Present and Prospective Advancements in the Field of Deep Brain Stimulation Technology

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Abstract – Deep brain stimulation (DBS) in the neurosurgery domain allows for precise control of particular neural circuits. DBS has shown significant therapeutic effectiveness in the management of essential tremor, dystonia, and Parkinson's disease (PD). Moreover, ongoing research is investigating the potential of DBS as a therapy modality for several additional conditions characterized by aberrant circuitry, including depression and dementia. Over the last two decades, there has been a gradual improvement in DBS (Deep Brain Stimulation) devices, which today integrate an extension wire, pulse generator, and intracranial electrode. These components have been borrowed from the field of cardiology. The present paradigm of DBS is expected to undergo significant changes due to recent breakthroughs in technology and imaging, as well as a more comprehensive understanding of brain illnesses. Anticipated advancements in the tolerability and efficacy of DBS may be attributed to progress made in several areas, including battery and electrodes designing, stimulation systems, on-demand and closed-loop stimulation, including sensor technologies. This review provides a comprehensive examination of the historical and projected trajectory of DBS technology. By retrospectively examining the progress of DBS, we may enhance our understanding and recognition of our current position, as well as proactively forecast the next obstacles and prospects.

Keywords – Deep Brain Stimulation, Implantable Pulse Generator, Spinal Cord Stimulation, Obsessive-Compulsive Disorder.

I. INTRODUCTION

Deep brain stimulation (DBS) refers to the surgical procedure of electrodes implantation into the brain. The electrodes are responsible for generating electrical impulses in order to regulate and manage excessive activity. Conversely, the endogenous cells and chemicals inside the brain may be influenced by the electrical stimuli. A device that is surgically placed in the upper chest, like a pacemaker, is responsible for regulating the degree of stimulation in deep brain stimulation. The present device establishes communication with neural electrodes through a subcutaneously implanted wire. DBS has shown to be beneficial for patients suffering from various mental health conditions, such as obsessive-compulsive disorder (OCD), essential tremor, and movement disorders, dystonia, and Parkinson's Disease (PD). The Food and Drug Administration (FDA) has furthermore granted authorization for the use of this treatment in managing cases of severe epilepsy that are unresponsive to conventional medications. Although there is a lack of empirical data to indicate any specific hazards associated with deep brain stimulation, it is important to acknowledge that any surgical treatment inherently harbors the possibility of complications. There is also the potential for negative outcomes resulting from the stimulation of the brain.

Deep brain stimulation (DBS) is presently under investigation for various treatment-resistant states like Alzheimer's disease, depression, anorexia nervosa, addiction, Tourette syndrome, and schizophrenia. Furthermore, it has obtained FDA Humanitarian Device Exemption and CE approval for Obsessive-Compulsive Disorder (OCD) subsequent to a favorable random guided trials, which were conducted by Fan, Eisen, Rasmussen, and Boisseau [1]. The minimally invasive nature and low incidence of severe, debilitating side effects associated with DBS have prompted much research into its potential uses in the treatment of several medical conditions like sleep disorders, arterial hypertension, and tinnitus. Chronic stimulation leads to a diverse neuroplastic, molecular, and cellular alterations, alongside its direct impact on brain circuits.

As the understanding of deep brain stimulation's intricate mechanism of action continues to advance, so does the comprehension of the potential impact of long-term stimulation on the neurological system.

Following the beginning of DBS's modern era in the 1980s, a span of more than twenty years transpired without any notable advancements or enhancements in DBS technology (refer to **Fig 1**). The aforementioned technology was developed by the modification of cardiac pacemakers. Historically, the limitations associated with DBS technology, including the substantial size of batteries, restricted battery longevity, and the requirement for systematic battery replacement, have influenced advancements in the scientific domain. Nevertheless, the proliferation of many manufacturers of DBS technology in the international market has ignited massive global rivalry, leading to rapid advancements in the field. In the next years, it is anticipated that there will be the emergence of innovative hardware designs, advanced technologies, and updated stimulation algorithms. The clinical and scientific applications of DBS are expected to expand as the technology continues to advance, potentially offering many benefits. These advancements are expected to enhance the market's receptiveness towards DBS and improve the accessibility of therapy for patients in need, particularly those residing in low-income nations. However, advancements in electronics and computers may give rise to new concerns, including the possibility of regulating cognitive and decision-making processes, as well as the potential for data exploitation and brainjacking.

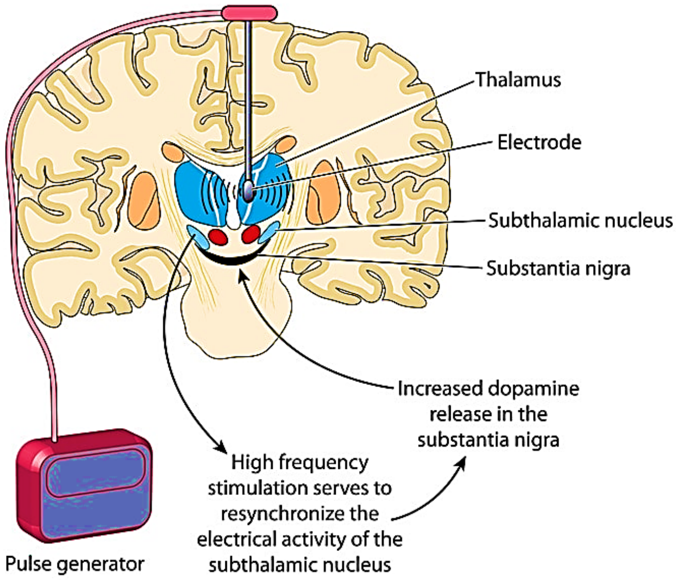

Fig 1. Deep brain stimulation technology

This article offers an analysis of the historical and present environment around DBS technology. It also explores possible future advancements in this field and examines the therapeutic implications associated with these technological interventions. The subsequent parts of the article are organized in the following manner. Section II presents a discussion of the present and future of deep brain stimulation. Section III reviews the advances of IPG design and electrodes. In Section IV, a discussion of the advancements in stimulation techniques is provided. Section V reviews closed-loop systems and adaptive DBS. Section VI focusses of DBS stimulation modelling and imaging. Lastly, Section VII concludes the paper and presents directions for future research.

II. PRESENT AND FUTURE OF DEEP BRAIN STIMULATION

The research conducted by Westerink et al. [2] was published in 1991, specifically focusing on the use of thalamic DBS as a tremor treatment. Subsequent investigations have shown that bilateral thalamotomy, specifically, has a higher level of risk compared to DBS targeting the thalamus. Similarly, the medical procedure known as pallidotomy, first proposed by Kalhoro, Sattar, Hashim, and Saleem [3] as a potential PD treatment that proved to be resistant to conventional medical interventions during the early 1990s, has been shown to possess a lower level of safety compared to globus pallidus stimulation. The DBS has been widely regarded as a safe therapy in these locations, leading to a progressive decline in the usage of lesional operations. The sub-thalamic Luys nucleus developed as a potential target for PD treatment, with Emmi, Antonini, Macchi, Porzionato, and De Caro [4] initiating its stimulation in 1994. The effectiveness of DBS in alleviating symptoms such as bradykinesia, tremor, and stiffness has been shown. Furthermore, a study conducted by de Oliveira, Vaz, Chamadoira, Rosas, and Ferreira-Pinto [5] examined the use of subthalamic nucleus targeting (SNT) and globus pallidus stimulation as therapeutic treatment interventions of global and segmental dystonia. DBS has been widely utilized and examined as a therapeutic intervention for the management of persistent pain, as well as motor dysfunctions. Consequently, it obtained official acknowledgement from the FDA in the year 1989.

The three thalamic nuclei are the Ventral Intermediate Thalamic Nucleus (VIM), Globus Pallidus Pars Interna (GPi), and Subthalamic Nucleus (STN). DBS has been proved to be the best treatment approach for movement disorders. The effectiveness of DBS has been shown over a significant duration of time in relation to several elements of movement disorders, like quality-adjusted life expectancy (QALY), quality of life, and motor symptoms. In the United States, a total of over 60,000 individuals diagnosed with PD, Tourette syndrome, dystonia, and essential tremor have had DBS implantation. On a worldwide scale, this number exceeds 160,000 individuals who have received DBS treatment. The globus pallidus pars interna (GPi), ventral oralis posterior (VOP) nuclei, thalamic ventral intermediate (Vim), and subthalamic nucleus (STN) have traditionally served as the three main DBS targets (see **Fig 2**) for the management of movement disorders.

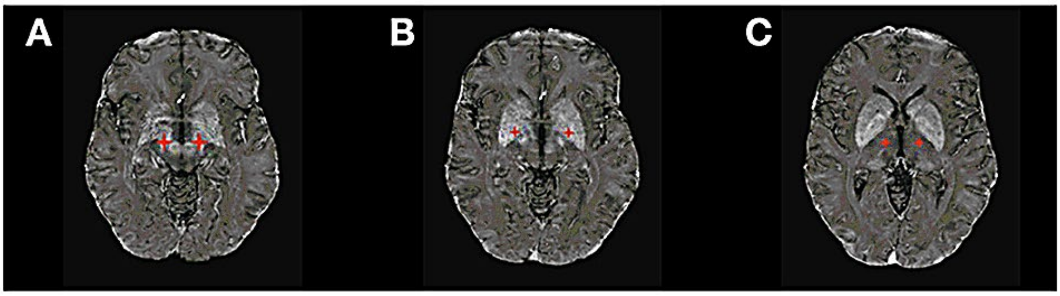

Fig 2. DBS targets for movement disorder

Despite several clinical studies, e.g. [6], that have shown evidence of the effectiveness of DBS in movement disorders treatment, there are still some unresolved issues that persist. The efficacy of DBS has been shown in people with PD who do not respond to medicinal treatment, leading to improvements in both the quality of life and motor function, as previously discussed. Nevertheless, the effect of these techniques on non-motor aspects of the illness remains uncertain. Furthermore, it is essential that we possess the capability to accurately identify the specifitc instance in which a patient is classified as unresponsive to medication and ascertain if early DBS intervention might potentially halt the progression of the ailment. A comprehensive experiment was conducted to evaluate the efficacy of DBS targeting the globus pallidus for primary dystonia. However, the available literature on DBS for secondary dystonia is limited to a limited number of minor reports. However, it is important to note that the efficacy of SNT stimulation in treating this particular illness has been well shown in previous studies.

The success of BDS in treating movement disorders has led epileptologists to take notice of its potential in the treatment of intractable epilepsy. The first findings on SANTE experiment has to provide a basis for diverse use of DBS in the treatment of epilepsy, specifically targeting the anterior thalamic nucleus. The sub-thalamic nucleus, caudate nucleus, cerebellum, centro-median nucleus of hippocampus, and thalamas have been identified as potential targets for future investigation, however the results so far have been equivocal.

The use of DBS has lately seen an expansion in its indications, including a broader range of illnesses. This development has created promising prospects for the exploration of novel treatment approaches in the future. Refractory Tourette syndrome, a complex disorder featured by the availability of multiple motor tics and a single or multiple vocal/phonic tics persisting for a duration beyond one year, has been managed with the use of bilateral thalamic stimulation. Shen et al. [7] have reported first positive results indicating improved clinical features. DBS has been proposed as a therapeutic intervention for severe mental disorders, including obsessive-compulsive disorder (OCD) and refractory depression. In addition to mental disorders, DBS has been considered as a possible therapeutic strategy for eating disorders, drug-resistant hypertension, and obesity. Although DBS for pain has principally fallen out of favor, the Milanese group has conducted research on the application of DBS to the posterior hypothalamus as a treatment for cluster headache. Furthermore, there has been a recent re-evaluation of DBS in the context of individuals with minimally conscious states after severe traumatic brain injury, as discussed by Banoei et al. [8].

III. ADVANCEMENT IN IPG DESIGN AND ELECTRODE

Electrode design

The underlying concept of DBS involves the precise localization of certain regions inside the brain and the application of electrical impulses via a minuscule electrode. The important features of electrodes are durability, inertness, long-term stability, and biocompatibility, suitability for surgical procedures, outstanding conductivity, desirable electrical features, tractability, optimal spatial layout and effective current delivery. The compatibility with magnetic resonance imaging (MRI) and the capacity for sensing are further considerations.

The DBS electrodes consist of nickel alloy connectors and platinum-iridium wires, which are encased in a polyurethane sheath. The choice of platinum-iridium was based on its low toxicity and exceptional conductivity properties. Currently, a wide range of electrode configurations is accessible. The tip of the probe has a diameter of 1.27 mm and is equipped with four stimulating electrode connections arranged in the quadripolar standard electrode configuration. The spacing between connections is either 0.5 mm or 1.5 mm, with every cylindrical contact that measure a length of 1.5 mm. By using various electrode configurations, it is possible to program different combinations of anodes and cathodes in order to provide an electric field along the lead z-axis.

Since 2015, the introduction of directed electrodes has enabled the flexible manipulation of the electric field, resulting in enhanced efficacy, reduced adverse effects, and an expanded treatment timeframe. The manipulation of the stimulation field might include horizontal plane displacement or the use of anodes and cathodes to shape the current's direction. Directional electrodes, characterized by radially segmented contacts, are used for this purpose, in contrast to the cylindrical shape of normal DBS electrodes. The electrodes and their capacity should be seen as a whole entity, closely associated with the technical features of the coupled IPG. In theory, the use of many independent sources linked to every electrode contact provides more tractability in the programming of electric domains compared to devices that rely on a single source and are either current-driven or voltage-driven.

Although the availability of a greater number of connections enhances possibilities, the use of directed electrodes introduces complexities in surgical insertion and poses challenges in programming. The Sapiens electrode exemplifies the constraints associated with the benefits and feasibility of augmenting contact quantities. The electrode in question has not been previously used for long-term stimulation and has a total of 64 connections, hence presenting challenges in terms of surgical integration with the extension cable. Increased current amplitudes also hinder the capacity to generate the stimulation domain in orientations other than the longitudinal course. In order to fully capitalize on the advantages offered by innovative electrode designs, it will be imperative to make breakthroughs in programming algorithms. This will include a shift from manual programming to automated programming methods.

The hand assembly of electrodes is a laborious and costly task in the existing production process of commercial DBS devices. While modern manufacturing techniques like as film printing have the potential to enhance the flexibility in electrode design and facilitate downsizing, they also raise some issues concerning the long-term resilience and safeguarding of new materials. The use of nanocoating techniques has the potential to enhance the stability of impedance.

Biocompatibility

Upon the implantation of the electrode, a transient connection is established and subsequently undergoes alterations with the surrounding brain tissue. The electrical features of electrodes-tissues interface under chronic conditions are influenced by many factors, including electrode glial encapsulation, electrode field protein adsorption, and the ionic environment at the electrode-electrolyte interface. In order to achieve enduring therapeutic outcomes with commercially available deep brain electrodes, it is essential to mitigate the inflammatory foreign body response that often arises from the long-term implantation of these electrodes inside the brain. Regardless of the duration of lead implantation, research conducted on these devices has consistently shown the occurrence of a response characterized by multinucleate giant cells. This reaction is believed to be associated with the presence of a polyurethane coating on the surface of the electrode. The available global evidence so far suggests that long-term DBS is generally considered safe, while further study is required to further investigate these findings.

There is a limited number of documented cases pertaining to idiopathic delayed-onset edema with leads surrounding, which is believed to indicate a sub-acute foreign body reaction following the implantation of electrodes. The origin, risk factors, and prognosis of peri-lead edema remain uncertain in the academic literature. However, recent evidence suggests that its occurrence may be more prevalent than first believed, since a considerable proportion of cases have been identified by routine postoperative MRI scans.

Programming and IPGs

The DBS sector has a significant need for technical innovation in the form of IPG. In order to enhance treatment outcomes, ensure patient safety, and optimize comfort, it is imperative to include novel waveforms and patterns, optimize programming techniques, increase energy economy, and achieve downsizing. DBS is now implementing advances that have previously been used in SCS for an extended period of time. One example of a technique is the use of multiple independent current control, whereby distinct lead contacts are combined with a dedicated present source to accurately tailor the dimensions and configuration of the stimulation field. The application of sophisticated waveforms such as 10-kHz HF-10 (high frequency) and BurstDR therapy, together with the adjustment of field shape, has significantly enhanced the effectiveness of neuromodulation in pain management. These innovative stimulation models are expected to be further discovered in DBS research in the next years.

One of the many techniques now under analysis in the neuromodulation field pertains to the enhancement of programming via the process of standardization. Both HF-10 and BurstDR use standardized approach, so replacing the potentially time-consuming and labor-intensive process of programming with a more straightforward approach. This approach is expected to be used into DBS programming due to its aim of establishing efficient feedback loops and using artificial intelligence for programming optimization. Automated programming has already made its presence known to a certain degree in the field of software-defined cyber-physical systems (SCS). A feasible and instructive IPG (implantable pulse generator) for SCS (spinal cord stimulation), for example, employs position data obtained from an embedded accelerometer to iteratively navigate and autonomously choose the optimal pre-determined parameters.

The utilization of artificial intelligence or computational models will be imperative in order to enhance the optimization of the progressively intricate implanted electrode systems. Clinicians have the option to choose the anticipated VTA (volume of tissue activated) by using a commercially accessible system provided by Boston Scientific. Subsequently, the programming software will control the technique determining contact activation. While wireless DBS programming is now the standard practice in clinics and requires physician supervision, it is expected that automated or self-programming devices, as well as remote monitoring and telemetry applications, will become more prevalent in the future.

Concomitant with enhancements in delivery methods, modifications to IPGs must be implemented to enhance the acceptability of DBS among prospective patients and doctors. Two advancements in this field are miniaturization and reduced charge load. The minimum weight of the IPG utilized in SCS has been reduced to 29.1 grams, whereas the typical weight range for DBS devices falls between 40 and 67 grams. Moreover, the increase in charge time and the deterioration of capacity have become noteworthy factors in the renewed attention towards rechargeable DBS devices. The current SCS IPGs available on the market exhibit a charging time of one hour from empty to full, along with a battery capacity of over 95% even after a span of nine years. However, these specific attributes have not yet been included into the DBS IPGs. The IPG technology, which is capable of harnessing energy, has the capacity to fully eliminate the need for traditional battery charging.

The potential emergence of cranium or burr hole-mounted implantable pulse generators (IPGs) should be considered in light of the ongoing trend of IPGs becoming more compact. By using this approach, the occurrence of wire breakage and wire passage would be eliminated, but, it would present novel issues such as cranial IPG infections.

Patient safety concerns

Ensuring the safety of patients holds paramount significance within the domain of neuromodulation. There is an expectation that manufacturers will soon acquire the capacity to provide MRI-safe systems that are compatible with comprehensive full-body imaging. Potential alleviation of concerns regarding the heat impacts of deep brain stimulation (DBS) systems during magnetic resonance imaging (MRI) scans could be achieved through hardware implant modifications, specifically by eliminating extension cords. Moreover, it is imperative to take into account the prevention of infections associated with implanted devices, which now affect persons with chronic deep brain stimulation (DBS) at a prevalence ranging from 5% to 10%.

Antibacterial envelopes have been employed as a measure to minimize the incidence of infections in cardiac pacemakers. A recent randomized controlled study conducted on patients with cardiac implanted devices revealed that the utilization of antibacterial envelopes resulted in a significant decrease in infection rates. The application of antimicrobial coatings on neurostimulation devices possesses the capacity to offer protection against infection and diminish the necessity for device extraction.

Moreover, the occurrence of symptoms such as tremor or depressive mood, accompanied by sudden malfunction of hardware, can have substantial adverse effects, potentially resulting in the emergence of a neuroleptic-like malignant syndrome among patients diagnosed with Parkinson's disease. In the context of future considerations, the inclusion of error-detecting servomechanisms may be seen as a crucial factor. The latest advancements in intelligent power grids (IPGs) have resulted in enhanced battery capacity assessments, facilitating more precise identification of the ideal moment for proactive replacement.

IV. ADVANCEMENTS IN STIMULATION TECHNIQUES

In recent years, there has been a notable emergence of regulated present IPGs, different stimulation waveform shape, and new temporal stimulation patterns. This progress follows a prolonged period of little advancement in hardware development. Due to the aforementioned technological improvements, there has been a reevaluation of stimulation techniques and the considerations of advanced models for stimulation treatments. While most of these techniques are already present, their efficacy and safety have not been sufficiently tested. In order to evaluate the therapeutic effectiveness of different stimulation paradigms, it is necessary to conduct research that include blinded comparisons.

Controlled voltage versus controlled current

Despite the limited number of studies that have directly compared the clinical results of regulated current DBS and regulated voltage DBS, a consensus article published in 2015 made a prediction that current DBS will likely exhibit more consistent effects than voltage DBS when confronted with dynamic variations in load impedance. As previously mentioned, the presence of an inflammatory response and gliosis in the vicinity of implanted DBS electrodes leads to changes in their impedance over a period of time.

Stimulation waveform shape

The stimulation waveform, which refers to the temporal profile of the stimulation current (or voltage), has the potential to influence both the number and kind of neuronal components that are activated. Stimulation patterns may be generated by repeating waveforms or pulses at varying interpulse intervals. Research comparing different types of stimulation patterns and waveforms has indicated that the symmetrical biphasic pulse, while leading to more battery depletion, are more efficient in reducing motor signs and symptoms linked to PD compared to standard asymmetric DBS waveforms that have a longer anodic recharging time. In a manner similar to this, it was shown that the use of symmetric biphasic pulses resulted in a greater decrease in tremor compared to the utilization of typical asymmetric DBS waveforms in patients with essential tremor (ET) who underwent thalamic nucleus Vim DBS. The activation of neurons during electrical stimulation is influenced by both the anodic and cathodic stimulus waveform phases. In this context, symmetric biphasic pulses have a higher likelihood of activating a greater neurons number than asymmetric pulses, given the same stimulation intensity.

The inclusion of waveform polarity, where convolutional pulse stage order is reversed, along with the incorporation of a gap between the 2 stages of charge-balance biphasic pulsations, are potential factors that might potentially augment neuron activation and entrainment. The impact of waveform shape on the desynchronizing impact of DBS techniques, where the pulse amplitude is controlled by close-looped controls based on linear/non-linear delayed response, is an additional factor to consider.

The thresholds for subthalamic nucleus deep brain stimulation (STN DBS) to induce adverse impacts and minimize motor symptoms in PD were found to be higher with anodic stimulations in comparison to cathodic stimulations. This finding is consistent with previous studies on tremor Vim nucleus DBS. However, it is worth noting that anodic stimulation, at amplitudes slightly below the threshold for negative effects, resulted in a higher symptoms suppression in comparison to cathodic stimulations.

Stimulation patterns

There is an increasing body of study indicating that the temporal pattern of stimulation, particularly in PD, could have an effective on the medical results after DBS. The choice of an optimal pattern presents significant model concern due to the difficulty in evaluating the impacts of symptoms stimulation pattern. This challenge is particularly pronounced whenever the feedback are apparent and rapid, such as in the context of tremor in ET or bradykinesia in PD. Nevertheless, in circumstances where the outcomes need a significant amount of time to become apparent and are difficult to observe, such as in the case of dystonia where improvements in tonic symptoms are sometimes delayed, or in epilepsy where modification in the frequency of seizure may take several months to become evident, the evaluation of these effects becomes very challenging. Furthermore, as shown in previous studies, the reaction to stimulation has exhibited temporal inconsistency. Moreover, a multitude of diverse temporal patterns may occur, hence potentially rendering it impracticable to determine the most therapeutically advantageous pattern using empirical means. The use of model-based optimization for the temporal pattern is a viable approach. However, it is important to note that this technique requires the construction of a highly accurate model that can effectively capture the relationship between the stimulation pattern and the corresponding alterations in a particular symptom.

In order to mitigate the anomalous synchronization of brain activity, computational techniques have been devised to generate stimulation approaches. Neuronal populations have intricate dynamics and may maintain stability in states characterized by either strong or weak connections and synchronization, particularly in the availability of timing-dependent spike plasticity. The use of desynchronizing stimulation in simulations and theoretical models has been seen to decrease neuronal coincidence rates. This reduction in coincidence rates, in turn, may result in a decrease in synaptic strength due to the influence of spike timing-dependent plasticity. Coordinated reset stimulation has the potential to induce acute desynchronizing effects and facilitate the unlearning of faulty brain synchronization and synaptic connections. This is achieved by the implementation of high-frequency short-term pulse trains over several stimulation contacts. The enduring implications of desynchronization have been shown by both preclinical and clinical studies, indicating that this phenomenon persists and accumulates even beyond the termination of synchronized reset stimulations.

The results, which are both promising and new, show the potentials for temporal patterns to boost the effectiveness of stimulations and extend the relief of symptoms via plasticity regulation.

V. CLOSED-LOOP SYSTEMS AND ADAPTIVE DBS

Modern DBS devices use a style of stimulation known as open-loop stimulation, whereby the stimulation is continuously activated. The efficacy of closed-loop adaptive neuromodulation is contingent upon the presence of a control signal that initiates timely modifications to the stimulation parameters. Biomarker-controlled DBS has the potential to provide assistance in managing the fluctuating symptoms seen the whole day in various neuropsychiatric and neurologic disorders. In the context of essential tremor (ET), tremors manifest during movement. On the other hand, in PD, tremors are seen at rest and stiffness is experienced while initiating movement. Neuropsychiatric illnesses, such as treatment-resistant obsessive-compulsive disorder (OCD), exhibit diurnal symptom fluctuations and substantial inter-individual variability in terms of the intensity of obsessive fixations and repeated compulsive behaviors.

While the symptoms of this illness exhibit significant variability, it has been shown that symptoms associated with TRD (treatment-resistant depression) tend to be highly noticeable during periods of stress and less discernible during periods of rest. Tics in individuals with Tourette syndrome (TS) tend to manifest at periods of heightened stress, exhibiting variability in location, duration, and intensity. Therefore, the use of on-demand stimulation paradigms has the potential to enhance the effectiveness, efficiency, and tolerability of neuromodulation approaches in treating a range of medical conditions. The aims of Adaptive Deep Brain Stimulation (aDBS) include addressing the individualized combination of symptoms experienced by each patient, mitigating the adverse effects of stimulation, especially those that disrupt sleep, and optimizing energy consumption to prolong battery life.

The primary focus of research on DBS mostly revolves on PD. Certain organizations argue that subthalamic nucleus adaptive deep brain stimulation (STN aDBS) is comparable to or not substandard to open-loop or continuous deep brain stimulation (cDBS) in minimizing the UPDRS (Unified Parkinson's Disease Rating Scale) score. Based on specific study findings, it has been shown that aDBS leads to greater reductions in scores compared to cDBS. The use of externally placed leads and experimentation pulse generator in a managed study environment during the initial period after lead implantation may represent a significant limitation in these investigations.

Additional study is necessary in order to determine the applicability of these results in long-term researches and non-medical contexts. The neurocognitive features of PD are also significant in the context of adaptive DBS. In [9] conducted a study in which they investigated a binary paradigm of DBS, characterized by the activation and deactivation of electrical stimulation. The study included eight patients diagnosed with PD who had bilateral subthalamic nucleus (STN) leads implanted. The researchers in [10] used beta oscillations, which have a frequency range of 13-30 Hz, to develop an algorithm based on thresholds. This system was designed to autonomously activate and deactivate, with a gradual increase or decrease in intensity over a period of 250 milliseconds.

In order to evaluate the speech-related adverse effects and enhancements, Stipancic, Wilding, and Tjaden [11] conducted a speech intelligibility test (SIT) at the initial stage, during cDBS, and during aDBS sessions lasting for a period of 15 minutes. When comparing aDBS to baseline and cDBS, it was seen that aDBS was associated with significantly higher SIT scores (baseline SIT: 67%; cDBS: 60%; aDBS: 70%; p = 0.02). Various researches have documented the results of zona incerta DBS or unilateral ventral intermediate nucleus (VIM) in conjunction to recordings from subdural stripelectrodes placed across the primary motor cortex in investigations of essential tremor (ET). Bocci et al. [12] have shown that aDBS is comparable to or not inferior to cDBS in its ability to suppress tremors. In contrast, Piña-Fuentes et al. [13] discovered that the use of aDBS resulted in a decrease in tremor control in comparison to cDBS.

Dystonia presents both challenges and opportunities in the application context of DBS. In a study conducted by Roodbol, de Wit, Aarsen, Catsman-Berrevoets, and Jacobs [14], it was shown that the implementation of short-term GPiaDBS did not provide significant clinical modifications or immediate fluctuations in low frequency oscillations (4-12 Hz). Nevertheless, the manifestation of dystonia often demonstrates a postponed reaction to conventional deep brain stimulation (cDBS), hence posing difficulties in extrapolating the impacts of aDBS within the framework of short stimulation. Due to the inherent complexities associated with DBS programming for persons with dystonia, as compared to those with PD or ET, it is plausible that the use of robust and efficient closed loop stimulation approaches might potentially provide favorable outcomes for these patients.

Variations in power spectra have been seen in a range of illnesses by the collection of local field potentials (LFPs) from implantable electrode contacts. The investigation of LFP response within the beta frequency dimension has been a primary area of interest in the study of adaptive DBS for PD. This research aims to establish a connection between LFP response in the beta frequency dimension and symptoms such as stiffness and bradykinesia, as shown by Denker et al. [15]. Additionally, dyskinesia, another symptom of PD, has been linked to gamma activity, which may be detected using a cortical strip electrode. Beta activity recordings may be processed in order to preserve rapid fluctuations in the signal or smoothed down over a duration of several seconds88. The smoothed signal exhibits a strong correlation with the dynamics of drug treatment and effectively captures the fluctuations in motor on-off states. Research has shown that the use of this particular kind of input for driving DBS has the potential to reduce on-state dyskinesias and decrease power requirements by around 50%.

The primary emphasis of research has mostly been on the LFP due to its ability to be captured from contacts in the distal end of similar electrodes utilized for chronic stimulations, hence obviating the need for additional electrodes or equipment. The subthalamic nucleus (STN), which is often the site of LFP recordings, offers a signal that is representative of the population while exhibiting a high degree of spatial specificity and confinement. The perceived benefit is in its ability to capture lower frequencies compared to single-unit recordings, since the influence of electrode interface and local geometry is less at these lower frequencies. Fortunately, there is an increasing body of study that consistently shows a substantial correlation between the LFP potentials and the activity of individual neurons. This correlation is particularly evident after the administration of medication, when there is a coordinated pattern of neuronal bursting that occurs in synchrony with a 13 to 30 Hz beta activity. One can raise the issue of whether the signals are effective for tracking intricate state changes, considering that LFP activity is an aggregate measurement across a population of neurons.

Nevertheless, it is important to emphasize that there is a notable convergence of data processing from various areas of the cortex towards a restricted location inside the basal ganglia, particularly the subthalamic nucleus (STN), as seen in the LFP recordings. Considering the fact that several states are represented throughout populations rather than inside individual neurons, it may be argued that a measure based on population activity may provide some advantages over single unit recordings. This is a probabilistic case, especially when monitoring overall state modifications in Parkinson's disease rather than the complex and particular motor coding required for precise voluntary movements. Local field potentials (LFPs) may, in some cases, provide a more accurate depiction of movements compared to individual units. Given these considerations, together with the established long-lasting stability of DBS at the tissues-electrodes interface, local field potentials (LFPs) emerge as highly sought-after response control metrics for receptive DBS.

VI. DBS STIMULATION MODELLING AND IMAGING

Over the past ten years, advancements in neuroimaging techniques have facilitated the precise localization and visualization of targets and leads for DBS. These technological improvements have facilitated precise surgical targeting and postoperative programming of DBS. The advancement of innovative imaging techniques has contributed to a comprehensive knowledge of the approaches of DBS actions.

The magnetic resonance imaging (MRI) scans commonly used for surgical planning purposes exhibit limitations in accurately visualizing specific DBS targets. T2-weighted images are capable of visualizing the subthalamic nucleus (STN), however the demarcation of its ventral boundary adjacent to the substantia nigra may not always be distinctly discernible.

Nevertheless, the internalized medullary lamina, which separates the globus pallidus externus and internus, cannot be identified on typical T1-weighted patterns. In order to mitigate these challenges and enhance the visibility of DBS targets, researchers have developed enhanced field strengths and novel sequencing techniques. For instance, the imaging of subthalamic nuclei (STNs) can be significantly improved by employing QSM (quantitative susceptibility mapping) on gradient-echo patterns, as QSM exhibits high sensitivity to iron content.

Moreover, the visualization of thalamic substructures and globus pallidus internus is most effectively achieved by the utilization of the rapid acquisition of the grey matter T1 inversions recovery sequence. This particular imaging approach was specifically designed to enhance neuroimaging methodologies. Diffusion-weighted imaging (DWI) is increasingly becoming recognized as a valuable targeting tool, particularly in the context of ET. This imaging modality has gained appeal due to its ability to precisely identify and focus on white matter tracts. There is a potential for the utilization of 7 T ultra-high-field (UHF) MRI to improve target visualization. The utilization of UHF MRI in DBS surgery for tremor provides significant advantages, as it enables the visualization of intrathalamic nuclei, among other benefits. Ultra-high frequency (UHF) magnetic resonance imaging (MRI) offers enhanced visualization of the borders of the STN compared to conventional MRI techniques. The susceptibility of UHF MRI to distortion artifacts, especially in the central brain region, requires the use of robust distortion correction methods. This limitation represents a significant drawback of the technique.

In order to achieve accurate targeting and ascertain the neuronal substrates that are crucial for therapeutic outcomes, it is imperative to guarantee exact electrode localization. Given the increasing prevalence of segmented and directed leads, medical professionals are faced with the task of determining the most appropriate approach to guide the current during programming. Consequently, it becomes imperative to ensure precise reconstruction of electrode placements in relation to adjacent anatomical structures. Due to this rationale, several programs have been introduced and methodologies have been developed to retrieve electrode localization from imaging modalities such as CT and MRI. Furthermore, the development and testing of algorithms were conducted in order to ascertain the recovery of the direction of segmented leads. The available evidence indicates that the classified directional DBS contacts leads frequently deviate significantly from their planned implantation orientation. As a result, precise electrode localisation becomes particularly important in these cases.

A novel approach has been developed to assess DBS electrodes positioning within the brain, even in the presence of metal artifacts. This strategy involves using the artifacts generated by the items of interest as part of the estimation process, rather than eliminating them from the computed tomography (CT) image. The localization approach is dependent on the identification of the primary points of intersection formed by the streak artifacts present in the image. The anticipated location of the electrodes is expected to lie between these two points, as will be further elucidated in the subsequent discussion. The images in the DICOM stack have a resolution of 600x600 pixels and are now undergoing evaluation. The current implementation of the concept involves the utilization of Matlab, facilitated by the incorporation of the Image Processing Toolbox.

The initial phase of the relevant procedure, known as brain extraction, has similarities to analogous methodologies. There exist multiple methodologies to address this issue, the majority of which yield outcomes that are sufficiently proximate to be deemed satisfactory for this particular context. The process of identifying unobstructed pathways for detecting straight lines within the image is impeded when the background and skull elements have not been removed beforehand. The Laplacian operator of Gaussian convolution is utilized on the masked image, resulting in a binary representation of the image and the filling of all voids, creating the illusion of a cohesive sphere representing the brain. This procedure entails an internal-exclusive, contingent expansion. The monochromatic shot predominantly centers its composition on the subject's cranial region. If all elements within the image possessing a surface area smaller than that of the head are eliminated, the remaining content solely comprises the head. The technique of morphological opening is employed to effectively mitigate any irregularities present within the internal region connecting the background and the subject's head. The extraction of the cranium necessitates the subsequent procedure of fabricating a protective facial covering. Considering the skull as the background is not a viable option due to its overlap with the brain and the similarity in intensity between its image and some regions of the brain artifacts.

A suitable threshold value is utilized on the grayscale image, enabling the distinction between the skull and regions affected by artifacts. The application of the morphological opening technique serves to eliminate streak artifacts. Following the completion of the preceding procedure, a segment of the cranial region was excised. The process of morphological opening is employed to alter the shape of the object. Subsequently, the disk-shaped structuring element is employed as a morphological closure operator to eliminate any remaining artifacts. Theoretically, if parts with a surface smaller than the skull were further eliminated, it is possible that all remaining components of the brain and artifacts would be removed. This would occur when the skull is perceived as a large interconnected object. The aforementioned technique has led to a reduction in skull thickness in certain areas, however it has also resulted in skull separation. Ultimately, a dilatation procedure employing a structural component of a disk is performed in order to verify the absence of any section of the cranium that has been excised. After the application of both the backdrop mask and the skull mask, a residual section of the image persists, encompassing the skin and muscles in proximity to the skull.

The Hough transform, as described in reference [16], is a computational technique that takes an input image and produces a matrix containing the possible representations of straight lines present in the image. Please refer to **Fig. 3** for an illustration of the several straight lines observed in the image. However, it should be noted that not all of these lines are linked to the metallic artifacts.

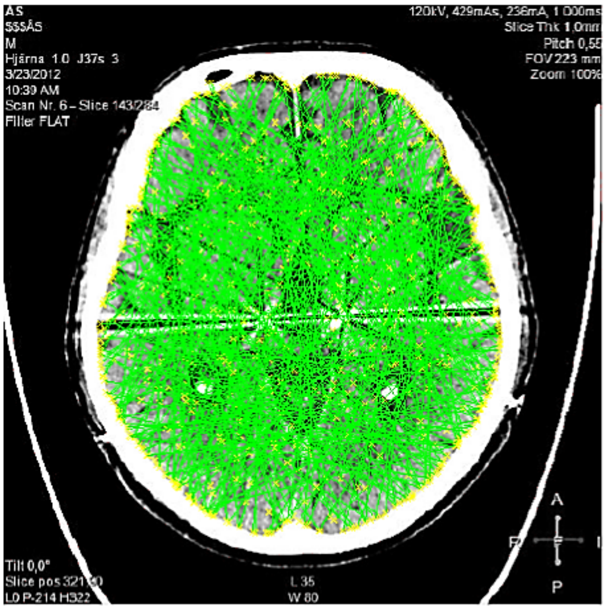

Fig 3. Computed tomography (CT) image of the brain

In **Fig 3**, the lines detected by the use of the Hough transform are overlaid onto the image, prior to the implementation of any selection criteria. Yellow indications are included to demarcate the starting and ending points of each line. A potential avenue for acquiring a deeper understanding of the functioning of DBS is retrospectively examining the accurate locations of electrodes in a significant number of patients. The utilization of neuroimaging techniques has enabled the precise alignment of patients' brain images with a standardized brain template, such as the Montreal Neurological Institute brain template, through non-linear normalization. Additionally, this has facilitated the accurate localization of DBS electrodes and the estimation of the ventral tegmental area. These advancements have greatly supported the conduction of group-level analyses. Group-level research with a substantial number of participants enable the identification and assessment of robust "sweet spots," referring to optimal patterns of connections.

These findings have significant potential for the prediction of outcomes in subsequent instances. The identification of the most efficient substrate of neuroanatomy within a significant group of patients may be achieved by the computation of probabilistic maps that include clinical outcomes and efficacious networks. These maps incorporate clinically weighted contact sites or ventral tegmental areas (VTAs). It is important to acknowledge that the VTA is a concept derived from a model-based theoretical framework, which is based on a visual approximation. The reliability and accuracy of the VTA are contingent upon the specific model used. Moreover, the estimation of the ventral tegmental area (VTA) fails to account for the fluctuations in intrinsic dynamics and localized impedance of neuronal demographics.

The place of electrode insertion and stimulation has been directly associated with clinical improvements in PD, ET, dystonia, and OCD. The findings of this study have led to the identification of "sweet spots," which are optimum locations for stimulation and surgical interventions. These sweet spots have been shown to have a statistically-relevant and direct linkage with medical outcomes. Research conducted by [17] has reached a consensus on a single optimal target for the therapy of PD.

The perception of track-based or network-based targets has been developed by incorporating functional or structural connectivity information into the identification of brain areas that are crucial for therapeutic outcomes. Clinical improvement has been associated with the modulations of targets physically-linked to supplementary motor field in individuals diagnosed with PD. In terms of symptoms, the connection profiles can be further categorized as follows: enhancements in bradykinesia and rigidity were observed in relation to connectivity with the primary motor cortex, whereas alleviation of tremors was associated with connection from active contacts within the subthalamic nucleus to the complementary motor area. The enhancement of ET's discrete tremor was shown to be associated with higher degrees of differential connectivity. Enhancements in both manual and cranial tremor were shown to be associated with augmented structural connectivity between the ventral intermediate nucleus (Vim) and the hand area within the primary motor cortex, as well as the cerebellum. Conversely, amelioration of head tremor was connected to the control of head regions via connectivity-mediated mechanisms.

In the field of mental surgery, where there is currently a lack of consensus about the objectives, the role of connectivity may be of heightened significance. The development of dependable connection profiles has the potential to assist surgeons in identifying more accurate surgical targets. In [18], it was shown that the observed connectivity patterns of DBS electrodes exhibited a clear correlation with the clinical amelioration seen by persons diagnosed with OCD. The researchers successfully found a distinct region inside the anterior limb of the internal capsule that had a significant association with positive clinical outcomes. Significantly, a subsequent study discovered that the proximity of the electrode to either the internal capsule anterior limb or the subthalamic nucleus (STN) exhibited predictive capabilities regarding efficacy in two distinct cohorts of patients with OCD. In the aforementioned scenario, it is seen that many DBS targets, when used for a particular illness, have the ability to modulate a common tract or network, hence alleviating identical symptoms.

As shown in our previous findings, gaining insights into the processes behind DBS may be facilitated by revisiting studies that investigate the relationship between the location of stimulation and its corresponding clinical outcomes. A potential avenue for obtaining a more comprehensive understanding of the brain modifications induced by DBS is the collection of prospective data from patients undergoing DBS. For example, using functional magnetic resonance imaging (fMRI) while DBS is active might provide valuable real-time observations of the changes occurring inside the brain. Until recently, the potential risks associated with exposing active implanted clinical instruments to the magnetic field produced by the MRI scanner have hindered the collection of functional neuroimaging dataset in individuals who have completely active and internalized DBS devices. In the majority of instances, safety rules impose restrictions on the MRI equipment used in these inquiries, such as a maximum magnetic field strength of 1.5 T. Recent research has demonstrated the safety and feasibility of acquiring functional MRI data at a magnetic field strength of 3 Tesla (using a body transmitting coil) in large patient groups with DBS systems. This advancement enables the collection of a wide range of functional neuroimaging dataset and presents opportunities for further exploration in the field of neuromodulation research.

VII. CONCLUSIONS AND FUTURE RESEARCH

The design of novel DBS hardware and the development of stimulation methodologies are being influenced by the increasing comprehension of the brain system circuit anomalies that are responsible for the clinical manifestations of neurological and psychiatric disorders. In the foreseeable future, it is anticipated that the use of neuromodulation will see a broader application among patients who have not responded to traditional therapeutic interventions. This is primarily attributed to its enhanced safety profile, less invasiveness, and heightened precision and efficacy. Anticipated advancements are foreseen in the realm of electrode technology, characteristics of implantable pulse generators (IPGs), as well as programming and stimulation approaches. The use of contemporary imaging methods enables the enhancement of target identification, validation of target engagement, and confirmation of the successful achievement of the planned physiological circuit effect of stimulation. In order to mitigate unforeseen consequences, it is imperative to concurrently evaluate ethical, privacy, and security considerations alongside technological advancements, as is customary with previous influential and transformative technologies.

It is imperative to steer clear of the technical and ethical errors that have marred the historical era of neuroscience, since DBS does not fall within the category of contemporary psychosurgery. The objective of DBS is to restore equilibrium in impaired neuronal circuits by selectively and reversibly manipulating (through stimulation) specific brain structures. These structures, when altered, can contribute to both neurological deficits and behavioral issues, as observed in conditions like Tourette's syndrome. In contrast, psychosurgery involved non-selective and irreversible manipulation of a particular brain region, as exemplified by Egas Moniz's proposal of lobotomy in 1935 and its subsequent variations. The psychiatric signals of obsessive-compulsive disorder and refractory depression are supported by evidence of organic alterations that underlie these conditions. This provides a sufficient explanation for why DBS, which aims to rebalance specific neurophysiological substrates, can effectively improve these behavioral disorders. As a result, DBS helps to align the physical and psychological manifestations experienced by individuals with these conditions.

Data Availability
No data was used to support this study.

Conflicts of Interests
The author(s) declare(s) that they have no conflicts of interest.

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Competing Interests
There are no competing interests.

References

[1]. Y. Fan, J. L. Eisen, S. A. Rasmussen, and C. L. Boisseau, “The relationship between obsessive-compulsive disorder symptom subtypes and social adjustment,” J. Obsessive Compuls. Relat. Disord., vol. 38, no. 100826, p. 100826, 2023.
[2]. L. G. Westerink et al., “Deep brain stimulation of the subthalamic nucleus in Parkinson’s disease after 15 years: clinical outcome and caregiver burden,” Deep Brain Stimulation, 2023.
[3]. A. Kalhoro, A. B. Sattar, Abdul Sattar M. Hashim, and A. Saleem, “Pallidotomy In Parkinsonian Disease: The Renaissance,” J. Univ. Med. Dent. Coll., vol. 12, no. 2, 2021.

[4]. A. Emmi, A. Antonini, V. Macchi, A. Porzionato, and R. De Caro, "Anatomy and connectivity of the subthalamic nucleus in humans and non-human primates," Front. Neuroanat., vol. 14, 2020.
[5]. F. de Oliveira, R. Vaz, C. Chamadoira, M. J. Rosas, and M. J. Ferreira-Pinto, "Bilateral deep brain stimulation of the subthalamic nucleus: Targeting differences between the first and second side," Neurocir. (Engl. Ed.), vol. 34, no. 4, pp. 186–193, 2023.
[6]. F. Magrinelli et al., "Reply to: Juvenile PLA2G6-parkinsonism due to Indian 'Asian' p.R741Q mutation, and response to STN DBS," Mov. Disord., vol. 37, no. 3, pp. 658–662, 2022.
[7]. J. Shen et al., "Does head tremor predict postural instability after bilateral thalamic stimulation in essential tremor?," Cerebellum, 2022.
[8]. M. M. Banoei et al., "Using metabolomics to predict severe traumatic brain injury outcome (GOSE) at 3 and 12 months," Crit. Care, vol. 27, no. 1, p. 295, 2023.
[9]. S. Ayub, R. Boddu, H. Verma, S. Revathi B, B. K. Saraswat, and A. Haldorai, "Health Index Estimation of Wind Power Plant Using Neurofuzzy Modeling," Computational and Mathematical Methods in Medicine, vol. 2022, pp. 1–8, May 2022, doi: 10.1155/2022/9535254.
[10]. S. Little and P. Brown, "The functional role of beta oscillations in Parkinson's disease," Parkinsonism Relat. Disord., vol. 20, pp. S44–S48, 2014.
[11]. K. L. Stipancic, G. Wilding, and K. Tjaden, "Lexical characteristics of the Speech Intelligibility Test: Effects on transcription intelligibility for speakers with multiple sclerosis and Parkinson's disease," J. Speech Lang. Hear. Res., pp. 1–17, 2023.
[12]. T. Bocci et al., "Eight-hours conventional versus adaptive deep brain stimulation of the subthalamic nucleus in Parkinson's disease," NPJ Parkinsons Dis., vol. 7, no. 1, p. 88, 2021.
[13]. D. Piña-Fuentes et al., "Acute effects of adaptive Deep Brain Stimulation in Parkinson's disease," Brain Stimul., vol. 13, no. 6, pp. 1507–1516, 2020.
[14]. J. Roodbol, M.-C. Y. de Wit, F. K. Aarsen, C. E. Catsman-Berrevoets, and B. C. Jacobs, "Long-term outcome of Guillain-Barré syndrome in children: Roodbol et al," J. Peripher. Nerv. Syst., vol. 19, no. 2, pp. 121–126, 2014.
[15]. M. Denker et al., "LFP beta amplitude is linked to mesoscopic spatio-temporal phase patterns," Sci. Rep., vol. 8, no. 1, p. 5200, 2018.
[16]. J. Liu and Y. Li, "The visual movement analysis of physical education teaching considering the generalized Hough transform model," Comput. Intell. Neurosci., vol. 2022, p. 3675319, 2022.
[17]. P. Brundin and R. Olsson, "Can α-synuclein be targeted in novel therapies for Parkinson's disease?," Expert Rev. Neurother., vol. 11, no. 7, pp. 917–919, 2011.
[18]. S. Ayub, R. Boddu, H. Verma, S. Revathi B, B. K. Saraswat, and A. Haldorai, "Health Index Estimation of Wind Power Plant Using Neurofuzzy Modeling," Computational and Mathematical Methods in Medicine, vol. 2022, pp. 1–8, May 2022, doi: 10.1155/2022/9535254.
[19]. G. Li, S. Zhao, and X. Duan, "Full activation pattern mapping by simultaneous deep brain stimulation and fMRI with graphene fiber electrodes," Ko. Hsueh. Tung. Pao., vol. 65, no. 20, pp. 2071–2073, 2020.