**IRB # 17-1350**

Title: Stimulation Parameters and Non-motor Symptoms in PD Treated With DBS
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## Introduction

Deep brain stimulation of the dorsolateral Subthalamic Nucleus is a highly effective treatment for the motor symptoms of moderate to advanced Parkinson's disease. At the same time, however, this therapy is also associated with small but consistent changes in cognitive and affective function. The mechanisms underlying these unintended DBS side effects is unknown. The goal of this research is to systematically evaluate two aspects of stimulation (location and frequency) that may explain the non-motor changes associated with STN DBS.

### Background and Significance

A number of outcome studies have looked at neuropsychological and psychiatric function both before and after STN DBS. The overall picture has indicated small declines on verbal fluency tests, executive function, and verbal memory retrieval[1]. A number of studies have evaluated cognitive function with stimulation on or off, and there is clear evidence that stimulation does impact cognitive abilities including verbal fluency [2], facial affect recognition [3], timing [4], and response inhibition [5]. However, the mechanism underlying these changes is unknown.

One hypothesis is that changes in cognitive and affective function are due to spread of electrical stimulation to neighboring non-motor regions of the STN (Jahanshahi, Ardouin et al. 2000; Hershey, Revilla et al. 2004; Czernecki, Pillon et al. 2005; Funkiewiez, Ardouin et al. 2006; Halbig, Tse et al. 2009). The possibility that variability in on-off effects arises from a difference in stimulation location is corroborated by our prior work (____ et al., under review) and others' demonstrating that contact location is relevant to cognitive outcomes from STN DBS [6, 7]

An alternative hypothesis that could explain stimulation effects on cognition concerns the frequency of stimulation. The optimal benefit for motor function occurs with high frequency stimulation, on the order of 130 Hz, although there is some minor variation across patients. Stimulation at this frequency appears to interrupt the pathological beta oscillations that occur in the basal ganglia associated with motor impairments. LFP recording in PD patients suggests that oscillatory activity is important for cognitive function [8] and high frequency stimulation may interfere with cognitive processing. This fits with Wojtecki and colleagues [9] finding that verbal fluency performance worsens with high frequency stimulation and improves with low frequency stimulation.

This study will clarify prior observations of cognitive changes in patients with STN DBS[27] and opens the door to tailoring stimulation parameters to independently influence cognitive or motor function. For example, DBS technology could be designed to improve both cognitive and motor symptoms by stimulating at one frequency in dorsal STN, and another frequency in ventral STN.

**Aim 1. To evaluate the cognitive effects of high frequency stimulation at dorsal and ventral contact locations in PD patients with bilateral subthalamic nucleus DBS electrodes.** We hypothesize that, relative to OFF stimulation, performance on tasks involving executive functions will show greater change at ventral contacts than at dorsal contacts.

**Aim 2. To evaluate the cognitive effects of low frequency stimulation at dorsal and ventral contact locations in PD patients with bilateral subthalamic nucleus DBS electrodes.** We hypothesize that, for tasks where high frequency stimulation produces a *deficit* relative to OFF stimulation (e.g., verbal fluency), low frequency stimulation will *eliminate or reverse* performance changes relative to OFF stimulation.

**Aim 3. To characterize changes in cognitive network activity during alternative stimulation of the STN.** We will also collect scalp EEG data during task performance when stimulation is OFF compared to alternative DBS settings. Patients with Medtronic or Abbott/St. Jude DBS systems that have been MRI safety tested will also undergo fMRI on a second day to examine BOLD

responses during task performance while stimulation is OFF compared to alternative DBS settings.

## Study Design

This is a prospective cohort study. All data will be collected at the Cleveland Clinic over one or more study days. The Figure provides an overview of the study procedures and timing for patients.

Sample

We will recruit 15 patients diagnosed with Idiopathic Parkinson disease.

Inclusion Criteria:
1. Between 40 and 70 years of age,
2. Ability to provide informed consent,
3. Clinical diagnosis of idiopathic Parkinson disease (PD) by a movement disorders neurologist,
4. Disease duration of at least 4 years,
5. Treated with bilateral STN DBS for at least 3 months prior to study enrollment.

Exclusion criteria:
1. History of prior neurosurgical intervention for PD (e.g., DBS, thalamotomy, pallidotomy)
2. History of other central nervous system disease (excluding migraine),
3. Presence of active psychiatric symptoms meeting Diagnostic and Statistical Manual of Mental Disorders-4$^{th}$ Edition (DSM-IV) criteria for Axis-I disorder on formal psychiatric evaluation, with the exception of mild depression (Beck Depression Inventory-2 score below 19),
4. Cognitive impairment meeting Diagnostic and Statistical Manual of Mental Disorders-4$^{th}$ Edition (DSM-IV) criteria for dementia on formal neuropsychological evaluation,
5. Current alcohol or substance abuse,
6. Lack of fluency in English which would invalidate cognitive testing,
7. Hearing or visual impairment precluding cognitive testing.

Exclusion criteria for Imaging procedures:

8. Inability to safely undergo MRI procedure (i.e., metal objects like prostheses, pacemakers)

Controls

We will recruit 20 health controls without Idiopathic Parkinson disease to examine normal performance and EEG variability over repeated task administration.

Inclusion Criteria:

1. Between 3 and 70 years of age,
2. Ability to provide informed consent.

Exclusion Criteria:

1. History of central nervous system disease (excluding migraine),
2. Presence of active psychiatric symptoms meeting the Diagnostic and statistical Manual of Mental Disorders – 4$^{th}$ Edition (DSM-IV) criteria for Axis-I disorder on formal psychiatric evaluation, with the exception of mild depression (Beck Depression Inventory-2 score below 19),
3. Cognitive impairment meeting the Diagnostic and statistical Manual of Mental Disorders – 4$^{th}$ Edition (DSM-IV) criteria for dementia on formal neuropsychological evaluation,
4. Current alcohol or substance abuse,

5. Lack of fluency in English which would invalidate cognitive testing,
6. Hearing or visual impairment precluding cognitive testing

Exclusion criteria for Imaging procedures is not applicable. Healthy controls will only complete EEG monitoring and cognitive testing.

Research Procedures – Arm 1 (12 patients)

*Study Day 1:* Patients will be admitted to the Clinical Research Unit of the Clinical and Translational Research Center on Study Day 1 after withholding Parkinson's medications overnight. After admission, they will undergo initial stimulation threshold evaluation (for sensorimotor stimulation side effects) with a physician's assistant trained in DBS programming. An EEG technician will apply scalp electrodes and electroencephalogram (EEG) activity will be monitored throughout the Study visit using standard electrophysiological equipment under the supervision of Dr. ____. Subjects with then complete two test sessions, at different stimulation parameters (varying contacts and frequencies designed by Dr. ____ ____ at Case Western Reserve University) at the amplitude corresponding to 90% of side effect threshold.

*Test sessions:* Each testing session involves performance of several tasks including a phonemic fluency, semantic fluency, Simon task, Facial Affect Recognition task (FAR), Time Production task, Interval Judgment task, as well as a speeded finger tapping test and a group of visual analogue rating scales regarding current mood and well-being (anxiety, motivation, fatigue, physical discomfort).

There will be at least 30 minutes between each session for wash-in/washout of stimulation effects and to rest. Patients will be provided with lunch and additional rest breaks, as needed. At the end

of the last session, patients will take their regular PD medications and stimulation will be readjusted to their clinically-defined settings. Note that STN DBS therapy has a 'wash-in' period of seconds to minutes, while medication therapy typically has a 'wash-in' period of around 15 to 30 minutes. EEG electrodes will be removed and they will be discharged from the CRU when the patient subjectively feels that their stimulation therapy and medications have taken effect, and the supervising neurologist or movement disorder Physician's Assistant delegate observe that Parkinsonian symptoms have improved.

*Patient-specific stimulation settings:* Deidentified pre- and post-operative imaging will be shared with Dr. ____ ____ at Case Western Reserve University for creation of patient-specific stimulation parameters (Data Use Agreement attached). Patient specific stimulation models for the active cathode/anode that preferentially activate dorsal and ventral aspects of the Subthalamic Nuclei will be constructed prior to the patients' arrival. All stimulation adjustments will be completed by an unblinded Physician Assistant trained in DBS programming. Patients will be blinded to stimulator settings and all data collection will be completed by blinded study personnel. We recognize that it is likely not possible to complete the research sessions for DBS patients in a fully blinded manner: in particular, the off-stimulation state and the low frequency stimulation states may be obvious to both patients and study personnel in the absence of medications. At each session, we will assess patient blinding (i.e., query patients' belief regarding current stimulator setting) to identify those patients who remain blinded for possible subgroup analyses.

**ARM 1**

**Day 1 Clinical Research Unit**

| Start Time | Minutes | Procedure |
|---|---|---|
| 7:00 | 15 | Informed Consent and Admit to CRU |
| 7:15 | 60 | EEG leads applied |
| 8:15 | 15 | Threshold Evaluation |
| 8:30 | 30 | Setting 1 and wash-in |
| 9:00 | 30 | Test Session 1 |
| 9:30 | 30 | Setting 2 and wash-in |
| 10:00 | 30 | Test Session 2 |
| 10:30 | 60 | Meds resumed, Clinical settings applied, EEG leads removed, and discharge |

**Day 2 Clinical Research Unit**

| Start Time | Minutes | Procedure |
|---|---|---|
| 7:00 | 60 | EEG leads applied and admit to CRU |
| 8:00 | 30 | Setting 3 and wash-in |
| 8:30 | 30 | Test Session 3 |
| 9:00 | 30 | Setting 4 initiated |
| 9:30 | 30 | Test Session 4 |
| 10:00 | 30 | Setting 5 initiated |
| 10:30 | 30 | Test Session 5 |
| 11:00 | 60 | Meds resumed, Clinical settings applied, EEG leads removed, lunch, and discharge |

**Day 3 Research MRI at Mellen Center**

| Minutes | Procedure |
|---|---|
| 20 | Safety checklist and MRI prep |
| 20 | Setting 1 initiated and position in MRI |
| 30 | MRI scan with tasks |
| 20 | Extract from scanner, Setting 2 initiated, position in MRI |
| 30 | MRI scan with tasks |
| 20 | Clinical settings applied, meds resumed |

*Study Day 2:* On a second day (scheduled at the subjects' convenience, within 4 weeks of the first study day), patients will again be admitted to the Clinical Research Unit of the Clinical and Translational Research Center after withholding Parkinson's medications overnight. After admission, an EEG technician will apply scalp electrodes and electroencephalogram (EEG) activity from the Epilepsy Monitoring Unit, under the supervision of Dr. ____. Subjects will then complete the three remaining test sessions at different stimulation parameters (varying contacts and frequencies designed by Dr. ____ ____ at the Case Western Reserve University) at the amplitude corresponding to 90% of side effect threshold.

*Study Day 3:* On a third day (scheduled at the subjects' convenience within 4 to 6 weeks of the first study day), only subjects with MRI-safe DBS systems will undergo fMRI scanning at the Mellen Center Imaging Center after withholding Parkinson's medications overnight. Patients will have their stimulators adjusted (in a randomized order) to OFF and to the patient-specific stimulation parameters that induced maximal cognitive change on Study Day 1. Specific sequences for structural and functional MRI will be determined by Drs. ____ and ____ based on their prior studies demonstrating safety of intracranial electrodes and DBS equipment in MRI environments [10-12].

Research Procedures – Arm 2 Harmonics (3 patients)

Study Session 1. Patients with MRI-compatible DBS systems will be admitted to the Clinical Research Unit of the Clinical and Translational Research Center for Study Session 1. Patients will be tested while ON their regular Parkinson's medications. We will also record EEG from a sparse electrode array (Fz, Cz, Pz, Oz, F3, F4, C3, C4). At the first session, each patient will have bilateral STN DBS electrodes adjusted by a physician-assistant trained in DBS programming procedures. Settings are adjusted in randomized order to deliver stimulation bilaterally at six low frequencies – 2, 4, 8, 11, 17, and 32 Hz. All other clinical personnel and the patient will remain blinded to stimulation settings. At each setting, patients will remain seated and at rest for a 10-15 minute wash-in period while monitored for sensorimotor or other neurological side effects. They will then perform two of the tasks from the existing protocol (Simon task, Verbal fluency task) for 10-15 minutes. After this 20-30 minute period, stimulation settings will again be changed to another setting. After all 6 settings are completed, patients' stimulation will be returned to their clinically-determined settings and scalp electrodes removed.

**ARM 2**

**Session 1 Clinical Research Unit**

| Start Time | Minutes | Procedure |
|---|---|---|
| 7:00 | 15 | Informed Consent and Admit to CRU |
| 7:15 | 30 | EEG leads applied |
| 7:45 | 15 | Threshold Evaluation |
| 8:00 | 15 | Setting 1 and wash-in |
| 8:15 | 15 | Test Session 1 |
| 8:30 | 15 | Setting 2 and wash-in |
| 8:45 | 15 | Test Session 2 |
| 9:00 | 15 | Setting 3 and wash-in |
| 9:15 | 15 | Test Session 3 |
| 9:30 | 15 | Setting 4 and wash-in |
| 9:45 | 15 | Test Session 4 |
| 10:00 | 15 | Setting 5 and wash-in |
| 10:15 | 15 | Test Session 5 |
| 10:30 | 15 | Setting 6 and wash-in |
| 10:45 | 15 | Test Session 6 |
| 11:00 | 45 | Clinical settings applied, EEG leads removed, lunch, and discharge |

**Session2 Research MRI at Mellen Center**

| Minutes | Procedure |
|---|---|
| 20 | Safety checklist and MRI prep |
| 15 | Setting 1 initiated and position in MRI |
| 10 | MRI scan at rest |
| 15 | Extract from scanner, Setting 2 initiated, position in MRI |
| 10 | MRI scan at rest |
| 15 | Extract from scanner, Setting 3 initiated, position in MRI |
| 10 | MRI scan at rest |
| 15 | Extract from scanner, Setting 4 initiated, position in MRI |
| 10 | MRI scan at rest |
| 15 | Extract from scanner, Setting 5 initiated, position in MRI |
| 10 | MRI scan at rest |
| 15 | Extract from scanner, Setting 6 initiated, position in MRI |
| 10 | MRI scan at rest |
| 10 | Extract from scanner, Clinical settings applied |

Study Session 2. On the same or different day (scheduled at the subjects' convenience maximum of 6 weeks of the first study session), subjects with MRI-safe DBS systems will undergo fMRI scanning at the Mellen Center Imaging Center. Patients will be tested while ON their regular Parkinson's medications. Patients will have their stimulators adjusted (in a randomized order) to each of the six low-frequency stimulation parameters from Study Session 1 and resting-state fMRI scans lasting completed at each setting. Specific sequences for structural and functional MRI will be determined by Drs. ____ and

____ based on their prior studies demonstrating safety of intracranial electrodes and DBS equipment in MRI environments [10-12].

Research Procedures – Healthy Controls (20 patients)

*Study Day 1:* Controls will be not be admitted to the Clinical Research Unit of the Clinical and Translational Research Center; testing will take place in private laboratory space (T2-303). An EEG technician will apply scalp electrodes and electroencephalogram (EEG) activity will be monitored throughout the Study visit using standard electrophysiological equipment under the supervision of Dr. ____. Controls will then complete the remaining study procedures over one 3-hour period.

*Test sessions:* Controls will complete five 25-minute testing sessions separated by 10-15 minute break periods. Each session will involve performance of several tasks that may include phonemic fluency, semantic fluency, Simon task, Facial Affect Recognition task (FAR), or Interval Judgment task.

## Data Analysis

Behavioral Tasks: With the support of a Biostatistics consultant (____), we propose to evaluate the behavioral task data using a combination of methods for General Linear model and categorical data methods where appropriate. Selected details are presented with the relevant aims above. Statistical corrections will be applied to avoid any increase in family-wise error rate.

EEG: We will analyze event-related potentials (ERP) to trial events in individual tasks to investigate phase-locked activity. Non-phase-locked activity will be investigated by averaging power within alpha, beta, and gamma frequency bands with respect to the trial events. The latter analysis technique will permit identification of event-related desynchronizations (ERD) and synchronizations (ERS)[24] associated with non-clinical stimulation parameters.

BOLD: Event-related functional MRI data at all stimulation settings will be analyzed for individual subjects to evaluate patient-specific changes in activated networks. Group-level analyses will be dependent on the degree of similarity across patients in terms of specific cognitive performance changes and associated stimulation parameters.

Confidentiality: CCF study investigators will have sole access to the study data. To protect confidentiality, participants' data will be identified only by coded subject number and stored in a secure location in a de-identified manner. All data provided to Dr. ____ for construction of stimulation models will be de-identified and encrypted. A password-protected, electronic record linking subject numbers with identifying information will be maintained in a password-protected folder on a secure server and only CCF-based study investigators will have access to this file. Data analysis will be conducted by the study investigators in consultation with biostatistics (____), where appropriate. Dissemination of the results will largely involve aggregate data, although individual data points may be used where illustrative. All dissemination of the study findings will maintain confidentially and include only de-identified data, except in the situation where express written permission has been obtained from the patient in advance.

## Adverse Events and Safety

For Study sessions involving stimulation and EEG recording, the patients are admitted to the CRU with continuous monitoring by nursing staff. Given the minimal risk of the computerized tasks and EEG recordings, the likelihood of adverse events due to the behavioral task or scalp electrodes is very low. Non-clinical or no DBS delivery is expected to worsen some Parkinson's

symptoms temporarily. The Physician Assistant completing the stimulation adjustment and threshold testing will also monitor for patient safety and well-being during parameter changes. In addition, patients will complete ratings scales of their well-being and discomfort at each stimulator setting change, as an additional check on subject safety. For fMRI procedures, Drs. ____ and ___ will closely monitor data integrity and patient safety. They are experts in the safety of MRI scanning in patients with implanted DBS systems.

A Data Monitoring Committee is not planned for this study. The Principal and Co-Investigators, as well as other protections in place (i.e., CRU clinical staff), will continuously monitor subject safety and data integrity. Adverse events and Unanticipated Problems will be reviewed by the Principle and Co-Investigators. If an Adverse Event occurs, it will be recorded on the Adverse Event Summary Sheet, and this will be submitted along with the Adverse Event Report in accordance with the stated time limitations. No clinical electrophysiological report will be generated as the recordings performed do not constitute diagnostic studies. However, if an unexpected finding is observed during the electrophysiological analysis (e.g., seizure activity), consult to the Epilepsy Center will be ordered. Likewise, if an unexpected finding is observed during the MRI procedure (e.g., mass), Dr. ____ will consult with the patient.

**Consent**

The informed consent process for controls will be completed on the study day prior to EEG electrode application by Dr. ____ or the research coordinator. The informed consent process for patients will be completed by Dr. ____ or the research coordinator/technician in a 2-step process.

Step 1:

*For patients approached during a regularly scheduled clinical visit to CCF Main campus:* The full procedures, risks, benefits, and alternatives to participation will be reviewed with patients in a private setting (i.e., exam room). Potential participants will be given a copy of the full written consent document (either with or without Study Day 3, depending on the type of DBS system implanted) and are given the opportunity to review the document and ask questions or clarifications of the person conducting the consent interview. The patient is also permitted to discuss the matter with their spouse/caregiver privately before consenting to participate. Patients who wish to proceed will provide limited written consent to access their neuroimaging data obtained as part of routine clinical care for pre-surgical planning and post-operative electrode placement confirmation, de-identify those scans, and deliver them in encrypted format to Dr. ___ for creation of patient-specific stimulation parameters.

*For patients not seen in clinic:* A letter will be mailed to potential subjects (see Recruitment letter), which includes the screening consent and the main study consent. Study personnel will conduct a follow up phone call (See Screening Telephone Script) to ensure that patients received the letter and to review the main study and the initial screening consent. If the patient agrees to participate, he/she will be asked to sign the screening consent and return it via the self-addressed and stamped envelope provided in the mailing. Upon receipt of the signed screening consent, de-identified scans will be transmitted to Dr. ____ at CWRU. The appropriate confirmation letter (see Confirmation letters – ScreenIn or ScreenFail) will be sent to patient to inform them of whether personalized stimulation models could or could not be constructed. For those patients who screen in, there will be a follow up phone call to serve as the main study consent discussion (See Consent Telephone Script) and to schedule an appointment at the CRU, if the patient provides verbal consent to participate).

Step 2:

Patients will be consented with the full informed consent process when they arrive at the CRU for the first Study Day. The consent process will take place in a private CRU inpatient room.

When patients return for additional study sessions, they will be reminded, before study procedures commence, that they may withdraw consent at any time without consequences.

## References


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