Northwestern Med J. 2023;3(1):56-61
doi: 10.54307/NWMJ.2023.ID

Review

Deep brain stimulation in idiopathic Parkinson's disease

İdiyopatik Parkinson hastalığında derin beyin uyarımı

Canan Akünal Türel, **Murat Arıcan**

Atıf/Cite as: Akünal Türel C, Arıcan M. Deep brain stimulation in idiopathic Parkinson's disease. Northwestern Med J. 2023;3(1):56-61.

ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative and progressive neurological disorder characterized by tremors, rigidity, bradykinesia, and postural instability. Changes of disease in PD pathophysiology are observed in melanin-containing dopaminergic cells in the substantia nigra. While neuronal loss and gliosis are observed in this region, the remaining neurons may contain cytoplasmic inclusions called Lewy bodies.

Deep Brain Stimulation (DBS), is the method of application with the highest patient satisfaction among device-assisted treatments in advanced PD. The DBS method is frequently preferred in cases where the disease progresses, drug treatment does not respond, and freezing and on-off dyskinesias begin. The most preferred method among these is subthalamic nucleus (STN) DBS. DBS treatment improves not only motor symptoms but also non-motor symptoms.

The success of DBS is based on adequate response to levodopa, appropriate patient selection, successful neuroanatomical and radiological localization of the target area, and a team experienced in motion sickness.

Many studies are being conducted to understand the mechanism of action of deep brain stimulation, the effectiveness of which has been proven by various studies. The excitation and suppressive effects provided by the electrodes are processed with a complex neuronal network and clinical results are obtained. In this article, deep brain stimulation tricks, choosing appropriate patients, and mechanisms of action in Parkinson's disease will be summarized.

Keywords: Parkinson's disease, Deep brain stimulation, neurosciences

ÖZ

Parkinson hastalığı (PD), tremor, rijidite, bradikinezi ve postural instabilite ile karakterize ikinci en yaygın nörodejeneratif ve ilerleyici nörolojik hastalıktır. PD patofizyolojisindeki değişiklikler, en belirgin olarak substantia nigradaki melanin içeren dopaminerjik hücrelerde gözlenir. Bu bölgede nöron kaybı ve gliozis görülürken, sağlam kalan nöronlar Lewy cisimcikleri adı verilen sitoplazmik inklüzyonlar içerebilir.

İleri PD'de cihaz destekli tedaviler arasında hasta memnuniyeti en yüksek uygulama yöntemi olan Derin Beyin Stimulasyonu'dur (DBS). Hastalığın ilerlediği, ilaç tedavisinin önceki kadar yanıt vermediği, donma ve on-off diskinezilerinin başladığı durumlarda DBS tedavi yöntemi ile nöromodülasyon, sıklıkla tercih edilmektedir. Subtalamik çekirdek (STN) DBS, bunlar arasında en çok tercih edilen yöntemdir. DBS tedavisi sadece motor semptomlara değil aynı zamanda non-motor semptomlara da fayda sağlamaktadır.

DBS'nin başarısı, levodopaya yeterli yanıt, uygun hasta seçimi, hedef bölgenin başarılı nöroanatomik ve radyolojik lokalizasyonu ve hareket hastalıkları konusunda deneyimli bir ekibe dayanmaktadır.

Etkinliği çeşitli çalışmalarla kanıtlanmış olan derin beyin stimülasyonunun etki mekanizmasını anlamak için birçok çalışma yapılmaktadır. Elektrotların sağladığı uyarma ve baskılayıcı etkiler, karmaşık bir nöronal ağ ile işlenerek klinik sonuçlar elde edilir. Bu yazıda Parkinson hastalığında derin beyin stimülasyonu, tedavi başarısında püf noktalar, uygun hasta seçimi ve DBS'in etki mekanizmaları incelenecektir.

Anahtar kelimeler: Derin beyin uyarımı, Parkinson hastalığı, sinir bilimleri

Received: 04.12.2022
Accepted: 12.01.2023
Publication date: 01.02.2023

Corresponding Author:
C. Akünal Türel
ORCID: 0000-0001-8791-235X
Bolu Abant İzzet Baysal University, Faculty of Medicine, Department of Neurology, Bolu, Türkiye
✉ cananakunal@gmail.com

M. Arıcan
ORCID: 0000-0003-1728-6087
Bolu Abant İzzet Baysal University, Graduate School of Education, Department of Interdisciplinary Neurosciences, Bolu, Türkiye

INTRODUCTION

Parkinson's disease (PD), first described by James Parkinson in 1817, is the second most common neurodegenerative disease in the world. PD is a neurodegenerative and progressive neurological disorder characterized by tremor, rigidity, akinesia, bradykinesia, postural instability and cognitive, behavioral and non-motor complaints may also be present (1-3). PD affects approximately 1% of the population over the age of 65 and 3% of the population over the age of 80 (1).

Most of the changes in PD are observed in melanin-containing dopaminergic cells in the substantia nigra pars compacta (SNc). While neuronal loss and gliosis are observed in this region, the remaining neurons may contain cytoplasmic inclusions called Lewy bodies. As can be seen in Figure 1, the direct path ensures the initiation and continuation of the motion, while the indirect path ensures the destruction of the extreme motion (4). Hypotheses regarding direct and indirect pathways activation have been associated with subthalamic nucleus (STN) and globus pallidus internus (GPi) firing. While neuronal death in the SNc decreases direct pathway activation, it increases indirect pathway activation. This situation increases STN and GPi firing which results in bradykinesia. In PD, loss of dopaminergic neurons, reduced dopaminergic facilitation of the direct pathway, and inhibition of the indirect pathway result in increased firing and increased inhibition of pathways that produce bradykinesia (2-4).

Deep Brain Stimulation (DBS), which is the method of application with the highest patient satisfaction among advanced-stage treatments-device-assisted treatments in PD, has become more and more frequently used in our country and the world (4).

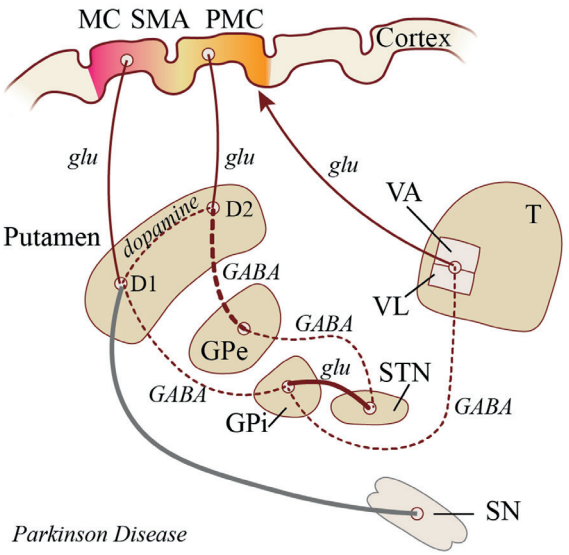

Figure 1. Demonstration of direct and indirect pathways in Parkinson's disease. Solid lines indicate excitatory pathways, dashed lines indicate inhibitory pathways. D1, Dopamine D1 receptor; D2, dopamine D2 receptor; GABA, γ-aminobutyric acid; glu, glutamate; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; MC, motor cortex; PMC, premotor cortex; SMA, supplementary motor area; SN, substantia nigra; STN, subthalamic nucleus; VA, ventral anterior thalamic nuclei VL, ventrolateral thalamic nuclei.

Clinical findings, patient status, and the course of the disease play an important role in determining the treatment method of PD (5). Commonly used treatment methods are given in Figure 2.

The drugs are primarily used in the treatment of Parkinson's disease. The pump option is used in cases where the patient cannot follow the medication regimen on their own. Pumps are surgically placed and allow the drug to be delivered to the body at the specified doses and times. DBS method is frequently preferred in cases where the disease progresses, drug treatment does not respond, freezing and on-off dyskinesias begin (6-10).

In this article, deep brain stimulation tricks and mechanism of action in DBS, which is an effective treatment method in Parkinson's disease, will be explained.

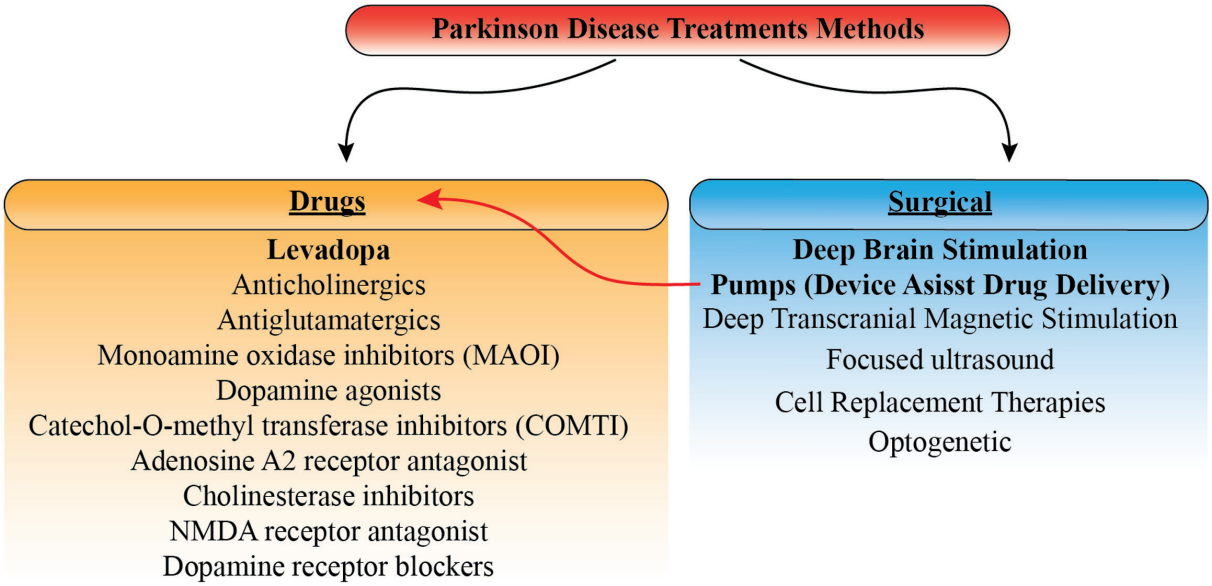

Figure 2. Commonly used methods in Parkinson disease treatment. Bold text indicates more commonly used methods.

Clinical Applications

The first use of DBS was for the treatment of psychiatric disorders and pain (11). It has been used in various fields of application from the middle to the last quarter of the 20th century for the treatment of psychiatric disorders such as depression, anorexia, schizophrenia, and pain (12-15). The first studies on its use in PD and movement disorders date back to 1966. However, chronic stimuli applied together caused lesion formation at the stimulation site. This problem was overcome with a reliable pulse generator (16).

The main purpose of deep brain stimulation is to modulate the anatomical points by giving electrical impulses to the target nuclei and thus to improve the symptoms that cause complaints in the patient. Today, for the motor symptoms of Parkinson's disease DBSis applied to STN, GPi, ventral intermediate (Vim) nucleus of the thalamus and pedunculopontine nucleus. However, STN DBS is most often preferred (7).

One of the most important factors in the success of DBS treatment is directly proportional to the response of patients to levodopa treatment. Thin-section neuroradiological imaging help to reach the target point in the most reliable way. Another factor in the success of treatment is to evaluate the DBS treatment option when the treatment response decreases and motor complications and on-off dyskinesias occur in patients using levodopa (8,17). Studies conducted in recent years have shown that DBS treatment improves not only motor symptoms but also non-motor symptoms (7).

When performed on the right patient, DBS surgery, one of the device-assisted treatments for advanced Parkinson's disease, significantly improves the quality of life for people with PD as measured by the Unified Parkinson's Disease Rating Scale (UPDRS). While the STN is the main neuroanatomical structure of this surgery, the thalamic Vim and GPi are other surgical targets. The usually preferred target for refractory essential tremor is Vim. The posterior subthalamic area and zona incerta are alternative targets to thalamic DBS in ET. In motion sickness in the form of dystonia, the GPi nuclei are more preferred as a DBS target (17-19).

During electrode placement in DBS surgery, patients are awake and operated under local anesthesia. With the Stereotactic Surgery method, when the surgical targets are the thalamus, zona incerta and pallidum, anterior and posterior commissure [AC/PC] coordinates are determined in stereotactic computed tomography (CT) or magnetic resonance imaging (MRI) images. The coordinates of the targets are calculated using the Schaltenbrand stereotactic brain atlas with indirect Cartesian measurement. The patient is checked for the effectiveness of the treatment and whether there are any side effects by performing a neurological examination.

After the electrodes are placed and electrophysiological recording is made, general anesthesia is applied to the patient and the neurostimulator generator is placed and its connections with the electrodes are provided (18).

Mechanisms of Action in DBS

Many studies are being conducted to understand the mechanism of action of DBS, the effectiveness of which has been proven by various studies. The excitatory and suppressive effects provided by the electrodes are processed with a complex neuronal network and clinical results are obtained (20,21).

Inhibition Hypothesis: The first finding regarding the DBS mechanism of action is that DBS suppresses the neuronal structure in the stimulation area. Surgical ablation and DBS show a similar effect on the target nucleus. This observation suggested that high-frequency stimulation has an inhibitory effect such as ablation and creates a functional lesion by suppressing neuronal activity. Subsequently, inhibition of somatic activity near the DBS site was demonstrated by microregistration of STN and GPi. This inhibition is thought to occur with the depolarization block, which is the inactivation of sodium channels and the activation of potassium channels. It can also occur with presynaptic depression of excitatory efferents or activation of inhibitory afferents (18-20,22).

Excitation Hypothesis: It has been explained by some studies that STN-DBS can also cause an ignition-enhancing activity in the basal ganglia. Despite the inhibition in the cell body and the intense γ-Aminobutyric acid [GABA] effect, this electrophysiological effect has been attributed to the triggering of some axonal stimuli that is above the threshold value. In some other studies, excitation and inhibition of GPi-DBS, it has been revealed that it contains some multiphasic responses involving Stimulating effects on axons are also seen in DBS complications. For example, in STN-DBS, the motor and visual side effects depend on the interaction between the optic pathway and the capsula interna. In a positron emission tomography study, the thalamus showed that DBS administered increased metabolism in cortical areas innervated by the thalamus. Interestingly, thalamotomy produces the opposite effect, decreased metabolism and, as a result, it causes decreased activity in the sensory and premotor cortex. STN DBS increases glutamate concentrations in efferent regions, suggesting that stimulation activates (20,21,23).

DISCUSSION AND CONCLUSION

DBS is mostly applied in STN nucleus and Parkinson's Disease in clinical practice. The mechanism of action of DBS is not based on a single hypothesis. Although the inhibition hypothesis prevails, it is understood that it has stimulant effects, neuromodulatory effects, and increases plasticity. It is thought that clinically used DBS causes a decrease in spontaneous neuronal activity and also stimulates the axonal pathways directly around the electrode, resulting in the release of inhibitory neurotransmitters and suppression of the relevant neural network. DBS is a symptomatic treatment modality that ultimately affects not only the local area but also the entire neuronal network, impacting various areas connected to the basal ganglia (20,21).

In the treatment of DBS, neuromodulation of nuclei with different gray matter islands in the brain has been studied, however, some attempts

were inconclusive; for example, Pallidal deep brain stimulation did not change upper extremity dystonia. New clinical trials, such as spinal DBS and brainstem pedunculopontine nucleus DBS, show promise as new therapeutic strategies that will enter our treatment fields in the future as the pathophysiology of treatment-resistant motion sickness is understood (23-25).

Side effects related to surgery and wound healing can occur, as well as speech disorder, visual complaints, psychotic symptoms, sensory complaints, imbalance, increased appetite, and suicidal thoughts. Knowing and applying the necessary tricks for DBS is extremely important for the success of the treatment. The eligibility of the patient, appropriate timing, selection of the appropriate anatomical location and surgical implantation, and then proper DBS programming will yield satisfactory results.

In conclusion, due to significant advancements in this fieldsector, fresh ideas in the field of neuromodulation and potential DBS modes of action have opened up new therapy options for the central nervous system. As DBS can promote hippocampus growth, increased neurotransmitter release, and long-term structural plasticity, studies on the disease have grown in recent years. Studies on its application in psychiatric disorders including obsessive compulsive disorder that are resistant to therapy have gained traction. The fact that DBS is seen as an intrusive operation with numerous dangers, including cerebral bleeding, infection, and behavioral and personality abnormalities, is a significant drawback of neuromodulation therapy. The processes underlying the therapeutic effectiveness and side effects of DBS must therefore be clarified through more extensive research, as the effects of stimulation in these nuclei are various and complex.

Conflict of Interest: The authors have declared that they have no conflict of interest.

Funding: The authors have declared that they have not received any financial support.

REFERENCES

1. Dawson TM, Dawson VL. Molecular pathways of neurodegeneration in Parkinson's disease. Science. 2003; 302(5646): 819-22. https://doi.org/10.1126/science.1087753
2. Rubino FA. Gait disorders: Recognition of classic types. In: Adler CH, Ahlskog JE, eds. Parkinson's Disease and Movement Disorders: Diagnosis and Treatment. Totowa: Humana Press; 2000: 411-25. https://doi.org/10.1007/978-1-59259-410-8_33
3. Parkinson J. An essay on the shaking palsy. 1817. J Neuropsychiatry Clin Neurosci. 2002; 14(2): 223-36; discussion 222. https://doi.org/10.1176/jnp.14.2.223
4. Jankovic J. Parkinson Disease and Other Movement Disorders. In: Jankovic J, Mazziotta JC, Pomeroy SL, Newman NJ, eds. Bradley and Daroff's Neurology in Clinical Practice. E-Book. Elsevier Health Sciences; 2021: 1498-534.
5. Jankovic J, Sherer T. The future of research in Parkinson disease. JAMA Neurol. 2014; 71(11): 1351-2. https://doi.org/10.1001/jamaneurol.2014.1717
6. Stoker TB, Barker RA. Recent developments in the treatment of Parkinson's Disease. F1000Res. 2020; 9: F1000 Faculty Rev-862. https://doi.org/10.12688/f1000research.25634.1
7. İnce Günal D. Deep Brain Stimulation in Parkinson's Disease: Candidate Selection. J Park Dis Mov Disord. 2016; 19(1-2): 1-4. https://doi.org/10.5606/phhb.dergisi.2016.01
8. Ulutabanca H. Derin Beyin Stimülasyonu: Yeni Teknikler ve Teknolojiler. Türk Nöroşirürji Derg 2021; 31(3): 343-7.
9. Connolly BS, Lang AE. Pharmacological treatment of Parkinson disease: a review. JAMA. 2014; 311(16): 1670-83. https://doi.org/10.1001/jama.2014.3654
10. Armstrong MJ, Okun MS. Diagnosis and Treatment of Parkinson Disease: A Review. JAMA. 2020; 323(6): 548-60. https://doi.org/10.1001/jama.2019.22360
11. Coffey RJ. Deep brain stimulation devices: a brief technical history and review. Artif Organs. 2009; 33(3): 208-20. https://doi.org/10.1111/j.1525-1594.2008.00620.x
12. Pool JL. Psychosurgery in older people. J Am Geriatr Soc. 1954; 2(7): 456-66. https://doi.org/10.1111/j.1532-5415.1954.tb02138.x
13. Heath RG. Electrical self-stimulation of the brain in man. Am J Psychiatry 1963; 120(6): 571-7. https://doi.org/10.1176/ajp.120.6.571
14. Litvan I, Chesselet MF, Gasser T, et al. The etiopathogenesis of Parkinson disease and suggestions for future research. Part II. J Neuropathol Exp Neurol. 2007; 66(5): 329-36. https://doi.org/10.1097/nen.0b013e318053716a

15. Heath RG. Modulation of emotion with a brain pacemamer. Treatment for intractable psychiatric illness. J Nerv Ment Dis. 1977; 165(5): 300-17. https://doi.org/10.1097/00005053-197711000-00002
16. Blomstedt P, Hariz MI. Deep brain stimulation for movement disorders before DBS for movement disorders. Parkinsonism Relat Disord. 2010; 16(7): 429-33. https://doi.org/10.1016/j.parkreldis.2010.04.005
17. Demiryurek BE. Deep brain stimulation in Parkinson s disease: The selection of appropriate patient candidate. J Bionic Mem. 2021; 1(1): 1-5. https://doi.org/10.53545/jbm.2021175566
18. Uhlhaas PJ, Singer W. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. Neuron. 2006; 52(1): 155-68. https://doi.org/10.1016/j.neuron.2006.09.020
19. Wallace BA, Ashkan K, Heise CE, et al. Survival of midbrain dopaminergic cells after lesion or deep brain stimulation of the subthalamic nucleus in MPTP-treated monkeys. Brain. 2007; 130(Pt 8): 2129-45. https://doi.org/10.1093/brain/awm137
20. Durdağ E, Kocabıçak E. DBS in Parkinson's Disease: Mechanisms of Action. Türk Nöroşir Derg 2021; 31(3): 271-7.
21. Türel CA. Idiopatic Parkinson's Disease and Parkinsonism. In: Parlar H, ed. Health & Science 2021-II; 2021: 49-58.
22. Welter ML, Houeto JL, Bonnet AM, et al. Effects of high-frequency stimulation on subthalamic neuronal activity in parkinsonian patients. Arch Neurol. 2004; 61(1): 89-96. https://doi.org/10.1001/archneur.61.1.89
23. Ünal Y. Deep brain stimulation: Practice, Follow-up, Difficult-to-treat patients. Parkinson Hast Harek Boz Derg. 2018; 21(1-2): 12-21.
24. Tutuncu M. Peripheral Silent Period In Cervical and Generalized Dystonia. Dicle Tıp Derg. 2021; 48(1): 205-11. https://doi.org/10.5798/dicletip.888781
25. Yakşi E, Yaşar MF, Türel CA, Balcı M. Are static posturography-assisted biofeedback exercises effective in Parkinson's disease? Arq Neuropsiquiatr. 2022; 80(9): 935-43. https://doi.org/10.1055/s-0042-1755325