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DEEP BRAIN STIMULATION AS THE TREATMENT OPTION FOR PARKINSON'S DISEASE

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Abstract:
Deep brain stimulation (DBS) has emerged as a very successful treatment for severe Parkinson's disease (PD) in recent years. A number of neurologic and neuropsychiatric conditions can be effectively treated with deep brain stimulation (DBS), which includes patient selection, postoperative stimulator programming, stereotactic electrode placement into specific brain areas for electrical stimulation delivery, and patient care. DBS is still an underappreciated treatment, even with its safety and effectiveness. Technological, mechanistic, and application advancements in DBS might increase its use and accessibility while simultaneously enhancing it therapeutically. Improvements in DBS technology, such as MRI compatibility and bidirectional DBS devices that can sense neural activity while stimulating the brain therapeutically.

Keywords: Deep brain stimulation, DBS, STN-DBS, dyskinesia, dopaminergic receptors.

Introduction:

A major reduction in quality of life is due to Parkinson's disease, one of the most disabling chronic neurologic conditions . Akinesia, tremor, stiffness, and postural instability are its clinical hallmarks, and they are mostly brought on by dopaminergic neuron degeneration of the substantia nigra [1]. In the early stages of the disease, levodopa and many dopamine agonists can be used as dopamine replacement medications that effectively relieve motor symptoms [2]. However, dyskinesia, or involuntary movements, and motor fluctuations, in which patients alternate between periods of improved mobility and times of decreased mobility & hamper long-

term levodopa treatment [3]. The key component of Parkinson's disease treatment is levodopa. A number of medications are available to effectively treat the disease's symptoms; however, the emergence of levodopa-induced motor complications generally complicates long-term medical management, resulting in sudden changes between periods of severe akinesia and periods of mobility that may be accompanied by problematic hyperkinesia [4] Amantadine, catechol O-methyl transferase (COMT) inhibitors, dopamine agonists, and other medications can successfully increase mobility and lessen dyskinesia at first, but they usually stop working after a few years [5] For most patients, these problems lead to impairment that cannot be adequately treated by medical therapy [6]. New therapeutic approaches to address these issues have been made possible by developments in our knowledge of the pathophysiology of the basal ganglia [7,8,9].

In 1986, people with Parkinson's disease (PD) with medically refractory tremor were treated with deep brain stimulation (DBS) of the ventral intermedius nucleus (VIM), a part of the motor thalamus [10]. Since then, DBS of different basal ganglia nuclei has been a very successful treatment for a number of movement disorders. DBS of the subthalamic nucleus (STN) and internal globus pallidus (GPi) were discovered to be safe and effective targets in Parkinson's disease. Neuronal activity in the globus pallidus and subthalamic nucleus becomes greater in animal models of Parkinson's disease, and lesions of these regions significantly enhance motor performance. [11,12,13]. Because it is linked to the likelihood of hemiballismus, the development of lesions in the subthalamic nucleus also benefits patients [13, 14]. Pallidotomy, which involves making lesions in the globus pallidus, has mild antiparkinsonian effects and improves contralateral dyskinesia. (20, 21). Chronic DBS used with standard PD stimulation parameters causes little to no tissue damage [15,16,17], making it mostly reversible when compared to surgical lesioning treatments. High-frequency deep-brain stimulation of specific brain targets simulates the effects of a lesion without intentionally damaging the brain [18]. It has been demonstrated that tremor can be controlled by deep brain stimulation of the thalamus[19,20]. Also, bilateral DBS can be used without significantly increased side effects, unlike lesioning. Along with the course of the disease and after surgery, stimulation settings can be changed. DBS basically replaced lesional surgery in developed countries because it demonstrated a superior functional outcome with fewer adverse effects in many randomized controlled studies [21,22]. Lesioning may still be the sole choice, though, because of financial

constraints in some nations. In people who suffer from severe stages of Parkinson's disease, it has been demonstrated that using a surgically implanted device that delivers high-frequency continuous electrical stimulation to the subthalamic nucleus improves motor symptoms 23,24,25]. For up to five years, mobility was significantly enhanced and dyskinesias were drastically decreased in open follow-up trials [26]. Only if the clinical advantages balance the inherent surgical risks and reduce the illness burden more successfully than ideal medication treatment will patients accept this therapy. Parkinson's disease has an influence on many aspects of quality of life, particularly those related to social and mobility[27,28,29].

Deep brain stimulation in both internal and external body regions:

Here are the inclusion and exclusion criteria:

A) Inclusion

(1) PD that is clinically idiopathic

(2) Substantial improvement (>30%) on dopaminergic medication

(3) Only minor symptoms during the ON-state Exclusion (relative)

(4) Refractory motor fluctuations or tremor

B) Exclusion

(1) Over 75 years of biological age

(2) Significantly lower life expectancy because of severe or malignant comorbidity

(3) Long-term immunosuppression;

(4) Significant brain shrinkage;

(5)Serious mental illness (depression, substance addiction, personality disorders, frontal dysexecutive syndrome, evident psychosis, cognitive deficits/dementia) (33)

Target points:

For DBS in PD, STN is now the primary target nucleus. STN-DBS can successfully cure all of the cardinal symptoms, such as tremor, stiffness, postural instability, and akinesia that primarily react well to levodopa. Stimulating the dorsolateral motor portion of the STN may yield the best outcomes [30,31], although there is evidence that stimulating the zona incerta also produces positive improvements [32] Bilateral STN-DBS is often recommended to reduce motor symptoms on both sides and enable the best possible medication decrease [33]

VIM Nucleus of the Thalamus:

VIM was one of the first nuclei targeted for DBS in the past [33,34]. The indication was PD and essential tremor [35,36]. VIM is still targeted for essential tremor today, but its use for PD is less common due to the discovery of other more effective target nuclei, STN and GPi, which participate in the three main symptoms of PD (akinesia, hypertonia, and tremor) rather than just tremor. VIM DBS has also been shown to alleviate orthostatic tremor [37].

Other Nuclei of Thalamus:

Tourette syndrome has been treated with bilateral thalamic DBS [38,39]. In patients with a minimally conscious state, a condition that falls within the spectrum of persistent vegetative state, very encouraging outcomes have been achieved. The central lateral nucleus, the posterior-medial aspect of the centro-median para-fascicularis nucleus complex, and the para-laminar parts of the median dorsalis are examples of midline thalamic nuclei that may be able to arouse a patient in a minimally aware state using DBS. This work remains preliminary [40,41].

The subthalamic core:

Presently, the vast majority of DBS treatment for severe Parkinson's disease includes bilateral electrode implantation in the STN [42,43,44]. With the STN being the most comprehensively verified target nucleus, this is by far the most meticulously validated use of DBS. Intractable epilepsy is one of the other indications for which DBS of the STN has been reported [45] Some case reports and a recent crossover double-blind multicentre study suggest that STN-DBS may be effective also in OCD [46,47].

GPi:

Dystonia and significant Parkinson's disease (PD) are the primary indications for GPi DB [48;49,50]. In addition to being utilized to treat Tourette syndrome, GPi DBS was also employed to alleviate writer's cramp [51,52,53]. The impact of the Centro-median Para-fascicular complex (CM-Pf) of the thalamus DBS has been contrasted with that of GPi DBS [54,55,56]. GPi stimulation has been demonstrated to provide a significant improvement in tics severity [57], with a reduction of 65% to 96% on the Yale Global Tic Severity Scale. Less successful was bilateral CM-Pf stimulation, which reduced tic severity from 30% to 64% [58,59,60].

Preoperative Steps in Deep Brain Stimulation :

The dopamine agonist is reduced a few days before surgery as a part of the preparation process. It is best to stop taking levodopa the night before the operation is performed. The impact of DBS must be assessed by a competent movement disorders expert using intraoperative test stimulation; hence, conscious patients should be maintained in a suitable OFF condition during the operation 61,62,63]. The target point is located using stereotactic coordinates [64,65, 66, 67] and is modified separately using cranial computed tomography (CCT) and cranial magnetic resonance imaging (cMRI) image fusion [68]. Direct observation of the target nucleus using high-resolution MRI with a voxel size <1.5 mm^3 and strong contrast may be more effective than indirect target point computation, but it needs axial/coronal T2 and/or inversion recovery sequences [69, 70]. It is necessary to conduct intraoperative investigations utilizing several neurophysiological methods in order to confirm the electrode location. A skilled specialist in movement disorders often performs test stimulation in the target region to determine the place of the best treatment impact.

The boundaries of the target nucleus can also be determined by mapping the side effects, such as oculomotor dysfunction, tetanic contractions, paresthesia, nausea, etc., that may arise after co-stimulation of nearby nuclei or fibers. Multi-trajectory microelectrode-recording (MER) can be utilized to better place the electrodes and capture the different activity patterns of the cells in the various nuclei [71, 72]. However, there is disagreement on whether MER raises the risk of brain hemorrhages [73, 74, 75]. There are four connections on the tip of the final DBS electrode used for chronic stimulation, and each one may be stimulated independently[76,77,78]. Even in cases

when the electrode is already implanted, this permits a slight alteration of the stimulated region[79]. For accurate targeting, intraoperative and postoperative controls of electrode location utilizing stereotactic x-ray, CCT, or cMRI are essential. Following electrode implantation, the electrodes are attached to the subcutaneously placed pulse generator at an abdominal or infraclavicular location [80,81,82].

Postoperative care and stimulator settings:

It still takes a lot of time to modify the stimulator settings in STN-DBS after surgery. The settings for stimulation and medicine often require frequent adjustments. . Without using the stimulator, symptoms may significantly and immediately improve after surgery. A micro lesioning effect is the reason for this clinical improvement, which eventually fades away. Although it generally fades away in the first few days and weeks, it can persist for several months. It is important to properly assess each of the four electrode connections once the micro lesioning impact has subsided. The contact with the best effect and the highest threshold for adverse effects should be chosen for long-term stimulation. Over the next several days and weeks, the stimulus amplitude will be gradually raised while the levodopa dosage is gradually decreased until satisfactory mobility and no noticeable dyskinesia occur [83]. For chronic DBS, typical stimulation settings include frequency 130-180 Hz, voltage 2.5-3.5 V, impulse length 60-90 ms, and monopolar stimulation. A number of considerations must be made while modifying the simulator's parameters. Changing to bipolar stimulation or activating a new contact may be required, depending on the negative effects that arise during chronic stimulation. Major modifications should not be made in the late evening or before the weekend since stimulation-induced dyskinesia may develop later after parameters have been raised. Sometimes it's hard to tell the difference between stimulation-induced dystonia and OFF-associated dystonia. In these situations, it is necessary to reevaluate the stimulating impact in the off condition. Additionally, it is well established that STN-DBS might have acute impacts on mood and subjective well-being [84]. Affective manifestations, such as pathological sobbing or humorous laughing, can even be directly induced by too-quick changes in stimulation parameters [85]. Reducing the dopaminergic drug too quickly may result in incapacitating mood disorders that may necessitate medical attention [86]. Due to the intricacy of STN-DBS, the patient's result is improved if the device is programmed by a movement disorders and DBS expert and if the implantation and

postoperative patient care are carried out in a specialized facility [86]. Although the medicine does not need to be modified, programming the devices for GPi-DBS and VIM-DBS is less complicated. The parameters may often be increased more quickly than with STN-DBS after the active contact with the optimal efficacy/side effect profile has been chosen. The stimulation settings for VIM DBS are comparable to those for STN-DBS, while GPi-DBS frequently calls for larger amplitudes and/or longer impulse durations [87,88]. When using regular simulator settings, the battery's capacity runs out after four to six years, necessitating a surgical battery replacement. A novel stimulation gadget has been released that enables wireless battery recharging without the need for surgery. Patients frequently require follow-up appointments with a physician knowledgeable in programming and optimization after they have had implants. This process is primarily empirical and necessitates a great deal of clinical expertise, which is only available at a select few specialized clinics. A common obstacle to DBS for prospective patients across all indications is limited or non-existent access to such facilities [89,90]. These difficulties show how urgently the DBS programming procedure has to be streamlined or automated so that a wide variety of highly qualified professionals may offer DBS patients high-quality treatment. The ethnic, gender, and socioeconomic differences in DBS usage further complicate people's access to DBS . According to studies, DBS results are correlated with income. This might be because patients with lower incomes find it difficult to take time off work, have limited access to transportation, or get enough assistance, which makes it difficult for them to attend numerous follow-up appointments for DBS programming optimization . Therefore, automated DBS programming may make DBS more accessible to vulnerable groups. When combined with sophisticated stimulation paradigms, such as CR and DBS, patients may notice better clinical results and require fewer clinic visits. [91].

Mechanism of action of DBS:

DBS's action mechanism is now thought to be caused by depolarization blockade , synaptic inhibition , synaptic depression , stimulation-induced interruption of pathological network activity , and stimulation of afferent axons projecting to the STN [92,93,94]. The similarities between the therapeutic efficacy of DBS and lesional surgery are probably due to depolarization blocking and synaptic inhibition. These theories are supported by recordings showing reduced somatic activity in the stimulated nucleus [95,96]. Nevertheless, these occurrences do not appear

to underlie the enhanced output of projection neurons [97,98]. Another widely accepted theory is that DBS hides aberrant signals by replacing defective spike train patterns with an un-physiological, high-frequency pattern. This leads to malfunction of the remaining components of the brainstem motor loop, thalamo-cortical system, and basal ganglia [99]. Abnormalities of the firing rate and pattern of basal-ganglia neurons, alterations in oscillatory activity, and excessive synchronization at multiple levels of the motor loop have been proposed as pathophysiological correlates of motor symptoms in Parkinson's disease (PD), although the precise nature of the aberrant signals and the relationship between stimulation-induced neuronal responses and intrinsic brain activity remain elusive [100].

Complications and side effects:

Although the safety of functional neurosurgery has significantly enhanced in recent years due to advancements in brain imaging methods, surgical complications are still a potential. Intracerebral hemorrhage (ICH), the most serious side effect of DBS surgery, is estimated to happen in 0.25 percent of cases. Hemorrhages can range in severity from asymptomatic ICH to severe ICH, which can cause fatalities or serious, long-lasting neurological impairments. There is a considerable range in postoperative infection rates; studies range from 1.8 to 15.2% of patients [101].The vicinity of the pulse generator is where infections most frequently arise [102]. In most cases, systemic antibiotic treatment and local surgery are enough, but, in extreme situations, the implanted device must be removed to stop the infection from spreading . The problems associated with electrode implantation and hardware that have been documented in studies involving over 100 patients are summarized in . Other hardware concerns include lead breakage or pulse generator dysfunction. Inadequate electrode placement and co-stimulation of nearby structures and fibers can result in stimulation-induced adverse effects. They might potentially happen, though, if current flows to nearby structures when the stimulation settings are increased. Typical side effects include tetanic muscular contractions, paraesthesia, oculomotor dysfunction, visual phosphenes, nausea, dizziness, dystonia, dyskinesia, or even a worsening of bradykinesia, depending on the anatomical location [103]. After STNDBS, weight gain is also typical and may result from DBS's notable decrease in dyskinesia [104]. Although there is a noticeable improvement in motor function, everyday living activities, and quality of life, STNDBS frequently does not lead to a successful social readjustment in the patient's household,

workplace, or personal life. As a result, meticulous preoperative psychosocial planning and postoperative psychosocial care are becoming more widely acknowledged as crucial components of patient care .

Conclusion:

DBS is a field that is constantly evolving. DBS is being used to treat a growing number of patients, mostly for Parkinson's disease. The progress of DBS has been wide and quick. DBS targeting strategies have been improved by advancements in atlases, imaging techniques, and connectomics. Improvements in lead design have made it possible to employ segmented contacts for directional stimulation, and these advancements have produced MRI-compatible batteries that are smaller and last longer. Software developments have made it possible to use a range of programming techniques to increase battery life and reduce adverse effects brought on by stimulation. In the future, brain sensing might serve as an additional programming technique and aid researchers and doctors in comprehending the physiological components of DBS. Customizing stimulation settings to each patient's symptoms may be possible with DBS. Virtual and remote programming could also become a more viable and available choice. Nowadays, DBS technology is widely used to treat a variety of illnesses and symptoms, and studies are being conducted to enhance existing designs. After DBS, the quality of life for individuals with advanced Parkinson's disease (PD) and significant "off" period impairment rises to the level of many people with moderate PD. The true benefit of STN stimulation is a reduction in the patients' social isolation. Further investigation is required to enhance targeting strategies and provide secure ways to pinpoint the exact anatomical position of electrode connections.

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