ACIBADEM MEHMET ALİ AYDINLAR UNIVERSITY
GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

QUANTITATIVE COMPARISON OF THE HEMODYNAMIC AND BEHAVIORAL CORRELATES OF IMPULSIVITY IN PARKINSON'S DISEASE PATIENTS BEFORE AND AFTER SUBTHALAMIC DEEP BRAIN STIMULATION: AN fNIRS STUDY

ÖZLEM ÖZTEL

M.Sc. THESIS

DEPARTMENT OF BIOMEDICAL ENGINEERING

SUPERVISOR
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DECLARATION

I declare that this thesis is my own work. I had no unethical behavior at any stage from the planning to the writing of the thesis. I obtained all the information in this thesis under academic and ethical rules. I cited all the information and comments that were not obtained with this thesis work, and I provided resources in the list of references. I also declare that there was no violation of any patents and copyrights during the study and writing of this thesis.

12.06.2025

Özlem Öztel

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LIST OF ABBREVIATIONS

ACC	Accuracy
AUC	Area Under The Curve
BA	Brodmann Area
CQ	Cognitive Quotient
DA	Dopamine Agonist
DBS	Deep Brain Stimulation
DDS	Dopamine Dysregulation Syndrome
DLPFC	Dorsolateral Prefrontal Cortex
DN	Dopaminergic Neurons
DPF	Differential Pathlength Factor
DRT	Drug Replacement Therapy
EEG	Electroencephalogram
fMRI	Functional Magnetic Resonance Imaging
fNIRS	Functional Near-Infrared Spectroscopy
GNG	Go/Nogo
GPCR	G-Protein Coupled Receptor
Gpe	Globus Pallidus Externus
Gpi	Globus Pallidus Internus
HbO2	Oxygenated Hemoglobin
HHb	Deoxygenated Hemoglobin
HbT	Total Hemoglobin
ICD	Impulse Control Disorder

ICRD	Impulse Control and Related Disorders
IQ	Intelligence Quotient
L-DOPA	Levodopa
LFP	Local Field Potentials
MNI	Montreal Neurological Institute
mPFC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
OCD	Obsessive Compulsive Disorder
OD	Optical Density
PCA	Principal Component Analysis
PD	Parkinson's Disease
PFC	Prefrontal Cortex
PG	Pathological Gambling
PPN	Pedunculopontine Nucleus
PSA	Posterior Subthalamic Area
ROI	Region Of Interest
RT	Reaction Time
SN	Substantia Nigra
SNpc	Substantia Nigra Pars Compacta
SNpr	Substantia Nigra Pars Reticulata
STN	Subthalamic Nucleus
UPDRS	Unified Parkinson's Disease Rating Scale
VIM	Ventral Intermediate Nucleus
VP	Ventral Pallidum
ZI	Zona Incerta

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ABSTRACT

Quantitative Comparison of the Hemodynamic and Behavioral Correlates of Impulsivity in Parkinson's Disease Patients Before and After Subthalamic Deep Brain Stimulation: An fNIRS Study

The neurophysiological basis of our behaviors, the behavioral outputs of neural networks and their relation with neurophysiology have been topics of interest for many years. The field of neuroscience has witnessed remarkable advancements in understanding the physiological mechanisms that govern the functionality of the human brain and its intricate workings from nanoscales to macroscales. Advancing technologies give scientists more opportunities for further research. Functional near-infrared spectroscopy (fNIRS) is a neuroimaging method that monitors changes in blood oxygenation levels to infer neural activity in a non-invasive way. This technique shows great potential in identifying unique patterns of cerebral hemodynamic activity. The objective of this study was to examine the impact of subthalamic nucleus (STN) deep brain stimulation (DBS) of Parkinson's disease (PD) patients on motor impulsive behavior and its neural correlates with an fNIRS system.

The primary goal of this research was to evaluate variations in both cognitive metrics and cerebral blood flow dynamics observed during a neuropsychological test battery that targets impulsivity induced by STN-DBS of PD patients with an fNIRS device for a deeper interpretation of how STN-DBS affects the functionality of cortical networks.

Keywords: Parkinson's Disease, Deep Brain Stimulation, fNIRS, Impulsivity, Go/NoGo.

ÖZET

Parkinson Hastalarına Uygulanan Subtalamik Nükleus Derin Beyin Stimulasyonu Sonrası Gelişen Dürtüsellik Davranışı Değişimlerinin fNIRS ile Karşılaştırmalı İncelenmesi

Parkinson hastalığı, beyindeki dopaminerjik nöronların dejenerasyonuna bağlı gelişen ilerleyici bir nörolojik hastalıktır. Hastalığın temel ve sık görülen semptomları, motor bulgulardır. Bu bağlamda derin beyin stimülasyonu (DBS) uygulamasıyla beyne elektrotlar yoluyla stimülasyon verilmekte ve motor semptomların hafiflemesine katkı sunarak ileri evre Parkinson hastalarına daha kaliteli bir yaşam elde etme imkanı sunmaktadır. DBS'in çalışma mekanizması, tam anlamıyla keşfedilmemiş olsa da sağladığı semptomatik iyileşmeler pek çok bilimsel araştırma ve klinik bulgular ile gösterilmektedir. Fakat karar verme hızını yavaşlatıp, dürtüsellik ve sağlıklı bilişsel fonksiyonlar anlamında önem arz eden bu alana yapılan stimülasyonlar her ne kadar motor semptomlarda rahatlama sağlasa da davranışsal anlamda hastalarda ameliyat sonrası süreçte nasıl bir yan etki yarattığı farklı bilimsel çalışmalarla da merak konusu olmuştur. Bu çalışmanın amacı, Parkinson Hastalarına uygulanan DBS ameliyatı sonrası kortikal beyin dokusundaki hemodinamik değişimleri davranışsal değişimlerle karşılaştırarak dürtüsellik anlamında değişimin beynin hangi alanlarında ne seviyede olduğunu gözlemlemek. İşlevsel yakın kızılaltı spektroskopisi (Functional Near Infrared Spectroscopy-fNIRS) cihazı ile eş zamanlı olarak uygulanan ve dürtüsellik metriğinde sıklıkla kullanılan Yap/Yapma testi esnasında girişim öncesi ve sonrası ölçüm alınmıştır. Böylece elde edilen davranışsal ve nörofizyolojik bilgiler, DBS müdahelesinin bilişsel ve hemodinamik etkilerini tanımlamaktır.

Anahtar Sözcükler: Parkinson Hastalığı, Derin Beyin Stimülasyonu, fNIRS, Dürtüsellik, Bas/Basma.

1 INTRODUCTION AND AIM

Parkinson's disease (PD) is a progressive neurodegenerative disorder which affects at least 1% of the population over the age of 60 (1). This neurodegenerative disorder is characterized by motor symptoms such as tremor, bradykinesia (slowness of movement), rigidity, and postural instability. These motor symptoms may also be accompanied with non-motor signs such as cognitive impairment, mood disturbances, and autonomic dysfunction (2). The disease is primarily induced by the degeneration of dopaminergic neurons in the pars compacta region of substantia nigra (SNpc), which interferes with the basal ganglia-thalamocortical circuits (3).

Treatment of PD includes pharmacological and surgical approaches. Dopaminergic medications are the main symptomatic treatment for PD. Levodopa is the primary medication. Initially, levodopa may control the symptoms well with 2-3 daily doses. However, after 3-4 hours of taking medication, the wearing-off period begins and the symptoms often re-emerge (4). The wearing-off periods become more frequent as the disease progresses. Additionally, prolonged usage can lead to motor difficulties and medication-induced dyskinesia. Dyskinesia is defined by involuntary, unintended, and uncontrollable movements such as jerking, twitching, or twisting. Dopamine agonists (DA) are also an option for treatment and help delay the onset of motor complications. While levodopa is converted in the brain into dopamine, DA mimics the effects of dopamine without having to be converted (5).

The underlying pathology of PD involves the progressive decline of dopamine-producing neurons located in the SNpc region of the midbrain. which leads to hyperactivity of the neuronal ensembles within the STN (3).

The cardinal motor manifestations include bradykinesia, resting tremor, muscular rigidity, and postural instability. However, not only motor symptoms but also non-motor complications are observed such as cognitive dysfunction, impulsivity, mood changes, and behavioral disorders (6). Due to environmental conditions, especially for

the aging population the burden of PD is increasing (7). DBS is an invasive method including electrical brain stimulation via an implanted electrode. DBS is widely used for the symptomatic treatment of a variety of neurological diseases and the brain targets are chosen depending on the diagnosis of the patients by neurologists and neurosurgeons. The target region for DBS stimulation for PD is most often selected as the STN region for the ultimate aim of regulating the hyperactivation in this region. However, although DBS stimulation is often accompanied by improvements in managing motor symptoms of PD, this therapeutic procedure may sometimes result in side and/or adverse effects associated with impulsive and cognitive behaviors. To analyze the behavioral and hemodynamic outcomes of DBS on cortical regions of the brain that are related to impulsivity, an fNIRS device is a suitable method, as being comfortable for the patients, tolerant to bodily movements and portable also suitable for all participants populations (8).

Cognition and impulsivity after STN-DBS have been studied in the literature previously. However, the neurophysiological mechanism of its impact and post-operation effects remain unclear. This study aimed to examine the outcome of DBS intervention on motor impulsive behaviors correlated with hemodynamic metrics via an fNIRS device. By using a device, our data will be more concrete and will not only be dependent on interpretation. Hopefully, this study can underline the importance of patient selection and contribute to a clearer understanding of cognitive alterations following DBS intervention, potentially guiding future research in the field. To date, there have been no studies that explored the efficacy/impact of DBS on prefrontal cortex (PFC) neurophysiology and impulsive behaviors via fNIRS.

While improving life quality, STN-DBS may cause neuropsychiatric side effects such as impulsivity (7). After STN-DBS, previous studies show increased response speed and increased action impulsivity with lower response accuracy (ACC). Healthy STN neuronal firing delays decision-making and allows time for evidence accumulation and appropriate behavioral policy (9).

Impulsivity can be described in many different ways. Impulsivity is described under two categories as cognitive and motor impulsivity (10). Impulsive behaviors can be described as a failure to resist an impulse, or a tendency to perform acts that are harmful to others and also can make the person's life more challenging (11-13). While making risky decisions and acting before analyzing the situation may have problematic outcomes.

Higher levels of cognitive control are typically associated with lower levels of impulsivity. This control mechanism is generally composed of three primary executive components: the ability to update information in working memory, to shift between tasks or mental sets, and to inhibit inappropriate responses (14). A healthy cognitive function can update information, shifting from task to task and inhibiting and suppressing prepotent responses (15). From a neuropsychological perspective, impulsivity reflects a diminished capacity to delay responses, often leading to rapid and unreflective decision-making (16). Detecting a patient's cognitive situation is crucial for his/her life quality and it is as important as motor functions.

Barratt distinguished three dimensions of impulse:

- Motor (action without thinking),
- Cognitive (quick cognitive decision-making), and
- Non-planning (decrease in orientation towards future) factors (17).

Measuring the cortical hemodynamic changes was targeted in the PFC during the Go/NoGo (GNG) task, before and 3 weeks after DBS surgery.

Subthalamic nucleus deep brain stimulation is a valuable intervention for improving the motor symptoms of DBS (9). However, patient selection is crucial for the post-operation period regarding neuropsychological risks. Related to the structural connectivity of the stimulation area, a cortical reorganization results in changes in cortical functional connectivity patterns and changes in the extent and amplitude of cortical hemodynamic activity localization. Suppose there are any changes in cognitive performance related to impulsivity; in that case, there will also be distinct

hemodynamic changes that can be detected and compared with fNIRS-derived biomarkers with task performance parameters.

To detect the cortical hemodynamic changes, subjects are performing these tasks, their cortical hemodynamic activity will be monitored with a 22-channel fNIRS device while their performance parameters, such as error rate and reaction time (RT) will also be considered.

In this study, the aim is to analyze the cortical hemodynamic difference during tasks as before and after STN-DBS, and by seeing the hemodynamic changes, forecasting post-operative cognitive and impulsive behaviors of the patient, and contribute to patient selection or maybe take preventive measures for the post-operation period.

2 BACKGROUND

2.1 Dopamine

Dopamine, whose receptors are members of the G-protein coupled receptor (GPCR) family, is a monoamine neurotransmitter, a chemical produced by dopaminergic neurons (DN) to transmit an electrical signal chemically between one neuron to the next. In the brain, DN are primarily found within the substantia nigra (SN) and the ventral tegmental area, as Levodopa (L-DOPA) and subsequently removed from the ethyl side chain, resulting in Dopamine. The death of DN in the midbrain causes neurological disorders including PD, addiction, schizophrenia, obsessive compulsive disorder (OCD), and Tourette's syndrome (18).

Dopamine receptors, classified into two main families: D1-like (D1R, D5R) and D2-like (D2R, D3R, D4R), are part of the G protein-coupled receptor (GPCR) family (19). D1-like receptors typically enhance intracellular signaling pathways that promote synaptic plasticity and excitability, while D2-like receptors tend to inhibit these pathways and reduce excitatory activity. In addition to functioning individually, dopamine receptors can also form functional dimers or oligomers, both with each other and with other neurotransmitter receptors such as serotonin, adenosine, and glutamate. These complexes may exhibit unique pharmacological properties that differ from their receptor counterparts, influencing various neurophysiological processes and behaviors.

Therefore, dopamine acts either as excitatory or inhibitory, depending on which receptors are present on the surface of the target neuron's membrane. Thus, the different functional roles of dopamine are expected to vary based on receptor subtype, cell type, synaptic properties, and interactions with other transmitters (15)

.

2.2 Mechanism of Parkinson's Disease

Postmortem analyses have identified the degeneration of nigrostriatal DN as a defining pathological aspect of idiopathic PD. PD is primarily marked by nigrostriatal pathway degeneration. A key pathological feature involves the selective degeneration of DN within the SNpc. The loss of DN within the SN particularly affects the ventral component of the pars compacta. Not only the loss of DN in SNpc, but also the axonal fibers that constitute nigrostriatal pathways, leads to the loss of dopamine in the striatum (20). The nigrostriatal system has the reserve capacity to endure deficits of over 50% without symptomatic manifestation. Abnormal burst activity within the STN contributes to hyperactivity in the basal ganglia circuitry, culminating in exaggerated inhibitory signaling toward efferent targets. Dopamine exerts an inhibitory influence on the activity of the STN; the output neurons of STN are glutamatergic and excitatory. These neurons project to the globus pallidus internus (Gpi) and pedunculopontine (PPN). The STN hyperactivity, reflecting the increase in firing rate is responsible for cardinal symptoms of PD (21).

Nigrostriatal Pathway: As an example, the action can be explained by these steps;

- At the moment a person tend to grab sth. the frontal lobe sends excitatory signals through glutamate to the striatum.
- The striatum then sends additional inhibitory signals to GPi and substantia nigra pars reticulata (SNr), so GPi and SNr lost their ability to inhibit the thalamus.
- The thalamus is now uncoupled (uninhibited) and is able to contact the cerebral cortex,
- The signals of motor neurons down the spinal cord resulting in desired movement.

Direct Pathway (D1 type): Dopamine binds to the D1 receptor on the neurons of the striatum, which stimulates these cells. Dopamine causes an increase in movement because it activates the striatum, which inhibits the internal segment of the globus pallidus.

Indirect Pathway (D2 type): Within the indirect basal ganglia circuitry, striatal output neurons primarily target the globus pallidus externus (GPe). D2-type receptors receive inhibitory dopaminergic innervation from the SNpc.

In normal conditions, the direct pathway plays a facilitative role in the initiation and execution of movement. In contrast, the indirect pathway functions to suppress or inhibit movement (Figure 1). Through the striatum, the two pathways diverge: the direct pathway projects directly to the internus part of the globus pallidus. Whereas the indirect pathway projects to the GPe, which later connects both the GPi and STN, which also connects back to the GPi. The Globus pallidus internus then sends inhibitory connections to the thalamus, which projects to the cortex, thus completing the basal ganglia loop. Activity in the direct pathway sends a "Go" signal to facilitate the execution of a response considered in cortex, whereas activity in the indirect pathway sends a "No-Go" signal to suppress competing responses (22).

Dopamine from SNc causes excitation via D1-type receptors, the direct pathway, and inhibition via D2 receptors. However, in PD, because of the imbalance, hyperactivity of the D2 indirect pathway occurs and lower activity of the D1 direct way is observed, as a result, an inhibition of voluntary movement occurs (Figure 1). Overactivity of the STN causes over-inhibition of the thalamus. In addition to input from indirect basal ganglia pathways, via the hyperdirect pathway, the STN is directly and rapidly innervated by monosynaptic projections originating from frontal motor cortical areas (23).

The hyperdirect pathway is unique as it bypasses the striatum and connects the cortex directly to the STN, which then sends excitatory projections to the GPi (Figure 2) (24, 25). The subthalamic nucleus is directly innervated by projections from frontal cortical areas via the hyperdirect pathway, associated with inhibitory control and executive functioning (26). It is detected in previous studies that STN is critically involved in cognitive processes and decisions that require the resolution of conflicting action plans. Distinct functional roles of the STN are thought to correspond to its anatomically segregated subregions; notably, the ventral portion is implicated in

complex decision-making under conflict, likely via its involvement in the hyperdirect pathway connecting to the PFC (27).

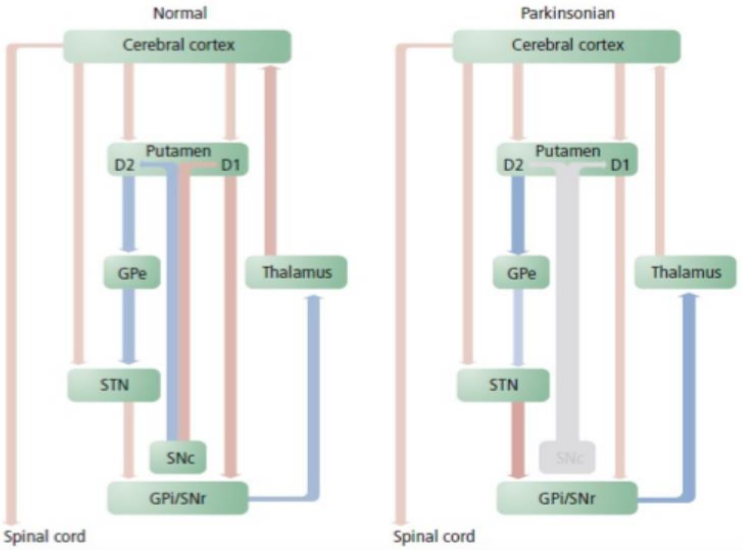


Figure 1. Comparison of healthy and Parkinsonian patients' nigrostriatal pathways due to dopaminergic activity (28).

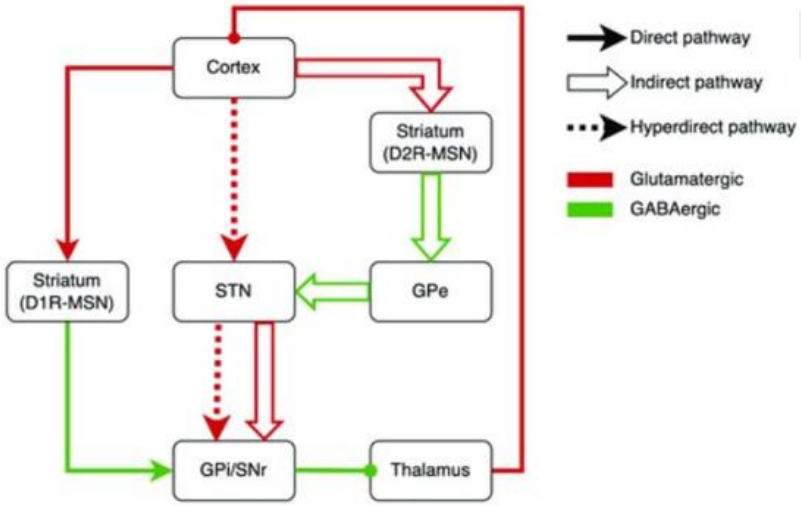


Figure 2. Schematic illusion of the D1 and D2 type receptors via direct, indirect and hyperdirect pathways (24).

Parkinson's Disease is a a chronically progressive neurological condition caused by the presence of Lewy bodies, results in overactivity of STN and the disability of motor movements such as bradykinesia, defined by the impairment of voluntary motor

control and slow movements of freezing, and at least one of the other symptoms such as tremor, rigidity, and postural instability. A scoring method can also be helpful for diagnosis. According to this method, to be able to say the case is Parkinsonism, there must be a total of at least 3 points, considering bradykinesia - 2, resting tremor - 2, rigidity - 1, postural instability - 1, and freezing - 1 (29). The main reason for Parkinsonism is PD. Freezing may last a few seconds to several minutes and tends to happen suddenly when walking, as if the feet become stuck on the ground (4). In addition to motor manifestations, PD is frequently accompanied by non-motor symptoms, including autonomic and sensory disturbances, hyposmia, pain, sleep disorders, as well as cognitive and mood impairments. Also, as a consequence of the reduction in regional blood flow, there is a high risk of dementia as the disease progresses. PD can be caused by the effect of accumulated neurotoxicants and also by risk genes.

Parkinson's disease affects at least 1% of the population over the age of 60 (1). Treatment of PD includes pharmacologic and surgical approaches. Dopaminergic medications are the main symptomatic treatment for PD. Levodopa is the primary medication, initially, levodopa may control the symptoms well with 2-3 daily doses. However, after 3-4 hours of taking medication, the wearing-off period begins and the symptoms re-emerge (4) (Figure 3). The wearing-off periods become more frequent as the disease progresses. Additionally, prolonged usage can lead to motor difficulties and medication-induced dyskinesia. Dyskinesia is defined by involuntary, unintended, and uncontrollable movements such as jerking, twitching, or twisting. Dopamine agonists (DA) are also an option for treatment and help delay the onset of motor complications. While levodopa is converted in the brain into dopamine DA mimics the effects of dopamine without having to be converted (5).

Figure 3. Mechanism of action of L-DOPA on PD medication (30).

The subthalamic nucleus is located at the bottom of all nuclei in the subthalamus. Findings indicate a connection between this nucleus and functions related to reward and suppression of impulses. The function of the STN in the basal ganglia motor circuits is well known. Situated centrally, the STN is anatomically embedded within both the associative and limbic pathways of the basal ganglia–thalamocortical system, serving as a key functional modulator of these networks (32). The STN has anatomically three subdivisions: the dorsolaterally located motor part, the ventromedially located associative part, and the medial tip representing the limbic part. The STN directly influences specific structures in the limbic circuit, such as the ventral pallidum (VP), a major limbic output region (32). In both associative and limbic circuits, the STN can regulate the basal ganglia output back to the thalamus and cortex, making it a potent regulation point in the basal ganglia circuits (33).

The electrodes of DBS are relatively large compared to the small size of the STN, and it may be difficult to selectively influence the motor part of the STN without affecting domains within the STN or in neighboring structures that are associated with motivational, emotional, and cognitive functions (34).

Modulating the STN through stimulation has been shown to impact not only regional neural activity but also broader circuits related to limbic and associative functions (35). The regions implicated include the left temporal gyrus, left inferior frontal and insular cortices, right anterior cingulate cortex, right ventral striatum, and right orbitofrontal cortex (35).

Unaffected by the loss of dopamine is the neural circuitry in the striatum of cholinergic neurons; cholinergic neurons inhibit the direct pathway and excite the indirect pathway.

2.3 Deep Brain Stimulation and Subthalamic Nucleus

Deep brain stimulation is a neurosurgical intervention for idiopathic PD, and the main targeted area is the STN, aiming to decrease hyperactivity. Electrical stimulation to the STN via electrodes is applied. The overactivity of STN may cause harm to GPi, PPN, and SNr over time. So, any medical or surgical intervention that helps decrease this overactivity or blocks glutamate receptors in SNc may be protective and also may slow down the progression of PD.

As a chronic and stereotactic surgical procedure, DBS involves the implantation of electrodes into specific brain regions, with the target site varying based on the clinical condition being treated. Lesioning and MRgFUS are also effective solutions for PD; however, due to their adjustability and reversibility, DBS is thought to be a more advantageous option. The electrical stimulation with different parameters has been given to the patient, and the optimization of the parameters has been arranged by the clinician by physical examination and feedback from the patient. The most preferred targets for stimulation include: Gpi for dystonia and dyskinesia as a medicational side effect, ventral intermediate nucleus (Vim), zona incerta (Zi), and posterior subthalamic area (PSA) for tremor, and STN for Parkinson's disease. STN-DBS has the advantage of promoting faster non-hypersynchronous activity in the basal ganglia, leading to clinical improvement and reducing the need for medication. Also, Gpi is essential for all the cardinal symptoms however, the amount of drug dosage in Gpi-DBS does not change (36). So, the stimulation of GPi will not be a solution to drug-dependent dyskinesias. The programming of Gpi-DBS is easier than STN-DBS due to its larger size; however, the battery life is lower. Also, some studies in the literature have suggested that STN stimulation is associated with a greater decline in letter verbal fluency compared to Gpi stimulation (37).

Over the past 37 years, more than 250000 patients have undergone DBS surgery worldwide. There are more than 19000 published articles on DBS in the literature. The factors that affect DBS outcome can be thought of as the position of the lead, programming technique, and surgical complications. With proper patient selection, improvements are seen with standard measures of disease, medication intake, and quality of life measures.

Patient selection is crucial for achieving good results of DBS surgery outcomes and is one of the most important issues to consider. A good PD candidate can be described as: Clear diagnosis of idiopathic PD, good response to Levodopa with improved the unified Parkinson's disease rating scale (UPDRS) motor score, significant motor fluctuations, medication intolerance, stable cognition and absence of dementia, good family support and realistic expectations, no co-morbid psychiatric problem. The candidate for DBS must be an advanced PD patient, have a levodopa response, be active for at least an hour after drug intake, and have a stable mental situation with good cognition for surgery. Also, structural brain changes such as brain atrophy or vascular changes are excluded because of the risk of mislocation of the implants.

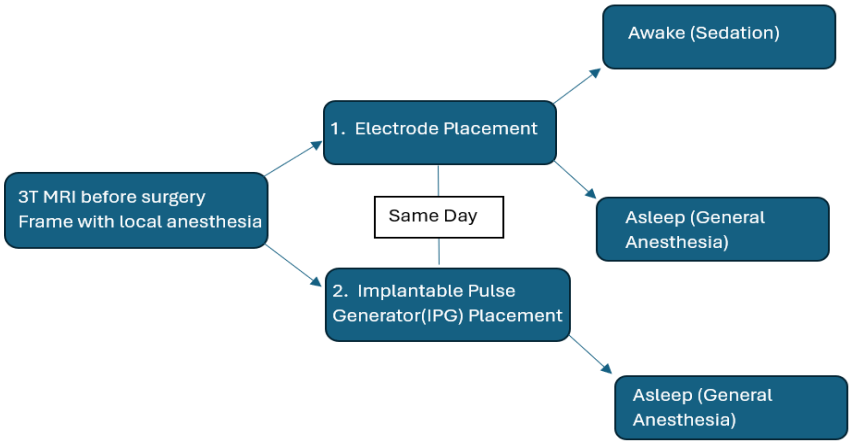


Figure 4. Surgery workflow

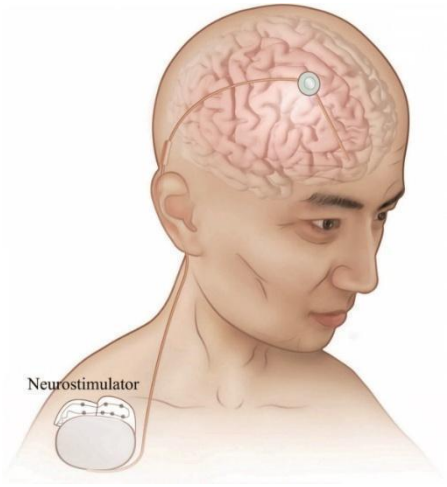


Figure 5. Illustration of DBS leads and neurostimulator (38).

Open-Loop, Closed-Loop, and Adaptive DBS approaches can be described as below;

- Open-Loop DBS Lead: This refers to the type of DBS in which the clinician sets the parameters, such as frequency, pulse width, and amplitude. This system gives continuous, constant stimulation, which may have the advantage of manual setting and the disadvantage of not being able to have quantitative feedback, and the primary feedback source is the patient.

- Closed-Loop DBS Lead: Includes on/off period according to the patient's situation and physiological condition. This system offers the potential to achieve better control of patients' symptoms and reduce side effects with lower power consumption than open-loop DBS.

- Adaptive DBS: The stimulation parameters are adjusted instantly in response to the signals corresponding to biomarkers. Effective in preventing unnecessary stimulation, however causes higher power consumption. It is a subset of closed-loop systems that follows clinical conditions through biomarkers such as beta oscillations.

2.4 Impulsivity in Parkinson's Disease

As an alternative invasive treatment, DBS is commonly employed in patients with advanced stages of PD; however, it has relevant side effects such as cognitive dysfunction, increased impulsivity, and apathy observed in the postoperative period (10), which have been associated with reduced metabolic activity in the orbitofrontal and dorsolateral prefrontal cortices (35).

In PD patients, impulse control disorders (ICD) are commonly seen, often compared to healthy individuals. Impulsive control disorder in PD are 1.7-6% for pathological gambling (PG), 2-10% for hypersexuality, 0.4-5.7% for compulsive buying, 4.3% for compulsive eating, and 3.9% for 2 or more ICDs (39).

As a class of medications, DAs exert their effects by activating particular types of dopamine receptors within the central nervous system. In PD, they target activating dopamine receptors, mimic dopamine's effect.

It is known that drug replacement therapy (DRT), especially with DA, may induce ICD (31). In a cohort of 3090 patients undergoing DRT, ICDs were found to be more prevalent among those receiving DAs compared to those who were not (32). Dopamin agonists are usually helpful for managing the symptoms of PD; however, when used for an extended period or in high doses, they can lead to unwanted side effects such as punding. Punding defines a condition in which an individual tends to engage in repetitive, automatic, and purposeless movements. Among these movements, constant manipulation of hands, continuous organizing of objects, or engaging in repetitive activities focusing on pieces or parts may be observed. Punding can be observed in individuals who exceed the recommended dosage or duration of medication use.

It has been increasingly recognized that STN-DBS might also induce ICD. So far, there is little information about the relationship between ICD, punding, and STN-DBS for PD patients. The subthalamic nucleus deep brain stimulation is known to increase response speed and lower response ACC in PD patients. The hyperdirect pathway

connecting STN to the cortex is thought to play a key role; however, identifying connectivity noninvasively in humans is not straightforward (40).

2.5 Literature Survey

During the literature survey (keywords: Deep Brain Stimulation, fNIRS, impulsivity, Parkinson's Disease, subthalamic nucleus), we could not find a comprehensive study comparing hemodynamic changes of cortical area, before and after STN-DBS intervention during an impulsivity task and including an fNIRS device. Some studies are comparing the impulsivity tasks before and after DBS due to the ACC or speed, without including a device for observation of hemodynamic metrics. There are some studies about the structural connectivity of STN-DBS and impulsivity, including diffusion tractography.

In studies including STN-DBS of PD patients, impulse control and related disorders (ICRD), including pathological gambling, hypersexuality, and dopamine dysregulation syndrome (DDS) are compared as before and after the intervention, it is seen that ages under approximate of 56 have more improvement compared to older operation ages (32). The results differ in different studies. While some studies report improvements in impulsivity following STN-DBS, others have observed a worsening of symptoms or even the emergence of ICDs postoperatively. To sum up, the main conclusion is the importance of patient selection. The results of previous studies give us a prediction and foresight of the patient's post-operative process.

The pathophysiological basis of impulsivity emerging as a side effect of treatment in PD has yet to be elucidated (41). Dysregulation within the mesolimbic dopamine pathway is considered a contributing factor, though DN plays a key role in modulating behavior in response to reward cues and task demands (42). Also most targeted area, the STN, has been implicated in the regulation of motor activity, cognitive processing, and emotional responses. The literature includes findings suggesting a link between STN-DBS and impulsivity, with some studies documenting either a deterioration or no significant effect following surgery, while some studies described improvement

(42). It is thought that each patient's previous distinctive factors such as; pre-operation psychological situation (ICD, depression, etc), genetic factors, age, gender, etc. may play a role in the post-surgery situation, on the other hand, the target location of the implantation also plays crucial role for patient's motor and cognitive outcomes after DBS intervention.

The available studies demonstrated that STN stimulation is linked with both favorable and negative outcomes in terms of impulse control and related disorders (32). This may be due to the location of the stimulated STN. Some authors have postulated the hypothesis that the resolution of DDS and ICD may reflect a direct effect of DBS on specific regions of the STN, in particular on the medial limbic part, e.g., the brain reward neural pathways (32). In a study, it is observed that their model accounts for the beneficial effects of STN lesions on oscillations of basal ganglion activity due to a decline in dopamine availability, which is the main cause of PD tremor, but suggests that this benefit may come at the expense of impaired decision making (22).

Studies including fNIRS and impulsiveness generally analysed data recorded from the dorsolateral prefrontal cortex (DLPFC). In a study, highly impulsive subjects have lower right DLPFC activity, vice versa in the left DLPFC, high-impulsive groups have higher activation (43). In another study analyzing hemodynamic changes with fNIRS during a delay discounting task, significant positive associations were observed between neural activation in the left prefrontal cortex and measures of delay discounting in contrast, activation in the right frontal pole was significantly negatively correlated with motor impulsivity, as measured by the motor subscale of the Barratt Impulsiveness Scale (BIS)(44).

Among the brain regions involved in executive functioning, the DLPFC is widely recognized as a key node in cognitive control. Tasks like decision-making, game of dice, GNG, beads, and delay-discounting have been used in the literature for understanding impulsivity.

The main reason for changes in impulsivity, whether it is because of the stimulation target, reduction of drug, or previous underlying reasons, remains unclear. It is obvious that STN-DBS improves motor functions and, by the way, life quality; however, evaluation of other behavioral and cognitive side effects is limited.

2.6 Subthalamic Nucleus-Prefrontal Cortex Circuitry

Studies show that the STN is critically involved in inhibiting premature responses and regulating decision thresholds. Research on non-human primates has demonstrated that STN receives converging input via the hyperdirect pathway from cognitive regions of the frontal cortex, including the PFC (45). It has been observed that STN local field potentials (LFP) can exhibit low-frequency coherence with prefrontal areas, and this hypothesis supports that human hyperdirect low-frequency interactions between the PFC and STN facilitate cognitive control (46).

According to a study by the University of Iowa, the involvement of the hyper-direct fronto-basal ganglia pathway contributes to various aspects of cognition in humans. They tested their hypothesis on patients undergoing surgical treatment. They demonstrated that the lateral and medial areas of the PFC are functionally connected with STN (46).

Another study published in the Journal of Neuroscience in 2016 highlights emerging data indicate coordinated oscillatory activity between the PFC and the STN (47).

2.7 Neural Mechanism and Design of Go/NoGo Task

Stopping is a neurocognitive process that overrides an initiated response tendency. The GNG task is a response inhibition task in which a motor response must either be executed or suppressed. A study conducted by the University of Swansea reveals that as the cognitive load on executive functions increases, inhibitory ability decreases..

While Go cells disinhibit the thalamus via GPi, thereby facilitating the execution of an action represented in the cortex (Figure 6). The No-Go cells have an opposing effect by increasing the inhibition of the thalamus, thereby suppressing actions from being executed. Dopamine from the SNc projects to the dorsal striatum, causing the excitation of Go cells via D1 receptors and inhibition of No-Go via D2 receptors (22).

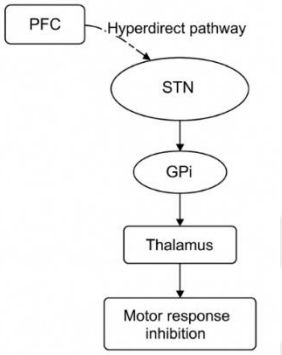


Figure 6. Hyperdirect pathway focused GNG cognitive inhibition circuit

In summary, during a No-Go signal, which can be described as cognitive inhibition, the DLPFC and the inferior frontal cortex are regarded as the primary control centers initiating inhibition. These regions transmit signals to the STN to suppress motor planning. This mechanism is considered a form of top-down, or higher-order, inhibition. The STN functions as a neural brake, receiving direct input from the prefrontal cortex via the hyperdirect pathway. It operates as a 'hold' or 'stop' command and is thus often referred to as a relay station in decision-making processes. In this circuit, the thalamus serves as the target of inhibition, it is the structure that must be suppressed to prevent motor execution. The STN influences the thalamus by connecting with the GPi, completing the inhibitory loop. This functional pathway accurately reflects the mechanism underlying cognitive inhibition (Figure 7).

Behavioral performance of the task was assessed by the errors of omission (not pressing any button when a participant should; on Go stimuli), errors of commission

(pressing the button when the response should be inhibited; on No-Go stimuli), correct rejections to the No-Go stimuli, and correct presses for Go signals (48).

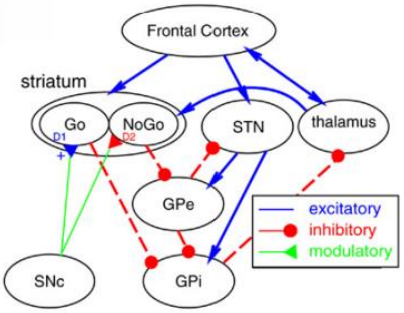


Figure 7. The striato-cortical circuitry.

Activation of Go pathway neurons leads to disinhibition of the thalamus through the GPi, thereby promoting the initiation of motor actions encoded in the cortex. In contrast, the NoGo pathway enhances thalamic inhibition, thus preventing the execution of undesired movements. Dopaminergic input from the SNc targets the dorsal striatum, where it facilitates Go pathway activity via D1 receptor stimulation and concurrently suppresses NoGo pathway neurons through D2 receptor activation (21).

In task design, there are 12 blocks; 6 blocks include 15 Go stimuli, and the other 6 blocks consist of 7 No-Go stimuli and 8 Go stimuli. The Go stimuli are represented as an orange square, while the No-Go stimuli are represented by blue (Figure 8). The Go and No-Go blocks are designed in order, one after another, and the stimuli are designed randomly. Totally 42 No-Go and 138 Go, a total of 180 stimuli make up the task.

Each stimulus remains on the screen for 0.5 seconds, followed by 1.5 seconds of rest before the next stimulus appears. The participant has to either respond or not respond in 2 seconds.

A) Image of Go stimuli B) Image of No-Go stimuli

Figure 8. Schematic representation of the image presented during A) Go stimuli and B) No-Go stimuli.

2.8 PsychoPy

PsychoPy is a widely used open-source software package designed specifically for the creation and execution of experiments in the field of psychology and neuroscience (Figure 9). In this experiment, PsychoPy was used as a GNG test due to its versatility for designing and implementing a wide range of experimental paradigms. It offers a user-friendly graphical interface that allows for the creation of precise and customizable stimuli, controls the timing and presentation of stimuli, and collects accurate and synchronized data. With its extensive library of built-in functions and support for various hardware devices, PsychoPy is a valuable tool in the field of experimental neuroscience. Its compatibility with different operating systems, such as NIRX, and the ability to be used as a trigger to display when stimuli were shown, as well as its ability to generate code in multiple programming languages, including Python, make it accessible and adaptable for this research experiment.

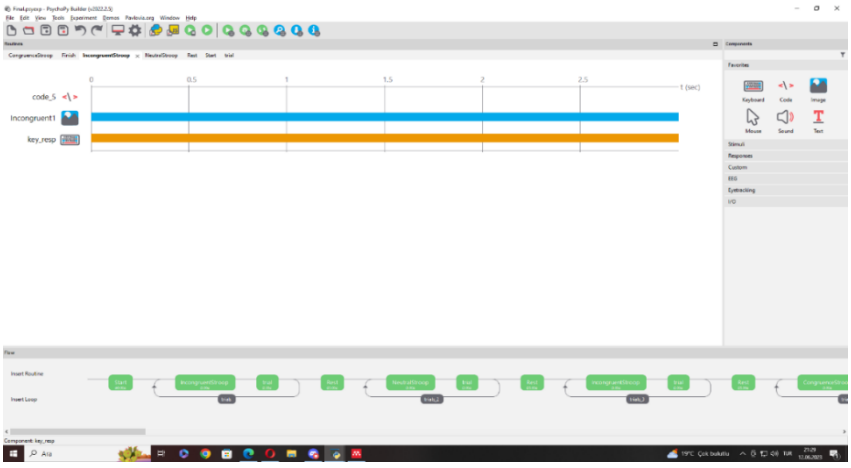


Figure 9. Psychopy interface.

2.9 Physical and Physiological Principles of fNIRS Methodology

As a non-invasive optical imaging technique, fNIRS enables the measurement of regional cerebral blood flow through hemoglobin-based signals. By measuring the concentration difference between oxyhemoglobin (HbO_2) & deoxyhemoglobin (HbR), a cerebral dynamic response can be measured. Decreases and increases in the site of interest infer cerebral activity. Unlike other devices used to measure cerebral activity fNIRS is more accessible, portable & accurate. It uses infrared light to measure cerebral activity. Which offers a greater insight into localized regions of the brain due to its high accuracy. fNIRS allows for the study of where exactly the brain activity is taking place. Since HbO_2 is directly linked to cognitive activity the measurement of the cerebral dynamic response is crucial. Since measuring in one frequency domain would yield insufficient results where multiple variables would be represented with one frequency, fNIRS generally uses two frequencies to measure cerebral activity. Beer-Lambert Law uses a modified version to calculate the concentration of HbR & HbO_2 .

3 MATERIALS AND METHOD

3.1 Subjects

The subjects were 7 right-handed whose ages were between 60 and 76 (mean age: 65 years, 3 females, 4 males) participated in the study (Table 1). Exclusion criteria were: the DBS surgery because of diseases other than PD, dementia, depression, any neuropsychiatric diagnosis, colour blindness, and neuropsychiatric drug usage. Inclusion criteria were: speaking Turkish language as native, being selected for DBS surgery as a PD patient.

All subjects signed informed consent before the experiment. The local ethics committee of Istanbul Medipol University, Istanbul, Turkiye, approved the study (Appendix).

Table 1. Demographic data of the patients.

Demographic Data of the Patients			
Subject	Age	Gender	Stimulation Target
S1	63	Female	STN
S2	60	Female	STN
S3	76	Female	STN
S4	67	Male	STN
S5	63	Male	STN
S6	63	Male	STN
S7	63	Male	STN

3.2 Experimental Procedure

Throughout the experiment, participants were seated comfortably in front of a computer positioned approximately 50 to 70 cm from their eyes, in a dimly lit, quiet

room to minimize external distractions (Figure 10). Prior to the onset of the experiment, all participants received a comprehensive briefing on the study protocol to ensure informed participation.

Figure 10. Patient at the beginning screen of GNG task

Each experiment is started with calibration of the NIRx device, then followed by 60 seconds of baseline recording, followed by Go Block, which contains 15 go stimuli with 0.5 seconds, including 1.5 seconds rests in between. Each block lasted 30 seconds with a 30-second inter-stimulus interval (ISI). The odd block numbers included 15 Go signals, even block numbers included 7 no-go and 8 go signals randomly. There are 12 blocks in the total experiment, including 6 Go, 6 No-Go blocks. The total experiment includes 180 stimuli. 60 seconds of baseline recording, 720 seconds of procedure, and 5 seconds of finish, form an approximate test of 13 minutes total.

3.3 fNIRS Data Acquisition

Neurovascular coupling reflects the temporal and regional linkage between cerebral blood flow and neural activity (50). Neurons in the activated region of the brain consume more oxygen. Oxygen is transported to neural tissue via oxyhemoglobin in the blood (Figure 11). The oxygen that oxyhemoglobin gives to the neural tissue is transformed into deoxyhemoglobin.

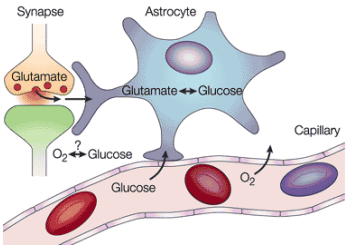
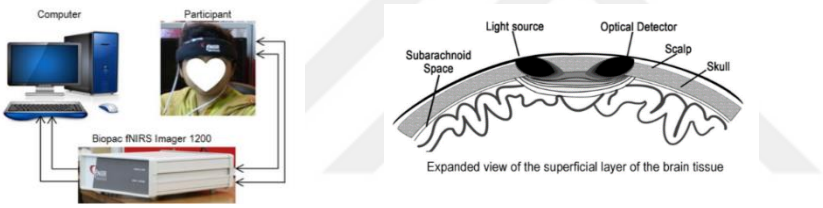


Figure 11. The interplay between oxygen supply and vascular response dynamics (52).

As a neuroimaging technique measuring fluctuations in HbO_2 , HbR, and total hemoglobin (HbT) concentrations in cortical tissue, fNIRS is a device that serves by using near-infrared light, and can penetrate tissue up to 5-6 cm (Figure 12B). A 750 nm source detects changes in HbR, and an 850 nm light detects changes in HbO_2 . The cortical activation related to hemodynamic changes can be observed.



A) B)

Figure 12. A) Monitoring hemodynamic responses in the PFC using the fNIRS modality, B) light penetrating cortical tissue detected by the optical detector (53).

Similar to functional magnetic resonance imaging (fMRI), fNIRS also monitores hemodynamic changes caused by cortical neuronal activation. Unlike magnetic resonance imaging (MRI)-based techniques, fNIRS is not affected by magnetic fields, and thus, in the context of this study, the presence of a pacemaker or implanted electrodes did not constitute exclusion criteria (35). Functional near-infrared spectroscopy is harmless, portable, low-cost, and suitable for all populations, including babies and elderly people. It can be used inside and outside the laboratory (54).

A 22-channel fNIRS device is used in this study. In the literature, impulsivity after STN-DBS has been studied using various tools and experimental designs, such as EEG

(Electroencephalogram), fMRI (Functional magnetic resonance imaging), and tractography.

Data were collected by using a NIRSport system (NIRx Medical Technologies, LLC, Berlin, Germany), with optodes strategically positioned over the PFC. The system utilized a forehead probe configuration comprising 22 channels, including 8 light sources emitting near-infrared light and 7 detectors. The wavelengths are 760 nm and 850 nm. Channel-forming optodes were placed 3 cm apart to ensure optimal signal penetration and coverage of the target brain regions. Sampling rate was set at 7.81 Hz, and data were recorded continuously throughout the experiment. Figure 13 depicts the spatial distribution of the probe's optical sensitivity over a standardized cortical surface model, aligned with the 10/5 international EEG electrode system. Channel positions were coregistered to the Montreal Neurological Institute (MNI) standard brain by using the NIRS_SPM toolbox (54).

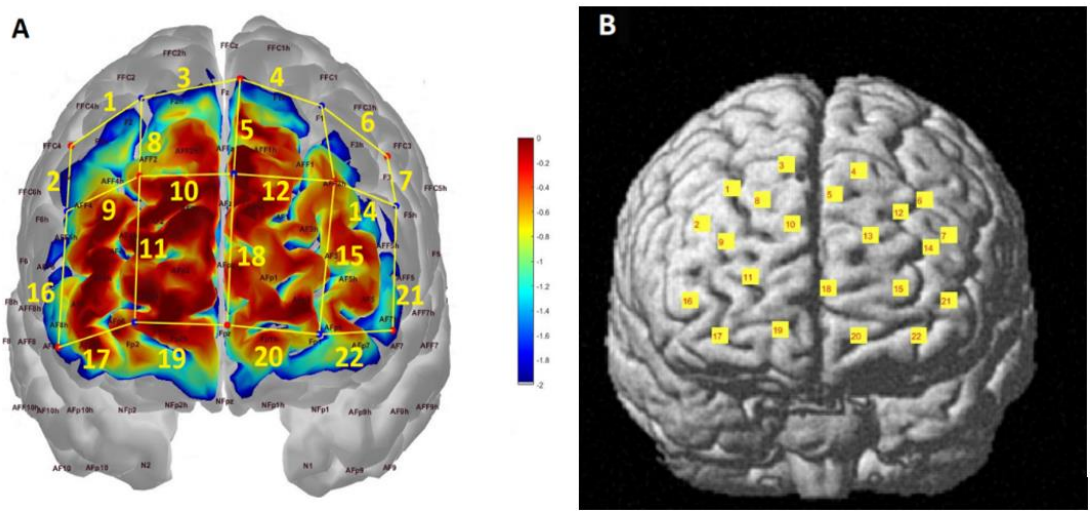


Figure 13. A) The configuration of the probe and its photon sensitivity profile are depicted. Red markers indicate light sources, while blue markers denote detectors. Measurement channels, shown as yellow lines and labeled accordingly, are formed by adjacent source–detector pairs. The probe's sensitivity to cortical hemodynamic responses is visualized as a heat map in log10 scale. B) The spatial distribution of channels is coregistered and registered to a standardized cortical surface within MNI space (55).

3.4 fNIRS Data Analysis

Preprocessing of fNIRS signals was conducted using MATLAB scripts (Mathworks, Natick, MA, USA) and functions from the Homer3 software (56). The light intensity signals of each channel were converted to optical density (OD) values using the hmrR_Intensity2OD function. The optical density data underwent motion correction using the hmrR_MotionCorrectSplineSG function with a parameter setting of p=0.99 and a frame size of 10 seconds. Following motion correction, the OD values were transformed to concentrations of HbO_2 and HbR utilizing the hmrR_OD2Conc function, applying a differential pathlength factor (DPF) of 1 for each wavelength. Bandpass filtering was applied with high and low cutoff frequencies. 0.01 Hz and 0.5 Hz was applied to for removing low-frequency drifts and high-frequency noise induced by heartbeat. A principal component analysis (PCA) was performed and the first principal component of all channel data was accepted as a regressor representing common systemic effects. The 1st principal component of the 22-channel HbO_2 data matrix was regressed out to isolate neuronally induced HbO_2 signal components from systemic physiological signals. HbO_2 time series data of each channel were segmented into Go and No-Go stimuli blocks with a pre-stimulus baseline of 3 seconds and a post-stimulus duration of 22 seconds, resulting in 55-second time traces for each stimulus block. Channel-specific HbO_2 signals corresponding to each stimulus condition were detrended prior to further analysis. Area under the curve (AUC) between 10th and 20th seconds after the stimulus onset was computed as the neurovascular coupling parameter representing oxygenation level and hemodynamic activity during each task.

To identify regions exhibiting statistically robust hemodynamic responses at the group level, one-sample t-test was applied on the channel-specific mean AUC parameters obtained for No-Go blocks of the 7 subjects. T-tests were applied for group-level mean AUC parameters of each channel separately, and they were conducted for all channel regions of the pre and post-DBS scans. Channels with t-values surpassing the statistical threshold ($p<0.05$) were accepted as significantly activated in response to the presented stimuli. T-values of significantly activated

channels were coregistered onto a standard brain template, which also depicted anatomical locations of the optode positions with respect to the 10-20 EEG system for electrode placement (Figure 14). For each subject, the change in AUC parameter of No-Go stimuli blocks between the fNIRS measurements obtained before and after DBS intervention was computed for each channel.

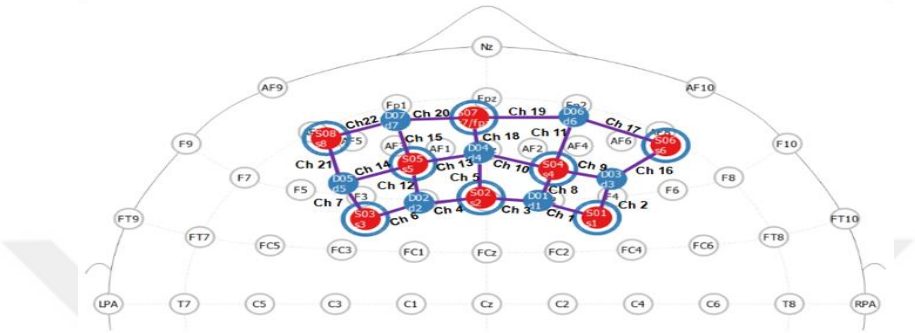


Figure 14. Spatial layout of the probe's optical sensitivity mapped onto a standardized cortical surface, co-registered with the 10/5 EEG system.

3.5 Behavioral Parameter Extraction and Analysis

For each No-Go stimulus block, ACC and RT were computed as the behavioral parameters that represented the response inhibition performance. A unified performance index, termed the Cognitive Quotient (CQ), was computed by dividing the overall accuracy (i.e., the percentage of correct responses across all No-Go trials) by the average RT obtained from the same trials.

The mean ACC for each No-Go stimulus block of each participant was determined by dividing the count of correct responses by the overall number of trials conducted within that block. ACC for go trials and No-Go trials were computed separately within a block. An overall ACC of each No-Go stimulus block was then computed as a weighted sum of the ACC for Go trials and No-Go trials where Go trial ACC was given a weight of 8/15 and No-Go trial ACC was given a weight of 7/15. The mean No-Go ACC of each participant was then calculated as the average ACC over the ACCs obtained from the 6 No-Go Stimuli blocks. Commission errors were trials when

the participants pressed their finger to the space key on No-Go trials (i.e., the trials on which they failed to withhold a response on No-Go trials). Omission errors were Go trials on which the participant did not press the space key (i.e., Go trials on which they failed to respond (48).

Reaction time has been calculated for the Go stimuli presented in the No-Go blocks. Mean RT for each No-Go block was computed as the average RT over the 8 Go trials presented within the block. Reaction time is taken as the time between the onset of an orange or blue square presentation on the screen and the moment that participant lift the finger from the space key. Reaction times that are shorter than 100 ms are counted as anticipatory errors, and any responses not made in 2 seconds (stimulus+rest) are counted as wrong for all Go trials. These trials were excluded from the mean RT computation procedure.

Cognitive quotient parameter for each No-Go block was computed as the ratio of overall ACC performance to the mean RT for the Go trials within the block. CQ is considered an efficiency metric since higher ACC performance obtained under shorter RTs would be indicative of higher neural efficiency. CQ is calculated as the ratio of ACC to RT.

For each behavioral performance metric, mean over the 6 No-Go blocks were computed for further analysis. For each behavioral parameter (i.e., ACC, RT, CQ), statistically significant differences between pre-intervention and post-intervention scores were analyzed using two-tailed paired t-tests. A significance threshold of $p < 0.05$ was applied in all statistical analyses. One sample t-tests were evaluated for pre and post-intervention group-level data of each behavioral metric separately to assess whether the performance of the group was statistically significant or not.

Correlations between changes in AUC and changes in ACC, RT and CQ scores of all subjects were then computed in terms of Pearson's Correlation Coefficient, and significant correlations were illustrated in scatter plots (Figure 16-20).

3.6 Limitations of the Study and Recommendations for Future Work

In future studies, the aim is to increase the number of participants and conduct this research more comprehensively with a larger dataset. Outcomes may exhibit inter-individual variability. This study aims to serve as a roadmap for future research. Increasing the number of patients and categorizing them into smaller subgroups based on factors such as age range, disease duration, and gender would probably be helpful to ensure a cleaner evaluation independent of other variables.

Besides, the patients also underwent the Stroop test; however, due to time constraints, the data analysis could not be included in this study, and it was planned to incorporate it into future research.

In addition to DBS applications, including patients who have undergone methods such as MRgFUS in the study, and comparing their pre-op and post-op behavioral and hemodynamic data with those of healthy individuals or patients using only medication can provide insights into the effects of interventional methods on these diseases.

Go-No/Go tests have not previously been conducted using fNIRS measurements in patients who have undergone STN-DBS, making this study a stepping stone for future research. Long-term results can be compared over extended periods, such as six months, one year, or longer, without time constraints.

Due to time limitations in this study, post-surgery data were compared with pre-surgery data over three weeks. In future studies, it is aimed to analyze potential long-term results that may emerge over time. One of the future goals is to establish an AI-supported system that analyzes data obtained through long-term post-operative observations, allowing us to predict patients' long-term conditions after surgery.

4 RESULTS

4.1 Behavioral Results

Figure 15, figure 16 and table 2 present individual ACC scores obtained during the No-Go task before (Pre-DBS) and after (Post-DBS) DBS. A consistent decrease in ACC is observed across nearly all participants following surgery, with the exception of one subject (Subject 6), whose post-DBS ACC remained comparable to pre-surgical levels (Figure 16).

Table 2. Accuracy scores for each subject for No-Go task.

Accuracy Comparison Of No-Go Blocks			
Subjects	Pre-DBS	Post-DBS	Post-Pre Difference
1	0.76	0.52	-0.24
2	0.60	0.53	-0.06
3	0.71	0.48	-0.23
4	0.64	0.42	-0.21
5	0.78	0.52	-0.26
6	0.58	0.60	0.02
7	0.74	0.58	-0.15
Mean	0.68	0.520	-0.16

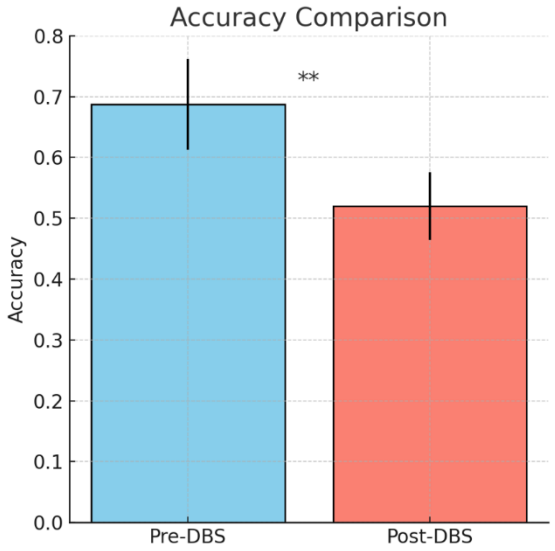


Figure 15. The bar graph illusion of subjects' comparative task performance as pre and post DBS for ACC (**=p<0.006).

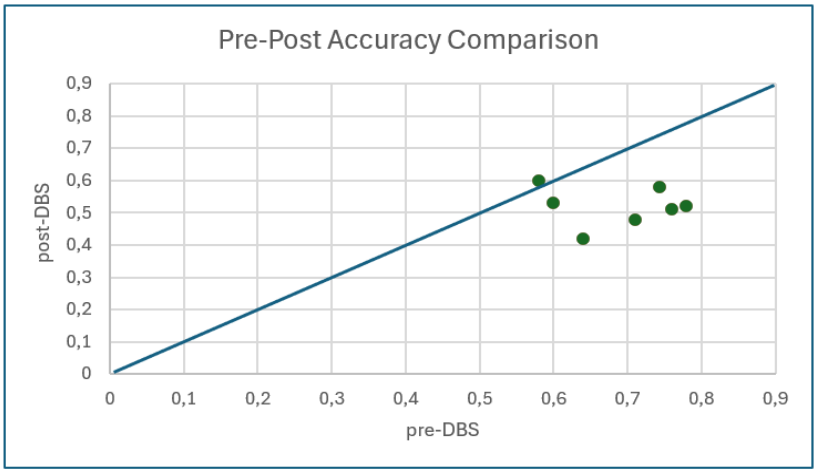


Figure 16. Scatter plots of ACC data. Each data point corresponds to an individual participant's pre versus post-intervention comparison for the specified behavioral metric.

The reduction in ACC after DBS intervention is particularly pronounced in Subjects 1, 3, 4, and 5, suggesting a potential decline in task performance related to inhibitory control or attentional processing. This trend is further supported by the group-level statistical analysis, which revealed a statistically significant decrease in ACC following DBS ($p = 0.006$).

These results may indicate that while DBS can modulate neural circuits involved in motor and cognitive processing, it may also compromise aspects of executive functioning required for maintaining task accuracy, such as sustained attention or error monitoring. The consistent decline across subjects underscores the need for careful evaluation of cognitive side effects in clinical applications of DBS.

Figure 17, figure 18 and table 3 demonstrate the individual RTs of participants to Go stimuli presented within No-Go blocks, which required participants to respond via button press. These data were also analyzed as part of the behavioral performance assessment compared between pre and post-DBS. Responses with a latency below 0.1 milliseconds (ms) were defined as anticipatory responses and were counted as errors. A general trend toward decreased RTs is observed following surgery, indicating improved response speed in the majority of participants.

Table 3. Reaction time scores for each subject for Go tasks in No-Go blocks.

RT Comparison of No-Go Blocks			
Subjects	Pre-DBS	Post-DBS	Post-Pre Difference
1	0.60	0.42	-0.18
2	0.74	0.67	-0.07
3	0.79	0.79	0.01
4	0.65	0.69	0.04
5	0.69	0.77	0.07
6	0.64	0.38	-0.25
7	0.64	0.43	-0.20
Mean	0.68	0.59	-0.08
STD	0.06	0.16	0.12
p value	<0.0001	<0.0001	0.13

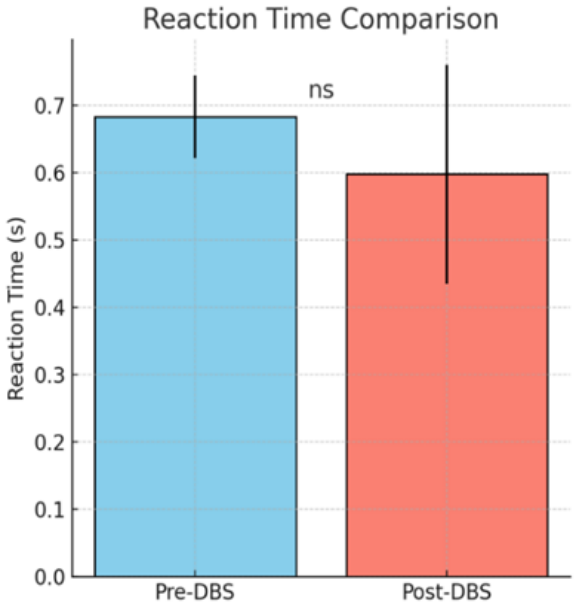


Figure 17. The bar graph illusion of subjects' comparative task performance as pre and post DBS for RT (ns: non-significant).

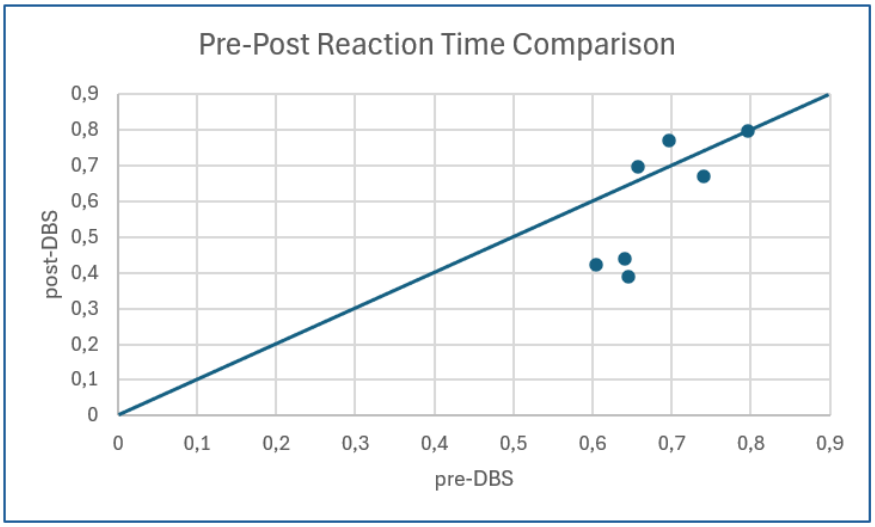


Figure 18. Scatter plots of RT data. Each data point corresponds to an individual participant's pre versus post-intervention comparison for the specified behavioral metric.

Specifically, subjects 1, 2, 6, and 7 demonstrated a notable reduction in RT post-DBS, suggesting enhanced cognitive processing or motor responsiveness. Subject 3 exhibited minimal change between pre and post-DBS measurements, indicating a

neutral effect of the intervention. In contrast, Subjects 4 and 5 showed slight increases in RT following DBS, potentially reflecting a mild decline in performance.

Overall, these findings suggest that participants tend to behave more impulsively after the surgery, shortening the phases of reflection and evaluation before responding. The comparison is statistically not significant, so it can be said that there is less effect of DBS on RT for most individuals. The variability among participants highlights the importance of considering individual differences in treatment outcomes.

Table 4, figure 19 and figure 20 demonstrate the individual CQ scores of participants pre and post-DBS. A consistent decrease in CQ is observed across nearly all participants following surgery, with the exception of one subject (subject 6), whose post-DBS ACC remained comparable to pre-surgical levels (Figure 16).

Table 4. Cognitive quotient scores for each subject for No-Go blocks.

Cognitive Quotients Comparison Of No-Go Blocks			
Subjects	Pre-DBS	Post-DBS	Post-Pre Difference
1	2.48	1.78	-0.70
2	1.12	0.93	-0.19
3	1.62	0.78	-0.84
4	1.58	0.63	-0.95
5	2.15	0.81	-1.34
6	2.00	2.25	0.25
7	2.01	1.85	-0.16
Mean	1.85	1.29	-0.56
STD	0.45	0.65	0.55
p value	<0.0001	<0.002	<0.005

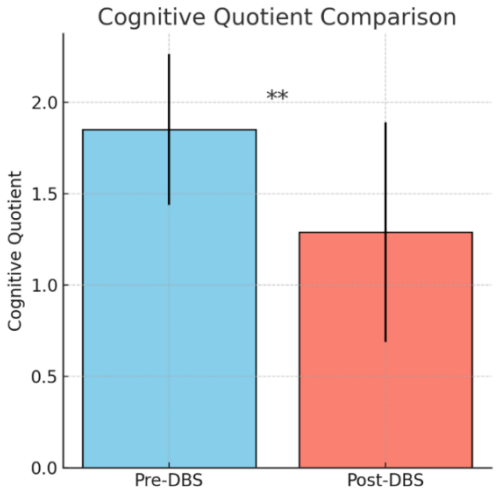


Figure 19. The bar graph illusion of subjects' comparative task performance as pre and post DBS for CQ (**=p<0.006).

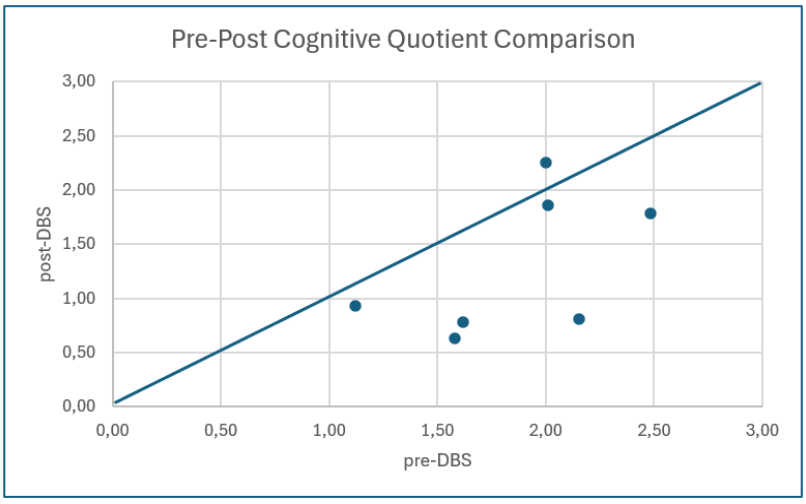


Figure 20. Scatter plots of CQ data. Each data point corresponds to an individual participant's pre versus post-intervention comparison for the specified behavioral metric.

The cognitive effort which is reflected as CQ index, described as a metric to complete a given task. Numerous metrics, indices, and quotients have been proposed to quantify such effort, typically involving combinations of neuropsychological task outcomes and, in some cases, physiological measures. In the presented work, CQ represents the compromise between ACC and speed. Therefore, higher CQ values indicate a better efficiency since the same ACC performance is obtained at a faster speed or shorter RT.

4.2 Hemodynamic Results

Figure 21 demonstrates localization of statistically significant PFC activation or deactivation during processing of No-Go stimuli, A) before DBS intervention, B) after DBS intervention and C) significant differences in hemodynamic activity between post and pre-intervention. The maps depict thresholded t-statistic scores.

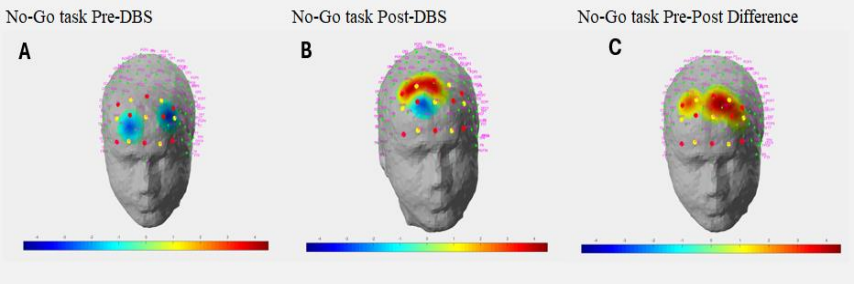


Figure 21. Group level hemodynamic activation maps during No-Go tasks, A) Pre-intervention, B) Post-intervention C) Significant differences in activation between post-pre DBS recordings. Thresholded t-statistics of channels with significant activation are projected onto a standard head model for each condition. The color bars represent t values.

Table 5. Location of PFC ROIs probed by the fNIRS headband and their relevant functions during No-Go stimuli processing. This figure/table presents the MNI coordinates of each projected channel, along with the corresponding percentage overlap with Brodmann Areas (BA).

Channel Number	EEG location of optodes	Brodmann Area	Main function	ROI	Hemodynamic Activity Information
Channel 1	FC4 (Right Precentral Gyrus) -F4 (Right DLPFC)	BA6 (1%) BA9 (99%)	Motor execution preparation (FC4) Cognitive Control-executive function (F4)	Right DLPFC	-No activity before DBS -Activated after DBS intervention -Significant activity increase after DBS intervention

Table 5. (continued) Location of PFC ROIs probed by the fNIRS headband and their relevant functions during No-Go stimuli processing. This figure/table presents the MNI coordinates of each projected channel, along with the corresponding percentage overlap with Brodmann Areas (BA).

Channel Number	EEG location of optodes	Brodmann Area	Main function	ROI	Hemodynamic Activity Information
Channel 2	F4 (Right DLPFC)	BA9 (8%) BA46 (1%) BA9 (72%)	Cognitive control, executive function (F4)	Right DLPFC	-No significant or non-significant activation have observed during pre and post No-Go or Go blocks.
Channel 3	F2 (Right DLPFC) Fz (Medial Superior Frontal)	BA8 (16%) BA9 (84%)	Working memory, attention (F2) Motor preparation, cognitive control (Fz)	Right DLPFC	-Significant activation after DBS intervention. There is no significant difference between pre-post hemodynamic activities.
Channel 4	F1 (Left DLPFC) Fz (Medial Superior Frontal)	BA8 (5%) BA10 (95%)	Working memory, attention (F1) Motor preparation, cognitive control (Fz)	Left DLPFC	-No activation before DBS intervention. -Significantly increased activation compared to pre-DBS.

Table 5. (continued) Location of PFC ROIs probed by the fNIRS headband and their relevant functions during No-Go stimuli processing. This figure/table presents the MNI coordinates of each projected channel, along with the corresponding percentage overlap with Brodmann Areas (BA).

Channel Number	EEG location of optodes	Brodmann Area	Main function	ROI	Hemodynamic Activity Information
Channel 5	AFz (Frontopolar PFC) Fz (Medial Superior Frontal)	BA9 (89%) BA10 (11%)	Cognitive control, response inhibition (AFz) Motor preparation, cognitive control (Fz)	Fronto-polar PFC Medial PFC (mPFC)	-Significant increase of activation after DBS intervention. - The hemodynamic and behavioral results are significantly correlated.
Channel 6	F1 (Left DLPFC) F3 (Left DLPFC)	BA9 (64%) BA46 (36%)	Working memory, attention (F1) Cognitive control, executive function (F3)	Left DLPFC Mid-superior part of the frontal lobe	-No significant activity in pre or post DBS intervention.
Channel 7	F3 (Left DLPFC) F5 (Left Middle Frontal Gyrus)	BA45 (42%) BA46 (58%)	Cognitive control, executive function (F3) Motor planning, verbal fluency (F5)	Left DLPFC Left Frontal Gyrus	- No significant activity in pre or post DBS intervention.

Table 5. (continued) Location of PFC ROIs probed by the fNIRS headband and their relevant functions during No-Go stimuli processing. This figure/table presents the MNI coordinates of each projected channel, along with the corresponding percentage overlap with Brodmann Areas (BA).

Channel Number	EEG location of optodes	Brodmann Area	Main function	ROI	Hemodynamic Activity Information
Channel 8	F2 (Right DLPFC) F4 (Right DLPFC) AF4 (Right Anterior Frontal Lobe)	BA9 (96%) BA46 (4%)	Working memory, attention (F2) Cognitive control, executive function (F4) Future planning, working memory (AF4)	Right DLPFC Anterior portion of the right frontal lobe	- No significant activity in pre or post DBS intervention.
Channel 9	F4 (Right DLPFC) AF4 (Right Anterior Frontal Region)	BA9 (2%) BA10 (27%) BA46 (71%)	Cognitive control, executive function (F4) Future planning, working memory (AF4)	Right DLPFC Anterior portion of the right frontal lobe	-No significant activity in pre or post DBS intervention.
Channel 10	AF2 (Right Anterior Frontal Region) F2 (Right DLPFC) AFz (Frontopolar PFC)	BA9 (21%) BA10 (79%)	Decision-making, future planning, and cognitive flexibility (AF2) Working memory, attention (F2) Cognitive control, response inhibition(AF z)	Right DLPFC Anterior portion of the right frontal lobe	-No significant activity before DBS intervention -Hemodynamic deactivation with respect to rest in post-DBS hemodynamic activity. -No significant difference in activity in pre-post comparison.

Table 5. (continued) Location of PFC ROIs probed by the fNIRS headband and their relevant functions during No-Go stimuli processing. This figure/table presents the MNI coordinates of each projected channel, along with the corresponding percentage overlap with Brodmann Areas (BA).

Channel Number	EEG location of optodes	Brodmann Area	Main function	ROI	Hemodynamic Activity Information
Channel 11	AF4 (Right Anterior Frontal) AF6 (Right DLPFC) FP2 (Right Frontal Pole)	BA10 (100%)	Future Planning, working memory (AF4) Cognitive Control-executive function, impulsivity control and working memory (AF6) -Decision making, social cognition (FP2).	Right DLPFC and right portion of the medial PFC	-Decreased hemodynamic activity with respect to rest, before DBS intervention. -No hemodynamic activity difference between pre-post No-Go tasks.
Channel 12	F1(Left DLPFC) AF1 (Left Anterior PFC)	BA9 (50%) BA46 (50%)	Working memory, attention (F1) Cognitive control, verbal reasoning, decision making (AF1)	Left DLPFC	-No hemodynamic activation or deactivation during pre and post tasks. -Significant difference has observed pre-post comparison of hemodynamic activation.
Channel 13	AFz (Frontopolar PFC) AF1 (Left Anterior PFC)	BA9 (15%) BA10 (80%) BA46 (5%)	Cognitive control, response inhibition(AFz) Left anterior PFC	Left region of the anterior frontal lobe Medial PFC	-No significant difference in activity in pre-post comparison.

Table 5. (continued) Location of PFC ROIs probed by the fNIRS headband and their relevant functions during No-Go stimuli processing. This figure/table presents the MNI coordinates of each projected channel, along with the corresponding percentage overlap with Brodmann Areas (BA).

Channel Number	EEG location of optodes	Brodmann Area	Main function	ROI	Hemodynamic Activity Information
Channel 14	AF3 (Left Anterior Frontal) F3 (Left DLPFC)	BA10 (1%) BA46 (99%)	Future Planning, working memory (AF3) Cognitive Control-executive function (F3)	Left DLPFC and left portion of the medial PFC	-Decreased hemodynamic activity with respect to rest, before DBS intervention. -Pre and post-intervention tests revealed significant changes in cerebral hemodynamic activity.
Channel 15	AF3 (Left Anterior Frontal Cortex) AF1 (Left Anterior PFC) F3 (Left DLPFC)	BA10 (89%) BA11 (11%)	Future planning, working memory(AF3) Cognitive control, verbal reasoning, decision making (AF1) Cognitive control, executive function (F3)	Left anterior frontal and DLPF region.	-No significant hemodynamic activation or deactivation during pre and post tasks.
Channel 16	F6 (Right middle frontal gyrus) F4 (Right DLPFC) AF8 (Right lateral frontal region)	BA10 (54%) BA46 (46%)	Motor planning, verbal fluency (F6) Cognitive control, executive function(F4) Social processing, verbal reasoning (AF8)	Middle and lateral-frontal region of right hemisphere	No significant pre-post differences or task-related activation/deactivation were detected following the test.

Table 5. (continued) Location of PFC ROIs probed by the fNIRS headband and their relevant functions during No-Go stimuli processing. This figure/table presents the MNI coordinates of each projected channel, along with the corresponding percentage overlap with Brodmann Areas (BA).

Channel Number	EEG location of optodes	Brodmann Area	Main function	ROI	Hemodynamic Activity Information
Channel 17	Fp2 (Right frontal pole) AF8 (Right lateral frontal) AF6 (Right anterior frontal cortex)	BA10 (25%) BA11 (%60) BA46 (3%) BA47 (2%)	Decision making, social cognition (Fp2) Social processing, verbal reasoning (AF8) Cognitive flexibility, emotional and social cognition (AF6)	Right anterior frontal region.	No significant pre-post differences or task-related activation/deactivation were detected following the test.
Channel 18	AFz (Frontopolar PFC) Fpz (Frontopolar PFC)	BA10 (%100)	Cognitive control, response inhibition(AFz) Future planning, self-monitoring, emotional regulation (Fpz)	Midline of the frontal pole.	No significant pre-post differences or task-related activation/deactivation were detected following the test.
Channel 19	Fpz (Frontopolar PFC) Fp2 (Right frontal pole)	BA10 (50%) BA11 (50%)	Decision making, social cognition (Fp2) Future planning, self-monitoring, and emotional regulation (Fpz)	Frontal pole of right hemisphere.	No significant pre-post differences or task-related activation/deactivation were detected following the test.

Table 5. (continued) Location of PFC ROIs probed by the fNIRS headband and their relevant functions during No-Go stimuli processing. This figure/table presents the MNI coordinates of each projected channel, along with the corresponding percentage overlap with Brodmann Areas (BA).

Channel Number	EEG location of optodes	Brodmann Area	Main function	ROI	Hemodynamic Activity Information
Channel 20	Fpz (Frontopolar PFC) Fp1(Left frontal pole)	BA10 (37%) BA11 (63%)	Future planning, self-monitoring and emotional regulation (Fpz) Decision making, social cognition (Fp1)	Frontal pole of left hemisphere.	No significant pre-post differences or task-related activation/deactivation were detected following the test.
Channel 21	AF7 (Left lateral frontal) AF5 (Left anterior frontal cortex)	BA10 (37%) BA46 (63%)	Social processing, verbal reasoning (AF7) Verbal working memory, cognitive flexibility (AF5)	Left frontopolar PFC	No significant pre-post differences or task-related activation/deactivation were detected following the test.
Channel 22	AF7 (Left lateral frontal) Fp1 (Left frontal pole) AF5 (Left anterior frontal cortex)	BA10 (33%) BA11 (53%) BA46 (4%) BA47 (10%)	Future planning, working memory (AF7) Decision making, social cognition (Fp1) Verbal working memory, cognitive flexibility (AF5)	Frontal region of left hemisphere	No significant pre-post differences or task-related activation/deactivation were detected following the test.

Table 6. Thresholded t-statistics of channels with significant activation or deactivation.

T Scores for NoGo Tasks	**Ch1**	**Ch3**	**Ch4**	**Ch5**	**Ch10**	**Ch11**	**Ch12**	**Ch14**
Tstats Pre	0	0	0	0	0	-2.75	0	-3.05
Tstats Post	4.07	2.89	0.00	3.06	-2.73	0.00	0.00	0.00
Tstats Post-Pre	3.96	0.00	2.65	3.65	0.00	0.00	2.54	2.50

Before the onset of the DBS intervention, significant HbO_2 deactivation was observed at channel 11 ($t = -2.75$, $p < 0.05$), and channel 14 ($t = -3.05$,$p<0.05$) which correspond to the right DLPFC and right portion of the medial part of the anterior PFC region and their bilateral homologous regions in left PFC (Table 6). More specifically, Channel 11 spans an ROI that covers AF4 (Right anterior Frontal), AF6 (Right DLPFC) and FP2 (Right Frontal Pole) regions in EEG 10-20 electrode system. Meanwhile, channel 14 covers an ROI spanned by AF3 and F3 locations that correspond to left DLPFC and left portion of the medial PFC. These bilaterally located PFC regions have critical role for processing cognitive tasks that involve response inhibition and impulsivity control such as the GNG task (Table 5). They are also involved in working memory, future planning and decision making tasks. A significant decrease in oxygenation with respect to baseline during processing of No-Go stimuli before surgery in two channels (channel 11 and channel 14) in BA10 and BA46 regions which maps bilateral DLPFC (Figure 21) (Table 5).

After the DBS intervention, significant HbO_2 deactivation with respect to baseline hemodynamics was detected at channel 10 (AF2, F2, AFz, in 10-20 EEG system) ($t = -2.73$, $p<0.05$) (Table 6) which is located in the right DLPFC, covered by BA10. This region has critical role in response inhibition and attention (Table 5).

There was an increase in oxygenation during the post-DBS No-Go task at channel 1 ($t=4.07$, $p<0.05$), channel 3 ($t=2.89$, $p<0.05$), channel 5 ($t=3.06$, $p<0.05$) (Table 6), which correspond to the BA8, BA9, and BA10 regions. These regions cover ROIs spanned by FC4, F4, F2, Fz, and AFz locations in the EEG 10-20 system and correspond to the Right DLPFC, frontopolar PFC, and medial superior frontal regions, which are responsible for cognitive control, attention, and response inhibition (Table 5).

When the differences in AUC parameter between pre-treatment and post-treatment fNIRS measurements were analyzed, a significant increase in hemodynamic activity was found at channel 1 ($t=3.96$, $p<0.005$), channel 4 ($t=2.64$, $p<0.05$), channel 5 ($t=3.65$, $p<0.05$), channel 12 ($t=2.54$, $p<0.05$), and channel 14 ($t=2.50$, $p<0.05$)

(Table 6). Channel 1 (FC4, F4) and channel 3 (F2, Fz) spans an ROI that is located bilaterally in DLPFC, BA9, and both associated with motor execution preparation and cognitive control-executive function (Table 5). Channel 5, located also in the region of BA9, corresponds to Fz, AFz electrode locations of EEG 10-20 (Table 5). The region of this channel (frontopolar PFC and medial superior frontal region) has been implicated in the execution of advanced cognitive functions, including cognitive control, inhibitory processing, multitasking, and planning for future-oriented behavior response inhibition, cognitive control. Channel 12 covers an ROI spanned by F1 (Left DLPFC) and AF1 (Left anterior PFC), the PFC of the left hemisphere, have a critical role in working memory, attention, and decision making (Table 5). This brain region, covered by BA9 and BA46 regions equally, has been implicated in high-order cognitive control and assists the function of easy switch between multiple tasks (Table 5). Channel 14 which showed significant deactivation before DBS intervention, which as mentioned correspond to left DLPFC and left portion of the medial PFC also showed significant pre-post difference in the hemodynamic measurements (Figure 21).

4.3 Evaluation Of Pre to Post-DBS Differences in Behavioral Performance and Hemodynamic Responses

A significant correlation between changes in behavioral performance and changes in hemodynamic activity has been observed in the region of channel 5 for all subjects during No-Go blocks tasks, which on the atlas projects to the medial frontal gyrus, medial prefrontal cortex (mPFC) (BA9/10), anterior and medial frontal regions of the brain. This region is highly involved in complex decision-making and strategic goal-directed planning (57) (Table 5). The STN may serve as a neural brake by modulating cortico-striatal circuitry during decision conflict, the mPFC exerts top-down executive control to guide appropriate behavioral responses. Therefore, increased activation in the mPFC likely reflects its role in supporting impulse control and cognitive regulation under demanding task conditions (58). The area is crucial for functions such as executive control, task switching, and attention control. mPFC may support the regulation of transitions from automatic to controlled action selection, particularly

under conditions of conflict or following recent errors as one of the target areas to analyse cognition and impulsivity (59).

To analyze the possible correlation between statistically significant alterations in HbO_2 response and behavioral parameters, correlations between changes in AUC parameter with respect to changes in ACC, RT, and CQ scores were evaluated for channels demonstrating a significant increase in activity between post and pre-DBS scans. Changes in hemodynamic activity of channel 5 demonstrated significant correlations with changes in ACC and CQ, marginally correlated with RT metrics of all subjects. Figure 22 shows the relationship between changes in ACC and AUC scores of all subjects induced by DBS intervention in the form of scatter plots. Similarly, the relationship between changes in CQ and AUC scores of all subjects is plotted in figure 23. Changes in hemodynamic and behavioral parameter values of all subjects are tabulated in Tables 7 and 8.

Table 7. Comparison of changes in ACC performance and changes in hemodynamic activation of channel 5 of all subjects.

Subject Number	Change in Hemodynamic Parameter (Post DBS-Pre DBS)	Change in Accuracy Performance (Post DBS- Pre DBS)
Subject 1	0.0001	-0.24
Subject 2	0.0002	-0.06
Subject 3	0.0001	-0.23
Subject 4	0.0001	-0.21
Subject 5	0	-0.26
Subject 6	0.0003	0.02
Subject 7	0.0002	-0.15
Correlation	0.93	
Significance (p value)	$p<0.006$	

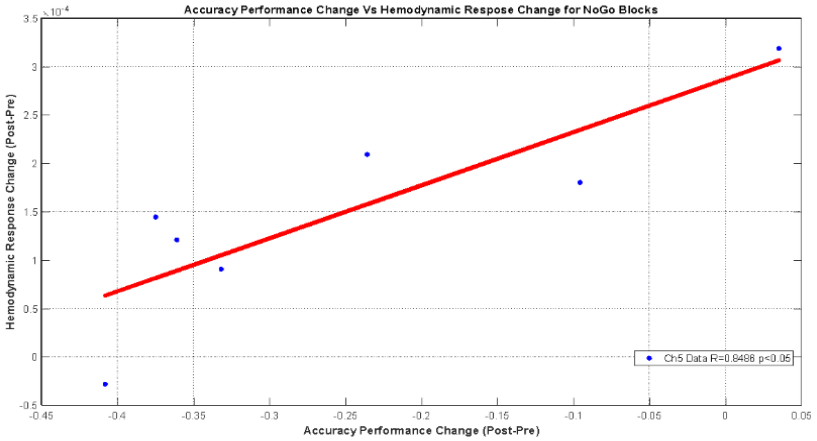


Figure 22. The scattered plot chart illustrates the correlation between hemodynamic responses observed at Channel 5 and the behavioral change in ACC calculated as the post–pre difference.

Table 8. Comparison of changes in CQ performance and changes in hemodynamic activation of channel 5 of all subjects. A statistically significant association was identified (R=0.98, p<0.03).

Subject Number	Change in Hemodynamic Parameter (Post DBS-Pre DBS)	Change in Cognitive Quotient (CQ) Performance (Post DBS- Pre DBS)
Subject 1	0.0001	-0.7
Subject 2	0.0002	-0.18
Subject 3	0.0001	-0.83
Subject 4	0.0001	-0.95
Subject 5	0	-1.34
Subject 6	0.0003	0.24
Subject 7	0.0002	-0.15
Correlation	0.96	
Significance (p value)	p<0.05	

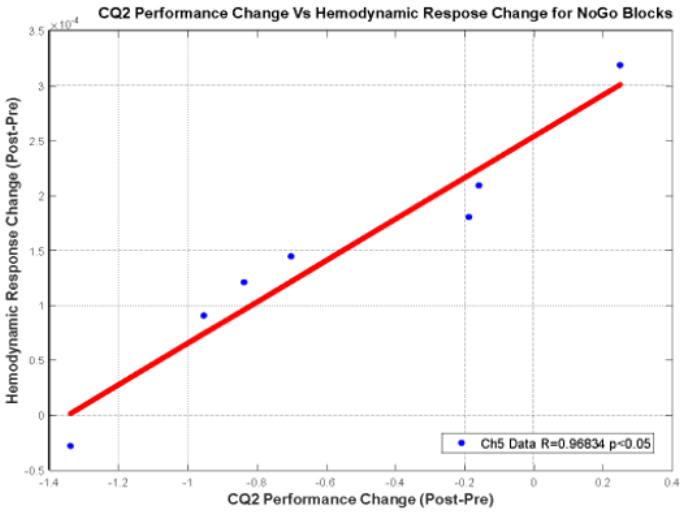


Figure 23. The scattered plot chart illustrates the correlation between hemodynamic responses observed at Channel 5 and the behavioral change in CQ calculated as the post–pre difference.

5 DISCUSSION

The increase of impulsive behaviours and impaired cognition can be explained by the spread of stimulation to adjacent regions. The posterior-dorsal-lateral STN is interconnected with a basal ganglia circuit devoted to motor functions (60). The main target of DBS for PD is the dorsolateral sensorimotor of STN, which is correlated with motor symptoms (61). Whereas the associative and limbic-related region is located in more anterior, ventral, and medial regions of the STN, which has an active role in stopping (60). The spread of stimulation through anterior and medial regions in STN, which is thought to delay decision-making and allow time for evidence accumulation, thereby facilitating more appropriate behavioral responses of the STN, might be impaired and affected (60). Although it is small in size, it can be subgrouped into regions such as limbic, sensorimotor, or cognitive through its functions. The benefit of STN stimulation for PD patients' cardinal motor features, such as impaired movement initiation, muscular stiffness, involuntary shaking, and compromised balance, is apparent; however, depending on the spread of stimulation, unwanted effects generally on cognition and impulsivity can be encountered (61).

A significant decrease in oxygenation with respect to baseline during processing of No-Go stimuli before surgery in two channels (channel 11 and channel 14) in BA10 and BA46 regions, which map bilateral DLPFC, bilateral anterior frontal, suggesting that the cerebrovascular reactivity for compensating the oxygen consumption was insufficient or impaired before the surgery. These PFC regions have a critical role in processing multitasking performance (62), cognitive tasks that involve response inhibition and impulsivity control, such as the GNG task (63). A significant decrease in oxygenation with respect to baseline, compensating for the oxygen consumption, was insufficient or impaired before the surgery.

After the DBS intervention, in post-operative measurements, significant deactivation concerning baseline occurred only in channel 10, corresponding to the right DLPFC area, BA10. Reduction may be attributed to insufficient oxygen supply, potentially

caused by increased oxygen consumption in the surrounding tissue, leading to an unmet local metabolic demand and inadequate perfusion in the ROI.

In three channels (channel 1, channel 3, and channel 5), there was a significantly increased activation in post-operative measurements compared to baseline, projecting frontopolar PFC, right DLPFC and medial frontal regions, the increased perfusion indicates a heightened oxygen demand, suggesting that the region was significantly more active during the task compared to baseline.

The comparison of pre and post-intervention analysis showed that no region demonstrated a decrease in hemodynamic activity after the intervention when compared to pre-task results. There were five channels (channel 1, channel 4, channel 5, channel 12, and channel 14) exhibiting a significant difference between pre and post-intervention. The observed increase between post-pre activation reflects heightened perfusion requirements in these areas, likely associated with increased cognitive load and metabolic demand. The response-selection and response-inhibition functions are critical in cognitive flexibility. The demand for oxygen in these regions is highly connected to the performance of tasks such as GNG. These regions were associated with motor execution preparation and cognitive control-executive function. The regions that showed significant difference were frontopolar PFC, medial superior frontal region, and DLPFC, which have been implicated in the execution of advanced cognitive functions, including inhibitory processing, reasoning, multitasking, planning for future-oriented behavior, response inhibition, working memory, attention, and decision making (64-66). The regions that project to BA9, BA10, and BA46 function similarly, and a healthy functioning individual shows easy switch between multiple tasks, considering options, high attention in goal-directed behaviours, delayed, inhibited, and accurate responding (67).

In this study, the analysis also shows that the hemodynamic activity in Channel 5 is highly correlated with the behavioral metrics. The region of channel 5 projects to the mPFC, covered by mostly BA9, which is linked with reward and short-term memory (68). Impulsivity typically emerges during reward-related tasks. The mPFC

is the brain region which critically involved in reward processing and considered highly relevant in the analysis of impulsivity, was identified in this study as the area where behavioral performance and hemodynamic activation were significantly correlated. This region is linked with a high level of cognitive control, decision making and planning, social cognition, and self-awareness. In most studies, this region is analysed with DLPFC for impulsivity and cognitive control.

The involvement of these regions, primarily within BA9, 10, and 46, reflects their integral role in cognitive control, motor inhibition, and goal-directed behavior, which are core demands of the GNG paradigm. The shared functional role of these regions, and the reason they are frequently selected as regions of interest (ROIs) in cognitive assessment studies, lies in their responsibility for critical executive functions such as cognitive control, response inhibition, task switching, and decision making, all of which are essential for evaluating an individual's cognitive capacity. Furthermore, during the observation of their performance, fundamental neurovascular indicators such as oxygenation and perfusion demand serve as key markers that are both sensitive and discriminative in task-based assessments.

This finding suggests that cerebral hemodynamics directly influence cognitive performance. Regions with increased perfusion are thought to reflect higher levels of activation. In this study, despite the observed increase in hemodynamic activity, patients exhibited greater cognitive fatigue and a higher tendency toward impulsive behavior compared to pre-operative levels. While hemodynamic blood flow increased compared to pre-op data, a decline in behavioral performance was detected. This indicates that, compared to pre-op data, the brain exerted more effort, which leads to neural efficiency, meaning the cost of performing the same task was higher, yet it still resulted in decreased test performance.

High cognitive performance is typically associated with adequate oxygenation in active brain regions. A decline in cognitive performance is expected when the oxygen demand of these regions is not sufficiently met. During task execution, cognitive load leads to an increased need for oxygen supply in the relevant brain areas. In this study,

a decrease in task performance was observed when comparing pre and post-operative assessments, highlighting this dynamic.

Neural efficiency tells us that brighter individuals invest less effort in the same task than individuals with less cognitive ability (69). In the literature, some studies tell us that intelligent individuals have less response time compared to individuals with lower intelligence quotient (IQ) levels. Besides, the significant detail here is the ACC of the response. People with higher and flexible cognitive functions are observed to have higher ACC and response time together in studies (69). Moreover, in the literature, it is explained that neural efficiency was primarily observed in the frontal cortex during less demanding cognitive tasks. As task complexity increased, cortical activation broadened, indicating higher resource utilization, a need for more nutrients, differing from the others in terms of brain operation and cognitive ability (70). A rapid response latency coupled with high response ACC is indicative of intact and advanced cognitive processing. In contrast, reduced response latency in the presence of diminished ACC may reflect impulsive behavior, rather than efficient cognitive control. Even if the comparison results of RTs were not significant, it is also observed that there is a decline in RT accompanied by a significant task ACC difference.
Notably, although cerebral perfusion increased, patients showed a higher propensity for incorrect responses rather than demonstrating appropriate cognitive flexibility and accurate analysis of the task. This suggests that STN stimulation following DBS surgery may contribute to cognitive strain and difficulties in behavioral adaptation. Consequently, the findings indicate that the negative impact of DBS on cognition, impulsivity, and behavioral performance via STN stimulation can be seen as increased hemodynamic activity caused by more oxygen needed for the same task than before, showing increased cognitive load.

Cognitive and impulsive outcomes following STN-DBS have been investigated in the literature in previous studies. However, the underlying neurophysiological mechanisms and postoperative cortical effects remain insufficiently understood. This study aimed to evaluate the impact of DBS in terms of cognition and impulsivity and

its cortical correlates using fNIRS, which provides objective, neurophysiologically grounded measurements beyond behavioral interpretation alone.

Unlike traditional behavioral assessments, the use of fNIRS allows for the monitoring of hemodynamic changes within prefrontal cortical areas, offering a more concrete understanding of the cognitive alterations associated with DBS. Identifying and analyzing the brain regions where hemodynamic activation and cognitive test outcomes are correlated has provided critical insights into the specific neural substrates associated with task success and impulsive responses.

Although STN-DBS has demonstrated efficacy in alleviating motor-related symptoms and overall quality of life in PD by regulating the overactivity of STN, it has also been associated with neuropsychiatric side effects, including increased impulsivity. Prior findings indicate that STN-DBS may lead to faster response times, increased action impulsivity, and reduced response ACC. In this study, a significant decrease in ACC and CQ has been observed, correlated with specific regions of the frontal cortex, which are responsible for impulsivity and decision making, also leading to cognitive flexibility.

6 CONCLUSION

As a slowly advancing neurodegenerative disorder, PD principally impacts the regulation and execution of voluntary movements due to the degeneration of DA. This study provides preliminary evidence that DBS is effective in improving motor symptoms in PD, but it may also be associated with changes in impulsivity-related cognitive functions. By integrating behavioral assessments with hemodynamic monitoring of the PFC via functional neuroimaging, the research offers a more quantitative and neurophysiological perspective on post-DBS cognitive alterations.

A significant decline in test performance was observed despite the increased perfusion, indicating a possible decrease in cognitive efficiency. These results suggest that STN-DBS may alter the balance between neural activation and behavioral output, particularly in domains related to response inhibition, working memory, and executive control.

The observed divergence between neural activation and behavioral performance underlines the importance of considering both behavioral and neurophysiological markers in evaluating post-DBS cognitive outcomes. These insights may contribute to more informed patient selection, better risk-benefit evaluation, and the development of predictive biomarkers to guide future neurosurgical interventions.

This study has further highlighted the importance of stimulation site selection in the context of patient-centered evaluation of postoperative side effects. If cognitive or behavioral side effects, such as increased impulsivity, are a major concern, alternative targets such as the GPi may warrant consideration. However, if substantial medication reduction remains a primary therapeutic goal, bilateral STN-DBS may still be considered the preferred option (36).

As mentioned previously, consistent with the existing literature, via the hyperdirect pathway, interactions with low-frequency between cortical areas and

anterior and ventromedial STN facilitate cognitive control (46). Post-stimulation alterations in the STN–PFC circuitry manifested as behavioral impairments, particularly in response inhibition and decision-making tasks. Also, mPFC-STN connectivity is thought to play a role in error-related feedback in tasks (59). These findings underscore the critical role of target site selection in DBS procedures and support the importance of a patient-centered approach to evaluating potential postoperative side effects. The findings, consistent with prior studies in the literature, demonstrate a predominance of increased activation in the DLPFC and medial frontal regions, its involvement in executive control, especially in the left hemisphere, further supporting its critical role in cognitive control processes affected by STN-DBS.

Given these implications, criteria such as accurate patient selection, post-operative caring, considering different targets, stimulation parameters (unilateral/bilateral), and various therapeutic approaches, and choosing the best timing are also critical for DBS operation (71)(72). By integrating behavioral outcomes with cortical hemodynamic markers, this study may help guide future clinical decision-making. In this present work, we aimed to explore the biomarkers of impulsivity that could aid neurologists and neurosurgeons in predicting the outcomes while selecting the DBS candidates and anticipating possible cognitive side effects. Ultimately, the findings of this study underscore the importance of integrating both neurophysiological and behavioral markers when guiding future patient selection and tailoring personalized DBS interventions. To maximize the therapeutic benefits of DBS, it is also essential to optimize stimulation parameters and accurately identify the target regions through advanced neuroimaging techniques, as these factors are critical for enhancing efficacy and minimizing potential side effects.

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8 APPENDIX

9 CURRICULUM VITAE