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Chapter

Deep Brain Stimulation Approach in Neurological Diseases

Dev Priya and Pathak Abhishek

Abstract

The technique was emanated in early 1960s; nowadays, deep brain stimulation (DBS) has become a huge practice in treatment of various movement disorders along with some psychiatric disorders. The advancement of DBS in different neurodegenerative diseases and managing patients with refractory brain disorders are closely related to the developments in technology. This development in regard with the device advancement along with the safe coupling of DBS to high-resolution imaging can help us to shape our knowledge in brain-wide networks and circuits linked with clinical aspects. DBS is found to be useful in learning and memory. On the contrary, traditional epilepsy surgeries are more complicated and technologically DBS is easier and more feasible. There are mild adverse effects of this DBS treatment, but a number of studies have shown positive treatment outcome with movement disorders and many kinds of psychiatric disorders too.

Keywords: deep brain stimulation, neuromodulation, brain, movement disorder, neurodegenerative disease, psychiatric disorder

1. Introduction

Neuromodulation is an increasingly rising field in the successful treatment of neurological disorders [1, 2]. Neurostimulation allows highly flexible alteration of disease symptoms. A number of medications fail due to severe side effects that outweigh the medication benefit, but neurostimulation has been so long to be potentially used as a treatment option for several movement disorders [2], with mild side effects with unknown mechanism of action in other disorders [3].

2. Types of Neuromodulation techniques

1. Deep brain stimulation (DBS) is an approved option for the treatment of intractable forms of various diseases. It involves inflecting the dysfunctional neuronal networks by long-term electrical stimulation, which utilizes implanting electrodes placed in the target neurological site that excites the neuronal circuits [4]. In recent years, evolution of DBS has revolutionized the treatment few neurological diseases especially in the treatment of movement disorders [5].

2. Vagal nerve stimulation (VNS) uses a device to stimulate the vagus nerve via electrical impulses. VNS is very helpful for people who have not responded to

intensive antiepileptic drug treatment and suffers from their adverse effects. FDA has approved VNS in 1997 for the treatment of epilepsy, depression, and various other disorders.

3. Transcranial magnetic stimulation (TMS) is a noninvasive brain stimulation by producing electrical impulses at a specific area of the brain through electromagnetic induction or by changing magnetic field [6].

4. Spinal cord stimulation (SCS) is useful in the treatment of long-lasting pain, which utilizes a stimulator that gives an electrical stimulus to the spinal cord.

5. Epidural motor cortex stimulation technique is highly useful in the treatment of intractable long-term neuropathic pain.

6. rTMS is useful in the treatment of experimental pain, neuropathic pain, and nonneuropathic chronic conditions.

7. Transcranial direct current stimulation is a highly used noninvasive technique altering neuronal plasticity. It is moderately used in treating neuropathic pain and fibromyalgia [7].

3. Deep brain stimulation (DBS)

DBS is an electrode implantation method using stereotactic techniques into the deep regions of brain for modulating neuronal function. An implantable pulse generator (IPG) is attached below the clavicle region, with an intention to treat neurological and psychiatric conditions. This attached IPG works on battery and delivers electrical stimulation, which is regulated externally by patients with the help of the remote. The electronic components like frequency, pulse, voltage, and other parameters can be altered to attain maximum efficacy of the treatment. It is believed that it works on excitation and inhibition of neurons present nearby the electrodes, but the exact mechanism is still unknown.

Low-frequency stimulation seems to excite nearby neurons, while high-frequency stimulation may decrease local activity leading to rescindable functional lesion. This simple-minded opinion for the mechanistic action has been a challenge in recent years, and more comprehensive knowledge may promote enhanced DBS treatments [8].

4. Brief chronicle of DBS

4.1 Early history

During the early 1900s' experiments, first stereotactic frame was designed that allowed stimulation of deeper regions of brain. In 1947, X-ray pneumoencephalography was developed that enabled surgeons to locate the target with the help of detailed stereotactic atlas that was developed later on. In 1950, stereotactic techniques were used for the tremor treatment. Later, in 1963, Albe Fessard reported high-frequency (~100–200 Hz) electrical stimulation for the first time in the ventral intermediate thalamic nucleus that could substantially alleviate Parkinsonian tremor [9].

4.2 The last 50 years

In 1960, levodopa treatment development was highly effective for Parkinsonian symptoms with lesser risk and expense compared to DBS implantation and this led the curtailing of early forms of DBS research.

Inspite of the drawbacks, the research for use of DBSnever stopped. DBS continued to observe restricted use in intractable chronic treatment, with Medtronic Inc. (Minneapolis, MN, USA) and released the first fully implanted DBS systems commercially accessible for this purpose in the mid-1970s [10].

Other study groups investigated the use of thalamic DBS to treat consciousness diseases and reported few benefits. By the end of 1980s, it was evident that using levodopa would not hold the promising effects, after years of therapy, and patients developed wearing off along with the side effects like dyskinesias. Meanwhile, the technology of implantable medical devices had improved to the stage that it was routinely used for chronically implanted devices like cardiac pacemakers and spinal cord stimulators. The animal model study eventually got translated into clinical practices, and the first subthalamic nucleus (STN) DBS study got published [11]. By the beginning of the century, clinical use of DBS in Parkinsonian disorders has begun to become common [8].

5. Rationale and mechanisms of action

Although the exact mechanisms of action of DBS are still elusive in spite of extensive research, several theories have been put forward. These proposed mechanisms can be divided according to the latency of onset of the effects from the time of stimulation into acute (seconds to hours) and chronic (days to months). The two major proposed mechanisms are as follows:

1. Electrophysiological and neurotransmitter modulation 395 likely explain the acute effects.

2. Plasticity and neurogenesis may explain the chronic effects [12].

However, there is a considerable overlap among the proposed mechanisms and one group of mechanisms has effects over the other, as described in detail in the following sections. Furthermore, depending on the methods used to investigate the mechanisms of action, different aspects of stimulation effects are tested. With an integrative approach combining investigations employing different modalities, one can understand the general effects of DBS.

5.1 Modalities used to study the mechanisms of DBS

Different methods have been used to quantify the changes produced by the DBS at the cellular, tissue and system levels to study the mechanisms of action of DBS. These modalities can be broadly classified into electrophysiological, imaging, biochemical, and molecular methods. Imaging techniques such as positron emission tomography (PET) and functional MRI (fMRI) provide information on both local- and system-level changes. These are complementary methods: functional imaging studies have high spatial resolution, whereas electrophysiological methods have high temporal resolution. Moreover, electrophysiological methods directly measure neuronal activities rather than indirect measures of neural activities using blood-flow changes measured by imaging methods [13].

There are several hypotheses proposed by different schools of thought, to explain the processes by which DBS works. Accepted and popular hypothesis relied on the alteration of pathological brain circuit activity induced by stimulation [12, 14]. The stimulating impacts that are accountable for this disturbance occur at protein, ionic, cellular, and network levels to produce symptom improvements [15]. While it is presently unclear that which of the DBS' wide-ranging impacts are needed and adequate to generate therapeutic results, it is evident that high-frequency (~100 Hz) pulse stations (~0.1 ms) produce network reactions that are essentially distinct from low-frequency (~10 Hz) stimulation. The electrodes implanted into the brain redistribute the charged particles (such as Na+ and Cl−ions) throughout the extracellular space, which generates electric field and ultimately leads to the manipulation of sodium channel protein's voltage sensor embedded in the neuron membrane [16]. The opening of sodium channels at the cellular level may generate a potential action for initiation of axons and can propagate in both orthodromic and antidromic directions. DBS causes, activated axons are able to follow very high fidelity stimulus rates at ~100 Hz, but these high-frequency synaptic transmissions are less robust and much complex than that of axonal transmission [17, 18].

Under such high-frequency activity, postsynaptic receptors can be depressed and axon terminals can exhaust their released pool of neurotransmitters [19, 20]. Even though these synapses appear to be active in DBS, theories of information processing suggest that they could become low-pass filters that can block low-frequency signal transmission [21]. This general mechanism, defined as "synaptic filtering," may play a crucial role in DBS, hampering the transmission of oscillatory activity patterns throughout the related networks of brain via neurons [22].

DBS' simple biophysical consequences offers a background where the patterns of network activity observed in patients can begin to be interpreted. The oscillation frequency of the stimulation signal is virtually zero as stimulation intensity remains unchanged during DBS, which could produce what is known as an "information lesion" in stimulated neurons [23]. According to this theory, action potential induced by DBS essentially bypasses some endogenous activity directly within the stimulated nerves and therefore slows down the transmission of oscillatory activity via the network. Nonetheless, not too many researches support the statement that high-frequency DBS causes lesion. Research with asleep and behavioral primates indicates how DBS can serve as a filter, which allows certain sensorimotor-related regulation of neuronal activity in the activated area, whereas specifically suppressing pathological low-frequency oscillation propagation [24, 25]. Certain basal ganglia activities, like those of reward-based decision-making or motor sequence learning, can often be retained during STN DBS or globus pallidus [26].

Certain factors may also have significant roles in treatment mechanism of DBS for PD like high-frequency DBS could provide an appropriate information lesion that inhibits the propagation of low-frequency oscillations, unlike low-frequency synchronization, could have no impact on broader network function [27, 28]. One of the advantages of this system is that high-frequency DBS is a standard device that can overcome various forms of clinical low-frequency excitations, like mobile tremor, dystonia, and akinesia rigidity [29].

The above proposed mechanism of DBS goes some way to explain only the acute effects of DBS in movement disorders, but this would not explain long-latency, chronic-adaptive alterations, which arise in individuals with dystonia following DBS and it may describe the psychological response to DBS. There might be possibility that low oscillating frequencies are strongly enhanced by long-term potentiation, while stimulation of high-frequency seems to have smaller plasticity effect. Therefore, replacing low-frequency patterns with high frequency can reverse

those symptoms associated with chronic disease [30]. DBS often takes months to get maximum benefit in various disorders, such as dystonia, depression, and epilepsy [31].

5.2 Open- vs. close-loop stimulation system

Nowadays, the open-loop system is embedded in many cases for DBS in which related parameters such as frequency, amplitude, and duty cycle can be adjusted by trained physicians. Stimulation, in this method, is fixed for initial months of treatment, then later can be adjusted based on patient's symptoms and overall conditions.

A closed-loop system receives continuous feedback from the patient's neuronal circuits of brain by a present and programmed algorithm and thus appears to be an effective stimulation, and the parameters are adjusted real time. The implanted device causes physiological changes, both over long and short term, via automatic therapeutic parameter delivery with the ability to sense brain signals. Though there are no randomized controlled trials, comparing the therapeutic effect of open- vs. closed-loop system, few researchers opine that closed-loop method are more effective than the open-loop system. Through their novel closed-loop method, to compare the effectiveness of open-loop systems using two neurons, they demonstrated that closed-loop system with implantable electrodes in GPi region has better results on the disease motor symptoms in PD patients than the open-loop and high-frequency systems [32, 33].

6. DBS in different neurodegenerative diseases

The common form of dementia, AD, treated with lesser efficiency of success in treatment via this technique has been used to modulate nonfunctional neuronal circuits with abnormalities seen in cortical and subcortical areas of the brain. Treatment helps in altering cholinesterase inhibitors and NMDA receptor antagonist [31]. DBS is a significant option for treatment of movement disorders that are intractable to drugs namely Parkinson's disease, essential tremors, dystonia, and have recently shown to be effective against treatment of OCDs, depression, and Tourette syndrome [5, 31].

7. DBS in movement disorders

DBS became the standard therapy refractory over the last 25 years for individuals with motor circuit disabilities, most notably PD, dystonia, and essential tremor. DBS use has now been confined to high-income and developing countries [34]. Hospital-discharge-based studies of US database has showed that >30,000 DBS surgeries were performed during 2002 and 2011, and the publications on DBS have also risen over the same period of time [35].

7.1 Parkinson's disease

Over the last 10 years, STN is used as a target for DBS in PD [36]. GPi is also used as a target, but the choice between STN and GPi is often guided by the biomedical group based on the medical context of the patient.

Multiple studies have already shown that STN DBS produces continuous symptom relief even after 5–10 years of treatment, although with cognition and gait regression due to the unremitting development of the underlying degenerative disorder [37]. In PD diagnosis, DBS is called the "second honeymoon"

(dopaminergic therapy is the first). Instability in posture and freezing can be improved by DBS at pedunculopontine nucleus region of the brain [38].

Based on previous studies, there is a general concept of DBS that it can improve PD patients with advance kind of symptoms like motor fluctuation, dyskinesias secondary to chronic levodopa as well as those with refractory and marked tremor. But based on studies of EARLYSTIM findings, DBS can also improve early stages of PD [39]. Due to these advantages of DBS, it is now been under clinical trials for those patients who are eliminated from surgery due to age factor, along with those patients with motor fluctuations in whom medication is effective. Due to the inherent risk of DBS like hemorrhage and infection, such trials face ethical issues [40].

7.2 Epilepsy

Earlier it was thought that DBS can switch open resective surgery in epilepsy, but after studies on DBS of the anterior nucleus of the thalamus (ANT), it was stifled. These researches imposed well on the efficacy of DBS but simultaneously also demonstrated that many patients did not attain seizure freedom after the DBS treatment [41, 42]. Closed-loop stimulation is a hopeful technology in epilepsy that can sense seizure activity with electrode and also can send electrical stimulations to brain to thwart propagation of seizure [43].

7.3 Essential tremor

After various studies, DBS was recommended by FDA in 1997 for the initial tremor symptoms of the movement disorder [44]. Along with DBS, other therapies such as lesional surgery have also been used for the treatment of essential tremors. DBS is a better choice due to its safety as well as adjustability of the stimulation, which is not provided by the lesional therapy [45]. Thalamic DBS is used in tremors of multiple sclerosis patients [46].

7.4 Dystonia

DBS had played a crucial role in dystonia treatment [47, 48]. Pallidal DBS, for instance, is the first-line treatment in childhood generalized dystonic disease. The most significant determinant of results was age at which surgery was performed and the duration of disorder [49–51]. Genetic makeup of patients has also been important in evaluating the outcome, as individual with DYT1 dystonia are benefited more than the DYT6 dystonia [52]. Therefore, genetic testing of patients undergoing DBS treatment would suggest which candidate is going to be benefited more [53]. The posteroventral lateral GPi in dystonia is the utmost recognized target for DBS [54]. GPi stimulation offers significant recovery in dystonic patients with adversarial effects on low frequency. The STN and the thalamus are two other targets for DBS. Despite of positive outcomes of STN DBS, the therapeutic use is still restricted [55]. An additional important target is sensorimotor thalamus, which in the age of radiofrequency lesioning, was considered as standard target [56, 57]. The mode of action of DBS in clinical improvement is quite intricate because of delayed and progressive effect exhibited over a period of months. The underlying mechanism for this was hypothesized as the alteration of maladaptive plasticity, progressive motor learning, and modification in pathological oscillatory activity in basal ganglia circuitry [58]. Dystonia can recur within minutes to hours after discontinuation of stimulation during the initial postoperative period; the advantages from stimulation that has been administered for several years can persist for days and weeks after

discontinuation [59, 60]. Therefore, DBS acts as a true treatment in case of dystonia where progressive treatments are absent or poorly successful. This rationale has contributed an EARLYSTIM study in dystonia [61].

7.5 Alzheimer disease (AD)

AD is perhaps the most prevailing neurodegenerative disease but is characterized with years of gradual reduction in neurocognitive parameters. Many DBS strategies have been identified for AD, including areas anterior to the fornix, entorhinal cortex, and the nucleus basalis of Meynert (NBM). Several studies suggest that DBS can affect cognitive function in AD. Nonetheless, outcome influencing factors such as baseline neuroanatomical substrates, surgical technique, placement of lead, and target population choice are the challenges for DBS [62].

8. DBS in psychiatric disorders

Psychiatric disorders are assorted conditions affecting multiple pathways with overlap. Such disorders have few (if any) biochemical markers that support treatment and outcomes, and there is a lack of data for its outcome assessment in patients. Thus, this affects the designing of clinical trial studies. In addition, the quality of surgical trials is also hindered due to significant selection barriers [63]. In an attempt to alleviate refractory psychiatric symptoms, numerous prospective studies have been done to evaluate if focal disruption at specific anatomic targets can impact circuit-wide or network-wide changes. Though the strategy is enticing, there are still some challenges.

8.1 Tourette syndrome

Due to the behavioral and cognitive issues in these patients, less than 300 patients have endured DBS treatment across the world. Patients with chronic symptoms are improved less than those with mild symptoms as per a meta-analysis [64]. A randomized controlled trial in 2017 did not report any significant improvement of tics in Tourette syndrome patients treated with anteromedial GPi stimulation during the initial blinded phase of the study; however, tics improvement was documented during the study's transparent period [65]. There is need of more randomized control trials for further development of DBS treatment in these patients.

8.2 Major depression

Major depression is a serious disorder that can impact quality of life day-to-day working and, eventually, life expectancy significantly [66, 67]. As a result of advancement of imaging techniques, there is a suggestion that depression occurs due to alteration in mood-related circuits, which can be reversed with neuromodulation along with other antidepressant therapies.

8.3 Bipolar disorder

Bipolar disorders are associated with acute and strong emotive condition, which are episodic and known as mood episodes; these disorders are less common than major depression but are linked with increased risk of suicide. Effective targets in bipolar disorders for DBS are thought to be SCC, the nucleus accumbens, and slMFB, but studies are less [68].

8.4 Obsessive: compulsive disorder

Obsessive–compulsive disorder (OCD) is a debilitating psychological condition, which is characterized by obsessions combined with time-consuming and subjectively anxiolytic behaviors. Several targets were proposed for OCD treatment, but STN DBS was found to be the most effective with significant reduction in OCD symptoms [69].

8.5 Anorexia nervosa

Anorexia nervosa is a severe, prevalent, and has one of the highest mortalities among any psychiatric disorder. The limbic and emotional circuits are involved activating and upholding the disorder. The limited availability of treatment in refractory anorexia nervosa and positive outcomes of DBS in mood-related circuits have led the curiosity for DBS targets availability in anorexia nervosa condition. Several research articles are published on SCC DBS target with significant reduction in depression and anxiety [70]. However, further studies are needed for convincing target for DBS.

9. Pain

For patients with pain, the analysis of DBS outcome is more challenging than in motor movement disorders due to rationality of pain self-assessment. Though nociceptive pain can usually be kept in check with opiate medication, DBS targets in the thalamus or cingulum are considered for patients with severe refractory neuropathic pain [30, 71, 72].

10. Positive influence of the DBS treatment

There are a number of side effects via medication that is highly reduced by neuromodulation technique. Seizure frequencies and mortality were decreased, but the results were not evaluated. Successful results of DBS on movement disorder and vagal nerve stimulation for epilepsy [73, 74]. DBS is a best way to treat extrapyramidal motor disorder namely dyskinesia, tremors, rigidity, and dystonia [75–77]. GPi-DBS, in primary generalized dystonia, was proved to be very successful, and it can be used as an effective treatment option [78]. Although with mild treatment side effects, a number of studies have shown positive treatment outcome in chronic disorders of consciousness with unknown mechanism of action [79]. DBS is found to beneficial in enhancing altered learning and memory. In rodents' model of dementia, mesial temporal DBS has shown positive results. Improvement in visual memory is seen in patients who underwent unilateral amygdalohippocampal DBS [80]. DBS helps in regaining of learning, memory, and altered communication skills in patients of postbrain injury with disorders of consciousness [81].

11. Negative influence of the treatment

Severe harmful effects of DBS are seen on dominant side of hippocampal region. Bilateral hippocampal DBS may cause memory dysfunction in epilepsy patients. Though DBS, is supposed to be safe, the adverse events can be seen in 7.5–8.5% of patients. The major adverse effects being, infections, intraoperative seizures and other complications [7].

12. Evolution in DBS technologies

Evolutions in technologies have led to the advancement in pain management in DBS. Several technologies related to spinal cord stimulation like Expanded MRI labeling, pulse modifier (generator as well as shrinker), dorsal root ganglia stimulating leads, and so on have benefited a lot due to high-frequency and high-density strategies of software [82–85]. The major problem in DBS is the inappropriate dose, for which no new technology has been developed for the past two decades; therefore, there is lack of competitiveness in DBS technology [30].

13. Summary

DBS is a neurosurgical procedure that utilizes lead-implanted electrodes that is placed chronically in the target areas of the brain well connected to pulse generator, which excites the neuronal circuits [1, 4, 5]. It is an invasive neuromodulation technique that was emanated in early 1960s [1]. Recently, DBS has become a huge practice in treatment of various movement disorders along with some psychiatric disorders [4, 5]. As compared to other neurosurgical options, lower chances of complications are seen with this technique [5]. Although with mild treatment side effects, a number of studies have shown positive treatment outcome in chronic disorders of consciousness with unknown mechanism of action [79]. Growth in DBS in respect to pathway and its impact on neuronal circuit has been mainly propelled by preclinical, neurophysiological, and computational research. Significant needs and prospect have evolved innovative techniques and technologies that have improved tolerability as well as research design, but DBS is still growing in many areas to manage cerebral diseases safely and efficiently.

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Conflict of interest

The authors have no conflict of interest.

Abbreviations

DBS	deep brain stimulation
VNS	vagal nerve stimulation
TMS	transcranial magnetic stimulation
SCS	spinal cord stimulation
rTMS	repetitive transcranial magnetic stimulation
AD	Alzheimer's disease
NMDA	N-methyl-d-aspartate
GPi-DBS	globus pallidus internus deep brain stimulation

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