Title
Evaluating target-specific pre-to-post DBS effects on brain function in Parkinson's disease using fMRI

Author
Vu, Katelyn

Publication Date
2023

Peer reviewed|Thesis/dissertation

Evaluating target-specific pre-to-post DBS effects on brain function in Parkinson's disease using fMRI

by
KATELYN VU

THESIS
Submitted in partial satisfaction of the requirements for degree of
MASTER OF SCIENCE

in

Biomedical Imaging

in the

GRADUATE DIVISION
of the
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Approved:

DocuSigned by:
Melanie Morrison
96FD0E65F33D4D9...

Melanie Morrison
Chair

DocuSigned by:
Ashish Raj
[illegible]4E0...

Ashish Raj

DocuSigned by:
Olga Tymofiyeva
[illegible]476...

Olga Tymofiyeva

DocuSigned by:
Ian Bledsoe
91CA3779276A40E...

Ian Bledsoe

Committee Members

Dedications and Acknowledgements

I dedicate this thesis to my unwavering source of inspiration, my parents, who's boundless love, and encouragement have propelled me forward every step of the way. Your belief in my potential has been the cornerstone of my journey.

I am profoundly grateful to my advisor, Dr. Melanie Morrison for her exceptional mentorship, guidance, and unyielding commitment to fostering my academic growth. Your expertise and patience have been pivotal in shaping the trajectory of my research.

I extend my heartfelt appreciation to my distinguished committee members: Dr. Olga Tymofiyeva, Dr. Raj Ashish, and Dr. Ian Bledsoe. Your insightful feedback and guidance have enriched this study and broadened my perspectives.

To the faculty members and my classmates of the MSBI program, I express my gratitude for imparting your knowledge and nurturing my intellectual curiosity. Your dedication to excellence has been instrumental in shaping my academic journey.

Evaluating target-specific pre-to-post DBS effects on brain function in Parkinson's disease using fMRI

Katelyn Vu

Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting both motor and non-motor neural circuits. Common frontline treatment includes dopamine agonists, but long-term levodopa use can cause dyskinesias and lower quality of life. Deep brain stimulation (DBS) is a second-line therapy to treat motor symptoms caused by movement disorders. Overall, the project aimed to better understand how DBS affects brain networks to improve patient outcomes. The repeatability of resting state functional magnetic resonance imaging (rs-fMRI) data was evaluated in patients with DBS and stimulation-induced longitudinal and immediate changes in brain activity and connectivity were related to symptom improvement. It was hypothesized that functional connectivity (FC) and variability would decrease with sub-thalamic nucleus (STN) or globus pallidus (GPi) DBS over time, and that these changes would be associated with symptom improvement. The two oldest patients with the highest MDS-UPDRS raw scores exhibited superior repeatability, while those with the worst MDS-UPDRS raw scores displayed lower repeatability. The Wilcoxon sign rank test's rejection of the null hypothesis suggested challenges in achieving group-level repeatability due to motion artifacts. Adjusting degrees of freedom may mitigate this issue. The study found a decrease in connectivity within thalamic regions, supplementary motor area and cerebellum Crus I and Crus II from pre-op to post-op, indicating neuroplastic changes in the brain. The variability metrics examined the

brain's network adaptability, with an overall decrease in variability in the post-op DBS off and on conditions.

Table of Contents

List of Figures

List of Tables

List of Abbreviations

all post-op DBS off1 ..... all patients' post-operative DBS off 1st scans

all post-op DBS off2 ..... all patients' post-operative DBS off 2nd scans

all post-op DBS on1 ..... all patients' post-operative DBS on 1st scans

all post-op DBS on2 ..... all patients' post-operative DBS on 2nd scans

BOLD ..... blood-oxygen-level dependent

DBS ..... Deep Brain Stimulation

FC ..... Functional Connectivity

fMRI ..... functional magnetic resonance imaging

GPi ..... Globus Pallidus Internus

GRE ..... Gradient Echo

MDS-UPDRS ..... Movement Disorder Society-Unified PD Rating Scale

PD ..... Parkinson's Disease

post-op DBS off ..... post-op DBS off1 and off2 averaged

post-op DBS off1 ..... post-operative DBS is turned off in the first scan

post-op DBS off2 ..... post-operative DBS is turned off in the second scan

post-op DBS on ..... post-op DBS on1 and on2 averaged

post-op DBS on1 ..... post-operative DBS is turned on in the first scan

post-op DBS on2 ..... post-operative DBS is turned on in the second scan

post-op ..... post-operative

rs-fMRI ..... resting state functional magnetic resonance imaging

STN ..... Sub-thalamic Nucleus

1. INTRODUCTION

Parkinson's disease (PD) is a progressive movement and neurodegenerative disorder affecting both motor and non-motor neural circuits. After Alzheimer's disease, PD is the most prevalent neurodegenerative condition. The onset of PD normally occurs in patients between the ages of 55 and 65, with approximately 90,000 Americans being diagnosed every year. However, due to the chronic and progressive nature of the disease, misdiagnoses or underdiagnoses can occur, thus the actual number of patients with PD is likely much higher [1].

The common frontline treatment for patients with PD usually includes dopaminergic medications, which can reduce motor fluctuations in patients, and increasingly levodopa is used early in the disease course[2]. Unfortunately, long-term levodopa use can cause dyskinesia and may be associated with other adverse effects at higher doses, including levodopa associated psychosis or orthostatic hypotension[3]. In the context of levodopa-associated adverse effects, deep brain stimulation (DBS) may be considered as an adjunctive treatment.

DBS is an invasive neuromodulation therapy used to treat motor symptoms caused by movement disorders such as PD by implanting electrodes in deep gray matter nuclei and delivering electric impulses to disrupt abnormal brain circuits and restore function. When successful, DBS can reduce daily fluctuations in motor symptoms including tremor, stiffness, and slowness[4]. However, because the mechanisms of DBS are not well understood, clinicians encounter challenges in identifying and refining therapeutic adjustments that could otherwise optimize patient

responses. This project aimed to better understand how DBS affects networks in the brain to further improve patient outcomes which are currently variable.

Our study 1) evaluated the repeatability of resting state functional magnetic resonance imaging (rs-fMRI) scans in patients with DBS while stimulation was turned on versus off and 2) identified the longitudinal and immediate effects of DBS on brain activity and connectivity in relation to symptom improvement. Repeatability is crucial in research, particularly in DBS. Quantifying repeatability will help neural network change assessments, distinguish the changes by therapeutic effects from measurement variability, identify patterns, aid in refining protocols, and tailor treatments to optimize the therapeutic outcomes. Gaining insight into functional network changes caused by DBS in PD patients can enhance our comprehension of the underlying mechanisms leading to symptom improvement. This knowledge, in turn, can guide clinicians in optimizing treatment approaches for future patients.

This has been one of the first investigations of rs-fMRI repeatability while the DBS device is implanted. Repeatability is crucial in research, particularly in DBS. Quantifying repeatability will help neural network change assessments, distinguish the changes by therapeutic effects from measurement variability, identify patterns, aid in refining protocols, and tailor treatments to optimize the therapeutic outcomes. We examined across multiple rs-fMRI scans the repeatability in the strength and synchrony of motor regions activated for two conditions 1) when DBS is off and 2) when DBS is on. The repeatability of the rs-fMRI scans will be evaluated for each patient and at the group level. It was hypothesized that rs-fMRI metrics calculated from scans acquired in the same imaging session would show correlation.

To understand the functional network changes brought on by DBS over time that contribute to variations in patient symptom improvement, we will compare pre-DBS imaging with 1) post-DBS imaging when DBS is on, and 2) post-DBS imaging when DBS is off. We expect to see functional connectivity (FC) between the sensorimotor motor cortices and thalamus, and between the sensorimotor motor cortices and cerebellum as these regions have been shown to be dysfunctional and hyperactive in PD patients[5]. We also expect to see decreased with sub-thalamic nucleus (STN) or globus pallidus (GPi) DBS over time and that the changes in the brain regions affected by DBS will be associated with symptom improvement[6]. This will be done by relating functional connectomes with clinical scores describing patients' symptom improvement with DBS, measured via the Movement Disorder Society-Unified PD Rating Scale (MDS-UPDRS)[7].

2. BACKGROUND

2.1 Parkinson's Disease

PD is a neurodegenerative disorder without a known cause but can be attributed to genetic and environmental factors such as pesticides[8]. This movement disorder is characterized by the loss of dopaminergic neurons, which produce dopamine in the substantia nigra of the basal ganglia, and the accumulation of misfolded Lewy bodies in the substantia nigra[3]. The substantia nigra is part of the basal ganglia, which is part of a group of brain structures that coordinate voluntary movement, reward functions and cognitive planning. In the classical rate model, the direct and indirect pathways of communication between the basal ganglia and cortex via the thalamus and striatum are under or overactive in PD, which leads to an increase in basal ganglia firing rates[9,10].

The four main motor symptoms that manifest as a result of this increase in firing rates, include resting tremors, rigidity, bradykinesia, and postural instability[8,11].

To remedy the loss of dopamine, dopamine agonists or levodopa treatments are used to reduce symptoms of involuntary motor fluctuations in patients. Given that levodopa can cause dyskinesia, dopamine agonists are sometimes used as the first line of therapy; however, because i f motor fluctuations and dyskinesia that sometimes become problematic after 5-10 years of PD, DBS can be combined with dopaminergic medications to address symptoms caused by prolonged use of dopaminergic medications and PD progression[3].

2.2 DBS Implant

DBS was first approved for PD in 2002 and has had remarkable success, leading to its rapid adoption to treat other neurological and psychiatric conditions. To date, over 230,000 patients world-wide have undergone DBS, and more than 12,000 more patients receive this surgery every year[12]. The DBS implant consists of three main components: electrode leads, extension cables, and the programmable neurostimulator, also called the pulse generator (Figure 1). The electrode leads are thin wires with multiple contact points that are surgically implanted into specific regions of the brain. The neurostimulator is placed under the skin in the chest region and delivers electrical impulses to the basal ganglia target via uni- or bi-lateral electrodes (Figure 1).

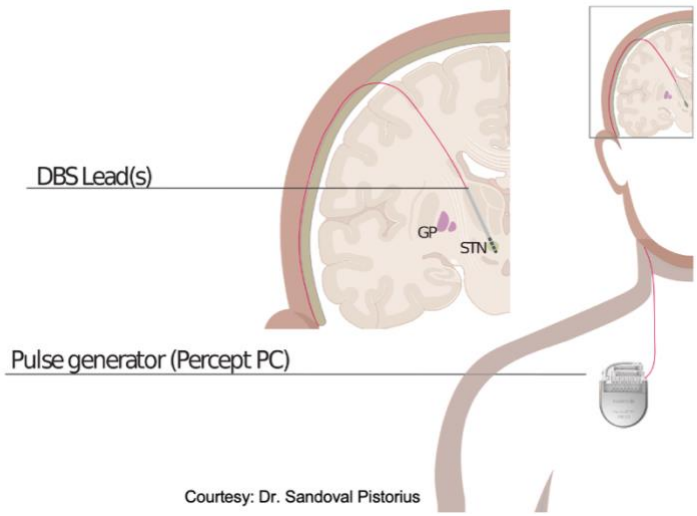

Figure 1: The DBS implant. The STN and GPi are current targets for Parkinson's Disease.

Approximately one-month after surgery, patients undergo device programming with a neurologist. This programming is done in a trial-and-error fashion and can go on for up to 6 months. The leads can be set into the monopolar or bipolar configuration. The monopolar configuration consists of the lead acting as the anode and the neurostimulator acting as the cathode, whereas the bipolar configuration has both the cathode and anode on the lead (Figure 2). Although it has been found that configurations have comparable effects on tremor suppression, most patients will have sufficient symptom improvement with the monopolar configuration[13]. It is noted that the monopolar configuration can reach a larger area than the bipolar configuration—which can cause the current to spread to unwanted areas[13].

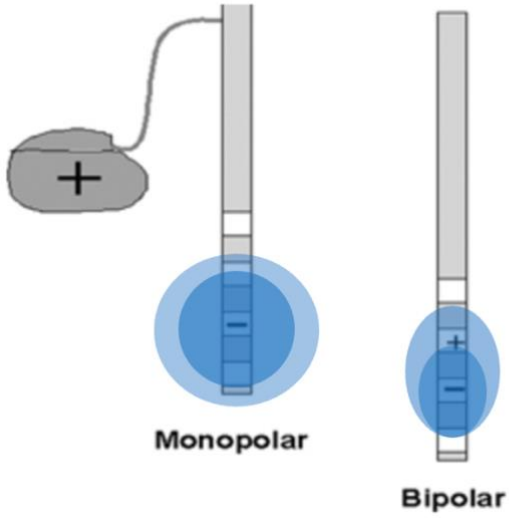

Figure 2: Configurations for Stimulation in the Leads. The monopolar configuration has the lead contact acting as the cathode (negative terminal) and the neurostimulator acting as the anode (positive terminal). The bipolar configuration both the anode and cathode are on the DBS lead. Adapted from Montogmery, 2009 [14].

The benefits of DBS combine with medications as therapy for PD has shown far more improvement for controlling the motor symptoms and dyskinesis than medications alone[15]. DBS has also been noted to have benefits that last over 10 years. Although DBS as a treatment for PD has seen success, the mechanisms of DBS modulation including its potential neuroplastic effects on brain networks leading to target-specific differences in outcome, is still unclear. It is presumed that the electrical pulses sent into the neurons in the target areas block the depolarization, thus disrupting the neurons connectivity network. However, the effects of DBS extend to neurotransmitters from neurons that are further away from the electrodes, indicating that DBS may work through multiple mechanisms[16].

DBS is implanted in the STN & GPi (Figure 1) as the preferred targets for treatment of PD, as approved by the Food and Drug Administration. Both the STN and GPi are effective targets in PD treatment to address the four main motor symptoms of

PD; several studies have found that there was no statistical difference in the degree of tremor suppression between the STN and GPi[16]. However, more verbal fluency impairments, stimulation induced dyskinesia and task-dependent cognitive side effects have been reported with STN-DBS, but a greater reduction in medication dosage is typically seen with STN-DBS compared to GPi-DBS[16,17]. Therefore, the GPi is typically selected for when risk for cognitive worsening is high and STN is favored in patients with higher medication dosage in hopes of decreasing patient dosage after the surgery[15].

In addition to individual patient differences, because target-specific DBS mechanisms are still not fully understood, there remains significant variability in patient response to treatment. Developing a better understanding of these mechanisms and their relationship to target-specific patient outcomes will help improve the DBS strategy for patients and clinicians by identifying biomarkers that can be used to aid candidate and brain target selection and guide device programming.

2.3 Functional MRI

Functional MRI (fMRI) is a promising imaging tool that can be used to study long-term neuroplastic changes in FC across the entire brain before versus after DBS implantation. The technique can non-invasively, but indirectly, measure the brain's response to DBS in real time by measuring the blood-oxygen-level dependent (BOLD) signal while the patient performing a task, exposed to a stimuli or at rest, but not sleeping[18].

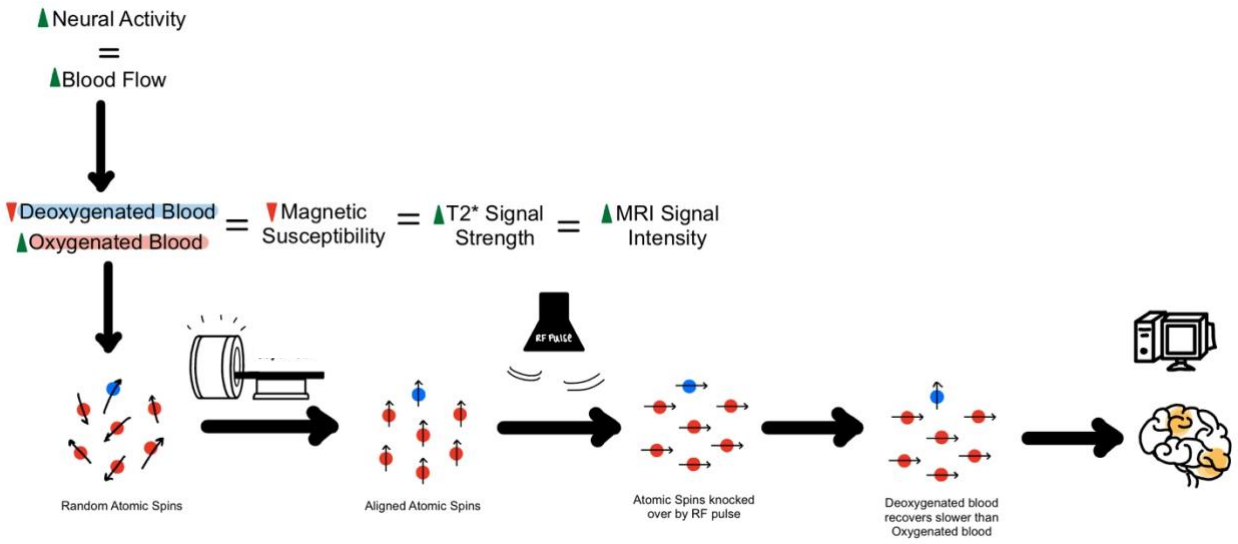

Figure 3: How the BOLD signal can be derived from fMRI. BOLD signal is created with an increase in neural activity which causes the blood to decrease in magnetic susceptibility to create a stronger signal. The fMRI aligns the atomic spins of the blood, and an RF pulse knocks the spins over and due to the nature of oxygenated blood, it will recover slower than deoxygenated blood creating a stronger signal.

Brain activation can be estimated using neurovascular coupling, where brain blood flow is coupled with blood oxygenation in areas of activation[18]. To measure this the powerful magnet in the MRI aligns the atom's spin to point in the same direction. The deoxyhemoglobin is paramagnetic and causes a localized change in brain blood flow which can be detected using fMRI T2* weighted gradient echo (GRE) sequence (Figure 3)[18]. The T2* weighted imaging is used because the T2* is affected by the changes in the local ratio of deoxyhemoglobin to oxyhemoglobin. A GRE sequence has a radiofrequency pulse and a gradient reversal, which helps to refocus the spins that were dephased by the initial pulse and highlight T2* image contrast[19,20]. The radiofrequency pulse changes the direction of the spins uniformly and as time passes, the oxygenated blood will recover to the aligned direction before the deoxyhemoglobin. This ratio is used to determine the BOLD signal, which is stronger in areas of brain activation because activation requires more oxygen[21].

Functional MRI studies involve imaging the subjects either while performing a task or being exposed to a stimulus—called task-based fMRI—or while the patient is at rest—called resting state fMRI. Task-based fMRI studies are often used to identify brain regions that are functionally active and involved in a specific task, whereas a rs-fMRI study is typically used to investigate intrinsically connected functional activity in brain networks and regions[22]. Given the characteristics of Parkinson's disease, task-based fMRI can prove overly demanding, heightening the risk of motion artifacts. In contrast, resting-state fMRI captures simultaneous spontaneous neural activity fluctuations during rest, while task-based fMRI concentrates solely on brain networks engaged in the specific task[23,24].

2.4 fMRI to evaluate DBS Mechanisms

MRI is commonly used in clinical practice and more broadly for diagnostics and neuroscience research, however, using fMRI to study patients with DBS implants is an emerging area of investigation. Recent improvements in DBS hardware have made imaging with fMRI possible. Currently the only DBS neurostimulation device that is approved by the Food and Drug Administration for use in 3T imaging while the device is turned on and actively stimulating is the "Percept™ PC" (B35200) DBS device by Medtronic[25].

To perform whole brain fMRI in DBS patients, it is imperative that heating is minimized as to not damage the electrodes or harm the patient. Patients DBS device must be 1) programmed into a special configuration that is equivalent to their clinical therapeutic settings, and 2) checked for an open or short circuit. The patients can also

only be actively scanned for 30 minutes in a 90-minute scanning window to reduce electromagnetic interference and lower heating effects[2].

There have been less than 45 fMRI studies where DBS is active during scanning, as only recent technological advancement has allowed for it[26]. Previous fMRI studies in patients with PD being treated with DBS found there is increased FC between the sensorimotor motor cortices, thalamus and cerebellum with the STN and GPi DBS that is associated with the improvement of motor symptoms associated with PD[6,26].

Currently the test-retest reliability of fMRI data remains a persistent challenge in the field. Furthermore, there is a lack of studies dedicated to analyzing the neuroplastic changes induced by DBS in the brain and their correlation with variations in treatment outcomes[27]. To address current needs for improved understanding of DBS mechanisms, this project will first assess the reliability of fMRI for studying DBS effects, then evaluate DBS effects on brain connectivity and activity in relation to symptoms.

2.5 Clinical relevance of the work

The investigation into the repeatability of fMRI scans in patients undergoing DBS and the exploration of neuroplastic changes induced by DBS in PD patients holds significance and has many implications. This investigation can extend its benefits beyond PD patients. The outcomes from this work can be translated to other DBS patient populations, such as those with essential tremor or dystonia, thereby expanding the clinical applicability of the findings. Moreover, the investigation of repeatability of fMRI scans has implications that can resonate across the entire fMRI community, contributing to the establishment of robust methodologies and enhancing the credibility of functional neuroimaging studies. At an individual patient level, the insights from this

research could directly influence patient care, potentially uncovering novel facets of neuroplasticity that can help optimize DBS therapy for improved clinical outcomes.

3. METHODS

3.1 Subjects:

This study recruited volunteers who were diagnosed with PD and have undergone DBS through UCSF's Neurology department. All volunteers were provided with written informed consent prior to participating, as approved by the UCSF institutional review board. Patients were selected for if they had or would be receiving the internal pulse generator "Percept^{TM} PC" (B35200) DBS device by Medtronic, as it is the only generator that has been approved by the FDA to be used in 3T fMRI scans while it is on. Table 1 contains the patient demographics regarding age, gender, year of PD diagnosis, DBS target (STN (n=7) or GPi (n=9)), the number of leads, and whether pre-operative (pre-op) and post-operative (post-op) fMRI & MDS-UPDRS data collected (n=6). All patients (n=16) had post-op fMRI and MDS-UPDRS data collected.

Table 1: Cross-sectional Patient Characteristics

Characteristic	Subject Proportions		
	$N_{pre\text{-}op}$=6	$N_{post\text{-}op\ DBS\ off}$ =16	$N_{post\text{-}op\ DBS\ on}$= 16
Age, mean(range)	59.26 (50.26-68.44)	64.87 (50.26-76.36)	64.87 (50.26-76.36)
Male, (%)	83.33	81.25	81.25
Race/Ethnicity, (%)	-	-	-
White	100	93.75	93.75
Other	-	6.25	6.25
Years with Diagnosis, mean (range)	7 (4-9)	8.53 (4-18)	8.53 (4-18)
STN targets	3	7	7
GPi targets	3	9	9
Bilateral Leads	6	14	14
Unilateral Leads	-	2	2

3.2 Data Collection

In this study the MDS-UPDRS clinical motor assessment scores (while DBS is off and on) and fMRI scans were collected during the clinical patient visit to UCSF prior DBS surgery (no DBS implant; n=6) and after DBS surgery (while DBS is off and on; n=16). During each visit to the UCSF facilities patients first underwent the MDS-UPDRS exam and received multiple fMRI scans. Figure 3 provides an overview of the entire workflow for each study visit which is elaborated on further in sections 3.2.1-3.2.2.

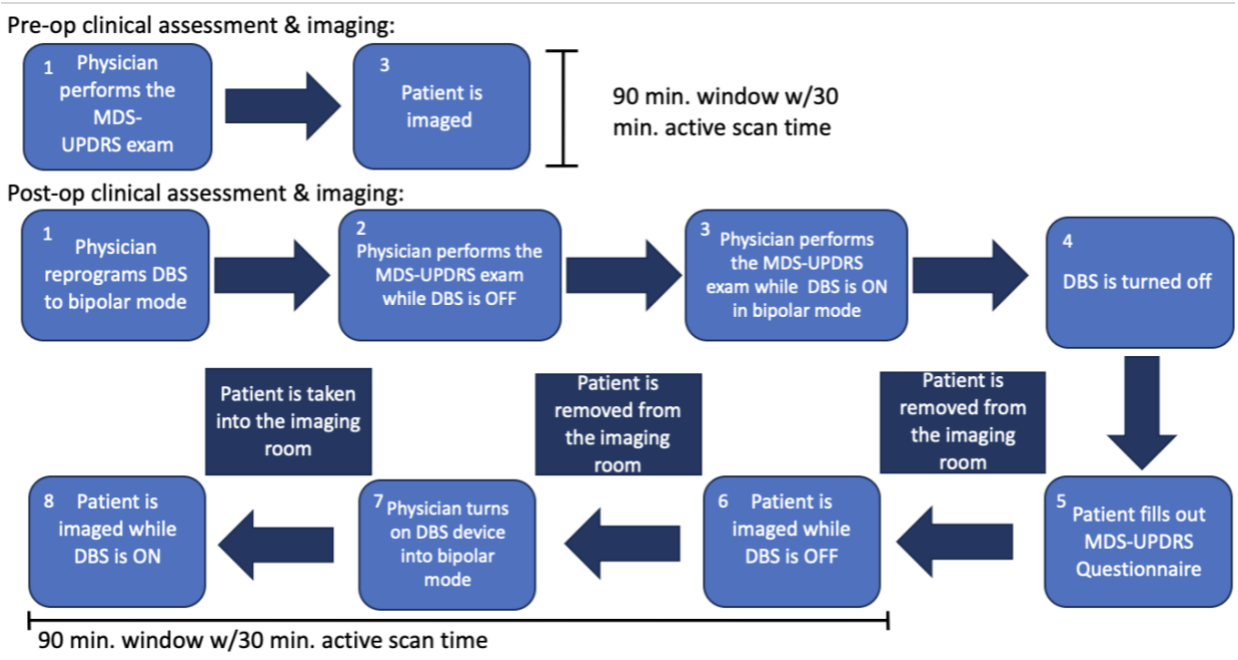

Figure 4: Study Workflow. The clinician administers the MDS-UPDRS exam, administers a questionnaire, and takes patients to the imaging room for scans. If it is a post-op visit, the clinician also reconfigures the patient into bipolar settings, administers the MDS-UPDRS exam with DBS off and DBS on in bipolar mode, then images the patient with DBS off, turns on the device into bipolar mode, and patient is scanned with DBS on.

3.2.1 Clinical Motor Testing and Bipolar Programming

During both pre-op and post-op patient visits, a comprehensive evaluation utilizing the MDS-UPDRS is conducted prior to the commencement of imaging

sessions. MDS-UPDRS scores collected for patients prior to surgery were performed in a virtual clinical visit, therefore the sections that assess motor skills was MDS-UPDRS sections were not performed—specifically the patient's rigidity and postural stability. To ensure a matched comparison, the post-op MDS-UPDRS total scores were calculated in the same way.

The MDS-UPDRS is a validated tool utilized for the comprehensive evaluation of motor and non-motor symptoms in PD patients, encompassing four distinct sections: 1) Non-motor Experiences of Daily Living, 2) Motor Experiences of Daily Living, 3) Motor Examination, and 4) Motor Complications. The assessment involves scoring individual and aggregated sections, with each component involving clinician-assessed behaviors and a questionnaire. Section 1 involves clinician-assessed behaviors, while Section 2 includes a questionnaire. In Section 3, patients replicate movements demonstrated by the clinician, and rates severity of motor complications. This scale helps elucidate a patient's symptoms and enhances patient care.

During the pre-op visit, the clinician conducted the MDS-UPDRS examination twice: once before the patient took their PD medication and once after, which was done to determine if they are at least a 33% decrease in MDS-UPDRS score to qualify for DBS[28]. In the post-op visit, the MDS-UPDRS examination was administered twice by the clinician once with DBS turned off and subsequently with DBS activated using bipolar settings. The device was then converted into a bipolar setting to minimize heating in the brain while being actively scanned the electrical current is confined between the two contacts that are adjacent, which minimizes current spread and the associated electrical field in comparison to the monopolar configuration[2]. Before the

fMRI acquisition, DBS was temporarily deactivated, and then the patient was instructed to complete the questionnaire component of the MDS-UPDRS examination 30 minutes prior to the imaging session.

3.2.2 Imaging Protocol

The pre-op fMRI scans were part of standard of care, with only one fMRI scan acquired pre-operatively. In the post-op scanning session, two T2* weighted fMRI scans where the patients' DBS device was turned off was imaged first (post-op DBS off1 & post-op DBS off2) (Figure 4).

MRI was performed on the 3T General Electric horizontal cylindrical system with H-imaging, at 128 MHz. The whole body transmit coil, and 8 or 32 channel receive coil was used. To minimize heating of the DBS leads and prevent patient injury, the RF power was lowered (B1+rms $\leq$ 2.5mT, SAR $\leq$ 1.0 W/kg), gradient strength and the spatial field gradient were adjusted (max slew rate = 200 T/m/s, SG_{MAX} = 20 T/m). The post-op scan protocol included a T1 weighted anatomical scan first followed by the T2* weighted fMRI scans acquired using an interleaved, GRE-EPI sequence with 168 time points, repetition time of 2.15s, echo time of 29ms, flip angle=84^{o}, voxel size of 3.75 mm x 3.75mm in plane, 4mm slice thickness, and 23cm FOV.

Prior to the initiation of the scans to ensure subject safety patients were asked to fill in and sign an MRI screening form before imaging sessions, review exam details, and verify implant location, serial number, and ID card accuracy. They were also asked about past falls, physical trauma, DBS revision surgery, or major changes. The body temperature was monitored to ensure it was below 100^{0}F, and no open or short circuits

were found. Patients were instructed to communicate with technicians, remain still, and not sleep. They were not provided with blankets for warmth to prevent extra heating.

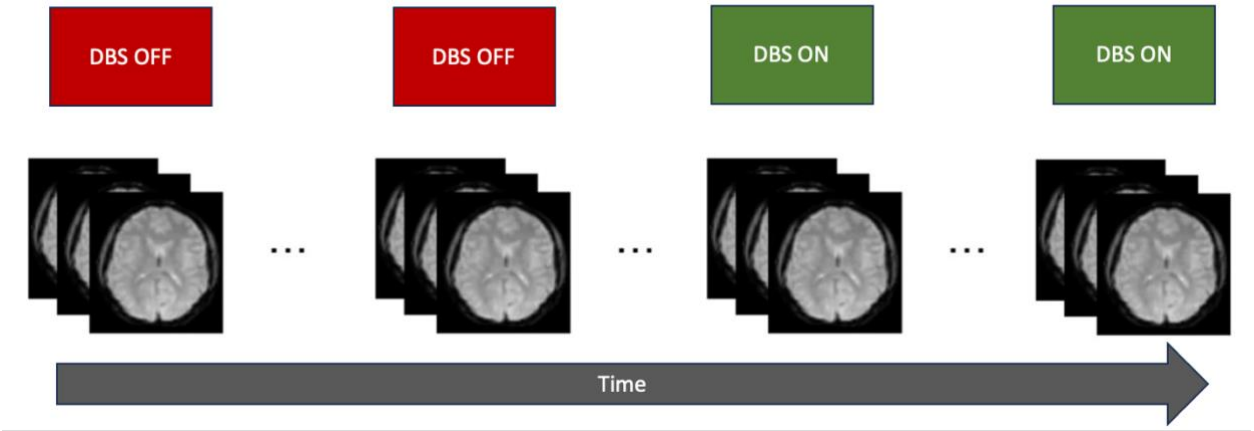

Figure 5: Post-op DBS fMRI Paradigm. During the post-op DBS imaging session, the patient is first scanned twice with DBS off and then scanned twice with DBS on. Duplicate scans were gathered for each post-DBS condition for a total of 4 scans: 1) post-op DBS 1st off scan (post-op DBS off1), 2) post-op DBS 2nd off scan (post-op DBS off2), 3) post-op DBS 1st on scan (post-op DBS on1), and 4) post-op DBS 2nd on scan (post-op DBS on2) for each patient (N=16) during the same fMRI session to assess the repeatability of resting-state fMRI data when there is a DBS implant in the brain.

Following the completion of the first two scans in the protocol, the patient was removed from the scanner room by detaching the bed from the MRI for the clinician to program the DBS device into the bipolar therapy setting that was determined by the clinician prior to the scanning session to be most like the patient's daily monopolar therapy settings. The patient was then scanned again while the device was turned on (post-op DBS on1, post-op DBS on2) (Figure 4). The active scan time was limited to 30 minutes during the 90-minute scan window.

3.3 fMRI Preprocessing and Parameter Quantification

To minimize sources of variance across the dataset, CONN was used to remove any motion artifacts and denoise the datasets[29]. All of the MRI data obtained underwent preprocessing in MATLAB using the CONN toolbox, encompassing correction for

distortion, motion, and slice timing, along with spatial smoothing and temporal filtering[29]. The preprocessing pipeline began by removing the first couple nonsteady-state volumes from each fMRI data set. The images were realigned to rectify any potential patient motion during the scans, and precise coordinates were assigned to the newly corrected image. To account for inter-slice differences in acquisition time, a correction procedure was applied. Then outlier detection was conducted using ART-based identification of outlier scans for scrubbing. The entire brain was segmented, and MNI-space normalization was applied, and then it was labeled with coordinates for precision in brain region identification. The atlases used to segment the brain were the default CONN atlas and a longitudinal deep gray matter atlas created from quantitative susceptibility mapping data were the two MNI[30]. Finally, the data undergoes normalization, facilitating the application of spatial convolution and Gaussian kernel smoothing.

3.3.1 Connectome Generation & fMRI Variability Calculation

For each patient's pre-op and/or post-op (DBS off & DBS on) pre-processed data, FC connectomes and network variability metrics (standard deviation of signal; thought to reflect brain network adaptability) were generated at two scales 1) within the sensorimotor network and 2) across the whole brain (Figure 5)[31].

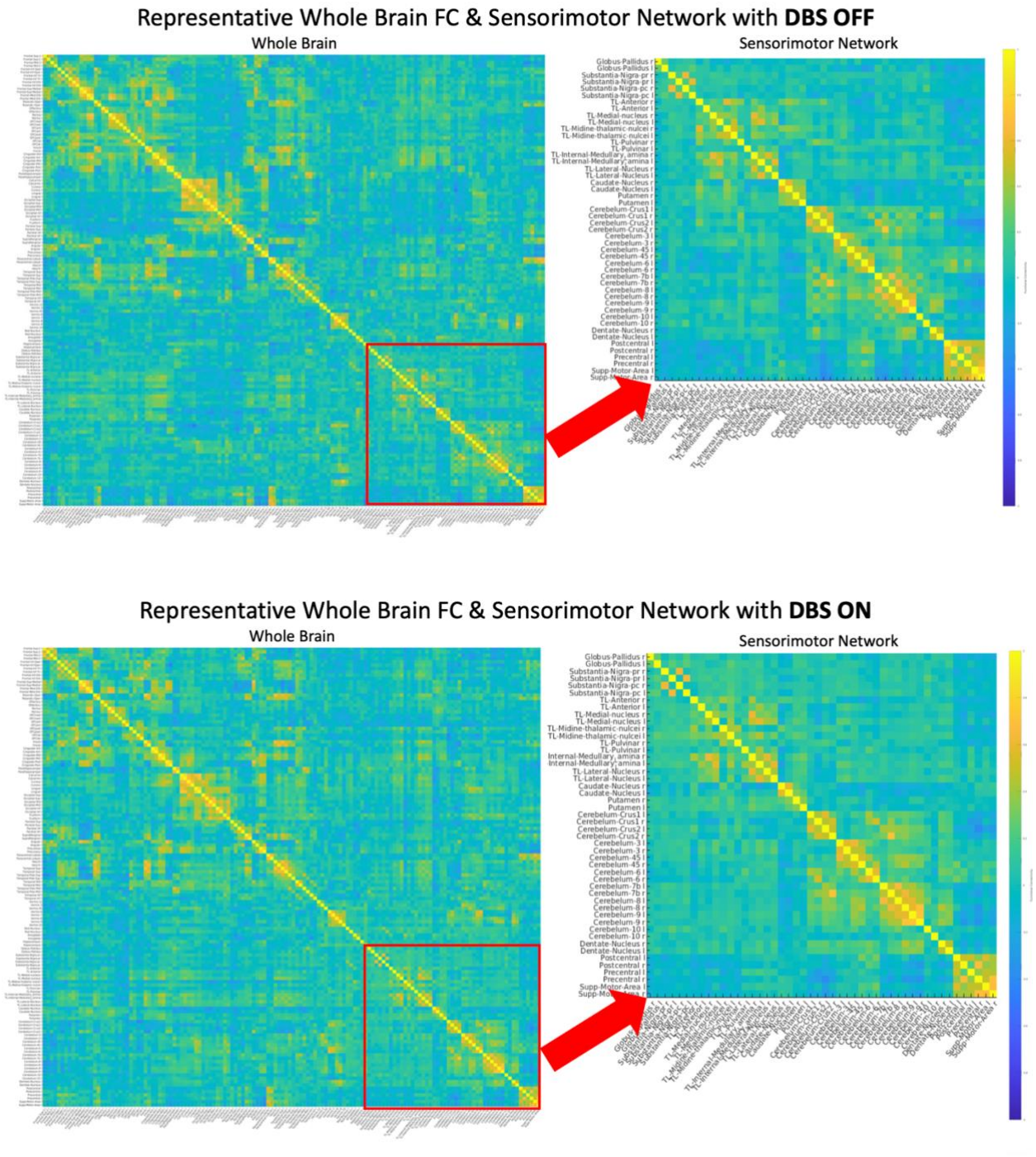

Figure 6: Whole Brain & Sensorimotor Network FC maps. These are the representative FC maps for the whole brain and sensorimotor network while DBS is ON and while DBS is OFF.

First, each patients' pre-op and post-op pre-processed timeseries data were loaded into MATLAB (MathWorks, Natick, Massachusetts). The FC matrices for all

patients were constructed by correlating each brain region using ‘corr()’ with all other brain regions including itself. All patients with preop fMRI data (n=6) also had FC matrices constructed for that timepoint. fMRI data for each DBS condition (post-op DBS off1, post-op DBS off2, post-op DBS on1, and post-op DBS on2) and repeat scans for all patients (n=16 was made into matrices. These matrices were thereafter Fisher’s transformed using, ‘tanh()’, to adjust the data set into an approximate normal distribution which then can be used in parametric tests. The variability metrics were computed as the standard deviation of each brain region’s average timeseries in specific brain regions of interest using ‘std()’.

3.4 Data Analysis

3.4.1 Repeatability Investigation

To assess the repeatability between two fMRI scans taken in the same patient, with the same conditions during the same scan session Spearman rank correlations calculated as,

$$\rho = 1 - \frac{6\sum d_i^2}{n(n^2-1)} \quad \textbf{(1)}$$

were utilized to assess the statistical similarity between post-op DBS off1vs post-op DBS off2 and post-op DBS on1 vs post-op DBS on2 for each subject (n=16). The difference between the two ranks of each observation (d_i) and number of subjects, or observations, (n), is used to calculate the Spearman’s rank correlation coefficient (ρ). Each patient’s all FC measurements that were made into matrices: (post-op DBS off1, post-op DBS off2, post-op DBS on1, and post-op DBS on2) were vectorized in MATLAB in order to do the Spearman rank correlation, and the function ‘corr()’ was used to return the rho and p-value. High rho values correspond to stronger the association between

the two data sets, and lower values correspond to weaker the association between the two data sets.

To assess the repeatability of the post-op off and on rs-fMRI scans at the group-level, the Wilcoxon signed rank test was implemented for nonparametric evaluation of the difference between the paired test-retest groups[32]. The test ranks the absolute difference of the paired observation of all the patients' first post-op DBS off and on scans to their repeated post-op DBS off and on scans, respectively, to find the test statistic, W. Using W, the z-value can be calculated, where n is the number of observations. The z-value of the Wilcoxon signed rank test calculated as,

$$z = \frac{(W - n(n+1)/4)}{\sqrt{\frac{n(n+1)(2n+1)}{24}}} \quad (2)$$

was used to examine the test-retest ability of multiple scans and patients taken with the same conditions. All of each patient's FC measurements were made into matrices: (post-op DBS off1, post-op DBS off2, post-op DBS on1, and post-op DBS on2) and then organized into four vectors that were concatenated across subjects: 1) all patients' post-op DBS off 1st scans (all post-op DBS off1), 2) all patients' post-op DBS off 2nd scans (all post-op DBS off2), 3) all patients' post-op DBS on 1st scans (all post-op DBS on1), and 4) all patients' post-op DBS on 2nd scans (all post-op DBS on2). To calculate Wilcoxon signed rank test and determine the 2 p-values and acceptance or rejection of the null hypothesis, the 'signrank()' function in MATLAB was used. All post-op DBS off1 FC maps were compiled to be ranked against all post-op DBS off2 FC maps and all post-op DBS on1 FC maps were compiled to be ranked against all post-op DBS on2 FC maps to find the group p-values. The p-value was then used to accept or reject the null hypothesis which stated the median of the difference between the paired

data is zero. A median of zero informs us that there is no difference between the paired observations.

3.4.2 Longitudinal Analysis

To understand how DBS has altered the brain response to the treatment over time, we performed longitudinal analysis by comparing pre-op DBS fMRI scans to post-op DBS fMRI scans. We expected to see FC between the sensorimotor motor cortices, and thalamus and between the sensorimotor motor cortices and cerebellum decreased with STN and GPi DBS over time[6]. To find these differences the average of all patients with pre-op and post-op data (n=6) FC matrices were created for the scans: pre-op, post-op DBS off1 and off2 averaged (post-op DBS off), and post-op DBS on1 and on2 averaged (post-op DBS on). The network variability metrics of the same patients were also calculated for the average of pre-op, post-op off1 and off2 averaged, and post-op on1 & on2 averaged scans.

The total MDS-UPDRS scores calculated during the pre-op and post-op clinical visits were used to see if the changes in FC and variability also align with patient symptom improvement. MDS-UPDRS scores were calculated for each visit by showing percent change from before treatment to after treatment (medication for preop and DBS on for post-op). The MDS-UPDRS exam was administered twice in both visits, where the first was done without medication (pre-op) or DBS turned on (post-op) and the second was done after the patient takes their PD medication (pre-op) or with DBS turned on (post-op). Pre-op MDS-UPDRS percent change was calculated using the pre-op MDS-UPDRS score without medication and the pre-op MDS-UPDRS score with medication and is used to determine who is a candidate for DBS. Post-op MDS-

UPDRS percent change was calculated using the post-op MDS-UPDRS DBS off score and the post-op MDS-UPDRS DBS on in bipolar mode score. It should be noted, patients also took medication with their post-op DBS treatment for daily treatment and took their medication during the post-op visit. Also, the post-op DBS on condition is with DBS in the bipolar configuration not their daily monopolar treatment configuration. To compare the scores within each condition, the percent change is calculated as,

$$percent\ change = \frac{(MDS{-}UPDRS\ score\ without\ treatment){-}(MDS{-}UPDRS\ score\ with\ treatment)}{(MDS{-}UPDRS\ score\ without\ treatment)} \times 100 \quad (3)$$

This percent change shows the effect that treatment has on the patient.

4. RESULTS

4.1 Repeatability Study

To determine the strength of association between the two rs-fMRI scans in one patient, the Spearman rank correlation test was calculated for each patient's (n=16) FC maps (Table 2). The post-op DBS off1 FC maps were tested against the post-op DBS off2 FC maps to calculate the rho value and determine repeatability (range=0.4198-0.6556, average=0.5659). Additionally, we evaluated the repeatability of rs-fMRI scans for the post-op DBS on1 FC maps against the post-op DBS on2 FC maps (range = 0.4283-0.6553, average= 0.5721). The p-values for all patients in both groups were below 0.05, indicating that there is a correlation between data sets: 1) post-op DBS off1 vs post-op DBS off2 and 2) post-op DBS on1 vs post-op DBS on2.

Table 2: Spearman Rank Correlation Test
Rho and p-values for each patient for DBS Off and DBS On Images for sensorimotor motor cortex

Patient ID	Spearman Correlation Post-op DBS off1 vs Post-op DBS off2		Spearman Correlation On1 Post-op DBS on1 vs Post-op DBS on2	
	Rho	p-value	Rho	p-value
1	0.5309	1.05E-167	0.6114	2.70E-236
2	0.6556	3.89E-283	0.6549	2.13E-282
3	0.6487	2.58E-275	0.5167	1.79E-157
4	0.6457	5.65E-272	0.6395	3.75E-265
5	0.6526	9.96E-280	0.6553	8.89E-283
6	0.5637	2.27E-193	0.4454	1.08E-112
7	0.4198	4.72E-99	0.4283	1.89E-103
8	0.5274	3.52E-165	0.5585	3.71E-189
9	0.6079	6.33E-233	0.4438	8.82E-112
10	0.5724	9.86E-201	0.5534	4.65E-185
11	0.4911	3.59E-140	0.5771	1.07E-204
12	0.4662	1.08E-124	0.6209	1.04E-245
13	0.5969	1.87E-222	0.6441	3.04E-270
14	0.5295	1.02E-166	0.6164	3.55E-241
15	0.5497	4.32E-182	0.6396	2.79E-265
16	0.5463	1.95E-179	0.5897	6.78E-216

By analyzing the rho scores, which serve as indicators of correlation strength, we can discern patients with the most robust and least consistent repeatability in their scans (Figure 6). Two patients, 2 and 5, had the highest two rho scores for both post-op DBS off1 correlated with post-op DBS off2 and post-op DBS on1 correlated with post-op on2. It is also interesting to note that both patients are the two oldest patients in the group (age = 76.36 and 76.12 years) as age is associated with lower repeatability[34]. Conversely, patient 7 had the lowest repeatability, as seen by the weakest rho scores in both conditions.

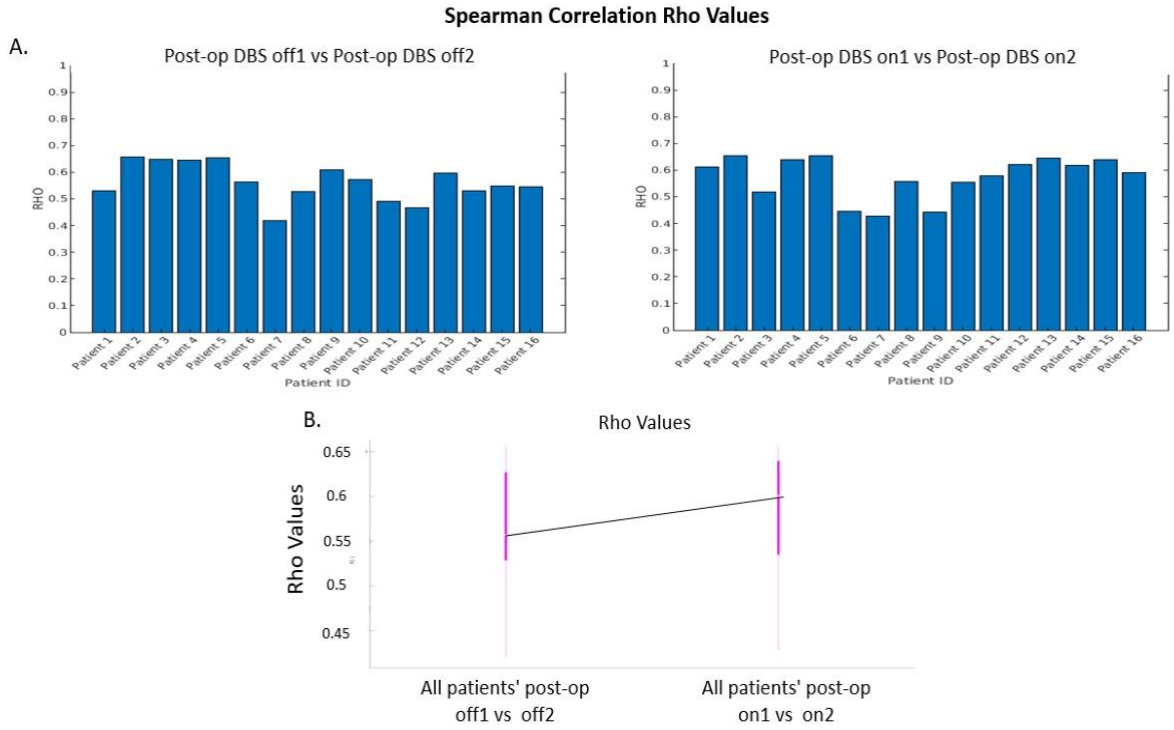

Figure 7: Spearman correlation rho values for repeatability. A) Bar graph of Spearman correlation rho values. The post-op DBS rho values for each patient's (n=16) post-op DBS off1 and post-op DBS off2 are shown in the bar graph on the left. The post-op DBS Rho values for each patient's post-op DBS on1 and post-op DBS on2 are shown in the bar graph on the right. **B) Box plot of Spearman correlation rho values.** All patient's rho values from post-op DBS off1 compared to post-op DBS off2 and rho values from post-op DBS on1 compared post-op DBS on2 are plotted. The median of each test group is shown with the black line between the two box plots.

To visualize the difference more clearly between the patients with the strongest and weakest repeatability in DBS off and DBS on of the FC matrices of each (post-op DBS off1, post-op DBS off2, post-op DBS on1, and post-op DBS on2) were plotted for patients 2 and 7 respectively (Figure 7). In patient 7's FC matrices, there are transitions from weak to strong connectivity and vice versa between post-op DBS off1 and post-op DBS off2, including an increase in FC in cerebellum 3 and 45, as well as a decrease in FC in the midline thalamic region and cerebellum 3. Furthermore, patient 7 has greater change from the post-op DBS off1 to in the post-op DBS off2 than patient 2, specifically with lower connectivity in the cerebellum 45 and 6 regions in the post-op DBS off1 than in the post-op DBS off2 FC maps. When comparing the post-op DBS on FC map for

patient 7, we can see that in the post-op DBS on1 FC maps there is stronger connectivity in the cerebellum 8, 9, and 10 regions than in the post-op DBS on2 FC map. In comparison, patient 2's change in connectivity between the post-op DBS off1 and post-op DBS off2 FC map and between the post-op DBS on1 and on2 FC map remain similar.

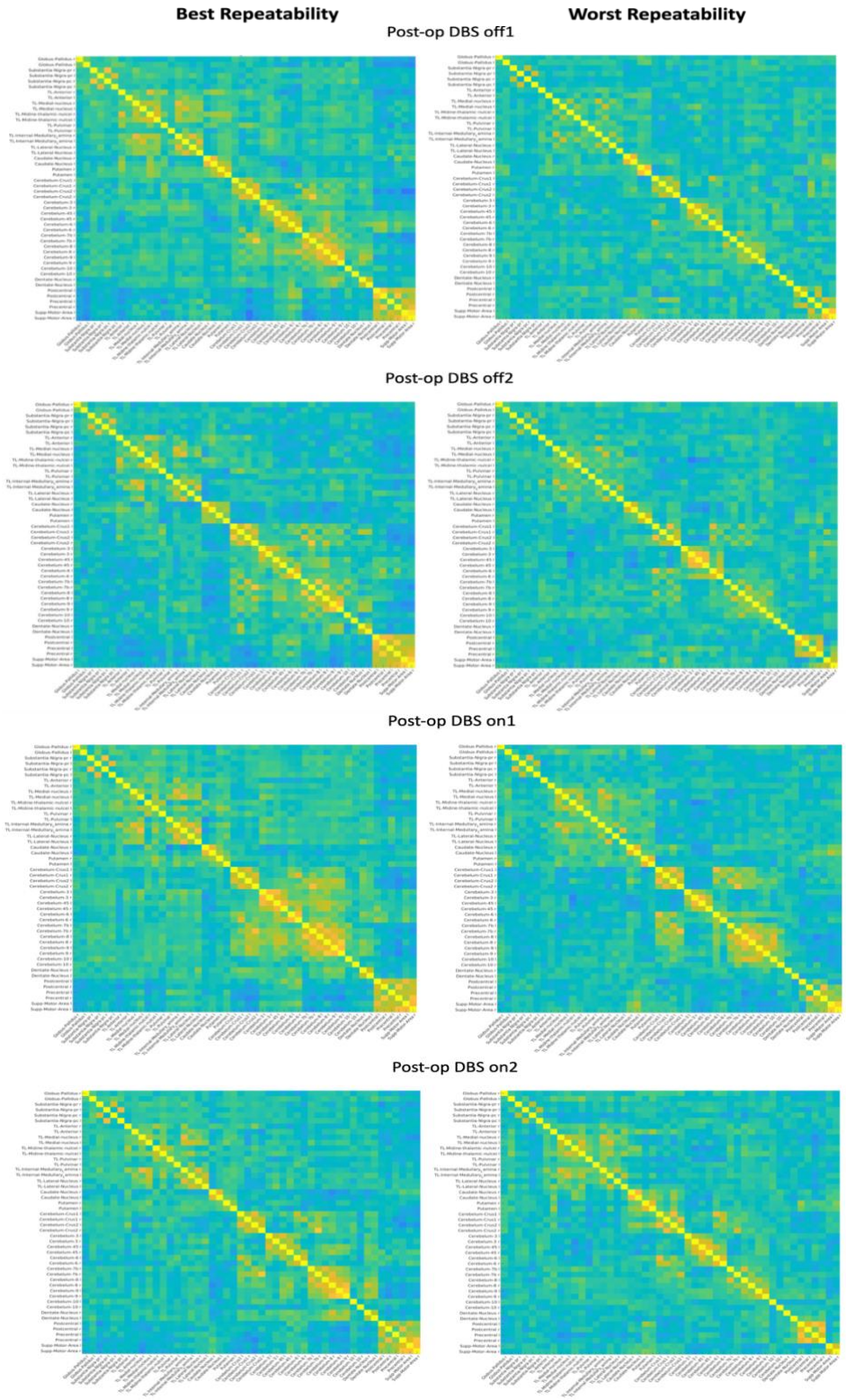

Figure 8: FC map comparison of patients with best and worst repeatability. The FC maps for post-op DBS off1, post-op DBS off2, post-op DBS on1 and post-op DBS on2 in the patients with the best (left column) and worst (right co column) repeatability.

To assess scan repeatability at the individual and group level, we further computed repeatability using the Wilcoxon signed-rank test. The Wilcoxon sign rank test was calculated for each patient's FC maps and for the average of all patient's FC maps (Table 3). The p-values of each test are used as a basis to accept or reject the null hypothesis states that the median of the data was zero.

Table 3: Wilcoxon Sign Rank Test
P-value and Acceptance or Reject Null hypothesis for each patient when DBS is Off and when DBS is On

	Wilcoxon Sign Rank Test Post-op DBS off1 vs Post-op DBS off2		Wilcoxon Sign Rank Test Post-op DBS on1 vs Post-op DBS on2	
	p-value	Null Hypothesis (1 = reject; 0 = accept)	p-value	Null Hypothesis (1 = reject; 0 = accept)
Concatenated FC matrix of all patients	1.90E-09	1	7.04E-11	1

At the group level, when testing the concatenated FC matrices into vectors of all post-op DBS off1 against all post-op DBS off2 FC matrices and when testing all post-op DBS on1 against all post-op DBS on2 FC matrices, the null hypothesis was rejected. This indicates that the difference of the paired data does not have a zero median.

4.2 Longitudinal analysis

To ascertain the impact of DBS on connectomes before and after treatment, we conducted an analysis where we averaged the FC matrices of all patients (n=6) across distinct stages: preop, post-op DBS off1 and off2 averaged (post-op DBS off), and post-op with DBS turned on1 and on2 averaged (post-op DBS on). Upon averaging, the FC maps revealed intriguing insights. Notably, the pre-op DBS matrix exhibited stronger connectivity among thalamic regions (anterior, medial nucleus, midline thalamic nuclei, pulvinar, internal medullary lamina and lateral nucleus) compared to both the post-op DBS off and post-op DBS on matrices (Figure 8). The stronger connectivity seen

between the putamen and the globus pallidus in the pre-op FC matrix was much weakened in the post-op DBS off and on matrices. There was also much less connectivity between the supplementary motor area and the cerebellum Crus I and Crus II within the post-op on FC matrix compared to both the pre-op DBS and post-op DBS off matrices.

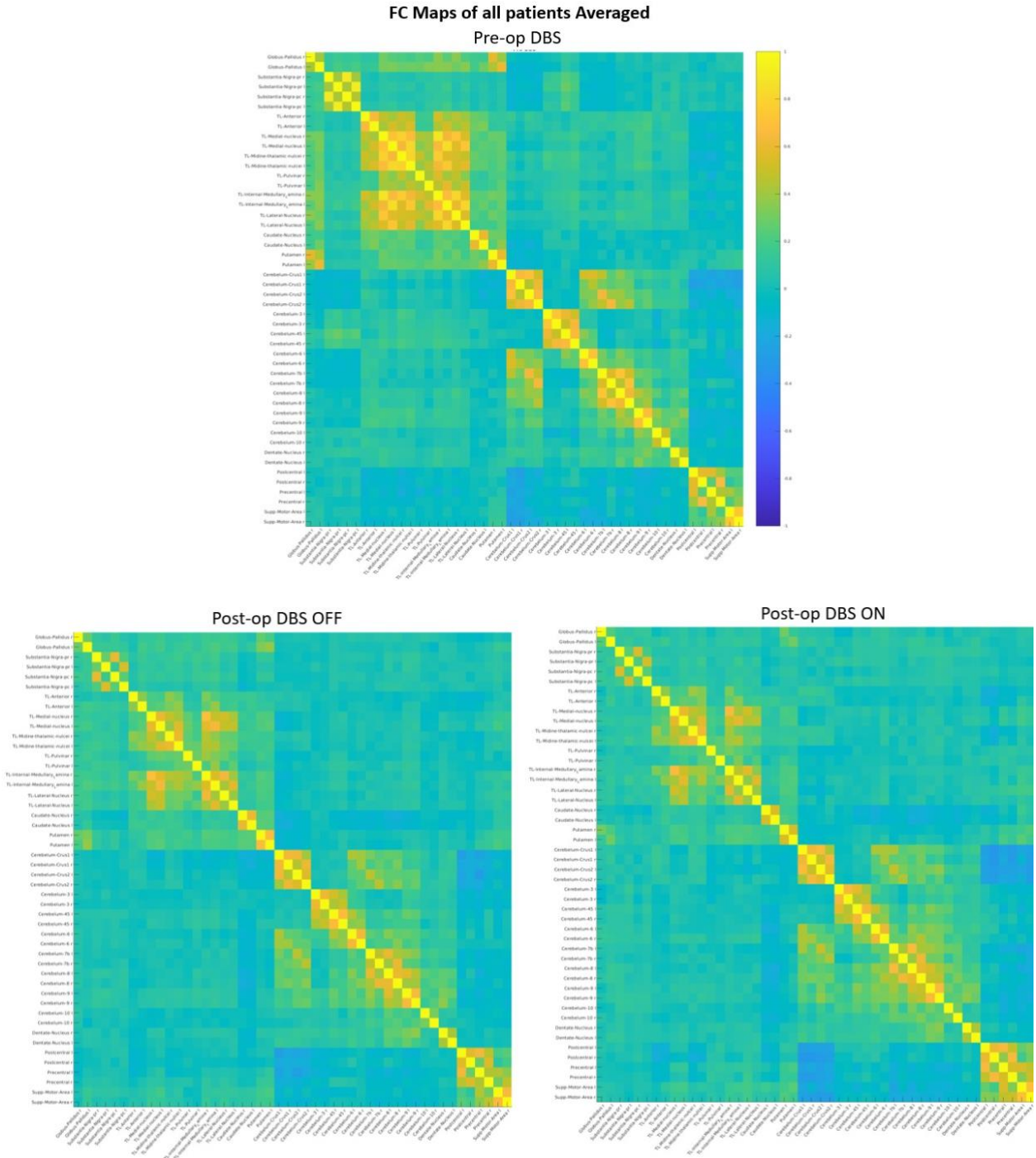

Figure 9: FC Maps of all patients (n=16). They are averaged for pre, post-op DBS on and post-op DBS off. These are FC maps for brain regions associated with motor and sensorimotor pathways. Pre-DBS, post-DBS-on, and post-DBS-off conditions are depicted in the maps, from left to right

The average of all post-op DBS off FC matrix had a lower median connectivity (median = 0.045) when contrasted with the pre-op and post-op DBS on (median =

0.056, 0.541) (Figure 9). Additionally, we see more outlier FC values in the post-op DBS on scan than in the pre-op and post-op DBS off scans (Figure 9).

These findings collectively illuminate the evolving dynamics of connectivity patterns induced by DBS treatment across PD patients.

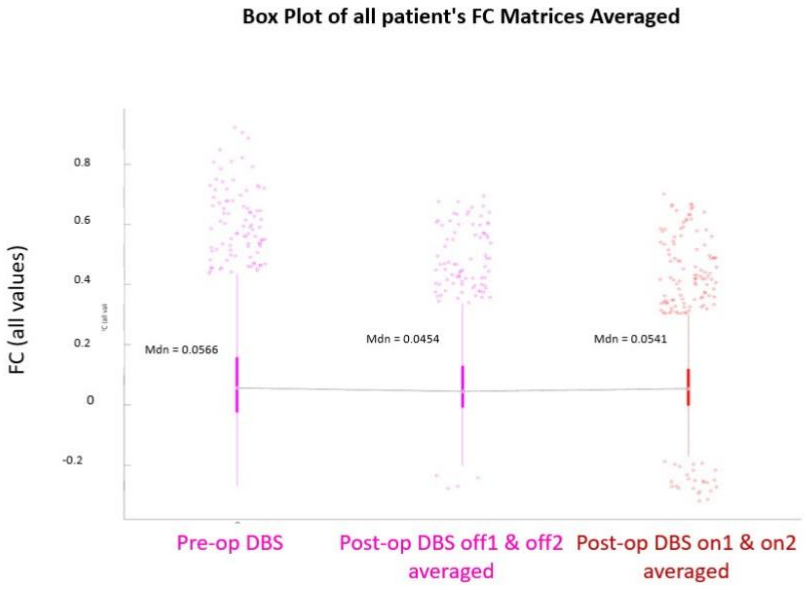

Figure 10: Box plot of the average of all post-op FC matrices. Groups are preop and all post-op DBS off1 & off2 averaged, and post-op DBS on1 & on2 averaged.

To better understand the trend in changes from pre-op DBS to post-op DBS off and post-op DBS on, each patient's FC matrix was individually visualized (Figure 10). Focusing on the medians of the pre-op, post-op DBS off, and post-op DBS on FC matrices for each patient, it is noteworthy that solely in the case of patient 3, the post-op DBS on FC matrix exhibited a higher median value (median = 0.0769) in comparison to both their pre-op and post-op DBS off medians (median = 0.0271, 0.0500). For patients 13 and 15, their respective highest median value in the post-op DBS off FC matrices (median = 0.0829, 0.0830), lowest median values in the pre-op FC matrices (median =

0.0563, 0.0504). Three patients (1,8 and 11) had the same trend, where the pre-op FC matrices have the highest median value (median= 0.1058, 0.0644, 0.0867) and the post-op off FC matrices have the lowest median value (median = 0.0444, 0.0292, 0.0448). While variations in pre-op and post-op connectivity values exist among patients, it is notable that, except for patient 3, the second highest median for their FC matrices was consistently observed in the post-op DBS on condition (medians: 0.0507, 0.0528, 0.0467, 0.0782, 0.0657) (Figure 10). Additionally, patients (1, 11, and 15) who underwent STN implantation exhibited the highest pre-op FC median and the lowest post-op DBS median. However, in the case of post-op DBS off, no distinct pattern emerged among patients with STN and GPi implants, as no single group displayed consistently larger or smaller medians.

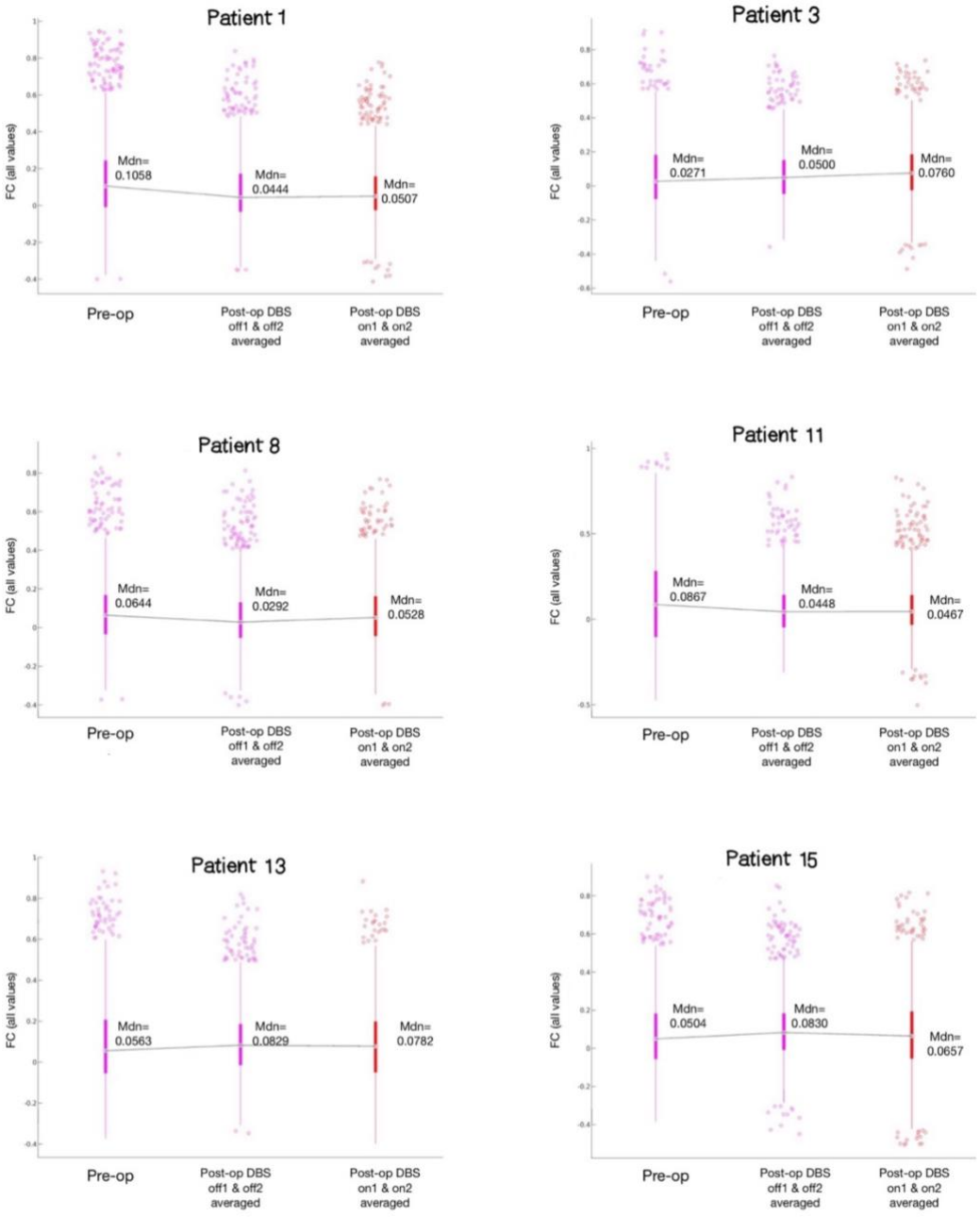

Figure 11: Box plot of FC matrices for each patient. In each patient the FC matrices for the pre-op, average of post-op DBS off1 and off2, and average of post-op DBS on1 and on2 were plotted and medians displayed.

To delve deeper into the exploration of potential neuroplastic changes induced by DBS, we computed the network variability metrics using the average of all patients for pre-op and post-op DBS states. Figure 11A demonstrates the presence of changes between pre-op DBS and post-op DBS off and on for all the patient's variability metrics

averaged together. After the patients had been treated with DBS, whether the device was on or off, there was a noticeable increase in variability observed in the substantia nigra and the anterior thalamus. There is a proportional increase in variability from post-op DBS off to post-op DBS on in the dentate nucleus, cerebellum region 3 and 10, cerebellum Crus I/ II. After DBS treatment, when DBS is off, the cerebellum 10 has similar variability as it did prior to DBS treatment. Additionally, there is a decrease in variability in the midline thalamic nuclei from pre-op to post-op DBS off and on variability metrics.

Although certain brain regions increase or decrease in variability from pre-op to post-op DBS off or on, the median variability from the pre-op variability metrics (median = 0.1895) is higher than the median variability metrics from the post-op DBS off and post-op DBS on (median = 0.1663, 0.1785) (Figure 11B). This indicates that after DBS treatment even though certain brain regions increase in variability, other brain regions decreased in variability.

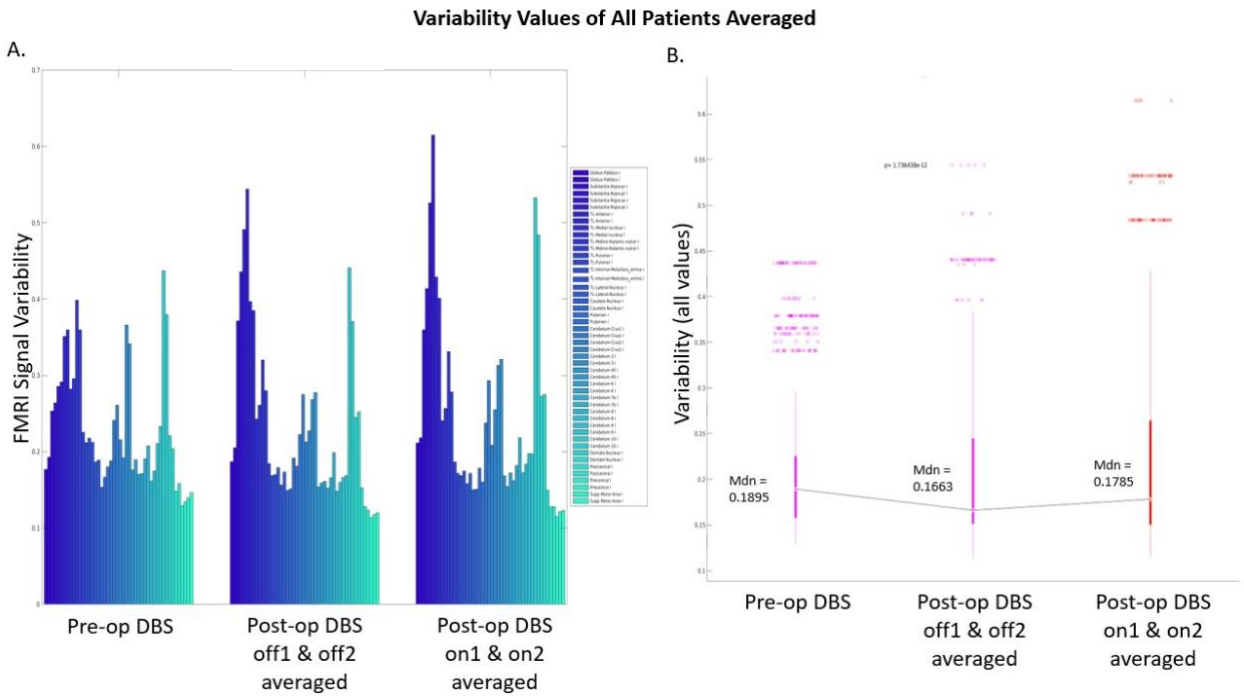

Figure 12: Average of Variability for all patients (n=16). A) Variability of all patients averaged for pre, post-op DBS on and post-op DBS off. These are variability metrics for brain regions associated with motor and sensorimotor pathways. Pre-DBS, post-DBS-on, and post-DBS-off conditions are depicted in the maps, from left to right. **B) Box plot of the average of all post-op variability metrics preop vs avg all pt post-op DBS off vs avg all patient post-op DBS on.**

The variability metrics were also computed for each patient (Figure 12). In contrast to the FC matrices, there are differences observed across all patients. When looking at the medians of patients 3, 11, and 15, their post-op DBS on variability metrics had the highest (median = 0.1505, 0.1641, 0.1854), their intermediate variability metrics was in the post-op DBS off scans (median = 0.1392, 0.1624, 0.1460), and their pre-op variability metrics were the lowest (0.1334, 0.1607, 0.0941) of all three scans (Figure 12). The pre-op, post-op DBS off, and post-op DBS on's median variability metrics for patient 1 (median = 0.1413, 0.1777, 0.1347), patient 8 (median = 0.2997, 0.1982, 0.1666), and patient 13 (median = 0.3150, 0.2076, 0.2652) do not follow similar increase or decrease in median from pre-op to post-op DBS scans.

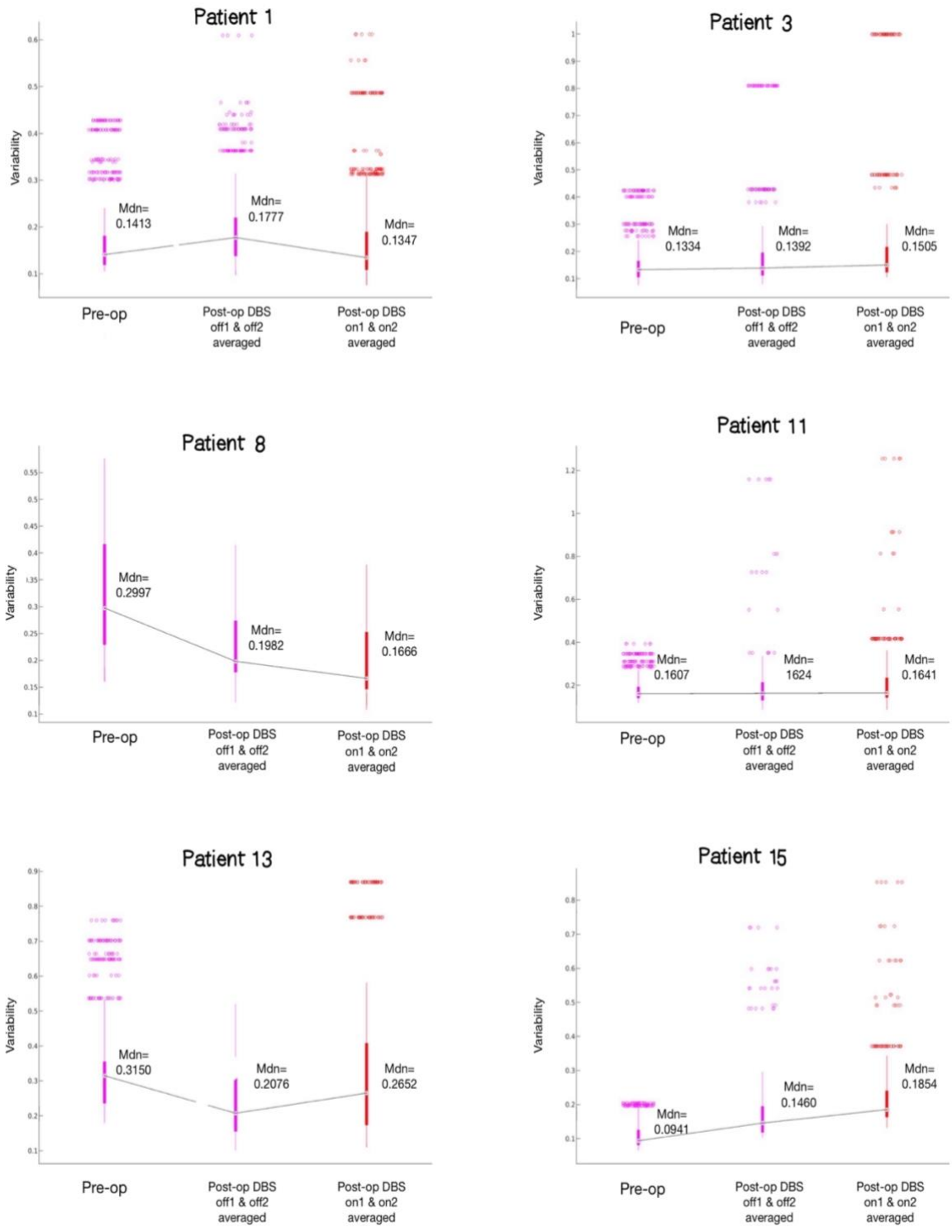

Figure 13: Box plot of variability metrics for each patient. In each patient the FC matrices for the pre-op, average of post-op DBS off1 and off2, and average of post-op DBS on1 and on2 were plotted and medians displayed.

4.3 MDS-UPDRS Scores

The percent changes recorded are the patient's MDS-UPDRS score without treatment to their MDS-UPDRS score with treatment (Table 4). In pre-op the treatment was medication and, in most post- op, scores the treatment was DBS on. All patients (n=16) had a positive percent change for both pre-op and post-op percent changes indicating symptom improvement with treatment.

Table 4: MDS-UPDRS Scores
MDS-UPDRS scores are reported for conditions: with and without treatment. Percent change is the change from without treatment to with treatment.

Patient ID	Pre-op without medication	Pre-op with medication	Percent change for Pre-op (%)	Post-op DBS off	Post-op DBS on	Percent change for Post-op (%)
1	27	16	40.74	30	19	36.67
2	23	12	47.83	18	16	19.05
3	28	11	60.71	42	34	60.71
4	23	7	69.57	28	18	47.62
5	35	21	40	34	15	50
6	36	24	33.33	21	11	40.74
7	64	42	34.38	24	12	33.33
8	39	16	58.97	27	16	34.69
9	33	16	51.52	41	34	38.46
10	60	42	30	49	32	29.27
11	40	29	27.5	39	24	33.33
12	56	35	37.5	41	39	39.58
13	54	23	57.41	41	29	31.25
14	31	10	67.74	24	16	28.95
15	14	6	57.14	48	29	24.32
16	34	8	76.47	48	33	26.32

However, the percent change for pre-op is higher than the percent change in post-op for most patients (patients 1, 2, 4, 7, 8, 9, 10, 13, 14, 15, and 16) (Figure 13). Only three patients (5, 6, 11 and 12), had a higher percent change in post-op than in pre-op. Only patient 3 had the same percent change in pre-op compared to post-op.

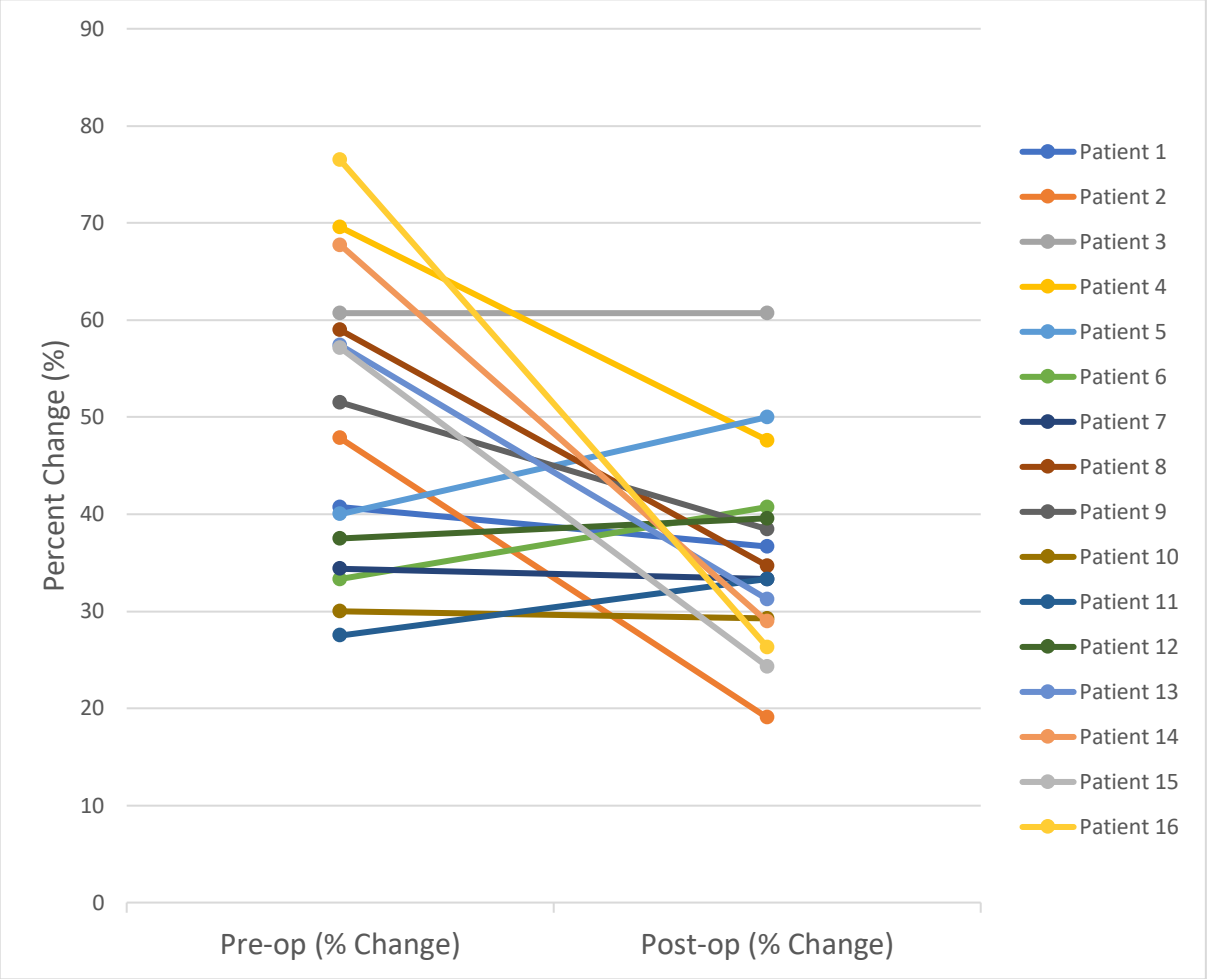

Figure 14: Comparing percent change in MDS-UPDRS from pre-op to post-op. The percent change is the change is the change in MDS-UPDRS without treatment to with treatment. This is calculated for the pre-op and post-op conditions.

5. DISCUSSION

In this investigation, fMRI in DBS patients with PD was used to examine the repeatability of rs-fMRI scans while DBS is turned on and to compare pre-DBS imaging with post-DBS imaging to better understand the FC network alterations that DBS makes over time and immediately when DBS is turned on. Patients were found to have fair to moderate ($0.4 < rho < 0.5$) repeatability with no clear trend in demographics that related them to the repeatability scores, but the two oldest patients had the best rho scores. Furthermore, at the group level, both the all post-op DBS off1 vs all post-op DBS off2

and the all post-op DBS on1 vs all post-op DBS on2 rejected the null hypothesis in the Wilcoxon signed rank test. To investigate longitudinal and immediate changes DBS makes on the brain, the study examined FC changes in the sensorimotor motor network and found a decline in connectivity in supplementary motor area and the cerebellum Crus I and Crus II in the post-op DBS on compared to both the pre-op and post-op DBS off. The pre-op DBS matrix also exhibited stronger connectivity among thalamic regions compared to both the post-op DBS off and post-op DBS on matrices. PD symptoms, as measured by MDS-UPDRS scores, improved with DBS on but pre-op percent change was higher than post-op percent change. Variability decreased, in both post-op DBS off and post-op DBS on in comparison to pre-op.

5.1 Repeatability

To best quantify the repeatability of rs-fMRI scans in DBS patients the Spearman rank correlation and Wilcoxon sign rank test were employed. The correlation between two FC matrices is quantified using the rho value, where the closer to 1 the rho is, the stronger the correlation between the FC matrices. All patients had fair to moderate repeatability, showing repeatability reliability in rs-fMRI scans in PD patients with DBS[33,34]. Patients 2 and 5 had the best repeatability for post-op DBS off1 vs off2 FC matrices (rho = 0.6556, 0.6526) and for post-op DBS on1 vs on2 FC matrices (rho = 0.6549, 6553). No clear age, DBS target, nor years with PD diagnosis- related pattern emerges in connection with the higher rho values. However, it is intriguing to observe that despite both patients being the two oldest patients (76.36 and 76.12,) as it has been found that test-retest reliability is reduced in older adults[35]. It can also be noted that patient 2 had the lowest post-op DBS off and post-op DBS on MDS-UPDRS raw

scores indicating that this patient had less severe PD symptoms. Having less PD symptoms can mean that the patient is able to keep still for longer than other patients and thus less motion artifacts occur. However, because patient 5 had the 6th lowest post-op DBS off and 8th lowest post-op DBS on MDS-UPDRS raw scores, which indicates other factors contribute to repeatability in rs-fMRI scans that are not age, DBS target, nor years with PD diagnosis- related pattern emerges in connection with the higher rho values. Conversely, patient 7 had the lowest rho score for the post-op DBS off1 compared to the post-op DBS off2 scans and for the post-op DBS on1 compared to the post-op DBS on2 FC matrices. Furthermore, patient 7's MDS-UPDRS post-op raw scores were the second highest, indicating the most severe PD symptoms of the group. This further supports the idea that patients with more severe PD symptoms are not able to remain still for multiple scans. Having motion can reduce the degrees of freedom because it introduces correlated noise, which reduces statistical analysis degrees of freedom, potentially affecting sensitivity and reliability of results[36]. Pre-processing can also impact test-retest reliability, as more degrees of freedom can introduce additional noise that may distort the data[37].

The Wilcoxon sign rank test is applied to compare the medians of paired FC matrices and determine if there is a significant difference between them. Both the all post-op DBS off1 vs all post-op DBS off2 and the post-op DBS on1 vs all post-op DBS on2 failed to reject the null hypothesis. The rejection of the null hypothesis indicates that the signed rank of DBS off and DBS on conditions does not possess a zero median. This means implies that group-level rs-fMRI repeatability was not achieved. This may be caused by motion artifacts that were introduced by some patients that affected the

overall test. This can be addressed by decreasing the degrees of freedom, however if the degrees of freedom are decreased too much, the signal may be simplified too much and some details may be lost[37].

5.2 Longitudinal Study

In this study, our primary aim was to investigate the alterations in FC within the sensorimotor motor network, cerebellum and thalamus following DBS procedures targeting the STN and the GPI. Consistent with our hypothesis and as previously seen in other fMRI studies the FC within these circuits decreased following the DBS treatments[6]. This is specifically seen in the medians of the average of all patient's FC matrices for pre-op, post-op DBS off and post-op DBS on, were compared and showed that the pre-op FC matrix had a higher median than the all post-op DBS off and all post-op DBS on FC matrices. However, the FC has also been found to have increased with DBS, which is mirrored in the individual patient's medians for pre-op, post-op DBS off and post-op DBS on, where half of the patients have a higher median in the post-op DBS off and post-op DBS on FC matrices than in the pre-op FC matrix[38,39].

The observed decrease in connectivity within thalamic regions (including anterior, medial nucleus, midline thalamic nuclei, pulvinar, internal medullary lamina, and lateral nucleus) from pre-op to both post-op DBS off and post-op DBS on matrices aligns with previous studies that found higher FC in the thalamus of PD patients[40]. In the context of PD, the observation of higher thalamic FC is an abnormal property compared to a healthy patient. Furthermore, the similarity between DBS on/off maps in certain cases may be due to washout times not being long enough between the MDS-UPDRS post-op DBS on evaluation and the post-op DBS off scans. The evaluation and scans were

conducted within an hour of each other. Without an adequate washout period, the effects of DBS may not dissipate from the brain, potentially confounding the interpretation of an "off" condition.

Thus, because DBS is effective, it is likely working to reduce this abnormal FC and normalize the brain's connectivity patterns. The increase in FC is consistent with other research findings and show neuroplastic changes in the brain[38,39,41].

There was also a decrease in FC between the supplementary motor area and cerebellum Crus I and Crus II that weakened from pre-op to all post-op DBS off and had the weakest FC in the all post-op DBS on FC matrix. Because increased connectivity between the Crus I and Crus II is associated with increased PD symptom severity[42], the alteration observed in Crus I and Crus II may play a crucial role in symptom improvement, as evidenced by the enhanced MDS-UPDRS scores when DBS is turned on, compared to when it is turned off. The decrease in connectivity in the supplementary motor area was previously recorded, and it has been found that DBS may improve connectivity, which can promote normal gait[5,43].

The variability metrics were also used to examine the brain's network adaptability. Like the decrease in FC there is an overall decrease in variability in the post-op DBS off and on conditions. Overall, there is more variability prior to DBS treatment than when DBS is off or on. However, when examining the pre-op, all post-op DBS off and all post-op DBS on variability metrics, there was a large spike in the substantia nigra and cerebellum regions 3 &10, for both the post-op variability metrics. The substantia nigra was previously found to have greater variability in patients with PD[44]. The increase in variability seen from pre-op to post-op DBS off and to post-op

DBS on in those brain regions are likely due to DBS's effect, as other brain regions either decreased or had the same amount of variability. Through the brain's network adaptability, the cerebellum is relied on for motor takes in PD patients more than in healthy patients[45]. The increases in these brain regions' variability can be attributed to those brain regions facilitating neural malleability or trying to create neuroplastic changes[31]. The median of the average of all patient's pre-op was higher than the average post-op DBS off1 and off2 and average post-op DBS on on1 and on2, showing that the pre-op condition has higher variability. With DBS, either on or off, the variability was lower indicating that some brain regions have lowered in variability. The cerebellum Crus II decreased in variability, meaning that brain region has greater neuroplasticity, which was also seen in the change in FC from pre-op to post-op DBS off and on. It should also be noted that patients did not have the same trend in variability from pre- to post-op DBS off to post-op DBS on. These differences in variability have no trends found in relation to the variability trends and age, sex, race, DBS target, MDS-UPDRS score or PD diagnosis length suggesting that variability may be due to another factor.

All patients showed improvement from DBS off to DBS on, re-confirming DBS as a successful treatment for PD. The percent change post-op is less than the percent change in patient's pre-op scores. Yet, considering the progressive nature of PD, the decrease in percent change and increase in raw MDS-UPDRS scores could potentially be attributed to this underlying progression.

5.3 Conclusion

In conclusion, our study assessed the rs-fMRI scan repeatability within DBS patients with the Spearman rank correlation and Wilcoxon sign rank test. The two

oldest patients with the best MDS-UPDRS raw scores had the highest repeatability, while patients with the worst MDS-UPDRS raw scores had the worst repeatability. The Wilcoxon sign rank test rejected the null hypothesis, suggesting challenges in achieving group-level repeatability due to motion artifacts. Adjusting degrees of freedom may mitigate this issue.

This study investigated the changes in FC within the sensorimotor motor network for pre- and post-op DBS targeting the STN and the GPI. Results showed a decline in FC within these circuits following DBS treatments, with a higher median in the pre-op FC matrix compared to all post-op DBS off and post-op DBS on matrices. However, functional connectivity increased with DBS, with half of the patients having a higher median in the post-op DBS off and post-op DBS on FC matrices than in the pre-op FC matrix.

A decrease in connectivity within thalamic regions and cerebellum Crus I and Crus II from pre-op to post-op, indicating neuroplastic changes in the brain and possible target for PD symptom improvement with DBS. This decrease may play a crucial role in symptom improvement, as evidenced by enhanced MDS-UPDRS scores when DBS is turned on. The decrease in connectivity in the supplementary motor area has also been recorded.

The variability metrics examined the brain's network adaptability, with an overall decrease in variability in the post-op DBS off and on conditions. However, a large spike in variability in the substantia nigra and cerebellum regions was observed, possibly due to the progressive nature of PD. All patients showed improvement from DBS off to with DBS on, confirming DBS as a successful treatment for PD.

One major limitation is the small sample size; however, these results may still be used to guide future research in the pre- to post-op effects that DBS has on the brain. In the future, more time points following DBS surgery may lead to greater insight as to what specific neuroplastic changes occur in patients with greater symptom improvement. This investigation has confirmed the decrease in functional connectivity and variability following DBS treatment, whether DBS is off or on, which may have possible implications for improving therapeutic approaches.

References

1. Willis AW, Roberts E, Beck JC, et al. Incidence of Parkinson disease in North America. *NPJ Park Dis*. 2022;8(1):170. doi:10.1038/s41531-022-00410-y

2. Boutet A, Chow CT, Narang K, et al. Improving Safety of MRI in Patients with Deep Brain Stimulation Devices. *Radiology*. 2020;296(2):250-262. doi:10.1148/radiol.2020192291

3. Rizek P, Kumar N, Jog MS. An update on the diagnosis and treatment of Parkinson disease. *CMAJ Can Med Assoc J J Assoc Medicale Can*. 2016;188(16):1157-1165. doi:10.1503/cmaj.151179

4. Cheng GX, Yin SB, Yang YH, et al. Effects of bilateral subthalamic nucleus deep brain stimulation on motor symptoms in Parkinson's disease: a retrospective cohort study. *Neural Regen Res*. 2021;16(5):905. doi:10.4103/1673-5374.297089

5. Rahimpour S, Rajkumar S, Hallett M. The Supplementary Motor Complex in Parkinson's Disease. *J Mov Disord*. 2022;15(1):21-32. doi:10.14802/jmd.21075

6. Zhang C, Lai Y, Li J, et al. Subthalamic and Pallidal Stimulations in Patients with Parkinson's Disease: Common and Dissociable Connections. *Ann Neurol*. 2021;90(4):670-682. doi:10.1002/ana.26199

7. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results: MDS-UPDRS: Clinimetric Assessment. *Mov Disord*. 2008;23(15):2129-2170. doi:10.1002/mds.22340

8. John van Geest Centre for Brain Repair, Department of Clinical Neurosciences, University of Cambridge, UK, Kouli A, Torsney KM, et al. Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis. In: John Van Geest Centre for Brain Repair, Department of Clinical Neurosciences, University of Cambridge, UK, Stoker TB, Greenland JC, John Van Geest Centre for Brain Repair, Department of Clinical Neurosciences, University of Cambridge, UK, eds. *Parkinson's Disease: Pathogenesis and Clinical Aspects*. Codon Publications; 2018:3-26. doi:10.15586/codonpublications.parkinsonsdisease.2018.ch1

9. DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci*. 1990;13(7):281-285. doi:10.1016/0166-2236(90)90110-v

10. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. *Trends Neurosci*. 1989;12(10):366-375. doi:10.1016/0166-2236(89)90074-x

11. Limousin P, Greene J, Pollak P, Rothwell J, Benabid AL, Frackowiak R. Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease. *Ann Neurol*. 1997;42(3):283-291. doi:10.1002/ana.410420303

12. Wong JK, Deuschl G, Wolke R, et al. Proceedings of the Ninth Annual Deep Brain Stimulation Think Tank: Advances in Cutting Edge Technologies, Artificial Intelligence, Neuromodulation, Neuroethics, Pain, Interventional Psychiatry, Epilepsy, and Traumatic Brain Injury. *Front Hum Neurosci*. 2022;16:813387. doi:10.3389/fnhum.2022.813387

13. França C, Carra RB, Diniz JM, Munhoz RP, Cury RG. Deep brain stimulation in Parkinson's disease: state of the art and future perspectives. *Arq Neuropsiquiatr*. 2022;80(5 Suppl 1):105-115. doi:10.1590/0004-282X-ANP-2022-S133

14. Erwin B. Montgomery Jr. *Movement Disorder Surgery: The Essentials*. Georg Thieme Verlag; 2009:b-002-56122. doi:10.1055/b-002-56122

15. Fang JY, Tolleson C. The role of deep brain stimulation in Parkinson’s disease: an overview and update on new developments. *Neuropsychiatr Dis Treat*. 2017;Volume 13:723-732. doi:10.2147/NDT.S113998

16. Wong JK, Viswanathan VT, Nozile-Firth KS, et al. STN Versus GPi Deep Brain Stimulation for Action and Rest Tremor in Parkinson's Disease. *Front Hum Neurosci*. 2020;14:578615. doi:10.3389/fnhum.2020.578615

17. Costentin G, Derrey S, Gérardin E, et al. White matter tracts lesions and decline of verbal fluency after deep brain stimulation in Parkinson's disease. *Hum Brain Mapp*. 2019;40(9):2561-2570. doi:10.1002/hbm.24544

18. Glover GH. Overview of functional magnetic resonance imaging. *Neurosurg Clin N Am*. 2011;22(2):133-139, vii. doi:10.1016/j.nec.2010.11.001

19. Markl M, Leupold J. Gradient echo imaging. *J Magn Reson Imaging*. 2012;35(6):1274-1289. doi:10.1002/jmri.23638

20. Elster AD. Gradient-echo MR imaging: techniques and acronyms. *Radiology*. 1993;186(1):1-8. doi:10.1148/radiology.186.1.8416546

21. Hillman EMC. Coupling Mechanism and Significance of the BOLD Signal: A Status Report. *Annu Rev Neurosci*. 2014;37(1):161-181. doi:10.1146/annurev-neuro-071013-014111

22. Chen JE, Glover GH. Functional Magnetic Resonance Imaging Methods. *Neuropsychol Rev*. 2015;25(3):289-313. doi:10.1007/s11065-015-9294-9

23. Kristo G, Rutten GJ, Raemaekers M, De Gelder B, Rombouts SARB, Ramsey NF. Task and task-free FMRI reproducibility comparison for motor network identification: Task and Task-Free fMRI Reproducibility Comparison for Motor Network Identification. *Hum Brain Mapp*. 2014;35(1):340-352. doi:10.1002/hbm.22180

24. Lee MH, Smyser CD, Shimony JS. Resting-state fMRI: a review of methods and clinical applications. *AJNR Am J Neuroradiol*. 2013;34(10):1866-1872. doi:10.3174/ajnr.A3263

25. Lozano CS, Ranjan M, Boutet A, et al. Imaging alone versus microelectrode recording–guided targeting of the STN in patients with Parkinson's disease. *J Neurosurg*. 2019;130(6):1847-1852. doi:10.3171/2018.2.JNS172186

26. Loh A, Gwun D, Chow CT, et al. Probing responses to deep brain stimulation with functional magnetic resonance imaging. *Brain Stimulat*. 2022;15(3):683-694. doi:10.1016/j.brs.2022.03.009

27. Heilicher M, Crombie KM, Cisler JM. Test-Retest Reliability of fMRI During an Emotion Processing Task: Investigating the Impact of Analytical Approaches on ICC Values. *Front Neuroimaging*. 2022;1:859792. doi:10.3389/fnimg.2022.859792

28. Artusi CA, Lopiano L, Morgante F. Deep Brain Stimulation Selection Criteria for Parkinson's Disease: Time to Go beyond CAPSIT-PD. *J Clin Med*. 2020;9(12):3931. doi:10.3390/jcm9123931

29. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect*. 2012;2(3):125-141. doi:10.1089/brain.2012.0073

30. Zhang Y, Wei H, Cronin MJ, He N, Yan F, Liu C. Longitudinal atlas for normative human brain development and aging over the lifespan using quantitative susceptibility mapping. *NeuroImage*. 2018;171:176-189. doi:10.1016/j.neuroimage.2018.01.008

31. Garrett DD, Samanez-Larkin GR, MacDonald SWS, Lindenberger U, McIntosh AR, Grady CL. Moment-to-moment brain signal variability: a next frontier in human brain mapping? *Neurosci Biobehav Rev*. 2013;37(4):610-624. doi:10.1016/j.neubiorev.2013.02.015

32. Kim HY. Statistical notes for clinical researchers: Nonparametric statistical methods: 1. Nonparametric methods for comparing two groups. *Restor Dent Endod*. 2014;39(3):235-239. doi:10.5395/rde.2014.39.3.235

33. Akoglu H. User's guide to correlation coefficients. *Turk J Emerg Med*. 2018;18(3):91-93. doi:10.1016/j.tjem.2018.08.001

34. Chan YH. Biostatistics 104: correlational analysis. *Singapore Med J*. 2003;44(12):614-619.

35. Song J, Desphande AS, Meier TB, et al. Age-Related Differences in Test-Retest Reliability in Resting-State Brain Functional Connectivity. Hampson M, ed. *PLoS ONE*. 2012;7(12):e49847. doi:10.1371/journal.pone.0049847

36. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage*. 2012;59(3):2142-2154. doi:10.1016/j.neuroimage.2011.10.018

37. De Zwart JA, Gelderen PV, Fukunaga M, Duyn JH. Reducing correlated noise in fMRI data. *Magn Reson Med*. 2008;59(4):939-945. doi:10.1002/mrm.21507

38. Kahan J, Mancini L, Flandin G, et al. Deep brain stimulation has state-dependent effects on motor connectivity in Parkinson's disease. *Brain J Neurol*. 2019;142(8):2417-2431. doi:10.1093/brain/awz164

39. Mueller K, Jech R, Růžička F, et al. Brain connectivity changes when comparing effects of subthalamic deep brain stimulation with levodopa treatment in Parkinson's disease. *NeuroImage Clin*. 2018;19:1025-1035. doi:10.1016/j.nicl.2018.05.006

40. Owens-Walton C, Jakabek D, Power BD, et al. Increased functional connectivity of thalamic subdivisions in patients with Parkinson's disease. *PloS One*. 2019;14(9):e0222002. doi:10.1371/journal.pone.0222002

41. van Hartevelt TJ, Cabral J, Deco G, et al. Neural plasticity in human brain connectivity: the effects of long term deep brain stimulation of the subthalamic nucleus in Parkinson's disease. *PloS One*. 2014;9(1):e86496. doi:10.1371/journal.pone.0086496

42. Mirdamadi JL. Cerebellar role in Parkinson's disease. *J Neurophysiol*. 2016;116(3):917-919. doi:10.1152/jn.01132.2015

43. Grafton ST. Contributions of functional imaging to understanding parkinsonian symptoms. *Curr Opin Neurobiol*. 2004;14(6):715-719. doi:10.1016/j.conb.2004.10.010

44. Jesse S, Kassubek J, Müller HP, Ludolph AC, Unrath A. Signal alterations of the basal ganglia in the differential diagnosis of Parkinson's disease: a retrospective case-controlled MRI data bank analysis. *BMC Neurol*. 2012;12(1):163. doi:10.1186/1471-2377-12-163

45. Wu T, Hallett M. The cerebellum in Parkinson's disease. *Brain J Neurol*. 2013;136(Pt 3):696-709. doi:10.1093/brain/aws360

Publishing Agreement

It is the policy of the University to encourage open access and broad distribution of all theses, dissertations, and manuscripts. The Graduate Division will facilitate the distribution of UCSF theses, dissertations, and manuscripts to the UCSF Library for open access and distribution. UCSF will make such theses, dissertations, and manuscripts accessible to the public and will take reasonable steps to preserve these works in perpetuity.

I hereby grant the non-exclusive, perpetual right to The Regents of the University of California to reproduce, publicly display, distribute, preserve, and publish copies of my thesis, dissertation, or manuscript in any form or media, now existing or later derived, including access online for teaching, research, and public service purposes.

DocuSigned by:
Katelyn Vu
6F1C1FB468F7476...
Author Signature

8/21/2023
Date