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COMPILATION

Deep Brain Stimulation: History, Indications and Future

Derin Beyin Stimülasyonu: Tarihçe, Endikasyonlar ve Gelecek

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ABSTRACT

Deep brain stimulation is a surgical technique with proven efficacy in the treatment of movement disorders-most notably-as well as psychiatric diseases and refractory epilepsy. In this review, we discuss the history of the deep brain stimulation technique, its indications for various diseases, stimulated anatomical targets, and the mechanisms of action involved in the stimulation. Additionally, the potential complications associated with different stimulation parameters are outlined. Finally, we summarize advancements in medical device technology, various surgical techniques, and the future trajectory of deep brain stimulation.

Keywords: Deep Brain Stimulation, Movement Disorders, Epilepsy, Psychosurgery.

ÖZET

Derin beyin stimülasyonu; hareket bozukluklarının tedavisi başta olmak üzere, psikolojik hastalıklarda ve dirençli epilepsi tedavisinde etkinliği kanıtlanmış bir cerrahi tekniktir. Bu derlemede, derin beyin stimülasyonu tekniğinin tarihçesini, farklı hastalıklarda uygulanan endikasyonlarını, her bir hastalığın tedavisinde hedeflenen anatomik bölgeyi ve stimülasyonun etki mekanizmasını tartıştık. Ayrıca farklı stimülasyon parametrelerinin olası komplikasyonları ortaya konuldu. Son olarak, medikal cihaz teknolojisindeki gelişmeler, farklı cerrahi teknikler ve derin beyin stimülasyonu tekniğinin ilerleyen süreçte ne yönde gelişim göstereceği derlendi.

Anahtar Sözcükler: Derin Beyin Stimülasyonu, Hareket Bozuklukları, Epilepsi, Psikocerrahi.

Deep brain stimulation (DBS) is a reversible surgery, which includes electrodes implantation into a specific target deep within the brain to modulate abnormal activity through stimulation. Then these electrodes are connected to a battery that generates electrical stimulation. Since its improvement, DBS has been proved to be an essential therapeutic choice for multiple disorders. Stimulation parameters are planned with different amplitudes, frequencies, and pulse width depending on the target and the disease being treated.

The exact mechanism of DBS remains unclear. However, from recurrent applications, it has been understood that deep brain stimulation affects multiple circuits that have a role in neuronal function. The therapeutic results depend on variety of characteristics, such as the physiology of the cells and the pathophysiology of the disease itself. It has been suggested that deep brain stimulation increases neural activity at the target site. (1)

History

Deep brain stimulation was first developed in 1987 and used for the treatment of essential tremor and Parkinson's disease (PD); however, physicians understood the important therapeutic effects of neurostimulation decades prior and explored different brain regions for ablative surgery since the 1930s. Montreal procedure was one of the earliest developments in functional neurosurgery by the neurosurgeon Wilder Penfield to treat epilepsy. During the surgery patients were awake, and the neurosurgeon stimulates different areas within the cerebral cortex to localize the seizure-causing area based on patient responses. Stereotactic neurosurgery was born after the development of the stereotactic apparatus in 1947, which enabled surgeons to explore deep brain regions. This advancement contributed to DBS becoming a therapeutic option. Approximately 25,000 stereotactic surgeries were performed for PD treatment by 1968 worldwide. During this era, surgeons used each electrode insertion not just for treatment, but also to study neurophysiology, and identify surgical targets through stimulation effects. However, the surgical approach declined by the introduction of levodopa in 1968 as a treatment for PD because it was noninvasive, effective, and cheaper compared to surgery.

In the period of experimentation, neurosurgeons understood the therapeutic effects of high-frequency stimulation. However, electronic stimulation could not be used alone because electrodes needed to be externalized and connected to a power source. This changed

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when Medtronic introduced the first available cardiac pacemaker in early 1960s, which contributed to the development of neurostimulation. Electrodes were implanted using stereotactic frames within the thalamus to treat chronic pain, then connected to a pacemaker by Hosobuchi in 1973, he reported that the results were satisfactory in three of the four original patients.
In 1970s, neurostimulation was used as a therapy for motor disorders, cerebral palsy, epilepsy, schizophrenia, severe depression, using the spinal cord, cerebral cortex, and deep brain regions as sites for stimulation. In the 1980s, there were technological advances like lithium batteries, improved leads and wireless programmable devices which enabled long-term implantation procedures. The need for clinical assessment tools led the Movement disorder society to create UPDRS as a standardized Parkinson's disease assessment in 1987. In 1997 FDA provided the initial approval for DBS as a treatment for tremor in Parkinson's disease and essential tremor, followed by European approval in 1998 (3).

Indications

While DBS in the first stages was used as a therapy for essential tremor and tremor of Parkinson's disease, now DBS is used for the treatment of more movement disorders, psychiatric disorders, epilepsy, with different targets deep within the brain. (1) All indications and targets are summarized in (Table 1).

Table 1. DBS indications and targets for DBS surgery.

Indication	Target
Parkinson's disease PD	Subthalamic nucleus, globus pallidus interna.
Dystonia	Globus pallidus interna subthalamic nucleus.
Essential tremor	Ventral intermediate nucleus, posterior subthalamic area.
Treatment resistant depression TRD	Subcallosal cingulate cortex, ventral capsule\ventral striatum, medial forebrain bundle.
Obsessive compulsive disorder OCD	Ventral capsule\ventral striatum, subthalamic nucleus.
Addiction	Nucleus accumbens.
Drug resistant epilepsy	Anterior thalamic nucleus, centromedian thalamic nucleus, hippocampus, subthalamic nucleus, caudate nucleus, cerebellum, posterior hypothalamus.
Alzheimer disease	Fornix, hypothalamus.
Tourette syndrome	Centromedian parafascicular thalamus, Globus pallidus interna ventral capsule ventral stratum.

Parkinson's disease (PD): Deep brain stimulation is used in the treatment of PD motor symptoms, particularly the same symptoms that respond to levodopa. Therefore, DBS outcome is related to how the patient is responding to levodopa. DBS benefits are not sufficient in the phase where the medication effects are stable during the day (honeymoon phase). However, once motor symptoms begin DBS can be considered. Subthalamic nucleus (STN) is the target for stimulation in PD treatment, especially in advanced disease with motor symptoms. Benefits of STN-DBS had been shown in patients younger than 60 years old, performed at the onset of mild motor symptoms. Dopaminergic medications are reduced gradually with the optimization of stimulation parameters which may lead to possible side effects such as apathy and dysphoria, in addition to subthalamic stimulation side effects such as dysarthria and postural instability. In addition to STN stimulation, globus pallidus interna (GPi) is also used. However, it is underutilized in comparison to STN stimulation. Medication is reduced minimally or not overall because pallidal stimulation works on dyskinesias directly. GPi-DBS is suitable for elderly patients or patients with contraindications to the stimulation of STN (4, 5).

Dystonia: Deep brain stimulation is used for dystonia when medical treatment is ineffective or not tolerated, or if the disease is severe to justify surgery. GPi is the target of stimulation, and it's effective for many dystonia subtypes. However, STN is another emerging target in which Bradykinesia caused by stimulation may be avoided (4, 5).

Essential tremor: Ventral intermediate nucleus VIM is the target for essential tremor DBS. Both unilateral and bilateral stimulation result in tremor improvement. However, Patients with VIM stimulation, specifically bilateral stimulation may experience adverse effects, such as dysarthria, paresthesia, and ataxia. In addition to the VIM, posterior subthalamic area PSA (zona incerta, prelemniscal) is emerging as a target because it provides results with lower adverse effects however, the studies are limited (4, 5).

Treatment-resistant depression (TRD): Deep brain stimulation is considered for patients with depression who fail multiple therapies such as antidepressants medications, and psychotherapy. Subcallosal cingulate cortex (SCC) is one of DBS targets for TRD treatment because increased SCC activity is correlated with depression symptoms, along with its association with emotional regulation networks. PET imaging showed metabolic differences after DBS in orbital frontal cortex, medial frontal cortex, anterior cingulate cortex, and posterior cingulate cortex, which suggests that DBS works at a network level instead of locally. Ventral capsule/ventral striatum VC/VS is also a target which was first observed in DBS treatment for OCD, where mood improvement was noticed. However, clinical benefits may require prolonged programming time. Moreover, Medial forebrain bundle (MFB) can be

targeted due to its involvement in pleasure, motivation, reward processing, and anhedonia (6, 7).

Obsessive-compulsive disorder (OCD): Deep brain stimulation targets in OCD is VC/VS, in which response is defined as more or equal to 35% reduction in Yale-Brown obsessive compulsive scale (Y-BOCS). Additionally, OCD improvement was seen accidentally in a patient with Parkinson's disease that undergone STN-DBS. Other psychiatric disorders treated with DBS are addiction (nucleus accumbens), Alzheimer disease (fornix/hypothalamus-Meynert nucleus), Tourette syndrome (centromedian parafascicular thalamus, GPi, VC/VS) (6, 7).

Drug-resistant epilepsy: DBS in the treatment of epilepsy works by modulating neuronal circuits that are involved in seizure generation. There are different targets for epilepsy, including anterior thalamic nucleus (ATN), especially targeted in focal and temporal lobe epilepsy. Centromedian thalamic nucleus (CMTN) is a common target in generalized epilepsy. Hippocampus is targeted in mesial temporal lobe epilepsy. STN primarily used in motor seizures. Other targets studied are caudate nucleus, cerebellum, and posterior hypothalamus (8).

Surgical and Technical Aspects

Finding the precise location to implant the electrodes for stimulation is essential therefore, DBS depends on multiple steps. Starting with stereotactic frame providing target coordinates using XYZ (Cartesian coordinate system). Preoperative magnetic resonance imaging (MRI) is merged with computerized tomography (CT) imaging obtained with the frame-mounted leads to accurate surgical navigation and target localization. The electrodes are inserted into the brain through burr holes to reach the target, according to planned trajectories, while avoiding blood vessels to reduce hemorrhage risk. The pulse generator is implanted in the infraclavicular or abdominal region through a subcutaneous tunnel from the head to the chest area using extension cables. Additionally, softwares can create a 3D model for the target and the surrounding area which provides simulation prior to the surgery, post-operative reconstruction, and visualization of the volume of tissue activated (9).

Complications

Deep brain stimulation surgery is considered safe with multiple advantages. However, there are potential complications that may be faced by the surgical procedure itself, hardware complications, or appearance of an underlying disease. The complications may be immediate or they progress later. Starting with infection, which is the most common complication after surgery, it can develop in the scalp incision extension wires or the pulse generator. While the most serious complication is intracerebral hemorrhage. It may occur during or after the insertion of the electrodes, however, it can be prevented by precise preoperative imaging and planning to avoid cerebral vessels. Some early-term neuropsychiatric complications may be faced post operatively specially with Parkinson's disease patients such as delirium and confusion. Advanced age, cognitive impairment, and severity of the disease can be risk factors. If the wires or battery are placed superficially underneath the skin this may lead to skin erosion and with time to secondary infection. Besides patient related complications, hardware problems may occur including wire fracture, disconnection, migration of the leads, device malfunction, and battery problems (10).

Future of DBS

Even though DBS has advanced noticeably offering therapy options for a range of diseases, to reach better future outcomes, more development and studies need to be established. The arising competition between DBS manufacturers is one way for these improvements. DBS programs that are model based have been proposed, in which a model of neural circuitry is used to achieve optimization of stimulation parameters. An arising approach is phase-controlled DBS, meaning that stimulation is sent at a certain phase to either suppress or enhance abnormal activity. Improving translation of the neural activity and brain circuits by providing higher resolution and more flexible electrodes is an essential area for improvement. Although internal pulse generators (IPGs) have substantially improved, miniaturized IPGs are developing providing smaller size to be implanted within the skull reducing surgical complications and increasing patients' comfort. A major focus for DBS' future is centralized patient registries to establish a database that can help the identification of therapy effects, clinical benefits, and safety measures. Obtaining an international registry would provide a chance for researchers and physicians to compare outcomes in a larger base (11-13).

Conclusion

Deep brain stimulation has positively affected the field of functional neurosurgery, offering a reversible surgical option for patients who could not benefit from medications alone. DBS progressed throughout the years extending beyond the treatment of movement disorders into psychiatric diseases and epilepsy increasing the quality of life for many patients. DBS success relies on multiple elements, starting preoperatively with proper patient selection, precise targeting, accurate surgical planning, and programming. Further DBS developments in multiple aspects will refine it and expand it is used in the future.

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