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Comparison of Apathy and Cognitive Symptoms in Pre- and Postoperative Period in Deep Brain Stimulation Surgery

Selim Polat[1], Miray Erdem[2], Melih Çekinmez[3]

[1]Department of Mental Health and Diseases, Adana City Training and Research Hospital, Adana, Turkey; [2]Department of Neurology, Adana City Training and Research Hospital, Adana, Turkey; [3]Department of Neurosurgery, Adana City Training and Research Hospital, Adana, Turkey

ABSTRACT

Background: The aim of the study was to investigatie apathy and cognitive functions in Parkinson's disease patients who underwent deep brain stimulation surgery on bilateral subthalamic nuclei.

Methods: This study included 18 patients with Parkinson's disease who were accommodated in the Parkinson's and Movement Disorders Center of Adana City Training and Research Hospital for treatment in 2022. Patients were evaluated by psychiatry, neurology and neurosurgery specialists with a multidisciplinary approach and found to be surgically appropriate. Standardized Mini-Mental Test and Montreal Cognitive Assessment Scale, Apathy Evaluation Scale, and Hamilton Anxiety and Depression Scale were administered to each patient before the operation and at 6 months after effective stimulation parameters were reached.

Results: The mean apathy score at the preoperative zeroth month was 47.77 ± 15.83 in patients having deep brain stimulation surgery and 30.83 ± 13.59 in the postoperative sixth month. Statistically that reduction was significant (P = .003) and showed clinical development. The average Hamilton Anxiety Scale scores at the preoperative zeroth month was 11.50 ± 5.14 and 10.22 ± 5.57 at the postoperative sixth month, with no clinical significance (P = .280). The determined value for the Unified Parkinson's Disease Rating Scale, on treatment, was 22.55 ± 7.53 in the preoperative zeroth month and 14.50 ± 6.99 in the postoperative sixth month, with statistical significance (P < *.001*). The Unified Parkinson's Disease Rating Scale, off treatment, score was revealed to be significant in the preoperative zeroth month (37.44 ± 9.85) in comparison to that of the postoperative sixth month (23.44 ± 7.86; P < .001).

Conclusion: This study showed that bilateral subthalamic stimulation improves nonmotor and motor symptoms in patients having Parkinson's disease. The mechanism is complex, and we believe that future studies focusing on pharmacological and nonpharmacological treatments involving more patient groups will be useful for clinicians.

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INTRODUCTION

Parkinson's disease is the most common disease after Alzheimer's disease and is characterized by degeneration of brain cells. The prevalence of this disease, which is classified among hypokinetic diseases, is 0.2%-0.3% in the general population and increases in older ages to approximately 1%-2% among people over 55 years of age.[1] In the clinic, there is usually an initial resting tremor, bradykinesia, which means a slowing of whole body movements, loss of fine motor skills, as well as rigidity and instability posturally. It should be remembered that they are assumed to be only the tip of the iceberg.[2,3]

Although Parkinson's disease (PD) is defined according to the cardinal motor symptoms that affect functional independence, it is classified as a neuropsychiatric disease because it includes non-motor symptoms including cognitive, autonomic, psychological and sleep disorders that directly affect the quality of life of the individual and are seen throughout the entire course of the disease.[4] This is why it has been described as a huge storm in which excessively bad things in bad situations happen simultaneously.

While the exact mechanism of etiopathogenesis has not been fully understood, the primary finding is the depletion of dopaminergic cells in the basal ganglia's substantia nigra pars compacta region, which results from the loss of structural and functional connections in the cortex, subcortex, and cerebellum.[5,6]

In addition, neuropathologic findings in the basal nucleus of Meynert, locus coeruleus, hypothalamus, and neocortex indicate that there is a widespread etiopathogenesis

Corresponding author: Selim Polat, e-mail: selim.md.polat@gmail.com

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underlying PD nonmotor and motor symptoms. Not only does the dopaminergic neurotransmitter system lead to all these abnormalities, but the irregular interactions of other neurotransmitter systems such as serotonin, noradrenaline, and acetylcholine also cause them.[7] There are some common nonmotor symptoms including impulse control, mood disorders, apathy, and cognitive deficits seen following the motor manifestations of the disease, and their severity and frequency increase along with the medications used for the treatment of time and PD. Psychiatric disorders have been shown to be a risk factor for Parkinson's disease in many studies.[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]

Over the past 10 years, there has been increased recognition of the role of neuropsychological and cognitive symptoms (including apathy) in the treatment of people with PD. Apathy is one of the most widespread neuropsychological disorders that precedes the onset of PD motor symptoms. It is characterized by a decrease in activity, often involuntary, and a decrease in reaction to stimuli, resulting in the manifestation of the apathetic symptoms (also referred to as affect flattened or mind dumbness). Apathy in PD ranges from 16.5% to 40% and appear in beginning period of illness. Regarding neurodegenerative disorders, apathy can be linked to atrophy in certain brain regions (anterior cingulate), including the brain's orbitofrontal and medial prefrontal cortices, or to dysfunction in the central nervous system (basal ganglia).[10]

Although there are a considerable amount of development in PD treatment, researchers have not found no effective neuroprotective treatment option to prevent or reduce the disease process the yet. In terms of the patient's age, reaction to treatment, side effects of the drugs used, quality of life, and many other factors, pharmacologic and surgical methods are applied to reduce the severity of nonmotor and motor symptoms. Many international treatment guidelines recommend deep brain stimulation to stabilize motor and neuropsychiatric non-motor symptoms that are refractory to pharmacotherapy, have rapid motor fluctuations during the day and occur with increasing drug doses, and to improve quality of life and maintain functional independence.[11]

MAIN POINTS

- Neuropsychiatric and cognitive symptoms, including apathy, are a very important part of the course of the disease.
- Electrodes iImplantation and electrical stimulation have a synergistic effect to foster the motor symptoms of PD.
- Appropriate programming of stimulation parameters in the postoperative period is among the most important parameters affecting the success of treatment.

Used for more than 50 years, DBS has been seen as a well-accepted treatment option in the scientific community due to its greater flexibility, fewer complications, and potentially reversible feature, thanks to the development of surgical and stimulation techniques, as well as the millimetric determination of the location of target areas in the brain.[12,13]

Subthalamic nucleus, medial globus pallidus, and ventral middle nucleus of thalamus DBS are the most relevant target areas. Among these, subthalamic nuclei have been the most extensively studied and experienced in recent years.

Although numerous theories have been proposed concerning the effects of DBS belonged to the brain, the precise mechanism of its action is not fully elucidated. However, it is generally accepted that the stimulation neutralizes abnormal brain activity, thereby improving brain function. The structural nervous system (STN) is composed of 3 divided subunits: the dorsolateral motor area, the ventromedial cognitive area, and the medial lateral area. The central location of the stimulation electrode in the STN is located in the thalamic region of the brain, which is connected to the basal ganglia and the cerebral cortex. The impact of STN DBS on motor symptoms and nonmuscular symptoms may be affected by more than just electrical stimulation. For instance, the stimulation of the dorsal part of the STN is possible to end up with symptoms associated with limbic interconnected circuits, such as hypomania- or mania-like states, which can be alleviated by stimulation of the dorsal area.[10]

Despite the fact that some studies have demonstrated cognitive impairment,[9] some others have demonstrated no proof for long-term cognitive decline,[14] while some have suggested that the long-term cognitive disorder is caused by the disease worsening rather than stimulation.[15] The majority of studies demonstrate that STN DBS leads to a decrease in verbal speech, memory, and executive functioning.[15]

The Montreal Cognitive Assessment (MoCA) Scale and Standardized Mini-Mental Test (SMMT) are quick, easy to administer, and highly sensitive to detect cognitive impairment. The MoCA Scale is particularly sensitive and sensitive in mild cognitive impairment, while the SMMT remains widely used in more advanced stages due to its ability to be administered to untrained populations for screening. However, as they are unable to define specific cognitive areas, we are unable to provide further comment except to note that our patients did not experience cognitive decline in the early phase of the study.[16]

In light of these findings, we set out to understand how DBS affected apathy and cognition, 2 of the most impairing nonmuscular symptoms of PD.

MATERIAL AND METHODS

Eighteen people with PD were monitored at Adana City Training and Research Hospital institution's Behavior and

Movement Disorder Unit. They were tested by a group of doctors who specialized in neurology, neurosurgery, and psychiatry for surgery. On April 10, 2022, Adana City Training and Research Hospital Clinical Research Ethics Committee approved the study (protocol number: 1928), and all of the participants consented to the study.

Patients who participated the study voluntarily, who could read and write, who did not have a psychiatric history such as mood disorder, suicidal history, personality pathology in the past and who did not have a history of psychiatric disorders such as mood disorders, suicidal history, personality pathology, and who had severe disease symptoms that would prevent surgery after biochemical and clinical evaluation were included in the study.

Deep brain stimulation surgery is done in 2 phases. In the first phase, electrodes are put in the target parts of the brain which use 3D neuroimaging techniques. This is done under local anesthesia. The patient is awake while stimulus parameters are adjusted based on their clinical condition. The second stage, the patient is placed under general anesthesia and a battery is placed under the skin in the chest area, which is connected to the electrodes to the brain.All these procedures take approximately 4-6 hours.

In the study, all patients were assessed at preoperative and postoperative zeroth month and sixth month, respectively. Every patient was given a Sociodemographic Data Form 5, a structured clinical interview [Clinical Version of the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition)], Sociodemographic Data Form (SDS-5), structured clinical interview [(DSM-5 Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) Clinical Version)], Hamilton anxiety and hamilton depression scales (Ham-A and Ham-D), apathy measurement (Apathy Rating Scale), motivation measurement (MoCA Scale) and standardized mini-mental test (SMMTMoCA) were applied to each patient. The neuropsychiatric evaluations were carried out by a trained clinical psychologist and psychiatrist. The assessment was conducted in this manner because the expected complications of motor function (such as dyskinesia) and nonmuscle function (such as apathy, depression, and hallucination) were observed at the beginning of the postoperative period, and successful stimulation parameters were achieved at 6 months.

There is no consensus on the time to start deep brain stimulation after electrode placement in the subthalamic nucleus, but different applications are seen. Appropriate programming of stimulation parameters in the postoperative period is among the most important parameters affecting the success of treatment. Empirically, many stimulation parameters have been tried to obtain the best clinical response. In order to see which stimulation parameter DBS responds better, the most common clinical response was based on the disappearance of rigidity, and in the absence of rigidity, the clinical response to bradykinesia and resting tremor. Studies investigating the specific effect of amplitude, pulse width and frequency have revealed that amplitude has a more significant impact upon improving motor symptoms in PD patients. Electrode implantation and electrical stimulation have a synergistic effect to foster the motor symptoms of PD. During this period, the doses of antiparkinsonian drugs are gradually reduced to avoid dyskinesias. Another important point is to wait for a while before starting electrical stimulation due to placebo and nocebo effects seen after electrode implantation. The process was performed through local anesthesia. Prior to the operation, special and permanent electrodes were inserted into the target areas of the brain. During the final phase of the procedure, a state-of-the-art battery was attached to the electrodes located in the chest area beneath the skin. In the third postoperative week, battery deployments were started as 60 μs pulse width, 130 Hz frequency, 1 mv, and the levadopa equivalent doses used by the patients were decreased and effective stimulation parameters were reached in the 6th month and planning was made to be in the range of 50-70 μs pulse width, 130-150 Hz frequency, 2-4 mv.

Statistical Analysis

Statistical Package for the Social Sciences version 25.0 (IBM SPSS Corp.; Armonk, NY, USA) program was applied for evaluation of the data. Descriptive statistics were revealed as mean value ± SD values; categorical variables were identified as frequency and percentage. Age, age at onset of PD, and disease process were analyzed as continuous variables; gender, comorbidity, marital status, and education level were analyzed as categorical variables.

Mainly, the participants consisted of 2 divided groups who were diagnosed before surgery and those who were not. The Kolmogorov–Smirnov test was used in the normality analysis variables. Dependent variables were continuous and ordinal. The paired-samples *t*-test was applied comparing dependent variables such as Apathy, Hamilton, UPDRS ON, MMST, and MoCA Scale. *P*-value was found to be statistically significant ($P < .05$).

RESULTS

The average age of the patients with PD was 55.22 ± 8.68 years in the study. 44.4% (n = 8) were female and 55.6% (n = 10) were male. All patients were married. When their employment status was questioned, only 4 (22.2%) were employed. The age at onset of PD was 40.39 ± 13.78 years and the disease process was 14.72 ± 9.39 years. When comorbidity status was questioned, diabetes was diagnosed in 4 (22.2%) patients and hypertension was diagnosed in 4 (22.2%) patients. None of the patients participating in the study was diagnosed with juvenile PD. Sociodemographic characteristics are shown in Table 1.

Table 1. Sociodemographic Characteristics of Parkinson's Disease Patients

Total Number of Patients (n)	18
Age (mean ± SD)	55.22 ± 8.68
Gender n (%) (female/male)	8 (44.40)/10 (55.60)
Education level, n (%)	
Not literate	1 (5.55)
Primary school	9 (50)
Middle school	3 (16.66)
High school	4 (22.22)
University	1 (5.55)
Employment status, n (%)	
Employed/unemployed	4 (22.20)/14 (77.80)
Age at onset of PD (mean ± SD)	40.39 ± 13.78
Disease duration (mean ± SD)	14.72 ± 9.39

PD, Parkinson's disease.

In terms of family history, there were 10 (55.57%) first-degree relatives with PD and 2 (11.08%) with a history of psychiatric illness. 9 (50%) of the cases had depressive symptoms and 5 of them were taking psychiatric medication. Nine of the patients experienced a history of depression, and none of them had any psychotic symptoms. The main symptoms were slow movement due to PD, not being able to do everyday activities due to dyskinesia or dystonia from drugs, somatic symptoms like pain and contractions in the arms and legs, and vegetative symptoms like sleep and food issues. None of the patients experienced depressive mood symptoms like harming oneself (Table 2).

Patients who had undergone a DBS operation had a mean apathy score that was lower than the preoperative value at the postoperative sixth month, i.e., at the preoperative zeroth month, the apathy score was lower than the postoperative value, i.e., it was lower than the sixth month by 30.83 ± 13.59. This decrease in apathy score was statistically significant, with a $P < .003$ value, and was indicative of clinical improvement. Seven of the 18 patients enrolled in the study had a HAM-D score higher than 14 prior to DBS, and there was a significant decrease in the HAM-D score after DBS, with the exception of 1 patient.

Table 2. Comorbid Features and Psychiatric History Associated with PD

	n (%)
Hypertension	4 (22.20)
Diabetes	4 (22.20)
PD in the family	10 (55.57)
History of psychiatric diseases	5 (27.80)
Family history of psychiatric illness	2 (11.08)
Depressive symptoms	9 (50)

PD, Parkinson's disease.

Hamilton anxiety HAM-A score was greater than 15 for 5 patients, and there was a significant reduction in HAM-A score after DBS with the exception of 3 patients. The mean HAM-A score at the preoperative zeroth was 11.5 ± 5.14 and was determined at the postoperative sixth month with no clinical significance. The UPDRS (Unified Parkinson's Disease Rating Scale), on treatment (ON), value was 22.55 ± 7.53 at the preoperative zeroth month and was statistically significant at the postoperative sixth month (14.50 ± 6.99; $P > .001$). The UPDRS off treatment (OFF) value was statistically significant at preoperative zeroth month at 37.44 ± 9.85 and at the postoperative sixth month at 23.44 ± 7.86. UPDRS motor scores of the patients were recorded in the off period in addition to the best on period. The regression detected in the scores for both periods was statistically significant ($p<0.001$).

The equivalent dose of levodopa (LED) was 1416.38 ± 341.72 mg in the preoperative zeroth month and 977.77 ± 317.60 in the postoperative sixth month (Table 3).

DISCUSSION

In our study, we investigated the effect of bilateral subthalamic nucleus DBS, which has a vital place in PD treatment, on apathy and cognitive functions.

Although it is a well-tolerated treatment option, it is extremely important to select cases that can respond well to surgical treatment. The first determinant in patient selection is the response to levodopa. It should be known that motor symptoms that do not respond to levodopa and deep brain stimulation. Studies show that disease lasts at least 4 or 5 years to determine continuous levodopa response and that good cognitive function before surgery is another factor that increases the success of treatment after surgery. Many centers consider 70 years of age as the surgical cutoff, and older age is considered contraindicated

Table 3. Pre-Op-Post-Op Comparison Results of PD Scale Values and Levodopa Equivalents

	Mean ± SD Pre-Op	Mean ± SD Post-Op	*P*
Apathy	47.77 ± 15.83	30.83 ± 13.59	.003
HAM-D	14.11 ± 7.52	11.22 ± 7.63	.025
HAM-A	11.50 ± 5.14	10.22 ± 5.57	.280
UPDRS ON	22.55 ± 7.53	14.50 ± 6.99	<.001
UPDRS OFF	37.44 ± 9.85	23.44 ± 7.86	<.001
L LED(mg ± SD)	1416.38 ± 341.72	977.77 ± 317.60	<.001
SMMT	27.05 ± 1.51	27.22 ± 1.69	.507
MoCA	23.05 ± 1.58	22.88 ± 1.49	.660

HAM-A, Anxiety; MoCA, Montreal Cognitive Assessment; SMMT, Standardized Mini-Mental Test; UPDRS OFF, Unified Parkinson's Disease Rating Scale, off treatment; UPDRS ON, Unified Parkinson's Disease Rating Scale, on treatmen. LED equivalent dose of levodopa, HAM-D Hamilton Depression.

as the surgical risk is associated with a greater amount of comorbidities, cognitive function loss, and further brain atrophy.

The current literature shows that DBS is effective in fostering motor performance, decreasing dyskinesias, the need for medication and thus increasing independence and improving life quality in patients with PD.[14,15] Nonetheless, its impacts on this procedure leading mood and behavioral disorders are complex and clearly multifactorial. Thus, articles being published have suggested conflicting results.[16] As far as we can see, there is no study involving a large number of patients in the literature. Drapier et al[17] conducted a study in 2006 in which 15 patients undergoing STN DBS underwent an evaluation of their apathy prior to and at 3 and 6 months post surgery. The researchers concluded that the STN DBS procedure had a direct influence on the limbic system, thus contributing to the onset of apathy.

The Earlystim (early stage stimulation) study, which was conducted with a relatively larger patient group in the literature, is a multicenter, randomized design study in which 251 PD patients were included and patients who received STN DBS were followed up for 2 years. In this study, patients were seen in 2 different groups as the group receiving STN DBS and medical treatment and the group receiving only medical treatment, and evaluations were made at the 5th, 12th, and 24th months. The study has 2 points that need to be emphasized. First, the group receiving only medical treatment has more neuropsychiatric fluctuations and therefore the need for more psychotropic use. The second important point is that despite developing acute withdrawal risk due to the reduction of dopaminergic treatment doses in the acute period in the patient group who received STN DBS, it was more stable in terms of both motor and nonmotor symptoms such as apathy, depression, and anxiety in the following years. No meaningful difference was observed between 2 groups only concerning apathy.[18]

Apathy, defined as the inability to perform goal-directed behaviors, or in other words as a motivation disorder, is a neuropsychiatric symptom associated with functional impairment. It is seen in many different brain diseases. It is noteworthy that it occurs in neurodegenerative diseases like Alzheimer's disease, focal lesions including cerebrovascular events, and psychiatric disorders. Although studies with drugs acting through the dopaminergic and noradrenergic neuromodulatory system are promising, the etiology has not been linked to dopaminergic deficiency in many studies. Although studies agree that dopamine-mimetic treatment leads to a decrease in apathy scores in PD patients in the acute period and decreased dopaminemimetic treatment after STN DBS leads to an increase in apathy scores, this effect is not permanent in the long term. Nevertheless, a few studies have reported that STN DBS causes apathy by directly affecting the limbic system, but the opposite result was found in our study. Apathy might be affected by the applied electrode position in the subthalamic nucleus, the intensity and direction of the stimulus, and this may explain the decrease in apathy scores in the study. The second important point is that despite the risk of developing acute withdrawal due to the reduction of dopaminergic treatment doses in the acute period in the patient group who received STN DBS, it was more stable in terms of both motor and non-motor symptoms such as apathy, depression and anxiety in the following years. The increase in apathy scores due to withdrawal caused by withdrawal of dopaminergic treatments provides a better cure while sustaining motivation and quality of life.[19,20]

Another point that should be emphasized is that apathy in PD patients decreases with dopaminergic treatments in the early stages, but this decrease is not permanent in the following years, on the contrary, it is seen as much more progressive over the years.[21-24] Although increasing dopaminergic activity is accepted as the most effective method to improve motor symptoms based on evidence, it has been shown that this activity decreases over time, leading to motor fluctuations and causing peripheral side effects including nausea, vomiting, orthostatic hypotension and arrhythmia. Considering cognitive and neuropsychiatric complications such as hallucinations, psychoticism, impulse control disorders, delirium, which are observed as central side effects, it should be known that the treatment target is much more than motor symptoms. In our study, when levodopa equivalent doses were evaluated preoperatively and at 6 months when effective stimulation parameters were reached, more than 50% reduction in doses was found, and at the same time more than 50% improvement in motor symptoms was observed and found to be statistically significant. Many studies investigating the effects of bilateral subthalamic DBS on motor symptoms also confirm our results.[25]

The process of apathy, which causes a decrease or blunting of emotional reactions to environmental events when viewed from the outside, is very similar to the loss of interest in depression, but the primary lack of motivation found in apathy is too deep to be attributed to emotional distress. Negative evaluations of one's self, environment, and future, which are found in depression, are generally not found in apathy. Studies have shown that apathy, whose frequency increases up to 70% in PD patients, is found alone in the absence of depression, claiming that different mechanisms have a part in the formation of depression and apathy.[26-30] Studies have shown that apathy and depression have common symptoms, but the connection between the 2 is still unclear. Researchers are trying to find new ways to treat apathy and depression through transmission systems. It is hard to tell the difference between the 2 because apathy and depression overlap so much with each other. In some cases, apathy may be a mask for depression and be mistaken for depression in severely depressed

people. A number of studies have suggested apathy to be an independent risk factor for depression in people with PD and cannot be just explained by dysfunction in the mesocortical nervous system.[27]

The association with depression is important in the clinical procedure of PD. Depression is a widespread neuropsychiatric disorder accompanying the diagnosis of PD. Depression is sometimes present long before the onset of motor symptoms and neurodegeneration during the course of the disease leads to an increase in the severity of prodromal mood disorders. Clinical management of depression can change the course of motor symptoms by reducing physical disability and improving quality of life. On the other hand, correction of motor symptoms contributes to the improvement of depressive symptoms.[31-33] In our study, similar to the literature, depression rates were found to be high and after bilateral subthalamic nucleus stimulation, a statistical decrease was found in depression scores in addition to motor symptoms.

Depression is a widespread symptom of PD. Parkinson's disease patients frequently face the feelings of less self-esteem, irritability, anxiety, guilt, and failure. This is because of changes in brain chemistry and physical disability, which can lead to depression. Some of the most common symptoms of depression among PD patients include slow movement before having DBS, limiting daily activities due to dystonia or dyskinesia caused by drugs, sleep problems due to changes in the pituitary–adrenal axis, and somatic symptoms like pain and contraction in the arms and legs. Our study found that people with PD with HAM-D scores above 14 had trouble sleeping, waking up, eating, and feeling pain. However, none of the patients experienced depressive mood symptoms or feelings of self-harm. Studies have shown that depression and suicidal thoughts are more likely to occur after having DBS. We think this is because the patient selection and stimulation parameters are high. Studies have also suggested that the basal ganglia not only regulate movement but also help improve mood through functional connections.[35,35] This uncertainty can be removed once the physiological mechanisms are fully understood. Losing daily activity through periods of inactivity; taking long-term, high doses of medication; social isolation; and autonomic complaints increase the likelihood of depression. The self-assurance developed with postoperative recovery, in terms of coping with their own needs and return to social life, improves complaints regarding depression that lead to loss of function.

Cognitive disorders are another difficult-to-manage nonmotor symptom in which dopaminergic and nondopaminergic systems have an important part in the etiology. Cognitive impairment is a condition in which speech is impaired, it is difficult to find words, and there is a loss of cognitive flexibility in a variety of areas. It may appear earlier than motor symptoms such as depression and may progress to dementia in later stages of the illness. In the literature, there are a considerable number of studies showing cognitive impairment at the onset of PD.[36,37] In our study, MoCA Scale and SMMT were utilized as screening tests to evaluate whether the patients were suitable for the operation, and no difference was found between before and after operation. However, given the simplicity of the scales used and the fact that they are for screening purposes, they lack detailed evaluation of cognitive functions.

Much progress has been made in understanding the etiopathogenesis and symptomatic treatment of the tip of the iceberg of motor symptoms of PD, the fastest growing neurological illness. However, the development of effective neuroprotective and disease-modifying therapies for nonmotor symptoms, which are the invisible part of the iceberg that directly affect the physical, mental, and social aspects of the person and impair quality of life, besides the economic burden of the disease, is the most challenging therapeutic obstacle.[38,39]

This study showed that in PD patients motor and nonmotor symptoms can be improved by bilateral subthalamic stimulation. The mechanism is complex and we believe that future studies focusing on pharmacological and nonpharmacological treatments involving more patient groups will be useful for clinicians.

Ethics Committee Approval: This study was approved by Ethics Committee of Adana City Training and Research Hospital Clinical Research Ethics Committee (Approval No.: 1928, Date: May 10, 2022).

Informed Consent: Written informed consent was obtained from the participants who agreed to take part in the study.

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REFERENCES

1. Parsons TD, Rogers SA, Braaten AJ, Woods SP, Tröster AI. Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: A meta-analysis. *Lancet Neurol*. 2006;5(7):578-588. [CrossRef]
2. Romito LM, Contarino MF, Vanacore N, Bentivoglio AR, Scerrati M, Albanese A. Replacement of dopaminergic

medication with subthalamic nucleus stimulation in Parkinson's disease: Long-term observation. *Mov Disord*. 2009;24(4):557-563. [CrossRef]

3. Williams A, Gill S, Varma T, et al. Deep brain stimulation plus best medical therapy *versus* best medical therapy alone for advanced Parkinson's disease (PD SURG trial): A randomised, open-label trial. *Lancet Neurol*. 2010;9(6): 581-591. [CrossRef]
4. Spalletta G, Robinson RG, Cravello L, et al. The early course of affective and cognitive symptoms in de novo patients with Parkinson's disease. *J Neurol*. 2014;261(6):1126-1132. [CrossRef]
5. Baba Y, Wrahen RE, Uitti RJ. *Surgeal treatment - Steretactic procedures. InManuchair S. Ebadi, Ronald Pfeiffer, eds. Parkinson's Disease*. New York: CRC Press; 2005:1158-1193.
6. Goetz CG, Koller WC, Poewe W, Rascol O, Sampaio C. Management of Parkinson's disease an evidence-based review. *Mov Disord*. 2002;17:1-2.
7. Kwon KY, Kang SH, Kim M, et al. Nonmotor symptoms and cognitive decline in de novo Parkinson's disease. *Can J Neurol Sci*. 2014;41(5):597-602.
8. Negida A, Elminawy M, El Ashal G, Essam A, Eysa A, Abd Elalem Aziz M. Subthalamic and pallidal deep brain stimulation for Parkinson's disease. *Cureus*. 2018;10(2):e2232. [CrossRef]
9. Halpern CH, Rick JH, Danish SF, Grossman M, Baltuch GH. Cognition following bilateral deep brain stimulation surgery of the subthalamic nucleus forParkinson's disease. *Int J Geriatr Psychiatry*. 2009;24(5):443-451. [CrossRef]
10. Massimo L, Powers C, Moore P, Vesely L, Avants B, Gee J, Grossman M. Neuroanatomy of apathy and disinhibition in frontotemporal lobar degeneration. *Dementia and Geriatric Cognitive Disorders*. 2009; 27:96–104
11. Krishnan S, Pisharady KK, Divya KP, Shetty K, Kishore A. Deep brain stimulation for movement disorders. *Neurol India*. 2018;66(suppl):S90-S101. [CrossRef]
12. Bronstein JM, Tagliati M, Alterman RL. Deep brain stimulation for Parkinson disease: An expert consensus and review of key issues. *Arch Neurol*. 2010;68(2):165.
13. Chiken S, Nambu A. Mechanism of deep brain stimulation: Inhibition, excitation, or disruption? *Neuroscientist*. 2016;22(3):313-322. [CrossRef]
14. Burchiel KJ, Anderson VC, Favre J, Hammerstad JP. Comparison of pallidal and subthalamic nucleus deep brain stimulation for advanced Parkinson's disease: Results of a randomized, blinded pilot study. *Neurosurgery*. 1999;45(6):1375-82; discussion 1382. [CrossRef]
15. Parsons TD, Rogers SA, Braaten AJ, Woods SP, Tröster AI. Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: A meta-analysis. *Lancet Neurol*. 2006;5(7):578-588. [CrossRef]
16. Sherwin BB. Mild cognitive impairment: Potential pharmacological treatment options. *J Am Geriatr Soc*. 2000;48(4):431-441. [CrossRef]
17. Drapier D, Drapier S, Sauleau P, Haegelen C, Raoul S, Biseul I, et al. Does subthalamic nucleus stimulation induce apathy in Parkinson's disease? J Neurol *2006*; 253: 1083–91.
18. Mestre TA, Espay AJ, Marras C, Eckman MH, Pollak P, Lang AE. Subthalamic nucleus-deep brain stimulation for early motor complications in Parkinson's disease: The EARLYSTIM trial: Early is not always better. *Mov Disord*. 2014;29(14):1751-1756. [CrossRef]
19. Østergaard K, Sunde N, Dupont E. Effects of bilateral stimulation of the subthalamic nucleus in patients with severe Parkinson's disease and motor fluctuations. *Mov Disord*. 2002;17(4):693-700. [CrossRef]
20. Erola T, Karinen P, Heikkinen E, et al. Bilateral subthalamic nucleus stimulation improves health-related quality of life in Parkinsonian patients. *Parkinsonism Relat Disord*. 2005;11(2):89-94. [CrossRef]
21. Drijgers RL, Dujardin K, Reijnders JS, Defebvre L, Leentjens AF. Validation of diagnostic criteria for apathy in Parkinson's disease. *Parkinsonism Relat Disord*. 2010;16(10):656-660. [CrossRef]
22. Limousin P, Krack P, Pollak P, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med*. 1998;339(16):1105-1111. [CrossRef]
23. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med*. 2006;355(9):896-908. [CrossRef]
24. Hariz MI, Rehncrona S, Quinn NP, Speelman JD, Wensing C, Multicentre Advanced Parkinson's Disease Deep Brain Stimulation Group. Multicenter study on deep brain stimulation in Parkinson's disease: An independent assessment of reported adverse events at 4 years. *Mov Disord*. 2008;23(3):416-421. [CrossRef]
25. Schüpbach W.M., Chastan N., Welter M.L. Stimulation of the subthalamic nucleus in Parkinson's disease: A 5 year follow up. Journal of Neurology Neurosurgery and Psychiatry. *2005* Dec;76(12):1640-4.
26. Lhommée E, Boyer F, Wack M, et al. Personality, dopamine, and Parkinson's disease: Insights from subthalamic stimulation. *Mov Disord*. 2017;32(8):1191-1200. [CrossRef]
27. Sockeel P, Dujardin K, Devos D, Denève C, Destée A, Defebvre L. The Lille apathy rating scale: A new instrument for detecting and quanrifying apathy: Validation in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2006;77(5):579-584. [CrossRef]
28. Kirsch-Darrow L, Fernandez HH, Marsiske M, Okun MS, Bowers D. Dissociating apathy and depression in Parkinson disease. *Neurology*. 2006;67(1):33-38. [CrossRef]
29. Wichmann T, DeLong MR. Deep brain stimulation for movement disorders of basal ganglia origin: Restoring function or functionality? *Neurotherapeutics*. 2016; 13(2):264-283. [CrossRef]
30. Robert GH, Le Jeune F, Lozachmeur C, et al. Preoperative factors of apathy in subthalamic stimulated Parkinson disease: A PET study. *Neurology*. 2014;83(18): 1620-1626. [CrossRef]
31. Pont-Sunyer C, Hotter A, Gaig C, et al. The onset of nonmotor symptoms in Parkinson's disease (The ONSET PD Study). *Mov Disord*. 2015;30(2):229-237. [CrossRef]
32. Aarsland D, Brønnick K, Alves G, et al. The spectrum of neuropsychiatric symptoms in patients with early untreated Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2009;80(8):928-930. [CrossRef]
33. Barone P, Antonini A, Colosimo C, et al. The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov Disord*. 2009;24(11):1641-1649. [CrossRef]

34. Burkhard, P.R., F.J.G. Vingerhoets, A. Berney, J. Bogousslavsky, J.-G. Villemure, and J. Ghika. Suicide after successful deep brain stimulation for move- ment disorders. *Neurology 2004; 63*: 2170–2172.

35. Kennedy, S.H., Giacobbe, P., Rizvi, S.J., Placenza, F.M., Nishikawa, Y., Mayberg, H.S. & Lozano, A.M. (2011). Deep brain stimulation for treatment-resistant depression: Follow-up after 3 to 6 years. *American Journal of Psychiatry*, 2011;168: 502–510.

36. Fraix V, Houeto JL, Lagrange C, et al. Clinical and economic results of bilateral subthalamic nucleus stimulation in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2006;77(4):443-449. [CrossRef]

37. Funkiewiez A, Ardouin C, Krack P, et al. Acute psychotropic effects of bilateral subthalamic nucleus stimulation and levodopa in Parkinson's disease. *Mov Disord*. 2003;18(5):524-530. [CrossRef]

38. Dujardin K, Langlois C, Plomhause L, et al. Apathy in untreated early-stage Parkinson disease: Relationship with other non-motor symptoms. *Mov Disord*. 2014; 29(14):1796-1801. [CrossRef]

39. Tarkstein SE, Ingram L, Garau ML, Mizrahi R. On the overlap between apathy and depression in dementia. *J Neurol Neurosurg Psychiatry*. 2005;76(8):1070-1074. [CrossRef]