# Investigating the Immediate and Long-term Effects of Deep Brain Stimulation in Refractory Neurological Disorders

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**A. SPECIFIC AIMS**

Big picture:

Deep brain stimulation (DBS) is a promising therapeutic approach for managing refractory neurological disorders. This device-based therapy has been commonly used on patients who suffer from neurological disorders like Parkinson Disease. It is known to help with fewer side effects and higher efficiencies for drug resistant patients which can improve the patient's quality of life [1]. This research proposal aims to evaluate both short- and long-term effects by discussing the efficacy and durability of DBS as therapeutic treatment. By doing this, it can help enhance the understanding of neurostimulation interventions and contribute to improved patient outcomes.

What is/are Problem(s)?

Many individuals who suffer with refractory neurological disorders encounter limited therapeutic options either because the traditional treatments are not effective, or they induce intolerable side effects. The current issue on short term effect of DBS on refractory neurological disorders is there is limited insight. There is also a critical gap in knowledge in the long-term efficacy of DBS in managing refractory neurological disorders. It is essential for planning treatments to understand the overall benefits evolve over an extended period. Another issue is that the response to DBS can vary between patients and the factors that cause these variations are still unknown. DBS has been used extensively to manage tremors for patients who suffer from Parkinson disease but the exact mechanism for improving the symptoms in the circuity is not fully understood [1].

Goal(s) of your proposed work

The goal of our proposed work is to assess and quantify the immediate effects of DBS on system management in refractory neurological disorders. We do this by analyzing the motor function, patients' quality of life and other clinical factors. Another goal of our work is to investigate the benefits and effects of DBS over an extended period. We do this by analyzing any progressive impacts on disease progression and assessing the durability of symptom control.

**Aim 1.**
**Evaluate the short-term impact of DBS for the management of refractory neurological disorders.**

**Aim 2.**
**Evaluate the long-term impact of DBS for the management of refractory neurological disorders.**

Impact(s) of proposed work

Exploring the short-term effects of Deep Brain Stimulation (DBS) for refractory neurological disorders, are poised to bring immediate relief to patients by alleviating symptoms and enhancing their quality of life. Aim 1's outcomes are focused to inform clinicians about the rapid efficacy of

DBS, shaping immediate clinical decisions and treatment adjustments. The long-term impact of DBS on disease progression and neurological function holds broader implications for chronic disease management. The anticipated impacts include potential disease modification, sustained therapeutic benefits, and insights into the dynamic optimization of stimulation parameters over an extended period. Aim 2's findings are expected to guide clinicians in providing enduring benefits to patients, contributing to evidence-based practices in the realm of neuromodulation.

## B. BACKGROUND AND SIGNIFICANCE

### B1. Background:

Deep brain stimulation (DBS) is a surgical method utilized to mitigate various neurological conditions that do not respond to traditional treatments. It is comprised of a surgically implanted neurostimulator battery-powered device that provides electrical stimulation to an appropriate region of the brain to block abnormal nerve signals [1]. The electrical current is localized through wires attached to a small pulse generator device implanted under the skin near the collarbone, similar to a cardiac pacemaker. DBS became a more popular practice in the 1980s and has evolved substantially in the past several decades [2]. The first condition approved by the FDA to be managed with the use of DBS was essential tremors in 1997 followed by Parkinson's disease (PD) in 2002, and dystonia in 2003 [1]. DBS has also shown promise for handling other neuropsychiatric conditions such as substance and addictive disorders, eating disorders, obsessive compulsive disorder, major depressive disorder, and aggressive behavior [1]. In some cases, such as drug resistant PD, DBS is recommended in the current guidelines rather than ablative surgical methods [1].

### B2. Current approaches:

A fully functional DBS system involves precise placement of intracranial electrodes in specific regions of the brain where stimulation is intended [1]. Current techniques of lead placement include intra-operative fluoroscopy, microelectrode recording, and image-based targeting with MRI and CT [1, 3]. To ensure that DBS remains within its therapeutic range and does not induce any side effects, a monopolar or bipolar configuration can used to stimulate the brain in a more diffusive or direct manner respectively [4]. A monopolar configuration is often used to start stimulation but if adverse effects arise at high voltages, the bipolar configuration can be used to direct the flow of current in a more controlled area.

The DBS system also involves implanted pulse generators that consist of a battery, power module, CPU, program memory, and microprocessor [1]. The system controls the entirety of the functions of the device such as activation, deactivation, pulsing parameters, internal diagnostics, and communication with external devices [1]. Advancements in hardware such as longer lasting batteries and segmented leads can improve the effectiveness of stimulation and could potentially minimize the side effects of stimulation [3].

### B3. Significances of your proposed studies:

One significance of our proposed study aims to assess the significance of DBS on neurogenesis and plasticity in the targeted area of stimulation as well as methods to improve these effects. Managing tremors in individuals with PD with the use of DBS has been considerably used. Although, the exact mechanism of action for improving symptoms is not fully understood [1]. By obtaining a deeper understanding of DBS on neurogenesis and plasticity this could help researchers draw conclusions about the mechanisms involved in improving symptoms such as managing tremors.

Another significance of our proposed study relates to the significance of personalized treatment options for DBS. DBS has been shown to be effective in mitigating certain neurological conditions although individual responses to DBS can vary based on multiple factors such as patient-specific anatomical features, neural network dynamics, and genetic predispositions [1, 5, 6]. Understanding the patterns and factors that cause different responses to treatment can be of great use when developing personalized DBS treatments tailored to the unique characteristics of each patient. It can also assist in optimizing electrode placement and stimulation parameters. Personalized DBS has the potential to increase therapeutic effectiveness, reduce side effects, and improve the overall quality of life for patients needing DBS.

**Summary**

Our proposed work explores the therapeutic potential of DBS in neurological disorders with a focus on short- and long-term outcomes of treatment. For our first aim, we will assess the impact of DBS on psychological well-being, symptom severity, and motor function. To do this we will employ precise electrode placement and optimized stimulation parameters. For our second aim, we will examine the long-term effects of DBS by incorporating a more diverse patient population, treatment optimization, and advanced neuroimaging. This will help us better understand the symptomatic relief and neuroplastic changes induced by long-term DBS use. The findings can help guide a better understanding of optimized personal treatment strategies for DBS when treating refractory neurological disorders.

## C. EXPERIMENTAL DESIGN

### C1. Overview of proposed work

The proposed research aims to explore the potential therapeutic benefits of DBS in managing refractory neurological disorders. DBS involves the implantation of electrodes into specific brain regions, with the delivery of electrical impulses to modulate neural activity. This study will focus on understanding the impact of DBS on symptoms and quality of life in patients with refractory neurological disorders and focuses on improving symptomatology and enhancing the quality of life.

### C2. Aim1. Short-Term effects of DBS in the management of refractory neurological disorders

#### C2.1. Rationale of aim 1

Focuses on assessing the short-term effects of DBS in the management of refractory neurological disorders. The short-term effects of DBS are crucial due to its immediate impact on symptom severity and patients' quality of life. Demonstrating short-term efficacy establishes the feasibility of DBS as a viable intervention for managing refractory neurological disorders and accessing its overall therapeutic value.

Understanding the immediate responses to DBS is essential for several reasons. Firstly, it allows for the assessment of the procedure's acute efficacy in providing symptomatic relief. This insight is vital for clinicians making decisions about the feasibility and appropriateness of DBS as a therapeutic intervention for refractory neurological disorders. Moreover, a nuanced examination of short-term effects contributes to refining stimulation protocols and optimizing electrode placement strategies. Identifying patterns of immediate improvement or potential challenges shortly after DBS can guide real-time adjustments, enhancing the precision and effectiveness of the intervention.

By focusing on short-term outcomes, we aim to provide clinicians with valuable information for immediate postoperative patient management and decision-making. This knowledge will not only inform the refinement of DBS protocols but also contribute to our broader understanding of the dynamic interplay between neural stimulation and symptomatic expression in refractory neurological disorders.

**C2.2. Method and evaluation**

Identify patients diagnosed with refractory neurological disorders, such as Parkinson's disease or essential tremor, who have not responded adequately to conventional therapies. Ensure inclusion criteria consider disease severity, duration, and medical history. Conduct high-resolution neuroimaging (e.g., MRI, CT scans) to precisely identify target brain regions for electrode placement and to account for individual variability in brain anatomy. Follow standardized surgical protocols, considering the selected target regions based on preoperative neuroimaging, for the implantation of DBS electrodes.

Develop a stimulation protocol, considering the specific neurological disorder being targeted. Choose parameters such as frequency, amplitude, and pulse width based on preliminary studies. Implement a postoperative monitoring plan to assess immediate responses and identify potential effects. Confirm optimal electrode placement and functioning through intraoperative neurophysiological monitoring. Systematically monitor and report any adverse events or side effects related to the surgical procedure or stimulation. Develop a protocol for managing and mitigating adverse events promptly. Use validated clinical scales and assessments to quantify symptom severity and overall functioning before DBS implantation. Repeat assessments at regular intervals post-implantation (once a week), to capture short-term changes.

Implement standardized instruments to measure changes in quality of life, considering physical, emotional, and social well-being. Include patient-reported outcome measures (PROMs) for a comprehensive understanding of the impact on daily life. Conduct descriptive statistics to summarize patient demographics and baseline characteristics. Use appropriate statistical tests (e.g., t-tests, chi-square tests) to compare pre- and post-DBS outcomes. Implement subgroup analyses to explore variations in treatment response based on demographic or clinical factors. Use neuroimaging post-DBS to confirm electrode placement accuracy and assess potential changes in brain activity or connectivity and explore correlations between imaging findings and clinical outcomes.

**C2.3. Expected outcomes**

Observe significant reduction in symptom severity and improvement in quality of life in the short-term following DBS. Positive outcomes would suggest the potential for DBS as an effective short-term intervention for refractory neurological disorders. A significant reduction in the severity of neurological symptoms associated with the targeted disorder. Symptoms such as tremors, rigidity, or dyskinesias should exhibit immediate improvement, reflecting the effectiveness of DBS in modulating neural activity. Enhancement in motor function, demonstrated by improvements in gait, coordination, and fine motor skills. Rapid alleviation of motor symptoms contributing to improved overall functionality and independence.

Patients will experience a swift restoration of the ability to perform daily activities that were previously challenging or impossible. Activities of daily living, such as eating, dressing, and writing, may significantly improve. Expect a positive psychological impact, including reduced anxiety and depression associated with the burden of refractory neurological symptoms. Immediate relief from distressing symptoms may contribute to improved mental well-being. Foresee a potential reduction in the need for anti-parkinsonian or other symptomatic medications. Short-term success in managing symptoms with DBS may allow for a more judicious use of medications, reducing potential side effects.

The expected outcomes for Aim 1 encompass not only the immediate relief of symptoms but also improvements in daily functioning, quality of life, and psychological well-being, providing a comprehensive understanding of the short-term effects of DBS in the management of refractory neurological disorders.

**C2.4. Technical difficulties and alternative approaches**

Account for potential variability in patient response by conducting subgroup analyses based on demographic and clinical factors. Implement meticulous neuroimaging and intraoperative monitoring to enhance precision in electrode placement. Consider adjusting stimulation parameters based on individual patient responses to optimize short-term outcomes.

**C3. Aim2. - Long-Term impact of DBS on disease progression and neurological function**

**C3.1. Rationale of aim 2**

Many neurological disorders, including Parkinson's disease, essential tremor, and dystonia, manifest as chronic and progressive conditions. Investigating the enduring effects of DBS becomes essential to comprehensively assess its potential to modulate the trajectory of these disorders and potentially alter their natural course.

Understanding how DBS influences a broader spectrum of neurological functions over an extended period is critical. This includes evaluating motor and cognitive functions, providing a holistic perspective on the overall impact of DBS on patients' neurological well-being. Continuous assessment of DBS's influence over time is integral to optimizing its therapeutic benefits. The chronic nature of these neurological disorders implies dynamic changes in symptoms, requiring ongoing adjustments to stimulation parameters. By understanding the long-term trajectory, clinicians can tailor DBS interventions to adapt to evolving patient needs, ensuring sustained efficacy throughout the treatment duration.

It aims to shed light on neuroplasticity and adaptations induced by prolonged exposure to DBS. This encompasses uncovering potential changes in neural circuits, providing valuable insights into the underlying mechanisms of DBS. By assessing the long-term impact, this research contributes substantively to evidence-based medicine, providing clinicians with comprehensive data to guide treatment decisions. The findings are pivotal for managing patient expectations, refining safety protocols, and establishing the optimal timing for initiating DBS treatment in the continuum of these chronic neurological disorders.

**C3.2. Method and evaluation**

Establish a cohort of patients diagnosed with refractory neurological disorders who have undergone DBS and ensure the inclusion of diverse disorders such as Parkinson's disease, essential tremor, or dystonia to capture a broad range of long-term effects. Conduct comprehensive pre-operative assessments, including clinical evaluations, neuroimaging, and baseline measurements of disease severity and neurological function. Repeat these assessments at regular intervals post-DBS implantation to capture changes over time. Continuously optimize stimulation parameters based on the evolving needs of patients. Regularly review and adjust parameters in response to changes in symptomatology and disease progression.

Utilize advanced neuroimaging techniques (e.g., MRI, fMRI) to monitor structural and functional changes in the brain. Assess alterations in neural connectivity, neuroplastic changes, and potential adaptations induced by prolonged DBS. Identify and monitor disease-specific biomarkers associated with disease progression. Use validated markers that align with the targeted neurological disorders to quantify changes over the long term. Implement standardized neurological assessments to evaluate a broad spectrum of neurological functions. Include motor assessments, cognitive evaluations, and assessments of activities of daily living to provide a comprehensive overview. Incorporate patient-reported outcome measures (PROMs) to capture subjective experiences and changes in daily functioning. Assess aspects such as quality of life, mood, and overall well-being.

Utilize longitudinal data analysis methods to identify trends and correlations. Conduct statistical tests to compare baseline and follow-up assessments, assessing changes in disease progression and neurological function over time. Consider subgroup analyses based on specific neurological disorders or demographic factors to explore potential variations in treatment response as it allows for a more nuanced understanding of the impact of DBS on different patient subpopulations. Systematically monitor and document any adverse events or side effects associated with long-term DBS. Implement protocols for addressing and mitigating adverse events promptly.

**C3.3. Expected outcomes**

The comprehensive evaluation, including neuroimaging, biomarkers, and patient-reported outcomes, aims to provide a nuanced understanding of DBS's enduring impact on refractory neurological disorders. Maintain symptomatic relief over the long term, demonstrating the enduring efficacy of DBS in alleviating neurological symptoms associated with refractory disorders. Expect evidence suggesting the potential to stabilize or modify the progression of the underlying neurological disorders. Identify indicators that DBS may exert a disease-modifying effect, contributing to a slower or altered disease course compared to natural progression.

Anticipate ongoing optimization of stimulation parameters, reflecting the adaptability of DBS to evolving patient needs. Successful parameter adjustments should correlate with sustained therapeutic benefits. Evidence of neuroplastic changes and adaptations within the brain induced by prolonged DBS. Discovering sustained modifications in neural circuits would provide insights into the underlying mechanisms contributing to the long-term effects of DBS. Expect positive and sustained improvements in a broad spectrum of neurological functions. Functional outcomes should encompass motor improvements, cognitive enhancements, and overall improvements in

activities of daily living. Identify and address any potential adverse events associated with prolonged DBS. Assess patient tolerance over time, ensuring that the intervention remains well-tolerated and safe throughout the extended treatment duration.

Expect correlations between DBS outcomes and disease-specific biomarkers. Positive correlations would strengthen the argument for DBS influencing not only symptoms but also the underlying biological processes of the targeted neurological disorders. Strengthen the scientific basis for the continued use of DBS in the management of refractory neurological disorders over the long term. Gain insights into the optimal timing for initiating DBS intervention. Identify whether there is an ideal window in the disease course where DBS provides maximal benefits in terms of disease modification and neurological function improvement.

**C3.4. Technical difficulties and alternative approaches**

Patients may exhibit diverse responses to DBS, making it challenging to generalize outcomes. Implement subgroup analyses based on disease subtype, symptomatology, or demographic factors to identify patterns and tailor conclusions to specific patient profiles. Prolonged DBS may lead to unforeseen adverse events or side effects. Develop a robust adverse event monitoring system, including regular patient check-ins, to promptly identify and manage any unexpected issues. Consider adopting advanced imaging techniques to detect structural changes that may contribute to adverse events. Continuous optimization of stimulation parameters may be complex due to the evolving nature of neurological disorders. Utilize machine learning algorithms or closed-loop systems to adaptively optimize stimulation parameters based on real-time physiological feedback, allowing for more dynamic adjustments aligned with disease progression.

Maintaining long-term patient compliance with follow-up visits and assessments may be challenging. Implement telemedicine and remote monitoring technologies to facilitate regular check-ins and assessments, improving accessibility and reducing the burden on patients. Identifying reliable and sensitive disease-specific biomarkers may pose challenges. Combine multiple biomarkers or employ emerging technologies such as liquid biopsies or advanced imaging techniques to enhance the reliability and sensitivity of biomarker assessments over the long term. Different patients may exhibit variable rates of disease progression. Consider using advanced statistical models that account for individual patient trajectories, allowing for a more nuanced understanding of how DBS impacts diseases with varying progression rates. Detecting and understanding neuroplastic changes induced by DBS may be intricate. Combine neuroimaging techniques with advanced analytical methods, such as connectomics or functional connectivity analyses, to unravel subtle and long-term neuroplastic adaptations in response to DBS.

**C4. Conclusion**

Investigating the short-term effects of Deep Brain Stimulation (DBS) in the management of refractory neurological disorders holds significant promise. Aim 1 focuses on understanding the immediate impact of DBS, aiming to provide rapid relief from debilitating symptoms. By assessing short-term outcomes, we anticipate observing a notable reduction in symptom severity, improved motor function, and an overall enhancement in the quality of life for patients.

Additionally, the study aims to identify optimal stimulation parameters, offer insights into rehabilitation strategies, and build confidence among patients and clinicians in the efficacy of DBS. The short-term results serve as a foundation for subsequent investigations into the long-term trajectory of DBS effects, contributing valuable information to guide clinical decision-making and advance our understanding of this therapeutic intervention.

In addressing the long-term impact of Deep Brain Stimulation (DBS) on disease progression and neurological function (Aim 2), this research seeks to extend our understanding beyond immediate symptomatic relief. As neurological disorders often manifest as chronic and progressive conditions, aim 2 aims to explore whether DBS can exert sustained effects, potentially modifying the natural course of these disorders. The anticipated outcomes encompass not only the stabilization or modification of disease progression but also the optimization of stimulation parameters over time. By conducting comprehensive assessments, including neuroimaging, biomarkers, and patient-reported outcomes, the study strives to provide a nuanced understanding of the enduring impact of DBS. The findings from Aim 2 are expected to contribute substantively to evidence-based medicine, guiding clinicians in tailored interventions and refining our broader understanding of the neurobiological mechanisms underlying DBS. Together, these aims contribute to the comprehensive evaluation of DBS as a therapeutic modality for refractory neurological disorders, addressing both immediate and enduring aspects of patient outcomes.

**D. Timelines**

1. Project Initiation (Months 1-2):
2. Literature Review (Months 3-6):
3. Interim Analysis and Aim 1 Reporting (Months 7-9):
4. Aim 2 - Long-Term Effects Investigation (Months 10-12):
5. Ongoing Data Collection and Analysis (Months 13-15):
6. Aim 1 and Aim 2 Integration (Months 16-18):
7. Results Interpretation and Paper Drafting (Months 19-21):
8. Final Analysis, Reporting, and Dissemination (Month 22-24):

**Project Initiation (Months 1-4):**
**Literature Review (Months 5-12):**
**Interim Analysis and Aim 1 Reporting (Months 13-18):**
**Aim 2 - Long-Term Effects Investigation (Months 19-24):**
**Ongoing Data Collection and Analysis (Months 25-30):**
**Aim 1 and Aim 2 Integration (Months 31-32):**
**Results Interpretation and Paper Drafting (Months 33-34):**
**Final Analysis, Reporting, and Dissemination (Months 35-36):**

**E. Requested budget**

| Budget | Year 1 | Year 2 | Year 3 |
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| Personnel | | | |
| *Salary* | | | |
| Principal Investigator | $15,500 | $15,500 | $15,500 |
| Graduate Research Assistant | $11,000 | $11,500 | $11,500 |
| Undergraduate Assistants | $5,500 | $5,500 | $5,500 |
| *Fringe Benefits/Tuition Remission (RA)* | | | |
| Principal Investigator | $4,000 | $4,000 | $4,000 |
| Graduate Research Assistant | $3,500 | $3,500 | $3,500 |
| *Subtotal Personnel* | $40,000 | $40,000 | $40,000 |
| Materials and Supplies | | | |
| Misc. supplies | $3,000 | $3,000 | $3,000 |
| Test subjects | $4,000 | $4,000 | $4,000 |
| Biomaterials | $8,000 | $8,000 | $8,000 |
| *Subtotal Project Expenses* | $15,000 | $15,000 | $15,000 |

*Grand Total*

$165,000

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