scientific reports

Check for updates

OPEN

Peripheral cytokine levels in patients with idiopathic parkinson's disease undergoing subthalamic nucleus deep brain stimulation

Ersoy Kocabıcak[1]✉, Sedat Sen[2], Hafize Uzun[3], Sait Ozturk[4], Mustafa Onur Yildiz[2], Erdem Tuzun[5], Onder Taskin[6], Dursun Aygun[2] & Yasin Temel[7,8]

Parkinson's disease (PD) is a movement disorder caused by dopaminergic neuron degeneration. In addition to L-DOPA and agonists, deep-brain stimulation (DBS) is also used in appropriate patients in the middle and advanced stages. The most common target for DBS is the subthalamic nucleus (STN). STN stimulation results in significant improvement in the clinical manifestations of the disease. In addition to its ameliorating effect on well-known clinical findings, stimulation has secondary effects that are not sufficiently known. This study aims to investigate the effects of STN-DBS on peripheral pro-inflammatory and anti-inflammatory cytokine levels in patients with idiopathic PD, and to explore whether changes in these biomarkers correlate with clinical improvements following DBS. The study included 32 patients with idiopathic PD who underwent STN-DBS at Neurosurgery Clinics. The mean Unified Parkinson's Disease Rating Scale (UPDRS) motor score improved from 45.71 (preoperative, Med OFF) to 17.90 (postoperative, STIM ON / Med OFF) and to 13.10 (6 months after surgery), corresponding to 60.8% and 71.3% improvements, respectively. LEDD decreased significantly over time ($p < 0.001$), and BDI scores improved significantly postoperatively. MMSE scores increased progressively at each follow-up. Medical treatment ameliorated the effect on UPDRS score by 49.1% in the preoperative period. However, no statistically significant changes were observed in serum cytokine levels (IL-1β, IL-6, IL-10, TNF-α) across the study period. No correlations were found between cytokine levels and clinical variables. STN-DBS is an effective and safe treatment for improving motor symptoms in patients with idiopathic PD, and it may also contribute to a reduced need for medication and gradual cognitive improvement. However, peripheral cytokine levels (IL-1β, IL-6, IL-10, and TNF-α) remained unchanged, suggesting that the clinical benefits of STN-DBS are unlikely to be mediated directly through peripheral immune modulation. Nevertheless, more complex immunological mechanisms cannot be excluded. Further studies with larger cohorts and longer follow-up are warranted to clarify these potential effects.

Keywords Parkinson's disease, Subthalamic nucleus, Deep brain stimulation, Neuroinflammation, Cytokine, IL-1beta, IL-6, TNF-alpha

Parkinson's disease (PD) is a neurodegenerative disorder caused by the degeneration of dopaminergic neurons in the substantia nigra pars compacta and striatum, affecting approximately 1–2% of individuals over the age of 60. L-DOPA and dopamine agonists have been used for the medical treatment of the disease for many years. However, drug-related complications develop in most patients after 5 years of medical treatment[1]. Deep brain stimulation (DBS) can be applied in appropriate patients with L-DOPA response[2]. In 1993, Pollak and colleagues performed subthalamic nucleus-DBS (STN-DBS) for the first time[3]. Since then, this method has been developed

[1]Department of Neurosurgery, Faculty of Medicine, Istanbul Atlas University, Istanbul, Turkey. [2]Department of Neurology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey. [3]Department of Biochemistry, Faculty of Medicine, Istanbul Atlas University, Istanbul, Turkey. [4]Department of Neurosurgery, Faculty of Medicine, Fırat University, Elazığ, Turkey. [5]Department of Neuroscience, Aziz Sancar Institute of Experimental Medicine, İstanbul University, İstanbul, Turkey. [6]Neurosurgery Clinic, Private Kolmed Hospital, Amasya, Turkey. [7]Department of Neurosurgery, Maastricht University Medical Center, Maastricht, The Netherlands. [8]Mental Health and Neuroscience Institute (MHeNs), Maastricht University, Maastricht, The Netherlands. ✉email: ersoy.kocabicak@atlas.edu.tr

and continues to be used in many patients. STN-DBS has gained an important place in the treatment of PD today thanks to imaging methods, neurophysiologic recording, and software technology[4].

The insertional effects of DBS represent a crucial yet underappreciated phenomenon with significant implications for optimizing therapeutic protocols and enhancing patient outcomes[5]. Chronic subthalamic nucleus stimulation in PD has been shown not to disrupt hypothalamic-pituitary (HP) function or the diurnal rhythm of peripheral cortisol secretion, indicating preserved neuroendocrine regulation despite DBS intervention[6]. In studies conducted in epileptic rats with status epilepticus, findings to better understand the mechanisms of action of DBS, it was found that DBS applied to the anterior thalamic nuclei may show anti-inflammatory and anti-apoptotic properties[7].

Interleukin-beta (IL-1β) is a pro-inflammatory cytokine that promotes fever, acute phase protein synthesis. IL-6 is a proinflammatory cytokine that provides B lymphocyte proliferation-differentiation and immunoglobulin (Ig) production. It is most important in fever and the acute protein phase production. Tumor necrosis factor-alpha and beta (TNF-α and TNF-β) are important mediators of the acute infectious response. It is the most important cytokine in Gram (−) infection[8]. IL-10 is one of the main anti-inflammatory cytokines as a factor that inhibits cytokine synthesis[9].

The role of inflammation and immune response in neurodegenerative diseases, such as PD, has been increasingly recognized. Cytokines are signaling molecules that mediate and regulate immunity, inflammation, and hematopoiesis[10,11]. Given that STN-DBS is an effective therapeutic intervention for PD, understanding how it influences immune responses could provide valuable insights into the broader effects of the treatment on brain function and patient health. Preclinical studies suggest that STN-DBS not only modulates motor circuits but also influences neuroinflammation, astrocyte activity, and peripheral immune responses. These findings support the relevance of exploring systemic immune markers, such as peripheral cytokines, in patients undergoing DBS[10–14].

We chose the 1-month and 6-month postoperative time points to capture both the early effects, including micro-lesion and immediate post-surgical changes, and the more stable intermediate-term effects of STN-DBS, providing a comprehensive assessment of clinical and immunological outcomes. There is no study in the literature that was done in such a manner. Thus, our clinicians decided on this timing solely depending on their clinical experience. The study aims to determine whether changes in cytokine levels, particularly pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) and the anti-inflammatory cytokine IL-10, are correlated with the clinical outcomes observed after STN-DBS. Additionally, the study aims to contextualize these findings within preclinical and experimental evidence on motor symptoms and levodopa-induced motor complications, exploring whether modulation of the inflammatory pathway through STN-DBS may contribute to symptom management and provide a potential therapeutic mechanism for improving patients' overall condition.

Materials and methods

Ethical approval

This prospective study was conducted in accordance with the ethical standards of the Institutional and/or National research Ethics Committee and with the principles outlined in the Declaration of Helsinki. Approval for this study was granted by Ondokuz Mayıs University, Faculty of Medicine Ethics Committee for Clinical Studies (Approval date: 29.04.2016; Number: B.30.ODM.0.20.08/260). Written informed consent was obtained from all patients included in the study.

Data collection

Patients with idiopathic PD who were eligible for STN-DBS and who met the inclusion criteria were consecutively enrolled in the study over a defined period between January 2016 and December 2018 at the Neuromodulation Unit of Ondokuz Mayıs University Faculty of Medicine and the Department of Brain and Neurosurgery at Firat University Faculty of Medicine. Thirty-six patients were included in the study. Specifically, four patients were excluded from the study due to hemolysis observed in their blood samples, which rendered the cytokine measurements unreliable. A total of 32 patients completed the study. The medications used by patients for PD were evaluated using the total L-DOPA equivalent daily dose (LEDD). Neuropsychological tests such as the Beck Depression Inventory (BDI) and the Mini-Mental State Examination (MMSE) were routinely evaluated before and after surgery. MMSE was selected for its practicality, wide use, and suitability for serial assessment.

Inclusion criteria

I) Age > 18 years old; ii) Patients with idiopathic PD according to the MDS-PD diagnostic criteria; iii) Implementation of STN-DBS therapy; iv) MMSE test score > 26; v) DBS treatment for more than three months; vi) Agreeing to shut down the deep brain stimulator.

Exclusion criteria

I) A formal diagnosis of dementia; ii) Refusal to accept DBS device deactivation or to provide informed consent; iii) Presence of persistent severe psychiatric disorders; Iv) Severe cognitive impairment determined through clinical evaluation, neuropsychological assessment, and imaging findings (e.g., diffuse atrophy or extensive ischemic lesions). Patients with mild to moderate cognitive deficits were eligible, reflecting real-world DBS practice; v) Presence of systemic diseases contraindicating surgery; vi) Hemolytic, lipemic, or icteric serum samples, which could compromise the accuracy and reliability of biochemical analyses.

Patients with severe cognitive impairment were excluded based on clinical evaluation, neuropsychological assessment, and imaging findings (e.g., diffuse atrophy or extensive ischemic changes). Patients with mild to moderate cognitive deficits were eligible for inclusion, consistent with real-world clinical DBS practice.

Diagnosis and discrimination

Ancillary tests are used to exclude other diseases included in the differential diagnosis[15]. The MDS-PD criteria are used to diagnose PD. An expert neurologist diagnosed each patient as having PD or non-PD, regardless of the International Parkinson and Movement Disorder Society criteria (gold standard, clinical diagnosis). Then, a second neurologist evaluated the presence/absence of each item from the International Parkinson and Movement Disorder Society criteria. According to these criteria, bradykinesia must be present in combination with either resting tremor or rigidity. In addition, supportive criteria strengthen the diagnosis, including a clear and dramatic beneficial response to dopaminergic therapy, the presence of levodopa-induced dyskinesia, rest tremor of a limb, and ancillary evidence such as olfactory loss or cardiac sympathetic denervation when available[16].

Clinical evaluation

Age, gender, disease duration, and disease subtype were recorded. Patients were evaluated preoperatively, at 1 month postoperatively, and again at a mean of 5.1 ± 0.6 months after surgery (range: 4–6 months). Unified Parkinson's Disease Rating Scale (UPDRS) part III motor scores, mini-mental test results, Beck depression scores, and medical treatment doses were recorded. Postoperative evaluations were performed under three standardized clinical conditions: (i) Stimulation Off – Medication Off (Stim OFF - Med OFF), where both DBS and antiparkinsonian medications were discontinued; (ii) Stimulation On – Medication Off (Stim ON - Med OFF), where DBS was active but medications were withheld; and (iii) Stimulation On – Medication On (Stim ON - Med ON), where both DBS and medications were active. When evaluating UPDRS III scores, Med OFF and Med ON assessments were performed preoperatively, and three consecutive assessments were conducted postoperatively based on stimulation and medication status (Stim OFF – Med OFF, Stim ON – Med OFF, Stim ON – Med ON). Med OFF examinations were performed at least 12 h after discontinuation of antidopaminergic treatment, and Med ON examinations were performed with 1.5 times the morning L-DOPA dose.

All patients underwent a clinical evaluation in the best ON- ON-medication state by a neurologist expert in movement disorders. Motor impairment and disease stage were assessed by means of MDS-UPDRS parts I–IV. and Hoehn & Yahr staging scale, respectively[17,18]. Section 1-mentation, behavior, and mood; Section 2-activities of daily living (scored for "on" and "off"); Section 3-motor exam; and Section 4-complications. Each subscale has a 0–4 rating, where 0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe.

Collection of samples

Fasting venous blood samples obtained from the participants in an EDTA anticoagulant tube were centrifuged at 4000 rpm for 5 min, and all biochemical parameters were analyzed in serum samples on the same day. Plasma cytokine levels were assessed preoperatively and at 1 month and 6 months after surgery. Plasma samples for IL-1β, IL-6, TNF-α, and IL-10 measurement were stored at − 80 °C until the study.

Measurement of plasma cytokine levels

The plasma IL-1β, IL-6, TNF-α, and IL-10 levels were measured by the immunoassay according to the manufacturer (Human Magnetic Luminex Assay, Human Premixed Multi-Analyte Kit, R&D Systems, Inc., Minneapolis, MN, USA). In this process, a Human magnetic premixed microparticle cocktail of antibodies (Kit Lot Number L141975) was used to magnetically label the samples.

Statistical analysis

Statistical analyses were performed using SPSS software version 21.0 (IBM Corp., Armonk, NY, USA) to evaluate the data. Results are given as mean ± standard deviation. The Kolmogorov-Smirnov test was used to determine whether the data fit the normal distribution. The statistical significance for dependent groups with normally distributed data was evaluated using the t-test. For comparisons across more than two points (preoperative and postoperative periods), repeated measures ANOVA was used for normally distributed data, and the Friedman test was applied for non-normally distributed data. Where a significant overall effect was observed, post-hoc pairwise comparisons were performed using the Bonferroni correction for ANOVA and the Wilcoxon signed-rank test with Bonferroni adjustment for Friedman test results. For parameters that did not fit the normal distribution, Spearman's correlation analysis was used to evaluate the direction and strength of the linear relationship between two continuous variables. $p < 0.05$ has been considered statistically significant.

Results

Among the patients with PD, 10 were female and 22 were male. The mean age was 56.32 ± 9.37 years (range: 37–71). Twenty patients had tremor-dominant PD, while 12 patients had a non-tremor-dominant subtype. The mean disease duration before surgery was 10.06 ± 4.13 years (range: 5–22 years) (Table 1).

In the preoperative period, the mean UPDRS motor score was 45.71 in the Med OFF state and 23.29 in the Med ON state, indicating a 49.1% improvement with medication. In the postoperative period, a statistically significant improvement was observed in UPDRS motor scores both under medication and with DBS stimulation. Repeated measures ANOVA revealed significant differences in UPDRS motor scores across the preoperative and postoperative periods ($p < 0.001$). Post-hoc pairwise comparisons with Bonferroni correction confirmed that postoperative scores were significantly improved compared to preoperative values (Table 2).

Similarly, changes in the total L-DOPA equivalent LEDD and neuropsychological outcomes (Beck Depression Inventory and MMSE scores) across time points were analyzed using the Friedman test due to non-normal distribution. These analyses showed statistically significant changes across the three evaluation points ($p < 0.001$). Post-hoc Wilcoxon signed-rank tests with Bonferroni adjustment indicated significant reductions in LEDD and

(n = 32)	
Gender (Female/Male)	(10/22)
Age (Year)	56.32 ± 9.37
Disease duration (Year)	10.07 ± 4.13
Age at onset of Parkinson's Disease (Year)	46.26 ± 8.66
Dominant / non-dominant tremor	(20; %62) / (12; %38)

Table 1. Demographic and clinical characteristics of patients with idiopathic Parkinson's disease.

	MED OFF	STIM OFF / MED OFF	MED ON	STIM ON / MED OFF	STIM ON / MED ON
Before surgery	45.71 ± 11.64	–	23.29 ± 6.88	–	–
1 month after surgery	–	43.58 ± 11.94	–	17.90 ± 5.50	12.26 ± 4.25
6 months after surgery	–	39.52 ± 5.85	–	13.10 ± 4.42	9.39 ± 3.71

Table 2. The Unified Parkinson's Disease Rating Scale (UPDRS) motor scores of idiopathic Parkinson's disease patients. MED OFF, Medication Off; STIM OFF, Stimulation Off; MED ON, Medication On;STIM ON, Stimulation On.

	Before surgery	1 month after surgery	6 months after surgery	*P* value
LEDD	1096.77 ± 216.06	706.45 ± 161.02[a]	438.71 ± 65.64[a,b]	***p* < 0.001**

Table 3. Comparison of L-DOPA doses in the preop and postop period. Post hoc test. a: Before surgery; b: 1 month after surgery. LEDD, L-DOPA equivalent daily dose.

	Before surgery	1 month after surgery	6 months after surgery	*P* value
BDI	23.29 ± 4.36	18.87 ± 3.99[a]	14.77 ± 2.86[a,b]	***p* < 0.001**
MMSE	21.42 ± 3.13	24.36 ± 2.94	27.90 ± 1.57	***p* < 0.001**

Table 4. Neuropsychiatric outcomes before surgery and the postoperative period. Post hoc test a: a. Before surgery; b: 1 month after surgery. BDI, Beck Depression Inventory; MMSE, Mini-Mental State Examination.

improvements in neuropsychological scores in both postoperative periods compared to the preoperative periods (Tables 3 and 4).

Postoperatively, significant improvements were observed in both depressive symptoms and cognitive function. The mean BDI score decreased from 23.29 ± 4.36 before surgery to 18.87 ± 3.99 at 1 month and further to 14.77 ± 2.86 in 6 months after surgery ($p < 0.001$). Similarly, MMSE scores progressively increased from 21.42 ± 3.13 preoperatively to 24.36 ± 2.94 at 1 month and 27.90 ± 1.57 at 6 months postoperatively ($p < 0.001$). Regarding inflammatory markers, no statistically significant differences were observed in serum levels of IL-1β, IL-6, TNF-α, or IL-10 across the preoperative and postoperative periods ($p > 0.05$ for all; Friedman test). Descriptive statistics for each cytokine are presented in Fig. 1.

No significant correlations were found between cytokine levels and clinical variables, including age (r = 0.135; $p > 0.088$), gender (r = 0.109; $p > 0.113$), disease subtype (r = 0.146; $p > 0.064$), or UPDRS (r = 0.086; p > 0.072) motor scores at any time point, as assessed by Spearman's correlation analysis.

Discussion

The main responsible factor in the pathogenesis of PD is dopaminergic neuron degeneration. There is widespread neuroinflammation. Increased synthesis of proinflammatory cytokines in PD is an indicator of this[19–22]. Due to this mechanism, anti-inflammatory therapies have been tried many times for the treatment of PD[23]. When the effects of bilateral STN-DBS on motor symptoms and neuropsychiatric symptoms in PD were evaluated in our study, it was observed that STN-DBS improved motor symptoms and levodopa-induced complications, as reported in previous studies[24]. No significant changes were observed in proinflammatory (IL-1β, IL-6, TNF-α) or anti-inflammatory (IL-10) cytokine levels before and after STN-DBS, nor were these levels correlated with clinical outcomes. This may be since peripheral blood cytokine levels have very low titers (3.2×10^3 pg/mL) and are affected by many factors such as sleep, vital signs, fasting, etc. The existence of many factors affecting peripheral blood cytokine levels should not be ignored. Peripheral blood cytokine levels can be affected by multiple factors, including sleep quality, circadian rhythms, fasting status, acute infections, medications, stress, and physiological parameters such as vital signs. In our study, some of these variables could not be fully identified

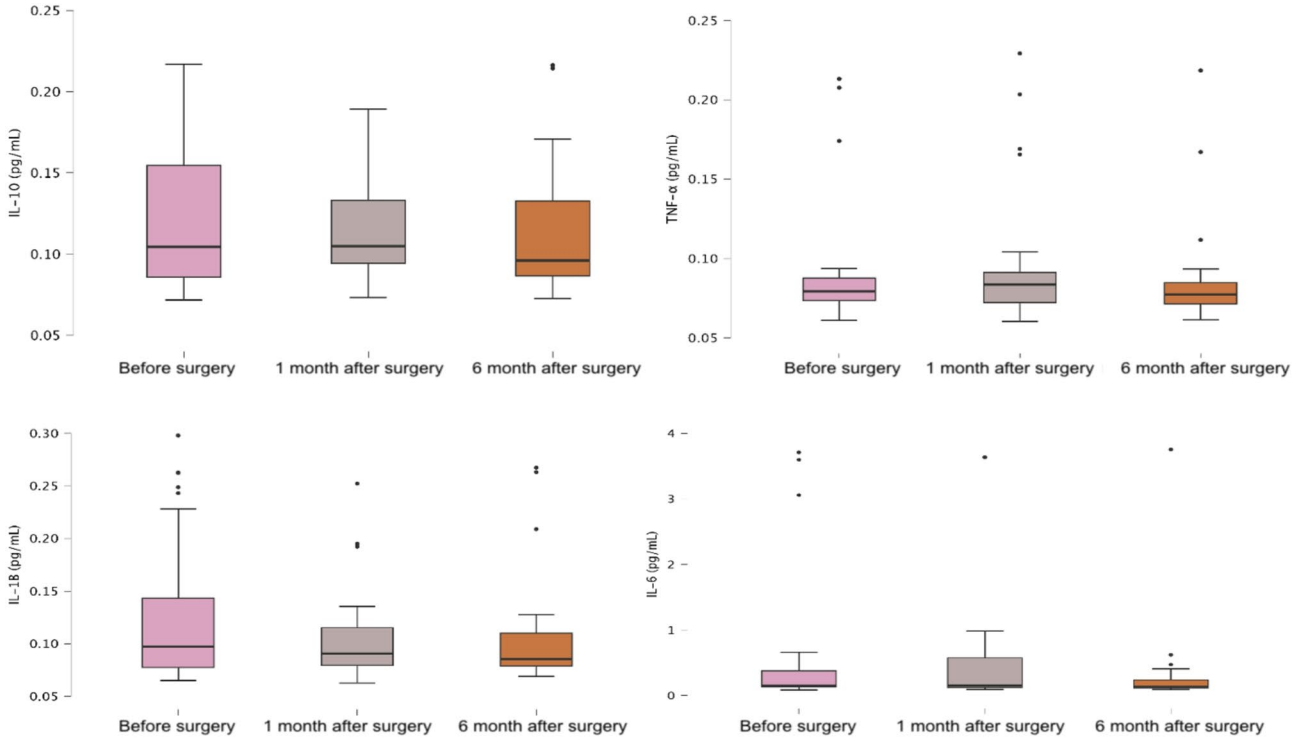


Fig. 1. Cytokine levels of patients with idiopathic Parkinson's disease (n = 32). IL-1β, interleukin-1beta; IL-6, interleukin; TNF-α, tumor necrosis factor-alpha.

or controlled due to practical limitations, such as the outpatient clinical setting, ethical constraints on invasive monitoring, and the inherent variability of patient behaviors. Additionally, our findings are supported by several preclinical and experimental studies (motor symptoms and levodopa-induced motor complications)[7,25–28]. The present study provides preliminary data on the peripheral inflammatory response following STN-DBS and highlights the need for long-term investigations to understand its immunological effects during PD.

DBS is an effective treatment method in PD[29]. It is known that bilateral STN-DBS applied in the early period provides better results on motor complications compared to medical treatment alone[30]. Patients were receiving either 5 or 12 daily doses of L-DOPA in combination with multiple dopamine agonists preoperatively, with the corresponding LEDD values presented in Table 3. There are many factors that cause this effect. The decrease in the patients' L-DOPA requirement and the decrease in complications related to medical treatment are among these factors. The decrease in motor fluctuations, the end-of-dose deterioration, and the absence of peak-dose dyskinesias are other factors. The patients in our study had a mean disease duration exceeding 10 years and were receiving high-dose LEDD therapy, indicating their suitability for STN-DBS. When the patient group included in our study is evaluated, while medical treatment in the pre-surgical period provides a 49% improvement on UPDRS III scores, this rate increases to 64% with stimulation alone (Stim ON-Med OFF) in the post-surgical period and to 75% with the addition of medical treatment. This observation may be attributed to residual neuroplastic effects induced by STN-DBS, optimized post-operative medication adjustments, and patient selection factors favoring more consistent responders. This benefit of STN-DBS on motor scores in the first year has also been shown in previous studies[31]. The 22% improvement between preoperative Med OFF and early postoperative Stim OFF/Med OFF scores is attributed to the micro-subthalamotomy effect created by microelectrode recording (MER) trajectories in the postoperative period, as reported in previous studies[32].

The MMSE is commonly used to evaluate cognitive status, especially in postoperative contexts[33]. In the present study, the significant reduction in BDI scores indicates an improvement in depressive symptoms after DBS. When interpreting BDI scores, the potential for exaggeration inherent in self-reported measures should be considered. Similarly, the increase in MMSE scores suggests enhanced cognitive function, likely influenced by both the effects of DBS and secondary factors such as improved mood and motor function. The observed postoperative improvement in MMSE scores may reflect not only the cognitive effects of subthalamic DBS but also confounding factors such as test–retest learning effects, improved motor function enabling better test performance, and overall improvement in mood, sleep quality, or general health status. It is important to interpret this improvement cautiously, considering these possible influences. MMSE was selected as the cognitive assessment tool in this study due to its wide clinical use, feasibility for repeated assessments, and ability to provide a global overview of cognitive status. Nonetheless, its limitations, such as ceiling effects and limited sensitivity to subtle deficits, are acknowledged, and future studies would benefit from incorporating more comprehensive neuropsychological evaluations. In addition to its effects on PD, studies in rat models have shown that STN-DBS inhibits serotonin neurons in the midbrain dorsal and median raphe nuclei[5,34]. Another

preclinical study found that STN-DBS reduced serotonin levels in the medial prefrontal cortex[35]. These data were found to be associated with mood changes after DBS[36].

In addition to these and similar factors, when the anatomical connections of the subthalamic nucleus with the hypothalamic pituitary axis are taken into consideration, possible effects on these systems are also possible. Steinhardt et al.[37] investigated the effects of STN-DBS on sleep–wake regulation and circadian rhythms in patients with PD. The study demonstrated that STN-DBS can influence sleep architecture and circadian rhythmicity, suggesting potential benefits beyond motor symptom control. A potential effect on corticosteroid synthesis may be one of the main reasons for this situation in rats[37,38]. In addition to the modulation applied to the medial thalamus region, similar effects may also occur in STN-DBS, and peripheral corticosteroid levels may be affected[6]. In our study, we aimed to explore the potential effects of STN-DBS on the hypothalamic pituitary axis indirectly, by assessing changes in peripheral pro- and anti-inflammatory cytokine levels, although corticosteroid levels were not directly measured. We did not find any difference in cytokine levels before and after surgery in patients who underwent STN-DBS. We also did not find any relationship between anti-inflammatory cytokine levels and their clinical reflections. There may be several reasons for this situation. Even if the HPA and corticosteroid synthesis are affected, it may not affect peripheral blood cytokine levels. Amorim et al.[7] investigated the anti-inflammatory and anti-apoptotic effects of DBS when administered during status epilepticus (SE). In their study, they showed that DBS has anti-inflammatory and anti-apoptotic effects when given to animals undergoing SE. However, they could not conclude a direct relationship between the reduced excitotoxicity, anti-inflammatory, and anti-apoptotic effects of DBS. Similarly, they could not explain why DBS only affected certain inflammatory cytokines (e.g., IL-6, but not TNFα). Our results differ from the findings reported by Chang et al.[28], who reported a postoperative reduction in TNF-α and other inflammatory markers in the central nervous system (CNS) of PD patients undergoing STN-DBS. In their study, TNF-α levels differed significantly between the three groups (preoperative DBS PD patients, postoperative DBS PD patients, and controls); however, no significant correlations were observed between TNF-α levels and clinical measures such as UPDRS III or Hoehn–Yahr stage in preoperative or matched patients. The results suggest that PD patients exhibit a persistent inflammatory profile, potentially involving activated immune cells in the CNS, and that DBS may exert therapeutic effects by modulating this central inflammatory environment. In contrast, our analysis focused on peripheral blood cytokine levels, which may not fully reflect central immune processes due to the selective permeability of the blood-brain barrier. These differences underscore the importance of evaluating both central and peripheral compartments when investigating the immunomodulatory effects of DBS in PD[28]. The fact that peripheral blood cytokine levels have very low titers and are affected by many factors, such as sleep, vital signs, hunger, etc., may also have caused this situation. The existence of many factors affecting peripheral blood cytokine levels should not be ignored.

In addition to dopaminergic neurodegeneration and neuroinflammation, recent studies have highlighted the critical role of innate immunity in the pathophysiology of neurodegenerative disorders, including PD. Chronic activation of microglia, the brain's resident immune cells, leads to sustained production of pro-inflammatory cytokines and oxidative stress, creating a self-perpetuating cycle of neuronal damage[38,39]. This suggests that PD is not solely a neurodegenerative disease but also a disorder with significant immune system involvement. Moreover, the orexin system—traditionally associated with sleep-wake regulation and arousal—has been increasingly recognized for its role in neurodegeneration. Dysregulation of orexin signaling may contribute to several PD-related non-motor symptoms, such as sleep disturbances, mood changes, and autonomic dysfunction. Recent evidence indicates that orexinergic pathways may interact with neuroinflammatory and neuroendocrine mechanisms, thereby influencing disease progression[39,40]. Including these perspectives helps to position DBS, particularly STN-DBS, within a broader neurobiological context, where its therapeutic effects may involve modulation not only of motor circuits but also of immune and neuroendocrine pathways.

The exact mechanisms through which DBS reduces inflammation and thus exerts a neuroprotective effect are not yet fully understood. However, the existing literature indicates that there appears to be a shared foundational effect, which involves the neuroprotective and potentially anti-inflammatory benefits of DBS in rats[7,40,41]. It should be considered that some of the findings are based on animal models and may not be directly generalizable to humans. Therefore, additional clinical research is required to better understand the mechanisms behind DBS that contribute to these neuroprotective and anti-inflammatory outcomes.

Limitations of the study

This study is subject to several limitations. One limitation of the study is its relatively small sample size and the absence of longitudinal measurements. Peripheral blood cytokine levels are known to fluctuate in PD[22,42], and the selective permeability of the blood-brain barrier may contribute to differences between central and peripheral cytokine levels. Examining cytokine values in the cerebrospinal fluid (CSF) could clarify this discrepancy; however, repeated CSF sampling was not performed due to ethical concerns and the practical challenges associated with serial lumbar punctures in PD patients. Additionally, although experimental studies in rats[12] have shown that STN-DBS can modulate peripheral immune responses, our findings in human patients did not reveal robust changes in peripheral cytokine levels, likely reflecting species differences and the high variability of these markers in clinical settings.

Conclusion

PD exhibits marked interindividual variability, influenced by factors such as disease progression, which can affect inflammatory markers. STN-DBS is an effective and safe treatment method for advanced PD, particularly in patients with motor complications unresponsive to medical therapy. Although experimental studies (in rodents) suggest neuroprotective and anti-apoptotic effects of DBS, its exact mechanisms remain unclear. STN-DBS did not significantly alter peripheral cytokine levels at 1 and 6 months postoperatively. Given the annual

increase in UPDRS motor sub-scores and the long-term use of DBS, longer follow-up is needed to assess delayed immunological effects. These findings suggest that the benefits of STN-DBS are unlikely to be mediated by peripheral immune mechanisms and may instead involve central pathways not detectable in peripheral blood. We recommend that future studies include longer-term follow-up, ideally extending beyond 12 months, with larger sample sizes and serial cerebrospinal fluid analysis, to fully assess delayed immunological effects and clarify whether STN-DBS modulates central or peripheral neuroimmune pathways in PD. An increase in the UPDRS motor sub-score per year by a certain number of points and the long-term use of DBS, longer follow-up is needed to assess delayed immunological effects.

Data availability

The original contributions presented in this study are included in this article. Further inquiries can be directed to the corresponding author ([ersoy.kocabicak@atlas.edu.tr](mailto: ersoy.kocabicak@atlas.edu.tr)).

Received: 29 May 2025; Accepted: 16 September 2025
Published online: 21 October 2025

References

1. Rademacher, K. & Nakamura, K. Role of dopamine neuron activity in Parkinson's disease pathophysiology. *Exp. Neurol.* **373**, 114645 (2024).
2. Porta, M., Servello, D., Zekaj, E., Gonzalez-Escamilla, G. & Groppa, S. Pre-dopa deep brain stimulation: Is early deep brain stimulation able to modify the natural course of Parkinson's disease?. *Front Neurosci.* **14**, 492 (2020).
3. Pollak, P. et al. Effects of the stimulation of the subthalamic nucleus in Parkinson disease. *Rev. Neurol.* **149**, 175–176 (1993).
4. Kocabicak, E. & Temel, Y. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: Surgical technique, tips, tricks and complications. *Clin. Neurol. Neurosurg.* **115**(11), 2318–2323 (2013).
5. Lawson McLean, A. & Nemir, J. Quantifying insertional effects in deep brain stimulation: Clinical outcomes and neurophysiological mechanisms. *Expert Rev. Med. Devices.* **22**(4), 285–291 (2025).
6. Seifried, C. et al. Diurnal variation of hypothalamic function and chronic subthalamic nucleus stimulation in Parkinson's disease. *Neuroendocrinology* **97**(3), 283–290 (2013).
7. Amorim, B. O. et al. Deep brain stimulation induces antiapoptotic and anti-inflammatory effects in epileptic rats. *J. Neuroinflam.* **12**, 162 (2015).
8. Mukhara, D., Oh, U. & Neigh, G. N. Neuroinflammation. *Handb. Clin. Neurol.* **175**(235–259), 3 (2020).
9. Wautier, J. L. & Wautier, M. P. Pro- and anti-inflammatory prostaglandins and cytokines in humans: A mini review. *Int. J. Mol. Sci.* **24**(11), 9647 (2023).
10. Magnusen, A. F., Hatton, S. L., Rani, R. & Pandey, M. K. Genetic defects and pro-inflammatory cytokines in Parkinson's disease. *Front. Neurol.* **12**, 636139 (2021).
11. Woo, K. A. et al. Parkinson's disease is associated with clonal hematopoiesis with TET2 mutation. *NPJ. Parkinsons Dis.* **10**(1), 168 (2024).
12. Chen, Y. et al. Subthalamic nucleus deep brain stimulation suppresses neuroinflammation by Fractalkine pathway in Parkinson's disease rat model. *Brain Behav. Immun.* **90**, 16–25 (2020).
13. Campos, A. C. P. et al. Unraveling the role of astrocytes in subthalamic nucleus deep brain stimulation in a Parkinson's disease rat model. *Cell Mol. Neurobiol.* **40**(6), 939–954 (2020).
14. Grembecka, B. et al. Subthalamic deep brain stimulation affects plasma corticosterone concentration and peripheral immunity changes in rat model of Parkinson's disease. *J. Neuroimmune Pharmacol.* **16**(2), 454–469 (2021).
15. Jankovic, J. et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov. Disord.* **30**(12), 1591–1601 (2015).
16. Postuma, R. B. et al. Validation of the MDS clinical diagnostic criteria for Parkinson's disease. *Mov. Disord.* **33**(10), 1601–1608 (2018).
17. Regnault, A. et al. Does the MDS-UPDRS provide the precision to assess progression in early Parkinson's disease? Learnings from the Parkinson's progression marker initiative cohort. *J Neurol.* **266**(8), 1927–1936 (2019).
18. Koçer, A. & Oktay, A. B. Nintendo Wii assessment of Hoehn and Yahr score with Parkinson's disease tremor. *Technol Health Care.* **24**(2), 185–191 (2016).
19. Di Lazzaro, G. et al. Differential profiles of serum cytokines in Parkinson's disease according to disease duration. *Neurobiol. Dis.* **190**, 106371 (2024).
20. Diaz, K., Kohut, M. L., Russell, D. W. & Stegemöller, E. L. Peripheral inflammatory cytokines and motor symptoms in persons with Parkinson's disease. *Brain Behav. Immun. Health.* **21**, 100442 (2022).
21. Jiang, S. S. et al. Cytokine and chemokine map of peripheral specific immune cell subsets in Parkinson's disease. *NPJ Parkinsons Dis.* **9**(1), 117 (2023).
22. Dzamko, N. Cytokine activity in Parkinson's disease. *Neuronal Signal.* **7**(4), e20220063 (2023).
23. Terzi, M. et al. The use of non-steroidal anti-inflammatory drugs in neurological diseases. *J. Chem. Neuroanat.* **87**, 12–24 (2018).
24. Bjerknes, S. et al. Subthalamic nucleus stimulation in Parkinson's disease: 5-year extension study of a randomized trial. *Mov. Disord. Clin. Pract.* **9**, 48–59 (2022).
25. Hwang, Y. S. et al. Long-term motor outcomes of deep brain stimulation of the globus pallidus interna in Parkinson's disease patients: Five-year follow-up. *J. Neurol. Sci.* **444**, 120484 (2023).
26. Mueller, K. et al. Brain connectivity changes when comparing effects of subthalamic deep brain stimulation with levodopa treatment in Parkinson's disease. *Neuroimage Clin.* **19**, 1025–1035 (2018).
27. Fundament, T. et al. Deep brain stimulation for parkinson's disease with early motor complications: A UK cost-effectiveness analysis. *PLoS ONE* **11**(7), e0159340 (2016).
28. Chang, L. et al. Deep brain stimulation improves central nervous system inflammation in Parkinson's disease: Evidence and perspectives. *CNS Neurosci. Ther.* **29**(8), 2177–2185 (2023).
29. Kocabicak, E., Tan, S. K. & Temel, Y. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: Why so successful?. *Surg. Neurol. Int.* **3**(Suppl 4), S312–S314 (2012).
30. Lhommée, E. et al. Behavioural outcomes of subthalamic stimulation and medical therapy versus medical therapy alone for Parkinson's disease with early motor complications (EARLYSTIM trial): Secondary analysis of an open-label randomised trial. *Lancet Neurol.* **17**(3), 223–231 (2018).
31. Luo, G. et al. Effects of STN-DBS surgery on cerebral glucose metabolism and distribution of DAT in Parkinson's disease. *Brain Behav.* **13**(8), e3172 (2023).
32. Aygun, D., Dere, U. A., Yildiz, O., Temel, Y. & Kocabicak, E. Characterizing the intraoperative microelectrode recording-induced microlesion effect on motor symptoms in patients with Parkinson's disease undergoing deep brain stimulation of the subthalamic nucleus. *Turk. Neurosurg.* **29**(3), 430–433 (2019).

33. Chen, J. W. et al. Electrode position and cognitive outcome following deep brain stimulation surgery. *J. Neurosurg.* **141**(1), 230–240 (2024).
34. Temel, Y. et al. Inhibition of 5-HT neuron activity and induction of depressive-like behavior by high-frequency stimulation of the subthalamic nucleus. *Proc. Natl. Acad. Sci. U. S. A.* **104**(43), 17087–17092 (2007).
35. Tan, S. K. et al. A combined in vivo neurochemical and electro- physiological analysis of the effect of high- frequency stimulation of the subthalamic nucleus on 5-HT transmission. *Exp Neurol.* **233**, 145–153 (2012).
36. Tan, S. K., Hartung, H., Sharp, T. & Temel, Y. Serotonin-dependent depression in Parkinson's disease: A role for the subthalamic nucleus?. *Neuropharmacology* **61**(3), 387–399 (2011).
37. Steinhardt, J. et al. The impact of deep brain stimulation of the subthalamic nucleus on sleep-wake function and circadian rhythms in patients with Parkinson's disease. *Mov. Disord. Clin. Pract.* https://doi.org/10.1002/mdc3.70160 (2025).
38. Calleja-Castillo, J. M. et al. Chronic deep brain stimulation of the hypothalamic nucleus in wistar rats alters circulatory levels of corticosterone and proinflammatory cytokines. *Clin. Dev. Immunol.* **2013**, 698634 (2013).
39. McGeer, P. L. & McGeer, E. G. History of innate immunity in neurodegenerative disorders. *Front. Pharmacol.* **2**, 77 (2011).
40. Alster, P. et al. Role of orexin in pathogenesis of neurodegenerative parkinsonisms. *Neurol Neurochir. Pol.* **57**(4), 335–343 (2023).
41. Schuhmann, M. K., Stoll, G., Bohr, A., Volkmann, J. & Fluri, F. Electrical stimulation of the mesencephalic locomotor region attenuates neuronal loss and cytokine expression in the perifocal region of photothrombotic stroke in rats. *Int. J. Mol. Sci.* **20**(9), 2341 (2019).
42. Reale, M. et al. Peripheral cytokines profile in Parkinson's disease. *Brain Behav. Immun.* **23**(1), 55–63 (2009).

Author contributions
EK, SS, MOY, OT, MT, YT, and HU performed the literature search, database set up and contributed to the writing of the manuscript. EK, SS, and HU reviewed the manuscript. EK, SS, MOY, OT, MT, and YT contributed to the study design and reviewed the manuscript. All authors agree on all aspects of the final manuscript.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations

Competing interests
The authors declare that they have no conflicts of interest.

Ethical approval
All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration. Approval for this study was granted by Ondokuz Mayıs University, Faculty of Medicine Ethics Committee for Clinical Studies (Approval date: 29.04.2016; Number: B.30.ODM.0.20.08/260).

Informed consent
Written informed consent has been obtained from all patients.

Additional information

Correspondence and requests for materials should be addressed to E.K.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

© The Author(s) 2025