

Cortical Network Modulation by Subthalamic Nucleus Deep Brain Stimulation (DOT DBS 2)

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A Introduction

A1 Study Abstract

Deep brain stimulation of the subthalamic nucleus (STN DBS) in Parkinson disease (PD) can provide substantial motor benefit yet can also produce unwanted mood and cognitive side effects. Although the neural mechanisms underlying benefits and side effects are not well understood, current hypotheses center on the potentially measurable yet currently undefined effects within downstream cortical networks. Limitations of current tools have impeded attempts to assess network connectivity directly and dynamically in humans with implanted DBS; PET lacks the necessary temporal resolution while fMRI is neither optimal nor safe for patients with implanted DBS. In this proposal, to overcome these significant limitations, we apply high-density diffuse optical tomography (HD-DOT) methods to investigate how STN DBS modulates cortical functional networks and behavior in PD patients. HD-DOT uses a collection of functional near infrared spectroscopy (fNIRS) measurements, free of radiation exposure concerns, and without electrical/metal artifacts or contraindications or safety concerns for DBS. However, common fNIRS systems are critically hampered by typically sparse measurement distributions that lead to poor anatomical specificity, unreliable image quality due to crosstalk with scalp signals, poor spatial resolution, limited field of view, unstable point spread functions, and uneven spatial coverage. HD-DOT solves these problems by using high-density interlaced source and detector imaging arrays that support densely overlapping measurements and anatomical head models that together result in higher spatial resolution, stable point spread functions, and greatly improved isolation of brain signals from scalp signals. We have demonstrated that HD-DOT accurately maps functional connectivity (FC) within and between cortical resting state networks (RSNs) in the outer ~1cm of cortex with comparable temporal and spatial resolution to fMRI. Preliminary data in older controls and STN DBS patients that directly establish validity and feasibility for the proposed studies are provided.

A recent comprehensive evaluation of FC in PD (without DBS) using fMRI found reduced within-network FC in visual, somatomotor, auditory, thalamic and cerebellar networks and reduced between-network FC involving predominantly cortical RSNs (somatomotor, sensory and association), some of which correlated with cognitive and motor dysfunction in PD. Notably, striatal RSNs were not abnormal. These data suggest that PD affects the interrelationships of cortical networks in a behaviorally meaningful way, far downstream of focal subcortical neuropathology. STN DBS is known to alter activity in downstream cortical regions that function as nodes within these dynamic cortical networks supporting movement and cognition. Thus, cortical network FC may play a critical role in mediating the impact of STN DBS on motor and non-motor behavior. Location of the stimulating contact may further modulate these downstream effects, due to the complex functional organization of the STN region.

Study procedures include motor and cognitive tests, questionnaires, HD-DOT scanning, and MRI scans.

A2 Primary Hypothesis

We propose to investigate how STN DBS influences downstream cortical network FC using HD-DOT.

A3 Purpose of the Study Protocol

This information could lead to more efficient clinical optimization of DBS, identify potential cortical targets for less invasive neuromodulation, and lay the groundwork for future more complex experimental manipulations to determine the full range of STN DBS-induced cortical network responses to up-stream focal electrical perturbations, revealing fundamental properties of functional network plasticity.

B Background

B1 Prior Literature and Studies

Preliminary Data. We have preliminary data supporting our hypotheses, the scientific rationale and feasibility of our proposed project, and the sensitivity and validity of our chosen methods. We show that STN DBS affects cortical blood flow/hemodynamics (using PET and HD-DOT) and cognitive function^{5,50,63}, provide extensive and varied data on the validity and feasibility of HD-DOT for measuring resting state FC and task-induced responses in controls and PD patients with implanted STN DBS in different DBS conditions^{27,29,31,64}, preliminary data suggesting that HD-DOT can capture the reduced within and between network cortical FC in PD, and their response to STN DBS, evidence that our contact localization procedure is reliable⁶⁵, examples of using our 3D statistical approach for testing whether contact locations are significantly associated with outcomes of DBS^{8,48,66} and data showing the utility of our movement monitoring and correction procedures for HD-DOT analyses. These data are described in the background and scientific approach sections and have been substantially expanded since our original application.

Background. Regional cortical effects of STN DBS: STN DBS affects cortical function in a clinically significant and anatomically plausible manner in PD. STN DBS-induced changes in regional cerebral blood flow (rCBF) have been measured with PET by our group and others^{5,45,63,67-70}. This approach assumes that changes in rCBF reflect changes in neuronal activity⁷¹⁻⁷⁵ in target synaptic fields, including local interneurons^{71-73,76,77}. We found that STN DBS decreases blood flow in cortical regions downstream from the site of stimulation (Fig 216,63). In addition, the degree of STN DBS-induced cortical blood flow change correlated with degree of motor benefit or cognitive impairment induced by DBS^{5,67}. However, behavior is known to be mediated by dynamic brain networks, not single, static regions, so these analyses likely provide an incomplete view of the brain's dynamic and integrated response to DBS. Recent reviews have emphasized the idea that DBS profoundly alters dynamics between distributed interconnected cortical brain networks^{2,16,17,46}. Based on evidence from EEG, limited fMRI, and animal studies^{17,78-81}, it has been suggested that a primary mechanism of STN DBS's effects may be to modulate or interfere with functional relationships in downstream cortical regions, driving behavioral responses¹⁶.

Cortical networks in PD: Given this premise, investigators have sought to assess functional networks in DBS using PET and fMRI methods. Eidelberg et al. have described resting glucose metabolism patterns measured with PET, that distinguish groups, change with DBS, or that correlate with cognitive or motor impairment^{45,69,70,82}. This approach has been useful but is limited in terms of its temporal resolution (each scan lasts several hours), ability to assess FC, and the ability to easily investigate multiple conditions (e.g. DBS settings) in an individual due to radiation exposure and time constraints. Resting state functional connectivity using fMRI, a more flexible methodology free of these limitations, is sensitive to the intrinsic spontaneous neural activity correlated on a time scale of tens of seconds (frequencies below 0.1 Hz) within constellations of regions distributed over widely separated parts of the brain. The corresponding topographic patterns are known as resting state networks (RSNs) and can be measured in the cortex equally well via fMRI BOLD or by HD-DOT^{27,29,30,83} (and preliminary data).

The measurement of RSNs within disease states and in response to treatments has led to profound insights into the neuropathophysiology underlying behavioral symptoms⁸⁴⁻⁸⁸. In PD, results from past studies have been varied, likely due to between subject clinical heterogeneity, small samples and limited motion control⁸⁹. However, a recent comprehensive examination of RSN abnormalities in PD (including members of our team) applied cutting-edge and converging analysis techniques and rigorous quality control measures to a large sample of non-demented PD patients, scanned while off medications, and controls. Analyses revealed reduced between-network FC involving predominantly cortical RSNs (somatomotor, visual, auditory, salience, and frontoparietal) and reduced within-network FC in predominantly somatomotor, visual, auditory, thalamic, and cerebellar networks³⁷. Some of these effects correlated with cognitive and motor dysfunction in PD. Notably, although there were some differences in subcortical-cortical FC, most of the largest differences were found in cortex; striatal RSNs were not abnormal³⁷ (Fig 3). Others have suggested that the abnormality of functional networks measured before DBS electrodes are implanted can predict the clinical response patients experience to DBS^{14,17}. These studies suggest the importance of functional networks in PD and DBS responses, but do not explore DBS-induced change in within and between-network FC.

Cortical networks in STN DBS: Notably, several groups have attempted to measure DBS-induced changes in FC using fMRI in small samples of DBS subjects on a low strength magnet (1.5T)^{81,90-92}. The largest of these 1.5T studies had 13 patients and found that STN DBS increased FC between left and right motor cortex and between motor cortex and thalamus and cerebellum⁸¹. However, data were collected only 1-3 days post-surgery and so could be confounded by microlesion or other surgical effects. In addition, significant signal artifact around the wires and electrodes limited analyses. Another study reported preliminary safety data from 3T fMRI¹⁵. Although no adverse events occurred and there was no evidence of heating at the tip of the electrode, the authors concluded that there was “significant artifact” from the electrode leads that impacted functional data quality and that more extensive testing for safety would be needed before this method could be recommended^{15,93,94}. Finally, one study on sedated pigs implanted with STN DBS electrodes used fMRI to measure the impact of short bursts of unilateral STN DBS in a quasi-event-related design (repeating trials of 6s DBS ON, 120s DBS OFF). For the hemodynamic response to DBS ON, they found increased BOLD response in many ipsilateral cortical regions (somatomotor, prefrontal) and contralateral temporal cortex (Fig 4), but they did not perform functional network analyses⁹⁵. Thus, despite strong interest in applying fMRI to these questions, we are currently unable to use it safely and effectively to measure DBS-influenced network properties in humans.

HD-DOT and FC: Functional imaging methods without the high magnetic field limitations of fMRI allow us to understand the impact of DBS on the FC of organized networks within the brain¹⁶. HD-DOT, which uses high density imaging arrays (>1800 SD-Pairs), coupled with anatomical-based tomography reconstructions, has been developed to dramatically improve the image quality beyond traditional fNIRS. Tomographic reconstruction techniques that incorporate subject specific anatomy derived from MRI structural scans provide three-dimensional simultaneous images of brain hemodynamics to a depth of 2 cm from the scalp (outer ~1 cm of cortex)²⁷. The Culver (co-PI) lab developed this HD-DOT technology through a series of improvements including new instrumentation capable of supporting the dynamic range and noise specifications needed for HD-DOT arrays, which enabled the first optically based angular and

eccentricity maps of the human visual cortex²⁴. Further developments in FC⁹⁶ such as registering HD-DOT data to anatomy^{27,29}, spatial normalization³¹ and large field-of-view instrumentation²⁷ has led to cortical mapping performance that is comparable to fMRI within the HD-DOT field-of-view. We have validated these measures with both task (Fig 5) and resting state (Fig 6) results in younger controls²⁷ and in our preliminary data from older controls (manuscript in preparation). We have developed portable systems that can go into intensive care units^{30,97} and also larger HD-DOT systems for dedicated imaging bays²⁷; the latter is used in this grant.

HD-DOT and STN DBS: Our previous study²⁷ and preliminary data (Figs 5-8) demonstrate that HD-DOT can measure activations and FC in PD and in response to STN DBS.

STN DBS activation: This dataset is new for this revision. In order to demonstrate HD-DOT's ability to detect cortical activations induced by STN DBS, we scanned 5 STN DBS patients (1 female, 4 males; ages 57-63, mean = 61.2) with HD-DOT while their DBS was turned ON and OFF in a classic block design, similar to the Min et al. paper⁹⁵. To make the testing maximally tolerable for these patients, they watched a 10-minute movie during the study, medications were not withdrawn, and the left DBS was in the ON condition throughout. The right DBS was turned ON and OFF repeatedly (n=22) in the following pattern: 8 sec ramp up, 18 sec ON, 16-24 sec OFF (OFF period randomly jittered between 16 and 24 sec (Fig 7a)). Clinically optimized settings were used for the ON conditions. Data were compared to a set of 5 healthy adult controls who were also scanned watching the same movie clip for the same amount of time. Data were censored for movement detected with accelerometers on the HD-DOT cap or observed in person. ON/OFF blocks were compared within 3 STN DBS patients with no overt symptoms in the ON or OFF states and identical timeframes were compared in Controls. Results (Fig 7) show that DBS decreased oxygenated hemoglobin in right primary motor cortex in patients (red arrow), similar to our previous PET study (Fig 1) and in the same region (although opposite direction) of the sedated pig study (Fig 4)⁹⁵. (Notably, anesthesia is known to reverse regional blood flow effects of pharmacological challenges⁹⁸.) The corresponding area in controls did not change. These new results suggest that HD-DOT can detect the expected regional decrease in blood oxygenation predicted by PET blood flow imaging, which is consistent with the known neurophysiology of STN-thalamocortical pathways.

STN DBS task and resting state: To determine the ability of HD-DOT to measure the impact of STN DBS on within and between network FC, we scanned 12 normal controls and 11 PD patients with STN DBS (Table 2). This dataset represents a 60% increase in subjects scanned since our original submission. PD patients were off PD medications overnight before the study and were scanned and tested in the DBS ON and DBS OFF state in a counterbalanced order. After each change in DBS settings, we waited 45min for symptoms to stabilize before scanning or testing. Controls were scanned and tested in 2-3 identical blocks, separated by a 45 min wait. For each block, HD-DOT data were acquired during visual stimulation (block design with flickering checkerboard, 8 min), auditory stimulation (block design with listening to words, 4 min) and 30 min of resting state (3x10 min blocks of fixating on a crosshair). The entire block took 45 min to perform. During scanning, movement was monitored with digital-video, eye tracking, and accelerometers. After scanning, kinematic and UPDRS assessments were also acquired. HD-DOT data were scrubbed for motion artifacts and analyzed according to procedures described in Methods, below.

We had sufficient data that survived motion scrubbing for resting state analyses (DBS OFF = 338 of 460 min, 73%; DBS ON = 350 of 690 min, 51%; Controls = 866 of 1130 min, 77%). These data suggest that we can acquire enough high-quality data in groups and conditions to perform reliable analyses. Task data yield lower percentage of high-quality data because data are excluded block-wise rather than frame-wise (DBS OFF = 29.2 of 135 min, 22%; DBS ON = 27 of 173.5 min, 16%; Controls = 115.5 of 338 min, 34%).

Results confirmed the validity and feasibility of collecting HD-DOT data sufficient to test our hypotheses. Auditory and visual activation tasks evoked anatomically appropriate patterns in both older adult controls and PD patients (Fig 5), consistent with our previous studies²⁷. In addition, PD subjects with DBS OFF had reduced within network FC in somatomotor, visual and auditory RSNs and between network FC with somatomotor and auditory RSNs, as found by Gratton et al.³⁷ (Fig 8, top row). We also observed that somatomotor to frontoparietal network connectivity was greater in PD than controls. Finally, turning DBS ON appears to alter FC within and between network connectivity for somatomotor, auditory, DMN, and other RSNs (Fig 8, bottom row). Interestingly, the region identified as having decreased blood flow in our activation study (Fig 7) was included in the somatomotor (SM) seed set (Fig 8, red arrow); DBS decreased FC in this region. Importantly, we have not applied any statistical tests to these comparisons, due to our limited sample size and so cannot definitively interpret these patterns. With the data collected in the proposed study, however, we will be able to confirm or rule out these initial observations and test our explicit hypotheses.

B2 Rationale for this Study

Deep brain stimulation of the subthalamic nucleus (STN DBS) in Parkinson disease (PD) can provide substantial motor benefit yet can also produce unwanted mood and cognitive side effects. Although the neural mechanisms underlying benefits and side effects are not well understood, current hypotheses center on the potentially measurable yet currently undefined effects within downstream cortical networks. Limitations of current tools have impeded attempts to assess network connectivity directly and dynamically in humans with implanted DBS; PET lacks the necessary temporal resolution while fMRI is neither optimal nor safe for patients with implanted DBS. In this proposal, to overcome these significant limitations, we apply high-density diffuse optical tomography (HD-DOT) methods to investigate how STN DBS modulates cortical functional networks and behavior in PD patients.

C Study Objectives

C1 Primary Aim

1. To determine cortical FC abnormalities in pre-surgical PD using fMRI and HD-DOT. We expect the PD group to have reduced within-network FC compared to controls in the somatomotor, auditory and visual RSNs, and reduced between-network FC replicating Gratton et al. fMRI will provide within and between-group validation of HD-DOT for cortical FC, and also allow assessment of the relationship between the cortical and the subcortical/cerebellar RSNs.

C2 Secondary Aim

2. To determine the impact of STN DBS on cortical FC with HD-DOT. After PD patients from Aim 1 undergo STN DBS surgery and clinical optimization, they will be scanned with HD-DOT in ON and OFF STN DBS states in a double-blind and counterbalanced manner. We hypothesize that STN DBS will alter FC within and between networks identified as abnormal in Aim 1. We also will compare pre and post-surgery (OFF DBS) HD-DOT scans to understand any effects of time/surgery on FC.

3. To determine how STN DBS-induced change in cortical FC relates to the anatomical location of DBS contacts. A 3D statistical mapping method with control for multiple comparisons will be applied to Aim 2 data. We hypothesize that STN DBS-induced changes in FC will be related to the location of the stimulating contact, with more dorsal contacts related to greater change in somatomotor FC and more ventral contacts related to greater change in frontoparietal FC.

4. To determine how STN DBS-induced change in cortical FC relates to change in behavior. PD patients will perform motor, cognitive, and mood testing in ON and OFF STN DBS states. We will test the hypothesis that motor response to DBS relates to changes in somatomotor FC, and that cognitive response relates to changes in frontoparietal FC.

C3 Rationale for the Selection of Outcome Measures

Cognitive Measurements: During the phone screening, for characterization and screening purposes, PD patients will be tested pre- and post- surgically and controls will be tested with the **Montreal Cognitive Assessment (MoCA; a brief screening instrument for mild cognitive dysfunction)**, those with scores <16 out of 22 will be excluded. After each scanning block, subjects will perform the NIH Toolbox tasks. To begin to establish a common test battery that could be used across future studies, we will perform a subset of the NIH Toolbox Tests that is appropriate for ages 3-85 and so will work for our age range (50-76) now and in the future, should they be followed further. A goal of this toolbox is to provide a “common currency” for cognition that can then be used to compare across studies, and monitor neurological and behavioral functions over time. Our decision to add tasks from the NIH Toolbox is motivated by a desire to establish some commonalities in tests going forward and to identify more specific cognitive components than is possible with typical multidimensional clinical neuropsychological tests. There is significant local expertise with the NIH Cognitive Toolbox based at WU that can be used to facilitate our use of this tool. The selected tasks are: 1) **Picture Vocabulary Test**; to be completed by the participant, measures receptive vocabulary (4 min). Accuracy will contribute to the Verbal IQ domain 2) **Picture Sequence Memory Test**; assesses episodic memory and takes 7 minutes. Percent accuracy will contribute to the Memory Domain. 3) **Flanker Inhibitory Control and Attention Test**; measures attention and inhibitory control (3 min). Accuracy will contribute to the Executive Function Domain. 4) **Dimensional Change Card Sort Test**; measures cognitive flexibility (4 min). Accuracy for switch and non-switch trials will contribute to the Executive Function Domain. 5) **List Sorting Working Memory Test**; assesses working memory and requires sequencing of visually- and orally presented stimuli. Accuracy will contribute to the Executive Function Domain. 6) **Oral Reading Recognition Test**; the participant will be requested to perform a brief reading test that provides an estimated IQ. 7) **Info Seeking Task**; task requires individuals to make choices between pictures of stacks of coins based on available information about risk.

Performance reflects an individual's risk tolerance and tendency to value information. These data will be used to ensure similarity of the overall cognitive level across groups and subgroups and may be covaried from certain analyses. STN DBS effects on these cognitive control processes have been investigated and replicated by other groups.

Mood Measurements: Subjects will be given the Geriatric Depression Rating Scale (GDRS; a questionnaire assessing the depression symptoms) and the Spielberger Trait Anxiety Instrument (STAI; questionnaire on lifetime symptoms). We used these measures in our previous studies of STN DBS. PD patients will complete these questionnaires pre- and post-surgically; controls will complete them at enrollment. During each imaging testing session, subjects will perform the Visual Analog Scales (VAS) which assesses the self-reported arousal and mood valence. This test is brief, repeatable, sensitive, and validated. VAS data will be used to determine the effects of stimulation location on overall change in mood valence and arousal, and the direction of these changes. We successfully used these methods in our previous PD and STN DBS studies.

D Investigational Agent

Not applicable.

E Study Design

E1 Overview or Design Summary

MRI, fMRI, HD-DOT, motor, and cognitive measures will be acquired from the Pilot Group, Pre-surgical PD patients, Post-surgical PD patients (no MRI, fMRI) and controls. MRI/fMRI is collected on the Pilot, Control, and Pre- and Post-surgical PD patient Groups. HD-DOT is collected on all subjects at all timepoints Pilot Group, Control, and Pre and Post-surgical PD patient Groups.).

E2 Subject Selection and Withdrawal

We use a within-subject and between-group study design. We will include up to 10 participants for the Pilot Group. Our target dataset is 30 PD patients with STN DBS, 30 PD patients intending to get STN DBS, and 30 age and sex-equivalent controls, based on power estimates and feasibility constraints. Under certain circumstances, the investigator or the NIH might decide to end a patient's participation in this research study earlier than planned. This might happen for no reason or because, in the PIs' judgment, it would not be safe for the patient to continue because their condition has become worse, because the patient became pregnant, because funding for the research study has ended, or because the sponsor has decided to stop the research.

2.a Inclusion Criteria

STN DBS: The group includes both the Pre- and Post-surgical DBS groups (see below). STN DBS patients will be males or females between 50 and 76 years of age who meet criteria for clinically definite PD. Approximately 40 PD patients undergo STN DBS implantation per year at our institution. We would need to recruit and successfully run 12 patients through our protocol per year to achieve our goal of 60 PD patients. Given the

possibility for data loss or subject drop out, we anticipate needing to enroll 25% more PD subjects (up to 75 or 15 per year) at the pre-surgical stage. In previous work, we were able to recruit and complete data collection on 80 STN DBS patients over 5 years (16 per year) in a significantly more complex, multi-day and invasive PET study.

Post-Surgical: Subjects with PD who have undergone bilateral STN DBS surgery will be recruited from the DBS program within the Movement Disorders Clinic at WUSM (directed by Dr. Ushe, co-I).

Pre-Surgical: Subjects with PD who have been clinically consented for bilateral STN DBS surgery but have not yet had the surgery, will be recruited from the DBS program within the Movement Disorders Clinic (MDC) at WUSM (directed by Dr. Ushe, co-I).

Controls: Controls will match the age and sex distributions of the DBS groups. Due to the possibility for data loss from motion, we anticipate enrolling up to 40 subjects in order to get 30 with sufficient high-quality data.

Pilot Group: Participants (ages 20-76 years) who enroll as part of the Pilot Group of up to 10, will follow the same inclusion criteria as the Control group with the exception of matching the age and sex distribution of the DBS group. The purpose of this group is to test the fluidity of the testing day as well as all of the measures, assessments and scans (DOT and MRI). The data from these participants could be included in the final data analysis and will be included in resulting publications.

2.a Exclusion Criteria

STN DBS:

Post-Surgical:

Patients who have had DBS surgery will have passed clinical screening for neurological and psychiatric comorbidities during their pre-surgical testing. In addition, post-surgical patients who experience clinically determined dementia manifesting after surgery, significant complications of surgery (e.g., stroke) and/or an inability to tolerate off DBS states will also be excluded for:

Pre-Surgical:

See exclusions for all groups below.

Control:

See exclusions for all groups below.

Pilot Group:

See exclusions for all groups below.

For all groups: potential participants may not participate in the study if:

- they have significant past or current neurologic or psychiatric diagnosis,
- they are currently experiencing untreated major depressive disorder with or without psychosis,
- they have had hallucinations in the past year that have stopped without any additional hallucination(s) in the last 6 months,
- they have any other condition which could interfere with testing (e.g., severe visual loss, non-English speaking, illiteracy),

- they are pregnant,
- if at any point in time prior to they score <23 out of 30 on the full MoCA or <16 out of 22 on the phone MoCA (administered over the phone during the screening call)and/or
- a condition that would disqualify the participant from having an MRI for health or safety reasons.

2.b Ethical Considerations

Not applicable.

2.c Subject Recruitment Plans and Consent Process

The enrollment process is very similar for each group. There are four participant groups: Pilot Group, Control Group, STN DBS PD Pre-OP Group, STN DBS PD Post-Op group. Study population consists of: 30 STN DBS PD, 30 Pre-Surgical STN DBS PD, 30 Control participants, and 10 Pilot Group participants

Recruitment Materials: In addition to providing postcards with study information on them to clinicians to pass along to interested patients in the clinic, we will utilize the television located in the waiting area of the WU MDC to advertise for the study. The advertisement will be a one-page slide that is a large slide of the postcard complete with study contact information for questions. This slide will run continuously in a loop with other studies. Many DBS patients are accompanied by another adult to their clinic visit, the slide will be used to recruit DBS, control, and pilot groups.

The following methods will be used to recruit participants:

A. If needed, Pilot subjects will be recruited from Volunteers for health. We will recruit up to 10 participants for the pilot group. It is possible that not all 10 participants will participate in all portions of the study. For example: if after 3 pilot runs the HD-DOT scan meets expectations and is ready to go, there is no need to test additional pilot participants on this portion of the study.

B. Appropriate Pre and Post DBS subjects will be identified by WU MDC physicians and nurses at their clinic visits. The clinician will tell them about the study and answer any questions that they can. The clinician will then offer the patient a postcard with study details and contact information for study staff and offer to pass their name along to the study coordinator to contact the patient. If requested, study coordinator will then contact the potential subject and review the study, assess interest and conduct the phone screen. If patient is interested and would like to proceed, their study visit will be scheduled as appropriate.

C. Patients of the WU MDC are entered into the MARS and EPIC patient databases as they are seen clinically in the Movement Disorders Clinic. MARS is controlled/managed by Karen Klumpp, Database Administrator (314-341-1395). In order to access this database, Karen Klumpp assigns designated study team members a username and password. Study staff are required to complete training on the rules/ regulations of using the MARS and EPIC database before accessing them. In order to generate a list of potential study candidates, a query with the study parameters is created and only the patients who meet these criteria will be generated into a list. This list will be reviewed for

any not so obvious exclusions and the remainder will be used to contact potential participants.

In addition, Pre and Post PD DBS patients and their accompanying controls will be handed a copy of the study informational postcard at their clinic visit. If they are interested, they can contact the study coordinator.

1. The general public is encouraged to voluntarily enroll in the Volunteers for Health Participant Registry managed by the Volunteers for Health office at Wash U. In order to utilize this database, the study protocol is submitted to VFH, the protocol accepted and then the study coordinator submits the parameters of the study and the volunteers who meet these criteria will be generated into a list. This list is then sent to the study coordinator and those potential subjects will be contacted. After all participants on the list are contacted (or multiple attempts made) then it is returned to VFH with notes saying such and, if needed, another list is generated.

2. The study team member (STM) then contacts the potential control participants and reviews the protocol as well as the inclusion/exclusion criteria and gives them an opportunity to ask any questions they may have. If the subject seems interested, the STM will ask to send them a consent form for their review and encourage them to call with any questions. A follow-up call is made by the STM to either answer questions or to schedule the subject to come in.

3. Once the subject is scheduled, they will be given the choice of receiving the consent form via e-mail or the USPS and will receive a confirmation of their study date and time. They will receive a reminder call 2-5 days before their scheduled visit. The participant will receive a call the day prior to the study visit to be screened for COVID 19 symptoms and then will be asked to complete an online screening for COVID 19 symptoms prior to arriving the day of their study visit via the REDCap link provided in their scheduling email. The control will be consented in-person prior to starting their study visit.

4. For Pre- and Post-surgical DBS patients a STM will obtain the participant's consent prior to starting their study visit. Participants are asked to remain on their PD medicine throughout the study. Study staff will provide participants with the name and contact information for the study neurologist (Dr. Ushe) and the study nurses who they can contact if they have any problems or questions while in the study.

* It is possible for DBS participants to be in both the STN DBS PD Pre-Op and Post-Op groups, or they can be in one or the other.

5. Payment for study participation is mentioned in the order that it is listed in the consent form and there is no special emphasis placed on compensation. Physician referral will be passed along to the study coordinator with the patient's permission. It will be made very clear to each patient that their decision to participate or not to participate in the study in no way impacts their clinical treatment.

If recruiting PD patients pre-surgically or keeping pre-surgical patients in the study pre to post surgery becomes unexpectedly difficult, we will consider recruiting additional STN DBS subjects post-surgically only. For these subjects, if a pre-surgical MRI is not available, we would still be able to analyze their HD-DOT data by adapting an atlas-based light model to generate the subject-specific sensitivity profiles. While atlas-based

light models may introduce errors due to internal structural differences we have found these to be <5mm.

Timeline: Year 1: IRB approval, instrumentation and testing materials assembled, team training, REDCap database set up, dry runs and problem solving with the Pilot Group. Begin enrolling and scanning individuals in the PD and Control Group. Year 2-4: Enroll and scan PD and Controls, score and enter behavioral data, process MRI/fMRI and HD-DOT data in pipelines to be ready for statistical analyses, make quality control determinations on collected data, determine number of additional datasets required to meet goals. Year 5: Finish data collection, perform planned statistical analyses, prepare manuscripts, report findings.

2.d Randomization Method and Blinding

Data collection will occur while DBS stimulators are ON or OFF. Conditions will occur in a counterbalanced order across patients. DBS patients and Dr. Ushe will be blind to the condition DBS stimulators are on during the data collection. A trained staff member will turn the DBS stimulators ON and OFF according to the counterbalance scheme.

2.e Risks and Benefits

HD-DOT Imaging: HD-DOT requires placement of optodes (optical fibers) onto the skin of the scalp. The light emitting diodes used to make the measurements have very low power. The intensity used to monitor brain hemodynamics will be considerably less than the amount of light the brain would receive during an outdoor walk on a sunny day and is therefore considered to be harmless. Thus far, no hazard has been observed.

Importantly, should the patient be uncomfortable or should any emergency arise, the patient is free to request a break from the imaging cap or that the experiment be paused or stopped. Patients will be in contact with an investigator at all times during the study.

Likely: Though there are no known risks involved with near-infrared imaging, patients may experience fatigue, short-term musculoskeletal discomfort (stiffness) or boredom from holding their head still for an extended period of time and performing repetitive tasks.

Less likely: The imaging cap is held on firmly with a chin strap. In some cases, the strap may push uncomfortably against the chin or the tight-fitting cap may make the patients' head warm. If these situations were to occur, the cap can be readjusted to improve comfort.

Rare: Though unlikely to occur, the tips of the optodes (sources and detectors) may press or scrape uncomfortably against the scalp. If the optodes becomes at all painful, patients may notify the investigator immediately, and the session will be terminated.

MRI imaging: Patients will undergo an MRI if they are in the Pilot Group, Control or Pre-Surgical Groups only. It is possible that not all participants in the Pilot Group will be scanned as the number of participants scanned will be limited to the number of scans needed to test the MRI imaging protocol. By administering the MRI safety form at the initial screening call and reviewing the MRI safety form again the day of the scan, it will be determined if it is safe for them to do the MRI scan. The MRI uses strong magnetic fields and weak radio waves. The magnitude of these and the duration of exposure will be similar to that used by a radiologist in standard clinical use of MRI. These exposures

are thought to be extremely safe, and presently no limit exists for the number of MRI studies one may have in a lifetime. Of course, there is the possibility that some unknown risk does exist.

Patients may be uncomfortable inside the MRI scanner if they do not like to be in closed spaces ("claustrophobia"). During the procedure, patients will be able to talk with the MRI staff through a speaker system. Patients can tell them to stop the scan at any time. We will also provide patients with a chance to get used to being in an MRI scanner before the scan is performed in our mock (practice) MRI scanner.

The MRI scanner produces a loud hammering noise, which has caused hearing loss in a very small number of patients. Patients will be given earplugs to reduce this risk.

There is a risk of burns that could be serious.

If patients have a device such as a pacemaker, bone hardware, or device placed in the uterus there may be additional risks. We will review what device patients may have and inform them of these risks. In general, these risks could be:

- heating or movement of the device
- device malfunction
- damage to the tissue that surrounds the device.

Likely: Lying in the MRI scanner for approximately 90 minutes may cause physical discomfort from trying to lie still. Some people get muscle aches and pains from lying on their back. This will be minimized by providing cushions at pressure points and beneath the knees as desired.

Less Likely: None

Rare: None

As mentioned above, there are certain criteria that could prevent patients from having an MRI as part of this study. Participants will undergo a thorough MRI screening on the screening call to ensure they are safe to proceed with the study. In addition, due to the following conditions, participants will be excluded from the study if they have any of the following:

- piercings on the head, shoulder or neck area that cannot be removed.
- any tattoos on the head, shoulder or neck area (including cosmetic tattoos such as eyeliner and/or lip-liner).
- medical devices such as an insulin pump or a continuous glucose monitor that cannot be removed for 90 minutes.
- a full set of braces (top and bottom).

Because many clothing items, such as sportswear, contain metal, as an extra safety precaution, before the MRI the study staff will ask patients to change into a disposable gown and pants. Patients will be provided with a private area to change into the MRI safe clothing and a private area to change back into their clothing after the MRI.

DBS Setting Changes: DBS patients will have their stimulators OFF or ON. The ON condition will be at the settings normally used for clinical care. Thus, risks are associated only with the OFF condition and with the actual switching of conditions, but typically not

with the ON condition. None of the commonly experienced side effects of OFF or switching ON/OFF are dangerous, permanent or require any intervention other than changing the stimulator settings.

Likely: In the OFF condition, patients may experience a significant increase in your motor symptoms.

Less Likely: When changing stimulator conditions, patients may experience temporary sensations, movements, difficulty with speech, general feeling of discomfort or unease, muscle cramps, blurred vision, eyelid closing, numbness, tingling or mood change.

Rare: None

Women capable of becoming pregnant: will be asked to have a pregnancy test before beginning this study. Women must use effective birth control methods and try not to become pregnant while participating in this study. If a woman does become pregnant, there may be unknown risks to the unborn child, or risks to the unborn child that we did not anticipate. There may be long-term effects of the treatment being studied that could increase the risk of harm to an unborn child. Patients must tell the doctor if their birth control method fails while they are on the study. If a patient believes or knows that they have become pregnant while participating in this research study, patients will be asked to contact the research team member identified at the top of this document as soon as possible.

Patients may not participate in this study if they are pregnant. If patients are capable of becoming pregnant, we will perform a pregnancy test before exposing them to research-related radiation. Patients must tell us if they have become pregnant within the previous 14 days because the pregnancy test is unreliable during that time.

If the patient is a sexually active male, it is important that their partner not become pregnant during their participation in this study. There may be unknown risks to the unborn child or risks we did not anticipate. The participant and their partner must agree to use birth control if they want to take part in this study. If the patient believes or knows that their partner has become pregnant during their participation in this study, they will be asked to contact the research team member identified at the top of this document as soon as possible

Breach of Confidentiality: One risk of participating in this study is that confidential information about the patient may be accidentally disclosed. We will use our best efforts to keep the information about patients secure. Please see the section in this consent form titled “How will you keep my information confidential?” for more information.

2.f Early Withdrawal of Subjects

Under certain circumstances, the investigator or the NIH might decide to end a patient's participation in this research study earlier than planned. This might happen for no reason or because in the PIs' judgment it would not be safe for the patient to continue, because their condition has become worse, because they patient became pregnant, because funding for the research study has ended, or because the sponsor has decided to stop the research.

2.g When and How to Withdraw Subjects

If a patient is too uncomfortable in any DBS condition, they will be withdrawn from the study. Dr. Ushe or trained staff will be present during all study days to supervise this aspect of the study.

2.h Data Collection and Follow-up for Withdrawn Subjects

Not applicable.

E3 Study Drug

Not applicable.

F Study Procedures

F1 Screening for Eligibility

Participants in all four groups will be screened using the Inclusion/Exclusion Screening form to determine study eligibility. Participants in the pilot, control and pre-surgical groups will be screened using the MRI screening form to determine MRI eligibility.

F2 Schedule of Measurements

Cognitive Measurements: For characterization and screening purposes, all participants will be tested with the phone version of the Montreal Cognitive Assessment (MoCA) at the screening call and will be excluded at this point if their score is <16 out of 22. In addition, PD patients will be tested post- surgically as well. The clinical version of the **Montreal Cognitive Assessment MoCA**) which is a brief screening instrument for mild cognitive dysfunction, those with scores <23 out of 30, currently or at any time in the past, will be excluded. In order to increase participant safety and minimize time spent in the testing environment due to COVID 19, the MoCA Blind (phone) version 8.1 (validated) will be administered to potential participants during the phone screen. To begin to establish a common test battery that could be used across future studies, we will perform a subset of the NIH Toolbox Tests that is appropriate for ages 3-85 and so will work for our age range (50-76) now and in the future, should they be followed further. A goal of this toolbox is to provide a “common currency” for cognition that can then be used to compare across studies, and monitor neurological and behavioral function over time. Our decision to add tasks from the NIH Toolbox is motivated by a desire to establish some commonalities in tests going forward and to identify more specific cognitive components than is possible with typical multidimensional clinical neuropsychological tests. There is significant local expertise with the NIH Cognitive Toolbox based at WU that can be used to facilitate our use of this tool. The selected tasks are: 1) **Picture Vocabulary Test;** to be completed by the participant, measures receptive vocabulary (4 min). Accuracy will contribute to the Verbal IQ domain 2) **Picture Sequence Memory Test;** assesses episodic memory and takes 7 minutes. Percent accuracy will contribute to the Memory Domain. 3) **Flanker Inhibitory Control and Attention Test;** measures attention and inhibitory control (3 min). Accuracy will contribute to the Executive Function Domain. 4) **Dimensional Change Card Sort Test;** measures cognitive flexibility (4 min). Accuracy for switch and non-switch trials will contribute to the Executive Function Domain. 5) **List Sorting Working Memory Test;** assesses working memory and requires sequencing of visually- and orally presented stimuli. Accuracy will contribute to the Executive Function Domain. 6) **Oral Reading**

Recognition Test; the participant will be requested to perform a brief reading test that provides an estimated IQ. 7) **Info Seeking Task;** task requires individuals to make choices between pictures of stacks of coins based on available information about risk. Performance reflects an individual's risk tolerance and tendency to value information. These data will be used to ensure similarity of the overall cognitive level across groups and subgroups and may be covaried from certain analyses. After each scanning block, subjects will perform the Flanker Inhibitory Control and Attention Test, List Sorting Working Memory Test, the Dimensional Change Card Sort Test and the Info Seeking Task. STN DBS effects on these cognitive control processes have been investigated and replicated by other groups.

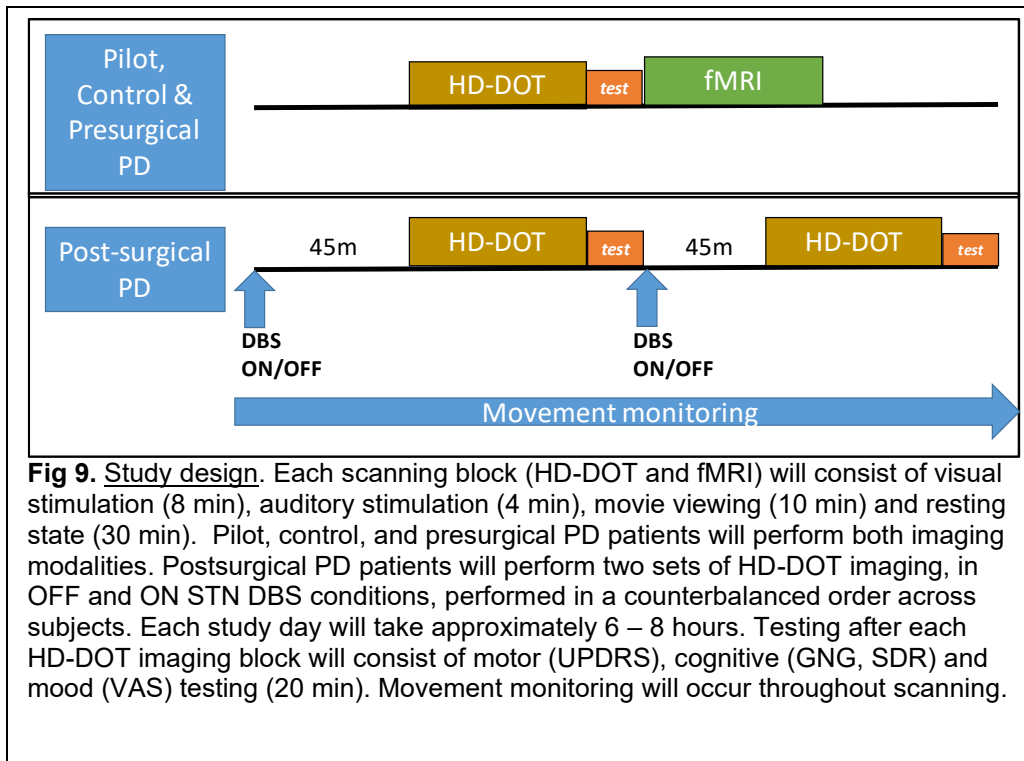
Mood Measurements: Subjects will be given the Geriatric Depression Rating Scale (GDRS; a questionnaire assessing the depression symptoms) and the Spielberger Trait Anxiety Instrument (STAI; questionnaire on lifetime anxiety symptoms). We used these measures in our previous studies of STN DBS. PD patients will complete these questionnaires pre- and post-surgically; controls will complete them at enrollment. During each imaging testing session, subjects will perform the Visual Analog Scales (VAS) which assesses the self-reported arousal and mood valence. This test is brief, repeatable, sensitive, and validated. VAS data will be used to determine the effects of stimulation location on overall change in mood valence and arousal, and the direction of these changes. We successfully used these methods in our previous PD and STN DBS studies.

Imaging acquisition: MRI/fMRI imaging: MRI scanning will be performed on Controls and pre-surgical PD patients. These images will be collected on a 3T Siemens PRISMA and include: (i) a 3D MPRAGE (T1) sequence (TR=2500 ms, TI=1070 ms, TE=2.9 ms, FA=8°, 1.0 mm³ voxels, *6:09-8:42 min); (ii) a T2-weighted sequence (TR=3200 ms, TE=564 ms, 1.0 mm³ voxels, *4:42-6:51 min); (iii) a BOLD sensitized fMRI (TR=1230 ms, TE=33 ms, 2.4 mm³ voxels, 11:10 min) for both task and rs-fcMRI, and (iv) an asymmetric spin echo (ASE) field map (TR=6470 ms, TE=60 ms, 2.4 mm³ voxels, 0:26 min), (v) and if time permits, two sets of 99 direction DWI at both b1500 and b3000 (TR=3500 ms, TE=83 ms, 2.0 mm³ voxels, 6:14 min) as it will better identify patient subcortical anatomy which is useful in contact localization. For T1 and T2 scans, short 3D echo-planar imaging volumetric navigators are embedded in a long 3D sequence, and the resulting image volumes are registered to provide an estimate of the subject's location in the scanner at a cost of less than 500 ms, ~ 1% change in contrast, and ~3% change in intensity. Minimum and maximum acquisition times are provided; actual times depend on the amount of motion correction required.

HD-DOT imaging: Our HD-DOT instrumentation provides a flexible infrastructure for expansion of the field-of-view to directly target additional areas within and around motor cortex that are expected to be modulated by STN DBS. We recently expanded two of our three large FOV HD-DOT systems to 128 sources and 128 detectors. We will move this DBS project to one of these 128x128 systems (Fig 11). To locate the cap on the head we will measure the distance between fiducials on the optode array and the head using an automated photometric approach. Anatomical landmarks based on the 10/20 international system (including nasion, inion, pre-auricular points and Cz) will be used for fiducials. To ensure adequate optode coupling across the cap, a display presents real-time readouts of the average light level in each optode and noise level of each source and detector pair. If either metric is poor (an optode with light level <1% of average values, or noise levels >7.5% cutoff), targeted individual fitting of the fibers is used to

improve data fidelity. Measurements are acquired to a depth of 2 cm from scalp (>1 cm into cortex) with a smooth sensitivity profile. To generate an accurate model of light propagation in a subject's head, the shape and internal structure of the head and the placement of sources and detectors must be estimated. The HD-DOT sensitivity for a given subject is modeled using head anatomy obtained from the subject's MRI. The T1 and T2 are used to segment the head into five putative tissue regions, each with unique optical properties: scalp (and soft tissue), skull, cerebral spinal fluid (CSF), grey matter, and white matter. FreeSurfer is used to perform an initial segmentation that is then refined and expanded to include the scalp and skull with in-house custom programs. High-density tetrahedral meshes (1.5 mm average internode distance) then are generated from the segmented volume using NIRVIEW. The source and detector positions for the finite element modelling (FEM) are placed on the head following spring relaxation approaches. A finite-element solution to the diffusion approximation to the radiative transport equation within the anatomical space of the subject is generated using the NIRFAST toolbox. This solution yields a sensitivity matrix that relates a change in light level measured at the surface to a local change in absorption at nodes throughout the volume. The sensitivity matrix is then re-sampled and interpolated to an isotropic two mm voxel space, and then inverted with spatially dependent regularization. To mitigate errors in the relative position of the cap placement we will use the evoked responses from the movie task as functional localizers to optimize the registration of the cap to the head.

Tasks: (fMRI and HD-DOT) Visual stimulation: Flickering checkerboard stimuli with radial, reversing (10 Hz), logarithmic black-and-white grids (10-Hz reversal) on a 50 percent gray background. A run will consist of 10 blocks, lasting 8 min. Auditory stimulation: A language paradigm to activate auditory cortex. Words (short simple nouns) will be presented in runs consisting of 6 blocks lasting 4 minutes. Movie: All subjects will be imaged while viewing a 10 min movie clip. Low-level visual and auditory processing will be used to map auditory and visual cortex while higher level processing of speech and bodies will be mapped using more specific features. These will provide additional functional localization within each subject. Commercial movies offer an engaging strategy for mapping brain functions as they are easy for subjects to comply with, reduce motion, allow for mapping multiple brain functions in parallel and have been validated against standardized stimuli and rest paradigms used in fMRI. Resting state: 3 runs of 10 min will be acquired with eyes open, fixed on a cross in the center of the screen at rest. For the pilot group only: The participant will fixate on a white crosshair at the center of the screen. At some predefined intervals, they will see the letters L or R in the middle of the screen. Corresponding to the letter presented on the screen, the participant will be required to tap their fingers onto their left (L) or right (R) palm for the duration that the letter appears on the screen. This session is about 7 mins.



This older population may tire before the end of the study day. If this is the case, the study day may be split into two visits instead of one. If this will make the study more tolerable and easier for the participant, we do have the flexibility to do this.

F3 Study Visits

TASKS & TIMES BY GROUP	Approximate Duration
Pilot & Control Group Study Visit	
Do NOT have Parkinson's Disease or Deep Brain Stimulators	
Complete –Consent form, medications list & demographics	20 mins
HD-DOT– cap fit & scan	75 mins
Cognitive – Picture Vocabulary, Oral Reading, Flanker, DCCS, List Sorting, Info-Seeking Task; Mood – VAS, GDRS, and STAI; Motor Assessments – UPDRS & Kinematics	90 mins
Lunch	30 mins
MRI – prep & scan (It is possible that not all participants in the Pilot Cohort will be scanned as the number of participants scanned will be limited to the number of scans needed to test the MRI imaging protocol.)	120 mins
Total	Approx. 6 hrs.
Pre-Surgical Group Study Visit	
Diagnosis of Parkinson's Disease AND scheduled for Deep Brain Stimulator surgery	
Complete – consent form, medications list & demographics	20 mins
HD-DOT– cap fit & scan	75 mins
Cognitive – Picture Vocabulary, Oral Reading, Flanker, DCCS, List Sorting, Info-Seeking Task; Mood – VAS, GDRS, and STAI; Motor Assessments – UPDRS & Kinematics	90 mins
Lunch	30 mins
MRI – prep & scan	120 mins
Total	Approx. 6 hrs.
Post-Surgical Group “ON” and “OFF” Study Visit	
Diagnosis of Parkinson's Disease AND currently have Deep Brain Stimulators	
Complete – consent form, medications list & demographics	15 mins
Pre-Setting Change Testing: Mood – GDRS, STAI; Cognitive – Picture Vocab & Oral Reading	50 mins
1 st stimulator change to OFF or ON and 45-minute wait period	50 mins
HD-DOT– cap fit & scan	75 mins
1 st Cognitive – Flanker, List Sorting, DCCS, and Info Seeking; Mood – VAS; Motor Assessments – UPDRS & Kinematics	90 mins
2 nd stimulator change to OFF or ON and 45-minute wait period & lunch	50 mins
HD-DOT– cap fit & scan	75 mins
2 nd Cognitive – Flanker, List Sorting, DCCS, and Info Seeking; Mood – VAS; Motor Assessments - UPDRS & Kinematics	90 mins
3 rd Stimulator change back to ON and take PD meds – 45-minute wait period.	45 mins
Total	Approx. 8 hrs.

F4 Safety and Adverse Events

4.a Safety and Compliance Monitoring

The PIs (Drs. Culver and Hershey) and Co-investigators (Drs. Ushe and Perlmutter) will monitor the study for adherence to protocol, data collection, and adverse events.

Reviews of Data and Safety Monitoring will be performed semi-annually. In addition, data and research monitoring will be undertaken annually with the local Institutional Review Board. Our plan includes but is not limited to the following features:

1. Review of adverse events: All personnel who will be in contact with participants and/or data are prepared to identify adverse events and have been instructed to report their occurrence immediately to the principal investigator(s).
2. Reporting of serious adverse events: In the unlikely event of a serious adverse event, the principal investigators, in collaboration with any relevant personnel, will take the

appropriate actions to report the event to the Human Research Protection Office as specified by the Washington University Medical Center's HRPO.

3. Criteria for stopping the study: Circumstances that would warrant stopping the study are not anticipated. However, should any circumstances arise that compromise the safety of the participants, they will be reported to the principal investigators who will suspend research until appropriate safeguards allow continuation of the study.

4. Qualified individual(s) monitoring the study: The principal investigator and collaborators have experience in this area of research and are qualified to monitor the study.

4.b Medical Monitoring

i Investigator only

Not applicable.

ii Independent expert to monitor

Not applicable.

iii Institutional Data and Safety Monitoring Board

Not applicable.

iv Independent Data and Safety Monitoring Board

Not applicable.

4.c Definitions of Adverse Events

The protocol will follow the established guidelines set by the IRB of adverse events.

4.d Classification of Events

i Relationship

Not applicable.

ii Severity

Not applicable.

iii Expectedness

Not applicable.

4.e Data Collection Procedures for Adverse Events

Data collection procedures for adverse events will follow the established IRB guidelines.

4.f Reporting Procedures

Reporting procedures will follow the established IRB guidelines.

4.g Adverse Event Reporting Period

Reporting procedures will follow the established IRB guidelines.

4.h Post-study Adverse Event

Reporting Post-study adverse events will follow the established IRB guidelines.

F5 Study Outcome Measurements and Ascertainment

Not applicable.

G Statistical Plan

G1 Sample Size Determination and Power

Power Analysis / Sample Size Justification: Our sample size (STN DBS=30; Pre-surgical STNDBS=30; Controls=30) should be sufficient for between and within group analyses, based on several estimations. Given the anticipated loss of data due to motion or other issues (we expect to keep the data from >75% of subjects), we will recruit higher numbers at the outset (n=75 PD, n=40 controls). Statistically significant DBS-induced cortical PET blood flow changes (~4%) are detectable with small sample sizes (n<11), and fcMRI can detect differences between PD and controls in relatively small samples (n=13). We expect the variance in fcDOT maps to be similar to fcMRI as seen in our previous studies and our preliminary data for both test-retest (standard dev. of $r < 0.2$ for contralateral homotopic connections) and the variance across subjects (standard error of $r < 0.1$ for contralateral homotopic connections with n=9 subjects). With similar variance, we expect to be sensitive to effect sizes of order $\Delta r \sim 0.233$. Furthermore, using our preliminary FC data, we estimate that we would achieve power of $> .80$ ($\alpha < .05$) to detect a group difference in within network FC with 51 subjects (34 PD and 17 controls). To detect a within subject change due to DBS in somatomotor FC, we would need at least 10 PD subjects. However, to be sensitive to other findings and within group correlations (e.g., location vs FC), we will benefit from much larger samples. We have ≥ 0.8 power to detect a partial Pearson r of 0.36 or smaller adjusting for 3 clinical variables with n=60 PD.

G2 Interim Monitoring and Early Stopping

Not applicable.

G3 Analysis Plan

fMRI and HD-DOT data processing streams are harmonized as much as possible to facilitate direct comparisons. fMRI: ASE field maps will be used to correct for distortion in the BOLD fMRI data. After applying motion correction procedures, data will be voxelwise demeaned and detrended within runs, while censored frames will be ignored. Nuisance waveforms (including the global signal) will be regressed voxelwise from the data. In frames marked for censoring, data will be replaced by interpolated values computed by least-squares spectral analysis. Interpolated data is included only for bandpass filtering and does not factor into correlation values. Finally, the data are spatially smoothed using a Gaussian kernel (6 mm full width at half maximum isotropic). HD-DOT. The light measurement data will be converted to log-ratio and high-pass filtered (0.02 Hz cutoff for task-based data, 0.009 Hz for resting state data) to remove long-term drift. Superficial signal regression will be performed to reduce systemic signals. A low-pass filter (0.5 Hz cutoff for task-based data, 0.08 Hz for resting state data) will be used to remove residual pulse and breathing signals. We will de-noise the data for motion artifacts by censoring

corrupted segments, where the bad quality segments are identified using a root mean squared value of the temporal difference between source-detector measurements analogous to the use of “DVARs” in fMRI. On average, a total of 1800 independent measurements will be used in each reconstruction. After image construction of each time point, the HD-DOT image data will be transformed to a standard MNI-based atlas space using an affine transform following standard processing used in fMRI. Next, the DOT image data are demeaned and detrended across each run. The average brain signal will be calculated using a brain mask created from each subject’s anatomical MRI and their DOT sensitivity profile and then regressed from each voxel’s time course.

Analyses: Clinical, behavioral and derived imaging data will be quality control checked and double-entered into a secure REDCap database. We will explore sex as a mediator of group differences and DBS-induced effects, although these effects are not specifically hypothesized. All statistical tests will be two-sided with significance level of 0.05 and performed with SAS 9.4 (SAS, Cary, NC) and R. Careful attention will be paid to ensuring that data satisfy assumptions required of a particular analytic strategy. When the required assumptions are violated, we will explore the use of data transformations and potentially, perform semi-parametric or non-parametric analysis. Planned analyses for each aim are as follows. Collectively, these analyses will define STN DBS-induced modulation of cortical functional networks and its relationship to STN DBS-induced changes in behavior.

1. To determine cortical RSNs abnormalities in pre-surgical PD. We expect the pre-surgical PD group to have reduced within and between network connectivity in selected cortical RSNs in both HD-DOT and fMRI analyses compared to controls, supporting the validity of HD-DOT and tying our data to the literature. We will compare within and between connectivity for select RSNs (somatomotor, visual, auditory, frontoparietal) between groups within each imaging modality using covariance pattern model (linear mixed effects model) adjusting for covariates such as age. We will explore use of object-oriented data analysis (OODA) a novel technique facilitating multidimensional comparison of the correlation matrix between PD and controls and between fMRI and HD-DOT. We will also take advantage of the whole brain fMRI data to determine if any additional cortical networks or subcortical-cortical RSNs are different in PD. We expect that, within fMRI data, thalamic and cerebellar networks will have lower connectivity in PD and will have less connectivity with visual and somatomotor networks.

2. To determine the impact of STN DBS on cortical RSNs. We hypothesize that STN DBS will alter connectivity within and between RSNs using HD-DOT. We focus on those RSNs that have been shown to have decreased FC in large recent fMRI analyses and our preliminary data (e.g., somatomotor, visual, auditory, frontoparietal). Covariance pattern model (linear mixed effects model) will be used to relate within and between network average FC to DBS states (ON and OFF) adjusting for patient clinical characteristic such as PD severity or time since surgery. In addition, we will use OODA to explore changes in the FC matrix between DBS conditions and over time/surgery (pre- vs post-surgical PD) to assess stability of OFF RSNs.

3. To determine how STN DBS-induced change in cortical FC relates to location of DBS contact. We hypothesize that STN DBS-induced alterations in network FC will be related to the location of the stimulating contact. Based on findings from Aim 2, we will use the mean connectivity of RSNs that show a significant effect of STN DBS in the 3D Stat analysis as the dependent variable and location of the contact as the independent, as

described in the 3D Stat methods section above. Significance testing (permutation test) will determine whether location of stimulation matters in predicting change in the selected connectivity measure, as described earlier. We will consider a Bonferroni-corrected p-value to indicate that DBS location significantly contributed to the dependent variable. We can also explore whether anatomical location relates to change in motor, cognitive or mood symptoms, although this would be replicating our previous analyses.

4. To determine how STN DBS-induced change in cortical FC relates to change in behavior. We will test the hypothesis that motor response to DBS (UPDRSIII, kinematics) relates to changes in FC involving the somatomotor RSN, and that cognitive (SDR [2 cue 15 sec error], GNG [Pr, high conflict condition]) and mood (VAS Arousal and Mood) response relates to changes in connectivity involving the association RSNs (frontoparietal). To determine whether differences in FC relate to cognitive and mood responses, pairwise partial correlation taking behavior and network FC responses as blocks will be reported adjusting for patient clinical characteristics. Partial-correlation p-values are FDR corrected for multiple comparisons.

G4 Statistical Methods

3D Statistical Analysis (3D Stat): 3D Stat, developed by members of our team, will be used to test hypotheses about the relationship between contact location (derived from ovid) and RSNs. For each dependent measure (e.g., change in RSN correlational strength, motor symptoms, cognitive function), 4 statistical maps will be generated: 1) An N-image, which shows the number of stimulated contacts that contributed data to each voxel of the map, i.e., within 1.3 mm. Voxels with $N < 6$ will not be included in further mapping steps. 2) A weighted mean image, containing the weighted mean of the dependent measure across subjects, with nearer contacts weighted higher. 3) A t-image depicting weighted t-values derived from single-sample t-tests comparing the dependent measure at each voxel to zero. 4) A p-image containing p-values for the t-test at each voxel (see Fig 16 for an example). Given the number of voxels tested in this manner, multiple comparison correction for Type 1 error and sample bias is necessary. To test whether the anatomical location of each DBS contact significantly contributed to the dependent variable, we use a permutation test. For each measure, a summary score reflecting the extent and amplitude of significant voxels in the p-image will be generated. This summary score will be compared to 1000 summary scores generated similarly but from randomly chosen pairings of the active contact locations and dependent variable. We will consider a p-value ≤ 0.05 (i.e., a summary score that would place it in the top 50 of the 1000 random data permutations) to indicate that the DBS location significantly contributed to the dependent variable.

G5 Missing Outcome Data

Not applicable.

G6 Unblinding Procedures

Dr. Ushe, the HD-DOT data collection staff and the patient will be blind to DBS condition during data collection for the post-surgical group. After raw data analysis is done, staff involved in analysis will be unblinded to DBS condition for each subject so that they can perform the next level of analyses.

H Data Handling and Record Keeping

H1 Confidentiality and Security

Confidentiality will be maintained in accordance with applicable state and federal laws. Subject data will be coded numerically to protect individual identity. No identifiers will be used in presentation or publications. All data will be stored in locked cabinets or on computers within a private, secure network protected by a PIX firewall with remote access only permitted through virtual private network connections, as per HIPAA guidelines. Patients will be informed of all risks prior to participation. Subjects will be told that they may discontinue participation at any time, that they have the alternative not to participate in the study, and that this will not impact their medical care. Insurance will not be charged. All key personnel involved in the design or conduct of research involving the human subjects will receive the required education on the protection of human research participants and HIPAA guidelines prior to funding of this project. Consent will be obtained in a private setting in the room where the experiment will take place.

H2 Training

Not applicable.

H3 Case Report Forms and Source Documents

Not applicable.

H4 Records Retention

Data (including videos) collected under this protocol will be kept for a minimum of 7 years after the study is complete.

H5 Performance Monitoring

Not applicable.

I Study Monitoring, Auditing, and Inspecting

I1 Study Monitoring Plan

See 4a.

I2 Auditing and Inspecting

Not applicable.

J Study Administration

J1 Organization and Participating Centers

Not applicable.

J2 Funding Source and Conflicts of Interest

National Institutes of Health (NIH)

J3 Committees

Not applicable.

J4 Subject Stipends or Payments

Subjects will be paid for being in this research study. Subjects will be mailed a check that will take approximately 2-4 weeks to arrive at their home address. Subjects will be paid \$25 an hour for completing the HD-DOT scan, the MRI, and study tasks. If participants are only able to complete a portion of the study visit, payment will be pro-rated to reflect that. We will reimburse for any parking fees and the cost of transportation for those in the DBS group who cannot drive.

J5 Study Timetable

Study Timetable Data collection will begin in October 2019 and finish by summer 2024.

K Publication Plan

Publications will be prepared once data collection and analyses are complete, likely fall of 2024.

L Attachments

L1 Tables

Not applicable.

L2 Informed consent documents

Attached to IRB submission.

L3 Patient education brochures

Not applicable.

L4 Special procedures protocols

Not applicable.

L5 Questionnaires or surveys

Attached to IRB submission.

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