^{th} month *(Table 3)*.

Discussion

In this study, the effect of bilateral sub-thalamic nucleus deep brain stimulation on apathy was investigated. The mean age of Parkinson's disease patients who underwent STN DBS in the literature varied between 50.4±9.8 to 63.4±6.4 years, and the duration of the disease was between 7.5±2.9 to 18.8 ±6.1 years *(10 – 12)*. In our study, the mean age was 55.22±8.68 years and duration of disease was 14.72±9.39 years.

Advanced age is considered a relative contraindication for DBS and 70 years old is considered as an advanced age in many centers as it is often associated with faster progression of PD leading to rapid decline in cognitive functions, increased burden of comorbidity and greater brain atrophy. A minimum duration of 4 years of motor symptoms is recommended to confidently accept the diagnosis and documenting a good levodopa response may not be possible earlier than this. DBS in PD is typically performed within 11 – 13 years of illness, with progression of the disease leading to an increase in motor complications and a decrease in quality of life. Recent studies denoted that DBS outperforms the best medical treatment in younger group of patients with lower surgical risk *(13)*.

In previous literature it was reported that sub-thalamic nucleus deep brain stimulation improved motor fluctuations, dyskinesia, and quality of life in advanced Parkinson's disease *(14, 15)*. However, its effects on the processes underlying mood and behavior disorders are complex and certainly multifactorial. Therefore, the published articles presented contradictory outcomes *(16)*. *Drapier et al. (2006)* enrolled 15 patients who underwent STN DBS in the pre – operative period and 3^{rd} and 6^{th} months post – operatively and found a deteriorated apathy scores and although there was a therapeutic improvement in motor symptoms. Regarding this STC DBS may directly contribute to the development of apathy by affecting the limbic system *(17)*.

The *EARLYSTIM* study, in which patients were treated with bilateral sub-thalamic stimulation plus medical therapy, evaluated behavioral outcomes in a relatively large group of patients. Less neuropsychiatric fluctuations were observed in those receiving STN DBS plus medical treatment. Although dopaminergic replacement has been reduced in the early period despite the risk of developing acute withdrawal *(including apathy, depression, and anxiety in the following years)*, both motor and non – motor symptoms were stabilized at a higher rate compared to the group that received only medical treatment. Additionally, antidepressant and antipsychotic requirements of the patients were reduced. In the same study, they stated that the frequency of apathy was not different in both patient groups, but they achieved higher apathy scores in patients who received subthalamic stimulation *(18)*. Similar to their findings the levodopa dose has also been reduced significantly in our study.

All previously published literature seems to agree that dopamine agonist treatment achieves a rapid reduction of apathy scores. In our study, a significant decrease was observed in apathy scores at the 6th month after the operation. Although studies have shown that dopaminergic neuromodulatory systems are primarily effective in the development of apathy, which is defined as inadequacy in goal-oriented behaviors or in other words, impaired motivation, it has not been attributed to dopaminergic deficiency.

The occurrence of apathy in neurodegenerative diseases such as Alzheimer's disease, focal lesions such as cerebrovascular events and psychiatric diseases is considerable. The idea that ventomedial stimulation of STN DBS directly spreads to the limbic system and causes apathy may be influenced by the position of the stimulating electrode in the STN and the stimulus intensity, as we have stated before, and may contribute to explain the decrease in apathy scores in our study. We think that the gradual reduction of dopaminergic

treatments is extremely important, and the accompanying medical treatment should be optimized for STN DBS in order to ameliorate apathy scores. Reduction of dopaminergic drugs in parallel with increased subthalamic stimulation after surgery and cautious re – introduction of dopaminergic drugs in case of withdrawal apathy enables a better recovery while maintaining motivation and quality of life *(19, 20).*

Another issue to be considered can be elaborated as the decrease in apathy after the initiation of dopaminergic treatment in early-stage Parkinson's disease *(but this decrease does not last permanently).* On the contrary, apathy increases to 40% in patients without dementia and 60% in patients with dementia 5 – 10 years after the onset of disease *(21 – 24).* Considering the behavioral complications of dopaminergic treatments such as impulse control disorders, hallucinations, or delirium, it is obvious that the target in treatment is not only the correction of motor symptoms. In our study, while the pre – operative levodopa equivalent dose was 1416.38±341.72 mg, it decreased to 977.77±317.60 mg in the 6^{th} month of the post – operative period and this decrease was found to be statistically significant. According to the outcomes of this study, while the BPHDS *(I – III)* Off period values w significantly decreased in the post – operative period. These figures indicated that the patients had the opportunity to reduce the dopaminergic treatment dose by up to 70%, and to improve their motor symptoms by 60%.

Similar to our study, it was previously shown that STS DBS improved motor scores by 50% on average *(25).* Although anhedonia overlaps to a large extent with an emotional expression of apathy *(26),* studies have shown that isolated apathy is a disorder not associated with cognitive impairment or depression in the early and advanced stages of Parkinson's disease *(27, 28).* Approximately half of the patients with apathy do not have accompanying depression or cognitive impairment. Therefore, apathy in PD patients can be considered as a separate clinical entity *(29, 30).* The relationship between apathy and depression, which has common symptoms with apathy, is not yet clear and new therapeutic relationships are being tried to be established through transmission systems. Although it has been shown in the literature that the absence of sadness and depressed temperament, the presence of hoarseness, and the more frequent occurrence of blunted affection in states of joy and sadness in apathy, it makes it difficult to differentiate because it overlaps with many somatic symptoms of depression *(26).* In this case, apathy may mask the underlying depression and may be misdiagnosed as apathy in severely depressed patients. Based on the hypothesis that apathy is caused by dysfunction of the dopaminergic mesocortical limbic system, the results of many studies have agreed that apathy occurs as a risk factor independent of depression in Parkinson's patients and cannot be explained only by subcortical dysfunction *(27).*

There is a strong relationship between parkinsonism and depression. Published articles indicated that depression is diagnosed in Parkinson's patients 2 times more often than the general population, and accompanying depressive symptoms are motor – related. Depression exerts a very important effect in terms of affecting the quality of life by aggravating the symptoms even more *(31 – 33).* Depression rates varied between 30% and 50% according to the methodological differences and was found to be 44% in our study. At this stage one should ask whether the accompanying depression developed as a reactive response to the current illness and psychosocial difficulties or is it due to neuro – degeneration. In our study, Hamilton depression scores decreased significantly at the post – operative period.

Depressive symptoms in Parkinson's patients are generally characterized by loss of confidence, anxiety and irritability, and less feelings of guilt and failure. Changes in brain chemistry, along with physical disability play an important role in the development of depression. Slowness of movement before DBS, limitation of daily living activities as a result of dystonia and dyskinesias due to side effects of the drugs used, sleep appetite problems as a result of changes in the hypothalamus pituitary adrenal axis, somatic symptoms such as pain, contraction in the extremities are very common symptoms in Parkinson's patients. In our study, sleep, wakefulness, appetite and pain complaints with somatic symptoms in the foreground were observed in patients with a HAM-D score above 14. None of the patients included in the study expressed depressed mood such as self-harm. In the literature, there are studies showing that depression increases and suicidal thoughts occur after STN DBS *(20,42).* However, we think that these symptoms occur with patient selection and generally high stimulation parameters. Studies strengthen the hypothesis that basal ganglia contribute not

only to the regulation of movement but also to the improvement of mood through their functional connections *(43,44)*. The complete elucidation of the physiological mechanisms may eliminate this uncertainty. While the loss of daily activity due to off periods, the use of long-term and high doses of medications, difficulties in social life, and autonomic complaints in patients increase the risk of depression, the increased self-confidence with postoperative recovery, meeting their own needs, returning to social life provides an improvement in depressive complaints that cause loss of ability.

Cognitive disorders are rarely diagnosed in Parkinson's disease. Even in the early stages, cognitive impairment increases and even progresses to dementia in the following years. Results from many studies have shown that executive dysfunction was correlated with apathy *(34, 35)*. In our study, the change in the mean of minimental test *(MMSE)* and Moca values in the pre – operative and post – operative period was not significant, and relatively high pre – operative scores affected the scores of post – operative cognitive impairment.

The presence of apathy is predictive of more severe motor symptoms, worsened cognitive status, poor quality of life, greater caregiver burden, and decreased functionality. The inability of the person to perform the activities of daily living, the decrease in the treatment response, means that the individual becomes dependent on someone else for the continuation of life *(36)*. A comprehensive and multidisciplinary approach based on the bio – psychosocial model for the recognition, assessment, and management of each psychiatric symptoms on the invisible parts of the iceberg makes an important contribution to calming the storm and tailoring interventions to the needs of each patient in Parkinson's disease *(37)*.

Conclusion

Regarding the results of this study, it was found that sub – thalamic stimulation led to stabilization of both motor and non-motor complications. Additionally DBS ameliorated apathy and depression symptoms of the patients significantly. Future studies with larger sample size that focus on both pharmacological and non-pharmacological treatments might provide better clinical aspects.

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There is no specific funding related to this research.

Competing interests

The authors declare that they have no competing interests.

Ethical Declaration

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution and informed consent has been obtained from all participants.

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Running Title: **APATHY & COGNITIVE SYMTOMS IN DEEP BRAIN STIMULATION**

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