CLINICAL PROTOCOL

Title: Cortical stimulation to treat mood and behavioral symptoms in Parkinson's disease patients

Protocol: **UCSF---PREFRONTAL---2020---08**

Study Sponsor/
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Protocol Synopsis

Title	Cortical stimulation to treat mood and behavioral symptoms in Parkinson's disease patients
Study Phase	Phase I
Device(s)	**Device Information:** Devices to be used in this study are grouped below according to FDA approval. All are Medtronic Devices. Investigational • Activa PC+S implantable pulse generator, Model 37604 • Sensing Programmer Model 8181 for Activa PC+S • Sensing Programmer Software Model 8180 for Activa PC+S • Lead extension Model 37087 • Nexus-D2/3 System • Nexus-D2/3 Application Programming Interface (API) • Nexus-E firmware and Activator • Intercept Patient Programmer, model 37441 • Summit RC+S implantable pulse generator (IPG), Model B35300R • Research Lab Programmer (RLP), Model 4NR010 • Clinician Telemetry Module (CTM), Model 4NR011 • Research Software Development Kit (RDK), Model 4NR013 • Patient Therapy Manager(PTM), Model 4NR009 • Recharge Therapy Manager (RTM), Model 97755 Approved for other indications • Medtronic Resume II paddle electrode model 3587A Approved for the intended indication • N'Vision Clinical Programmer Model 8840 • Clinician Programmer Software Model 8870 • Patient Programmer Model 37642 • Lead Model 3389 or 3387 • External Neurostimulator 37022 • Lead extension model 37086 • Activa SC 37603 single channel pulse generator
Indication	Adults with Parkinson's disease (PD) who experience inadequate relief of motor symptoms in the setting of optimal medical therapy by a movement disorders neurologist, who have been offered implantation of a deep brain stimulator system and who also suffer from one or more of the following non-motor symptoms: depression, anxiety and impulsivity.

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Medical Safety Monitor	The medical safety monitor (MSM) consists of a neurologist, Dr. Michael Okun (at the University of Florida, Gainesville), outside of our home institution, who has no direct involvement in this study but who has expertise in implantable devices. Treatment related adverse events assessed as definitely, probably, or possibly related to study procedures and either serious or unexpected, noted by any study personnel will be reported within 10 working days of their knowledge of the event to the MSM. The MSM will then advise the PI on potential changes in procedures to improve safety, or, in the event of multiple serious adverse events, may invoke stopping rules.
Treatment	Stimulation of the basal ganglia for treatment of the motor symptoms of Parkinson's disease patients, and stimulation of the prefrontal cortex for treatment of mood and behavioral symptoms.
Study Site	University of California, San Francisco 779 Moffitt, 505 Parnassus Ave San Francisco, CA 94143
Study Design	This is a single-center study of the neurophysiology of non-motor symptoms such as anxiety, depression, and impulsivity that are comorbid in Parkinson's Disease. The aims are to: 1) Determine the neural correlates of non-motor symptoms in PD patients. 2) Determine how open-loop cortical stimulation can reduce these symptoms and normalize the abnormal brain signals. 3) Develop closed-loop DBS paradigms by integrating the biomarkers of non-motor symptoms identified in the early phase of this project. 4) Teach patients how to voluntarily modulate cortical signals related to non-motor symptoms. In addition to their standard therapeutic DBS electrode(s) used to treat their motor symptoms, patients enrolled in this study will have a flexible 4-contact electrode (Medtronic 3587A Resume II paddle lead) placed over the prefrontal cortex. This cortical electrode will be advanced through the same burr hole used for the DBS lead implants and placed on the surface of the brain in the subdural space. The cortical electrode, as well as the standard therapeutic DBS electrode implanted on that side, will be attached to a Medtronic Activa PC+S pulse

	generator or a Medtronic Summit RC+S pulse generator placed in the ipsilateral pectoral area. On the contralateral side, for patients scheduled for bilateral DBS implantation, a standard therapeutic DBS electrode will be connected to a standard Medtronic single channel pulse generator (Activa SC). After electrodes implantation patients will undergo two phases: In Phase 1 (day 1 – 87 months) the aim is to identify a biomarker of non-motor symptoms and study the effect of continuous cortical stimulation on these symptoms. Therefore, patients will undergo long-term monitoring of their non-motor symptoms along with recordings of cortical (electrocorticography, ECoG) and subcortical local field potentials (LFPs). The patients' symptoms such as their emotion states may vary depending on medication state and/or cortical stimulation. Throughout this period, brain activity will be recorded frequently, and non-motor symptoms will be assessed using multiple rating scales and tasks engaging brain circuits related to emotional processing and cognition. This phase will be conducted in both the outpatient office setting and the patient's home environment. In phase 2 (8 months – 5 years), potential biomarkers identified in Phase 1 will be incorporated in a closed-loop paradigm. The stimulation parameters that optimally reduce symptom severity will be determined using Nexus-D and E systems, which have the capability to stream data non-invasively from Activa PC+S to an external computer in near real time and adjust the stimulation parameters, and to implement fully closed loop stimulation within the Activa PC+S or Summit RC+S IPG. During phase 2, patients will also be trained to voluntarily modulate the aberrant brain signals using Nexus-D and E.
Objectives	In ten patients undergoing DBS implantation for PD, we will implant a subdural cortical electrode in addition to the DBS electrode, and connect these to a novel implantable pulse generator that can store / stream field potential data (Medtronic Activa PC+S, Medtronic Summit RC+S). At multiple time points post-implantation up to 5 years, in our clinic or patients' homes, cortical and subcortical signals will be recorded. Data will be collected while patients are resting or engaged in emotion/cognition tasks and while cortical stimulation on and off. In addition to brain signals recordings, symptoms will be assessed using validated questionnaires and tasks to allow identification of neurophysiological correlates of non-motor symptoms. These signals will be used to determine the optimal stimulation parameters to disrupt symptom-related neural activity, and to implement feedback-controlled cortical stimulation *Hypotheses*: *1)* Characteristics of the prefrontal ECoG potentials (spectral power in specific bands, interaction between different frequency bands and/or between brain regions) correlate with severity of non-motor symptoms

	2) For patients who have non-motor fluctuations in mood, anxiety, or impulsivity in response to dopaminergic medication, characteristics of the prefrontal ECoG potentials will vary in relation to medication state. *3)* Cortical stimulation can reduce the severity of non-motor symptoms *4)* Patients can learn how to voluntarily modulate cortical signals related to non-motor symptoms
Patient Population	Study subjects will be adults with Parkinson's disease (PD) deemed appropriate candidates for the treatment of motor symptoms using deep brain stimulation. Study subjects will also have one or more of the following non-motor symptoms: depression, anxiety, or impulsive behavior.
Sample Size	10 subjects
Efficacy Assessments	Non-motor symptoms will be assessed by validated questionnaires: BDI= Beck Depression Inventory, BAI= Beck Anxiety Inventory, HADS= Hospital Anxiety and Depression Scale, QUIP= Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease, YBOCS= Yale-Brown Obsessive Compulsive Scale. Since these scales assess symptoms over the previous few weeks period, visual analogue scales (VAS) will be used to assess the non-motor symptoms at the time of the recordings. In addition, objective measure such as blood pressure, electrodermal activity, electromyography and/or task performance such as reaction time and error rate might also be used to assess non-motor symptoms.
Safety Assessments	1) Physical examination at all study visits 2) Baseline evaluation and regular clinical follow up with the study psychiatrist 3) Check of pulse generator stimulation parameters, impedance measurements, and battery voltage at all study visits 4) Surgical or nonsurgical adverse events as recorded on case report forms 5) Assessment of suicidality using the Columbia Suicide Severity Rating Scale, at protocol-defined outpatient visits 6) In visits where the Nexus D and/or E system will be used for closed loop stimulation, all possible stimulation settings are preselected by clinicians to avoid the possibility of producing major stimulation-induced adverse effects 7) When closed loop stimulation is used out of the clinic, patients can exit closed loop mode at any time, using a hand-held controller, and return to their normal clinical settings

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Protocol Signature Page

Dr. Starr is the Principal Investigator on this study:

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I have reviewed the following Food and Drug Administration (FDA) regulations: 21 CFR Part 812, Investigational Device Exemptions; 21 CFR Part 50, Protection of Human Subjects; and 21 CFR Part 54, Financial Disclosure by Clinical Investigators.

I agree and/or certify that I will conduct the clinical investigation in accordance with this agreement, all requirements of the investigational plan, IDE regulations, other applicable regulations of the FDA, and any conditions of approval imposed by my reviewing Institutional Review Board (IRB) or FDA. I agree to abide by all of the responsibilities of Investigators addressed under 21 CFR Part 812, Subpart E and Subpart G, including but not limited to the following:

a. I will obtain written approval from the authorized IRB for the institution at which this investigation will be conducted. If I am not also the sponsor-investigator of the corresponding IDE application, I will submit the certification of IRB approval and any conditions of this approval to the Sponsor (Sponsor-Investigator).

b. I will ensure that Informed Consent is obtained from each subject participating in this clinical investigation in accordance with the informed consent regulation found in 21 CFR Part 50, and that a signed copy of the informed consent is available to the Sponsor (Sponsor-Investigator) and the Sponsor's (Sponsor-Investigator's) designated monitor.

c. I will supervise all testing of the deep brain stimulation devices on human subjects and will allow only those physician co-investigators listed on the last page of this agreement to administer this devices and/or perform follow-up medical evaluations on the device.

d. I will be responsible for accountability of the medical devices at the study.

e. I will ensure the accurate completion of protocol case report forms and, if I am not also the Sponsor-Investigator of the corresponding IDE application, I will submit completed protocol case report forms, progress reports, and a final report to the Sponsor (Sponsor-Investigator) at the time frames specified in the Protocol and/or FDA regulations.

f. I will direct the retention of required records and documents related to the investigation.

Signature of Sponsor-Investigator _____

Phillip Starr, M.D., Ph.D Date

1.0 Introduction

Parkinson's disease (PD) is a common neurological disorder characterized by a constellation of motor and non-motor features, including cognitive and psychiatric symptoms.

Motor symptoms in PD have been well studied and several treatment options exist for their amelioration. One common treatment is deep brain stimulation (DBS), in which electrical stimulation is delivered through electrodes implanted in deep structures of the brain in order to modulate neural circuits. The two most important limitations of DBS currently used to treat PD are: 1) It does not treat non-motor features of the disease, and 2) contemporary DBS devices deliver "open loop" stimulation that is continuously on, and is unresponsive to fluctuations in brain physiology. 'On demand' or "closed loop" therapy is likely to overcome the limitations of the current 'open-loop' paradigm, reducing the side effects of stimulation and duration of programming sessions that are based on trial and error (1, 2). Both of these limitations are addressed in this protocol.

Depression and anxiety are among the most prominent non-motor symptoms in PD and greatly affect patients' and caregivers' quality of life. They occur organically as part of the fundamental circuit disruption of PD and often predate motor impairment (3, 4). In addition, impulsive behaviors frequently follow the addition of dopaminergic therapy (5). Increasingly recognized in PD is the development of impulse control disorders (ICD) such as gambling, hypersexuality, or punding. A subset of PD patients also suffers from a form of addiction, dopamine dysregulation syndrome (DDS), in which patients compulsively self-medicate with excessive doses of dopaminergic medication (6, 7). In total, these neuropsychiatric symptoms affect 35% of PD patients. In contrast to the motor symptoms, the pathophysiology of non-motor symptoms in PD is largely unknown. None of the currently available therapies for the motor signs of PD (i.e. dopaminergic medication, DBS) alleviate these symptoms. It is therefore crucial to investigate the pathophysiology underlying these symptoms in order to develop a comprehensive treatment for these patients. **We thus aim to identify neurophysiological signatures of non-motor symptoms in PD, and then incorporate these biomarkers in closed-loop stimulation paradigms and neurofeedback training to treat these symptoms.**

In PD, the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta leads to a depletion of dopamine, the principal neurotransmitter of both the nigrostriatal and the mesolimbic systems. The latter is associated with cognitive control, as well as emotional and motivational processes. A key structure in this limbic circuit is the prefrontal cortex (PFC). The PFC is involved in decision making, regulation of the emotional state in normal individuals, and in evaluating and comparing the expected rewards or punishments of an action (8-10). These mechanisms are essential for adaptive learning and their failure can lead to the inappropriate behavioral selection that can give rise to the mood and impulse control disorders often observed in PD (11, 12).

We will evaluate limbic circuits through chronic recording from the prefrontal cortex using a subdural strip lead, and manipulate this network using open and closed-loop cortical stimulation. Our extensive experience with intraoperative cortical recordings and acute brain stimulation supports the importance of PFC in these non-motor symptoms. We have also shown that acute intraoperative delivery of stimulation pulses in the PFC can induce a positive affect in PD (unpublished data). More importantly we showed that

this stimulation modulates mood in patients who were anxious or depressed at the time of stimulation, but did not induce changes in patients without these symptoms. Based on the literature and our results, PFC is a promising candidate for the development of a closed-loop stimulation paradigm to treat psychiatric symptoms.

This new study will utilize several investigational devices, as well as devices approved for other indications. We will use the investigational Medtronic Activa PC+S or Medtronic Summit RC+S implanted device, sensing programmer and associated software (13). The Activa PC+S is based on the FDA-approved Activa PC neurostimulator, but consists of additional sensing, stimulation and detection features (14). We will also use Medtronic's Nexus technology to develop closed-loop stimulation algorithms. Nexus D2/D3 systems are investigational devices providing a bidirectional, noninvasive interface between the Activa PC+S implanted device and an external computer. They mediate data streaming in real-time from the Activa PC+S to an external computer that extracts metrics that may be relevant to non-motor and behavioral symptoms (such as spectral power, coherence between brain regions or cross frequency interactions, such as phase-amplitude coupling (PAC)) and automatically adjusts the stimulation settings in the PC+S device, based on these metrics. Nexus E system allows for uploading fully closed-loop stimulation paradigms onto PC+S, without data streaming. The stimulation settings adjustments will always remain within allowable settings pre-programmed by a clinician using standard procedures (i.e. using the Medtronic 8840 programmer). Using Nexus-D2/3 and E, patients will also be trained to voluntarily modulate their abnormal signal in a way that minimizes their symptoms. The Summit RC+S is the second-generation bi-directional (sense and stimulate) interface which has a rechargeable battery, and an improved signal to noise ratio allowing detection of high frequency brain signals. It also has greater flexibility in the implementation of adaptive algorithms. All investigational devices contain the required statement: "CAUTION-Investigational Device. Limited by Federal Law to Investigational Use" and contain adequate information for the proposed investigational study, in accordance with § 812.5(a).

Preliminary work:

Acute human LFP recording:

We have performed acute prefrontal cortical LFP recordings in over 30 patients with Parkinson's disease and patients with epilepsy undergoing brain surgery, under an IRB approved protocol funded by The Defense Advanced Research Projects Agency (DARPA). For this study, in addition to the DBS lead implanted in the basal ganglia, a cortical electrode is temporarily placed over the PFC. Brain signals are then recorded for a short period of time while patients are resting or engaged in tasks. Cortical stimulation is then used to modulate non-motor symptoms such as anxiety and depression. We found that stimulation of the PFC induced positive affect in these patients. Although promising, these results are limited by the temporal and logistical constraints of human intraoperative studies, and chronic brain signals recordings are required to overcome these limitations and better understand and treat these symptoms. This will be achieved using Activa PC+S and Summit RC+S, the two devices allowing both long-term recording of brain activity and therapeutic treatment of the motor-symptoms.

Activa PC+S studies in animal models.

Several animal studies, including one from our group (13), have shown successful implantation of the Activa PC+S device. These animal data supported initiation of trials in human patient populations by showing:

1) Safety and maintenance of good health and motor function of the animals,
2) No underlying cortical damage as shown by a lack of cellular astrocytic and immuno-reactivity,
3) Lack of lead migration (based on stability of recording of characteristic M1 physiology),
4) Chronic stable recordings from the cortex using a subdural electrode connected to Activa PC+S may be maintained for 2 years

Activa PC+S and Nexus-D and E in patients with movement disorders.

As a part of another pilot clinical study investigating the effect of chronic DBS on *motor* cortex brain activity using the Activa PC+S and Nexus-D and E (covered in a separate IDE), we have gained substantial experience with long-term brain signals recordings and use in PD patients. In this protocol, Five PD patients have been implanted, from November 2013 to March 2016 (see **Table 1**) with the Activa PC+S connected to a standard DBS electrodes and a paddle electrode placed over the motor cortex (M1). Implantation has been well tolerated with no serious adverse events recorded over the past 2 years.

Patient #	Gender	Age (years)	Disease Duration (years)	Research Hemisphere	Baseline UPDRS Part III (off/on anti-parkinsonian medications)
1	F	47	15	L	68/16
2	M	62	8	R	30/14
3	F	56	4	L	46/35
4	M	59	7	L	29/14
5	M	60	14	R	44/31
6	M	53	12	R	60/13

Table 1: Demographics of the five Parkinson's patients implanted with Activa PC+S device.

With this pilot clinical study, we have data from the Activa PC+S demonstrating stable recordings from subthalamic nuclei and M1 over time (**Figure 2**). Indeed, the amplitude of the signal, as measured by the root mean square (RMS), did not decrease over time. Additionally, we found that the cortical electrode did not migrate over time, as shown by typical movement-related activity consistently observed in electrodes covering the primary motor cortex (**Figure 3**). Additional demonstration of the safety of implantation and lack of lead migration were documented by comparing intraoperative CT with a subsequent CT taken 1-2 months after surgery. Over the past 2 years, we have also gained extensive experience with the sensing programmer for recording and downloading data, as well as using the Nexus-D and E for closed loop DBS.

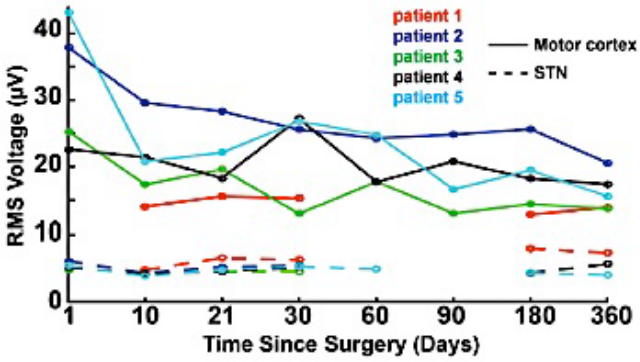

Figure 2: The amplitude of STN (dashed lines) and M1 (solid lines) signals recorded from Activa PC+S is stable over time, as shown by the root mean square voltage computed over time in 6 patients. Voltage does not decrease over a one year time period, indicating reliable signal quality over time.

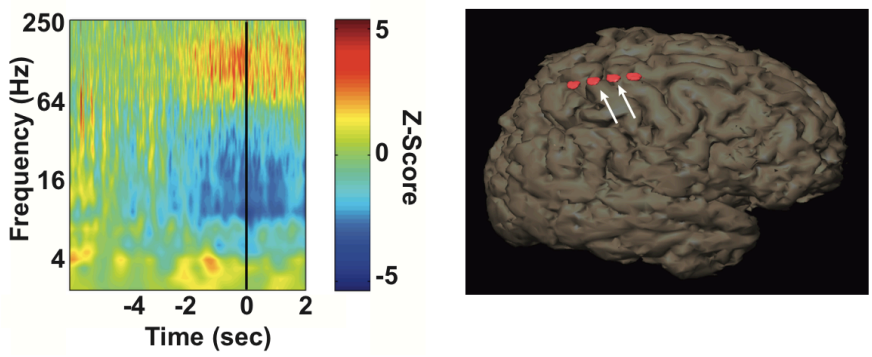

Figure 3: Movement-related changes in ECoG activity detected using Activa PC+S 6 months after implantation. Activity is observed in electrodes covering the primary motor cortex (right panel). A time-frequency plot (left panel) is aligned on movement onset (vertical line,). Movement onset is associated with a typical power decrease in the beta band (13-30Hz) and power increase in the gamma band (50-250Hz).

Other human studies using bidirectional neural interfaces

Several on-going human clinical trials currently implement the Activa PC+S for treatment-resistant depression (15), movement disorders (16) and Tourette's syndrome (17). Additional studies using a different closed-loop brain stimulation system (RNS, Neuropace Inc.) have been conducted in patients with epilepsy (18) and Tourette's syndrome (19). Currently, three similar and active research protocols using Summit RC+S have obtained FDA (G180097; G180203; G160018-S001) and IRB approval.

2.0 Clinical Study Outline

This study will use the Activa PC+S device in PD patients scheduled to undergo DBS implantation for the treatment of motor fluctuations, who also have concurrent non-motor symptoms. The PC+S will be attached to permanent ipsilateral prefrontal cortex and basal ganglia electrodes, to record cortical and subcortical brain signals during different mood/behavioural states (for example: anxious vs calm, depressed vs happy, impulsive vs thoughtful). The study design will allow us to identify abnormal neural activity corresponding

with non-motor symptoms associated with PD and investigate how stimulation can alleviate these symptoms. We plan to offer the Summit RC+S device or a standard Medtronic pulse generator to patients who have already been enrolled in the trial if their Activa PC+S devices are nearing end of battery life. The Summit System has not been evaluated for MR compatibility (like the PC+S). It also requires frequent recharge and stimulation programming for this device is restricted to the use of a special clinician programmer with limited distribution. These considerations will be discussed with patients before signing the consent form. Patients who do not qualify or decline the replacement of PC+S with the RC+S will be implanted with the commercially available DBS device compatible with their brain electrodes.

2.1 Study Objectives

This study will allow us to both define the neural correlates of non-motor symptoms as well as to test the efficacy of stimulation in alleviating these symptoms. The Medtronic Activa PC+S device will allow us to monitor cortical and subcortical brain signals while non-motor symptoms of PD are assessed by subjective (i.e. patient reports and questionnaires) and objective measures (blood pressure, electrodermal activity, and/or task performance in tasks that probe emotional state). Using Nexus-D and E, we will then develop closed-loop paradigm using the physiological biomarker underlying non-motor symptoms, identified in the first phase of this study, to automatically adjust stimulation parameters. Finally, using Nexus-D we will train patients to voluntarily modulate their abnormal brain signals to reduce symptoms. Summit RC+S will allow us to implement the fully closed-loop deep brain stimulation paradigm and neurofeedback components.

3.0 Investigational Plan

This is a single-center study of the neurophysiology of non-motor symptoms associated with Parkinson's disease with several goals: (1) define the electrophysiological correlates (potential biomarkers) of non-motor symptoms (i.e. abnormal oscillatory activity), (2) determine the stimulation parameters that can disrupt such abnormal oscillatory activity and reduce these symptoms, (3) integrate potential electrophysiological biomarker into a closed-loop DBS paradigm and into neurofeedback training.

In a cohort of 10 subjects, we will assess the feasibility of improving non-motor symptoms using closed-loop stimulation. Upon UCSF Institutional Review Board (IRB) approval of our investigational plan and protocol, we propose to conduct this study in two phases for each subject. In phase 1 (1-7 months), patients will undergo long-term recordings of brain signals from electrodes placed over the PFC and in the basal ganglia (subthalamic nucleus or globus pallidus) along with monitoring of the severity of their non-motor symptoms. Since non-motor symptoms may fluctuate spontaneously and in response to dopaminergic treatment or basal ganglia stimulation, neural data will be recorded at multiple time points, in medication on and off states as well as in stimulation on and off states. At each brain data recording session non-motor symptoms will be assessed. Brain signals and symptom assessments will then be analyzed in order to identify a neuronal correlate, a biomarker, of non-motor symptoms and determine how stimulation modulates this abnormal brain activity. In the latter part of phase I, the effects of acute and chronic open loop cortical stimulation will be assessed.

In phase 2 (8 months - 5 years), we will develop a closed-loop paradigm that will automatically determine stimulation settings that optimally reduce non-motor symptoms based on the biomarker identified in phase 1. Using that biomarker we will also train patients to voluntarily modulate these abnormal signals. Subjects will be asked to voluntarily minimize the aberrant signals as represented by the position of a cursor on a screen, while their non-motor symptoms are assessed

In both phases, data will be collected in clinic and/or at the patient's home. Non-motor symptom assessments will include both long-term and short-term time scales. Validated patient self-report questionnaires widely used by psychiatrists and neuropsychologists will be used to assess chronic symptoms over a 2 to 4 week time period. The Beck depression inventory-2nd edition (BDI-II), the Beck anxiety inventory (BAI), Hospital Anxiety and Depression Scale (HADS), Apathy Evaluation Scale (AES), Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease (QUIP), Yale-Brown Obsessive Compulsive Scale (YBOCS), and other well-validated questionnaires will be used. In addition, acute symptoms at the time of the recordings will be assessed using visual analogue scales and tasks engaging emotional and decision making processes, in which performance parameters such as accuracy and reaction time may correlate with non-motor symptoms**.**

4.0 Patient Eligibility

Inclusion criteria:

1.) Ability to give informed consent for the study
2.) Age 30-75
3.) Diagnosis of Parkinson's disease by a movement disorders specialist
4.) Movement disorder symptoms that are sufficiently severe, in the setting of best medical therapy, to warrant surgical implantation of deep brain stimulators according to standard clinical criteria
5.) UPDRS-III score off medication between 20 and 80 and an improvement of at least 30% in the baseline UPDRS-III on medication score, compared to the baseline off-medication score.
    OR
    Patients with tremor-dominant PD (a tremor score of at least 2 on a UPDRS-III sub-score for tremor), treatment resistant, with significant functional disability despite maximal medical management
    OR
    Patients intolerant to medication causing significant functional disability
6.) Have one or several mild to moderate mood or impulsive behavior as defined by:
    - depression (BDI>=13)
    - anxiety (BAI >=7)
    - impulsive behavior as indicated by a positive score on the QUIP-A (Questionnaire for Impulsive-Compulsive disorders in Parkinson's Disease) or as determined by clinical interview or informant report
    - Mood or behavior symptom fluctuations corresponding to minimum 30% improvement in non-motor symptoms when comparing visual analogue scales (VAS) scores in the on versus off medication state

7.) Stable doses of anti-Parkinsonian medications for at least 30 days prior to their baseline assessment.
8.) Patients considered for the replacement of the PC+S with the summit RC+S device would meet the following criteria:
    a. Ongoing clinical need as determined by clinical team. This would be defined as still having depression / anxiety causing significant discomfort.
    b. Cognitive capacity to take part in symptoms assessments associated with closed loop cortical stimulation.
    c. Clinical evidence of benefit from acute cortical stimulation.
    d. Cortical biomarker associated with depression and anxiety and identified in the early phase of this study.
    e. Evidence of benefit of closed loop cortical stimulation (as determined by quantitative visual analogue subjective self-reports).
    f. Ability to recharge the system (either patients and/or caregivers').
    g. Ability to receive re-programming care at UCSF or an institution with access to the clinician programmer that is specific to the investigational Medtronic Summit RC+S device and with limited distribution.
9.) Patient receiving the replacement under this protocol must be within the 5 year study duration that this protocol covers.
    a. The replacement will be provided so that the remaining time in the 5 year protocol can be completed.

<u>Exclusion criteria</u>:

1.) Pregnancy or breast feeding
2.) MRI showing cortical atrophy out of proportion to age
3.) MRI showing focal brain lesions that could indicate a disorder other than idiopathic PD
4.) Major comorbidity increasing the risk of surgery (prior stroke, severe hypertension, severe diabetes, or need for chronic anticoagulation other than aspirin)
5.) Any prior intracranial surgery except DBS surgery
6.) Significant cognitive impairment (MoCA<20).
7.) History of seizures
8.) Immunocompromised
9.) Has an active infection
10.) Requires diathermy, electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS) to treat a chronic condition
11.) Inability to comply with study follow-up visits
12.) Active suicidal based on Suicide Severity Rating Scale (SSRS) and no previous attempts
13.) Any personality or mood symptoms that study personnel believe will interfere with study requirements.
14.) For battery replacement, previous deep brain stimulation surgery using an RC+S incompatible system.

We are not setting a minimum on-medication UPDRS score, because in patients with severe motor fluctuation the on-medication score may be quite low. Such patients can be excellent surgical candidates because the major benefit of therapy is experienced in an effectively "off medication" state, which is of real benefit in patients who fluctuate between "on" and off" states in spite of frequent medication dosing.

5.0 Study Device(s)

Investigational

- Activa PC+S implantable pulse generator, Model 37604
- Sensing Programmer Model 8181 for Activa PC+S
- Sensing Programmer Software Model 8180 for Activa PC+S
- Intercept Patient Programmer, model 37441
- Activa PC+S lead extension model 37087
- Nexus-D2/3 System
- Nexus-D2/3 Application Programming Interface (API)
- Nexus-E firmware and Activator
- Summit RC+S implantable pulse generator (IPG), Model B35300R
- Research Lab Programmer (RLP), Model 4NR010
- Clinician Telemetry Module (CTM), Model 4NR011
- Research Software Development Kit (RDK), Model 4NR013
- Patient Therapy Manager(PTM), Model 4NR009
- Recharge Therapy Manager (RTM), Model 97755

Approved for other indications

- Medtronic Resume II paddle electrode model 3587A

Approved for the intended indication

- N'Vision Clinical Programmer Model 8840
- Clinician Programmer Software Model 8870
- Patient Programmer Model 37642
- Lead Model 3389 or 3387
- External Neurostimulator 37022
- Lead extension model 37086
- Activa SC 37603 single channel pulse generator

Nexus D2/3 – Wireless Adaptation

We propose to use an adapted version of the Nexus D2/3 interface to allow for wireless streaming (via Bluetooth) of brain data to a computer instead of the standard USB connection. This adaptation has been developed by our collaborators at University of Washington. Below we have provided information from Medtronic about the Nexus-D2/3 system and information from University of Washington about the Bluetooth streaming. This text is modified from the University of Washington's approved IDE.

Nexus-D2/3 System - Information from Medtronic

The Nexus-D2/3 System is a research tool that establishes a data and command conduit between a host computer and an Activa PC+S or Activa PC neurostimulator. This conduit can be utilized by researchers to receive sensing data (when used with the Activa PC+S) and also send low-latency stimulation update commands back to the neurostimulator. The Nexus-D2/3 System provides the following functionality:

- Transfer of data from an Activa PC+S or Activa PC neurostimulator
- Transfer of stimulation update commands to Activa PC+S and Activa PC neurostimulators

The Nexus-D2/3 System is designed for rapid, automated closed-loop algorithm prototyping. The system is a low-latency bi-directional data port between an implantable device and an external computer that processes data and algorithms. Nexus-D2/3 System data transmission is wireless to the implanted device and wired to the external computer. The Nexus-D2/3 API is software that resides on the host computer to enable a variety of software programs (e.g., Java programs, Matlab® scripts, and graphical Matlab Simulink® models) to communicate with the Nexus-D2/3 System. This architecture allows algorithms to be both flexible and safe: flexibility is enabled because algorithms on the host computer can be as complex as needed and also utilize data from sensors connected to the external computer (e.g, wearable accelerometers, gait and posture sensors, etc.); safety is ensured because updates to the implantable stimulator are limited to those permissible by the patient programmer and thereby constrained to ranges set by a clinician.

Wireless Modifications to the Nexus-D2/3 – information from University of Washington

The Nexus-D2/3 consists of a reprogrammed Medtronic sensing programmer telemetry module (SPTM) to create a communication channel to the implanted Activa neurostimulator. A host application on a desktop computer can access this communication channel through a commercially available USB to IrDA (infrared data association) bridge (an Actisys IR224UN). The Nexus-D2/3 system is comprised of this combination of the reprogrammed SPTM and the commercially available USB to IrDA bridge. It is important to note that the bridge is purely a translator between the USB interface from the PC and the infrared communication interface. No command generation, interpretation, or parsing of data is performed in the bridge of any kind. It simply passes any data communicated over USB directly to the Nexus SPTM and vice-versa.

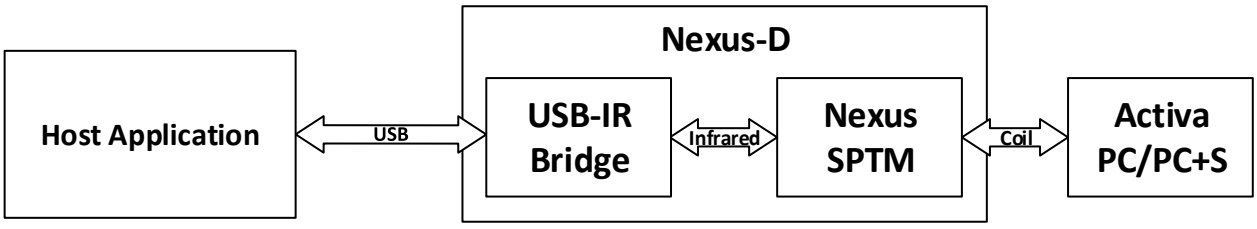

Figure 4 Nexus-D2/3 Block Diagram

Due to the fact that this bridge is a commercially available device that is unnecessary for the overall functionality that the Nexus-D2/3 system provides, developers from the University of Washington have

decided that it would be advantageous to remove it from the system. They have built a system that instead communicates directly with the Nexus SPTM over the infrared interface.

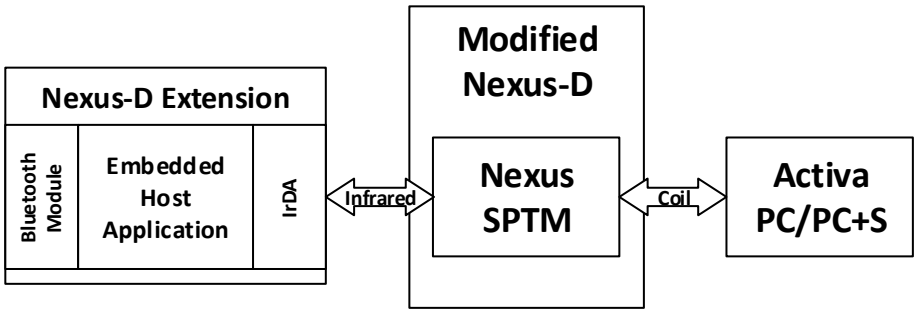

Figure 5 UW BRL Nexus Modification

In this system all of the safety mechanisms and functionality of the Nexus-D2/3 are maintained. However, this system gives us the advantage of building battery-powered embedded systems that will allow for studies on ambulatory patients that won't need to be tethered to a PC for the duration of the experiments.

RC+S Overview of functions of research devices and programming interfaces

RC+S communicates with peripheral devices via the Clinician Therapy Module (CTM), which must be within 2 meters of RC+S during communications. For clinical programming of the device, the research lab programmer (RLP) is linked to RC+S via the CTM. Most research related uses of RC+S are programmed on an investigator's windows-based computer using the Research Development Kit (RDK). The RDK is an application programming interface (API) that can be programmed to establish a data and command conduit between a host computer and RC+S. This conduit can be utilized by researchers to receive sensing data and also send low-latency stimulation update commands back to the neurostimulator, via the CTM. The patient recharges the device using the Rechargeable Therapy Monitor (RTM), and can interrogate it to check its function using the Patient Therapy Manager (PTM).

The RDK is designed for rapid, automated closed-loop algorithm prototyping. This programming interface provides for a low-latency bi-directional data port between an implantable device and an external computer that processes data and algorithms. The RDK includes software that resides on the host computer to enable a variety of software programs (e.g., Java programs, Matlab® scripts, and graphical Matlab Simulink® models) to communicate with RC+S. This architecture allows algorithms to be both flexible and safe: flexibility is enabled because algorithms on the host computer can be as complex as needed and also utilize data from sensors connected to the external computer (e.g, wearable accelerometers, gait and posture sensors, etc.); safety is ensured because updates to the implantable stimulator are limited to those permissible by the patient programmer and thereby constrained to ranges set by a clinician.

6.0 Study Procedure

Study Duration: The duration of this pilot study will be 5 years. We expect that all 10 patients will be recruited in the first 3 years, and data collection will be completed at 8 years.

Patient recruitment: PD patients will be recruited from the UCSF Surgical Movement Disorders Clinic. From this clinic population, 50 PD patients/year are typically offered DBS. Prior to the start of the study, an informal phone interview to schedule an in-clinic evaluation will take place, followed by the pre-surgical in-clinic evaluation. This baseline visit will be scheduled to: 1) confirm eligibility, 2) acquire patient demographics, 3) review medical history and report vital signs, 4) ensure patients are not currently pregnant or plan to become pregnant, 5) obtain a list of current medications being taken, 6) ensure MoCA score meets inclusion criteria ($\geq$20), 7) obtain a baseline clinical characterization of motor symptoms using the UPDRS III both on and off medication, 8) obtain a baseline clinical characterization of motor and non-motor symptoms on and off medication, 9) obtain an anatomical MRI for future surgical planning and to further determine eligibility under inclusion/exclusion criteria.

Clinical characterization: Study visits are summarized in **Table 2**. Motor and neuropsychological characterization will be performed by a movement disorders neurologist, neuropsychologist and psychiatrist at baseline (preoperative visit), at the one year and two years follow up visits. Motor symptoms will be assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) parts I-V and the dyskinesia rating scale (UDysR), on medication. The UPDRS part III will be performed both on and off medication (12 hours). At the one and two year visit, all patients will be assessed using the Clinician Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C) to adequately assess effectiveness that may not be captured by motor rating scales. Neuropsychological evaluation will include the following test battery: Montreal Cognitive Assessment (MoCA), the Columbia Suicide Severity Rating Scale (C-SSRS), Symbol-Digit Modality Test (SDMT, written and oral versions); Delis Kaplan Executive Function System (DKEFS Trail making test, Design Fluency), Neuropsychological Assessment Battery (NAB Digit Span, Memory, Visual Discrimination); Rey-Osterreith Complex Figure (ROCF Copy & Immediate Trials); Controlled Oral Word Association (COWA, FAS & Animal Fluency), Boston Naming Test; Beck Depression Inventory-2nd Edition (BDI-II); Beck Anxiety Inventory (BAI); Parkinson's anxiety scale (PAS); Hospital Anxiety and Depression scale (HADS); Apathy Evaluation Scale (AES), Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP), Yale-Brown Obsessive Compulsive Scale (YBOCS), and Visual Analogue Scales (VAS). Several of these tests (MoCA and Neuropsychological Assessment Battery) have alternative forms available, which will be used to avoid practice effects.

On all other study visits, clinical characterization will be performed by trained study personnel and will include non-motor symptoms evaluation using a subset of the scales listed above, depending on the patient's predominant non-motor symptoms. In addition the patient will perform tasks engaging emotion and/or decision processes. Rating scale examinations and task performance will be videotaped.

On all outpatient study visits we will also administer the Columbia Suicide Severity Scale (C-SSRS).

Study visits: Phase I consists of eleven study visits (**Table 2**). Eight occur during defined time points that coincide with normal clinical care visits (preoperative, day of surgery, day after surgery, 10 days, 4 weeks after surgery, 2-4-6-months after surgery), with four additional research visits (3 weeks and 3-5-7 months

after surgery). In Phase 2, ten study visits will take place (12 months to 60 months post-implantation), five of them coincide with clinical car visits. Some of the out-patient study visits require that PD patients stop their oral levodopa 12 hours prior to the visit which is frequently done for clinical assessment purposes, as well as research studies.

In addition, patients might be offered to participate in an optional minimally invasive sleep study that aims to understand how sleep might alter brain waves. During this sleep study, physiological signals, including brain signals, oxygen level, heart rate, breathing, eye and body movements, will be recorded overnight. Recordings will be done at the UCSF sleep laboratory at least 12 months after the DBS surgery. Additionally patients will stream neural data overnight using the RCS device at home with a paired wearable watch. During this sleep study patients will be on their regular medication dose. Understanding brain waves modulations during sleep in individual subjects is a crucial step in developing closed loop stimulation algorithms that might be use chronically.

Table 2. Summary of study visits

Study Visit	Time	Purpose	Therapeutic Conditions	Behavioral Conditions
Pre-surgery	Within 90 days prior to surgery	**Clinical**: Evaluation of motor and neuropsychiatric symptoms **Research**: Informed consent; ensure eligibility; Patient will perform computer-based tasks that engaged emotion and cognition	**Stimulation**: NA **Medication**: off then on	-Behavioral tasks -Symptom evaluation
1 (START OF PHASE I)	Day of surgery	**Clinical**: DBS Implantation and CT scan **Research**: Record brain signal during surgery; evaluate the severity of anxiety and depression; verification of electrodes placement	**Stimulation**: DBS off **Medication**: surgical anesthesia	-Rest -Symptom evaluation
2	1 day after implantation, prior to hospital discharge	**Clinical:** postoperative follow up **Research:** Record brain signals with and without dopaminergic medication in order to study the effect of antiparkinsonian medication on brain signals and patient's symptoms	**Stimulation**: DBS off **Medication**: off and on	-Rest and behavioral tasks -Symptom evaluation
3	10 days after implantation (+/- 5 days)	**Clinical**: Staple removal and wound check **Research**: Record brain signals with and without dopaminergic medication in order to	**Stimulation**: DBS off **Medication**: off and on	-Rest and behavioral tasks -Symptom evaluation

		study the effect of antiparkinsonian medication on brain signals and patient's symptoms		
4	3 weeks after implantation (+/- 10 days)	**Research**: Record brain signals with and without dopaminergic medication in order to study the effect of antiparkinsonian medication on brain signals and patient's symptoms	**Stimulation**: DBS off **Medication**: off and on	-Rest and behavioral tasks -Symptom evaluation
5	4 weeks after implantation (+/- 10 days)	**Clinical**: DBS initial programming **Research**: Record brain signals with and without dopaminergic medication in order to study the effect of antiparkinsonian medication on brain signals and patient's symptoms	**Stimulation**: DBS off **Medication**: off and on	-Rest and behavioral tasks -Symptom evaluation
6	2 months after implantation (+/- 10 days)	**Clinical**: CT scan **Research:** Record brain signals with and without dopaminergic medication in order to study the effect of antiparkinsonian medication on brain signals and patient's symptoms	**Stimulation**: DBS off **Medication**: off and on	-Rest and behavioral tasks -Symptom evaluation
7-10	3 to 6 months after implantation (every 1 months +/- 20 days)	**Clinical:** Follow-up at 4 months; 6 months; **Research:** Brain signals recordings with and without cortical stimulation in order to study the effect of brief cortical stimulation (<2h) on both brain signals and symptoms	**Stimulation**: cortical off, then on, then off **Medication**: on or off	-Rest and behavioral tasks -Symptom evaluation
11	7 months after implantation (+/- 20 days)	**Research:** Record Brain signals with regular medication and during cortical stimulation in order to study the effect of cortical stimulation (<2h) on brain signals and symptoms when patient is under regular medication; Initiation of chronic (4 weeks) cortical stimulation and set up the Activa PC+S in a recording mode that will automatically save a few minutes of brain signal every day (data will be stored in the Activa PC+S and downloaded at visit 12)	**Stimulation**: cortical on **Medication**: regular medication	-Rest -Symptom evaluation
12-14 (START OF PHASE II)	8 to 12 months after implantation (every 2	**Clinical:** Follow-up at 10 months, motor and non-motor symptoms evaluation at 12 months **Research: Download** data collected daily over the last month; **Record brain signals during** closed-loop cortical stimulation (<2h). During	**Stimulation**: cortical on with different settings	-Rest -Symptom evaluation

	months +/- 20 days)	closed-loop stimulation, stimulation will be delivered only when brain signals that are associated with anxiety/depression/impulsivity are abnormal. At visit 14, chronic (4 weeks) closed-loop stimulation will be initiated; The Activa PC+S will be set up in a recording mode that will automatically save a few minutes of brain signals every day (data will be downloaded at visit 15)	**Medication**: on	
15	At least 12 month after implantation	**Research:** sleep study; determine how sleep pattern alter brain waves	**Stimulation:** Cortical on with different settings **Medication**: regular medication	Physiological signals recorded during natural sleep
16-17	At least 12 month after implantation	**Research:** blind test of the effect of cortical stimulation on non-motor symptoms.	**Stimulation:** Cortical on and off **Medication**: regular medication	-Physiological signals - Symptom assessments
18-19	13 to 24 months after implantation (every 6 months +/- 20 days)	**Clinical: Follow-up at 18 months,** motor and non-motor symptoms evaluation at 24 months **Research:** Download data collected daily over the last month; Train subjects to voluntarily modulate their pathological brain signals using computer-based tasks.	**Stimulation**: off **Medication**: on	-Rest -Symptom evaluation
20-21	3 to 5 years after implantation (+/- 2 months)	**Clinical:** Follow-up at 3 to 5 years after surgery, motor and non-motor symptoms evaluation **Research:** Record brain signals at rest	**Stimulation:** On **Medication:** On	Rest -Symptom assessments
Study Visit	**Time**	**Purpose**	**Therapeutic Conditions**	**Behavioral Conditions**
Pre-surgery		**Clinical**: Evaluation of motor and neuropsychiatric symptoms	**Stimulation**: NA	-Behavioral tasks

	Within 90 days prior to surgery	**Research**: Informed consent; ensure eligibility; Patient will perform computer-based tasks that engaged emotion and cognition	**Medication**: off then on	-Symptom evaluation
1 (START OF PHASE I)	Day of surgery	**Clinical**: DBS Implantation and CT scan **Research**: Record brain signal during surgery; evaluate the severity of anxiety and depression; verification of electrodes placement	**Stimulation**: DBS off **Medication**: surgical anesthesia	-Rest -Symptom evaluation
2	1 day after implantation, prior to hospital discharge	**Clinical:** postoperative follow up **Research:** Record brain signals with and without dopaminergic medication in order to study the effect of antiparkinsonian medication on brain signals and patient's symptoms	**Stimulation**: DBS off **Medication**: off and on	-Rest and behavioral tasks -Symptom evaluation
3	10 days after implantation (+/- 5 days)	**Clinical**: Staple removal and wound check **Research**: Record brain signals with and without dopaminergic medication in order to study the effect of antiparkinsonian medication on brain signals and patient's symptoms	**Stimulation**: DBS off **Medication**: off and on	-Rest and behavioral tasks -Symptom evaluation
4	3 weeks after implantation (+/- 10 days)	**Research**: Record brain signals with and without dopaminergic medication in order to study the effect of antiparkinsonian medication on brain signals and patient's symptoms	**Stimulation**: DBS off **Medication**: off and on	-Rest and behavioral tasks -Symptom evaluation
5	4 weeks after implantation (+/- 10 days)	**Clinical**: DBS initial programming **Research**: Record brain signals with and without dopaminergic medication in order to study the effect of antiparkinsonian medication on brain signals and patient's symptoms	**Stimulation**: DBS off **Medication**: off and on	-Rest and behavioral tasks -Symptom evaluation
6	2 months after implantation (+/- 10 days)	**Clinical**: CT scan **Research:** Record brain signals with and without dopaminergic medication in order to study the effect of antiparkinsonian medication on brain signals and patient's symptoms	**Stimulation**: DBS off **Medication**: off and on	-Rest and behavioral tasks -Symptom evaluation

7-10	3 to 6 months after implantation (every 1 months +/- 20 days)	**Clinical:** Follow-up at 4 months; 6 months; **Research:** Brain signals recordings with and without cortical stimulation in order to study the effect of brief cortical stimulation (<2h) on both brain signals and symptoms	**Stimulation**: cortical off, then on, then off **Medication**: on or off	-Rest and behavioral tasks -Symptom evaluation
11	7 months after implantation (+/- 20 days)	**Research:** Record Brain signals with regular medication and during cortical stimulation in order to study the effect of cortical stimulation (<2h) on brain signals and symptoms when patient is under regular medication; Initiation of chronic (4 weeks) cortical stimulation and set up the Activa PC+S in a recording mode that will automatically save a few minutes of brain signal every day (data will be stored in the Activa PC+S and downloaded at visit 12)	**Stimulation**: cortical on **Medication**: regular medication	-Rest -Symptom evaluation
12-14 (START OF PHASE II)	8 to 12 months after implantation (every 2 months +/- 20 days)	**Clinical:** Follow-up at 10 months, motor and non-motor symptoms evaluation at 12 months **Research: Download** data collected daily over the last month; **Record brain signals during** closed-loop cortical stimulation (<2h). During closed-loop stimulation, stimulation will be delivered only when brain signals that are associated with anxiety/depression/impulsivity are abnormal. At visit 14, chronic (4 weeks) closed-loop stimulation will be initiated; The Activa PC+S will be set up in a recording mode that will automatically save a few minutes of brain signals every day (data will be downloaded at visit 15)	**Stimulation**: cortical on with different settings **Medication**: on	-Rest -Symptom evaluation
15	At least 12 month after implantation	**Research:** sleep study; determine how sleep pattern alter brain waves	**Stimulation:** Cortical on with different settings **Medication**: regular medication	Physiological signals recorded during natural sleep
16-17	At least 12 month after implantation	**Research:** blind test of the effect of cortical stimulation on non-motor symptoms.	**Stimulation:** Cortical on and off **Medication**:	-Physiological signals

			regular medication	- Symptom assessments
18-19	13 to 24 months after implantation (every 6 months +/- 20 days)	**Clinical: Follow-up at 18 months,** motor and non-motor symptoms evaluation at 24 months **Research:** Download data collected daily over the last month; Train subjects to voluntarily modulate their pathological brain signals using computer-based tasks.	**Stimulation**: off **Medication**: on	-Rest -Symptom evaluation
20-21	3 and 4 years after implantation (+/- 2 months)	**Clinical:** Follow-up at 3 and 4 years after surgery, motor and non-motor symptoms evaluation **Research:** Record brain signals at rest	**Stimulation:** On **Medication:** On	Rest -Symptom assessments

Surgery: PD patients will undergo staged bilateral or simultaneous bilateral DBS implantation. Subjects will have implantation of a permanent unilateral subdural cortical electrode (Medtronic Model 3587A lead) at the same time as their initial DBS lead (Medtronic model 3389 or 3387) is implanted. DBS leads are introduced through frontal burr holes. If possible, the subdural cortical electrode will be advanced through the same frontal burr hole as used for the ipsilateral DBS lead. However, if the clinically safe burr hole position for the ipsilateral DBS lead is far (>5 cm) from the cortical target we will make an additional burr hole closer to the cortical target, with a 2-3 cm extension of the frontal incision. Correct placement of the DBS leads and cortical lead is confirmed by intraoperative CT (20). Lead placement will be re-confirmed by CT at the 2 month visit, as post-operative standard of care. The cortical lead will be anchored to the skull near the burr hole with a 1 cm titanium plate, with a strain relief loop anterior to the site of anchoring to prevent movement or torque on the lead over time (**Figure 3**). Thus, the addition of the cortical electrodes may slightly alter the cranial surgical incisions that are routinely used for DBS lead insertion, and it will require one additional anchor point (titanium miniplate, **Figure 3**). We have used a similar surgical technique in five subjects who have had placement of permanent *motor* cortex paddle leads, in an existing PC+S protocol.

The free ends of the cortical lead and DBS lead are then placed in a subgaleal pocket, created by blunt dissection in the ipsilateral parietal area. After induction of general anesthesia, the ipsilateral head, neck and chest are prepped and draped, and the free ends of the lead and ECoG strip are accessed via a new 2 cm incision in the ipsilateral parietal area. The two electrodes are then attached to an Activa PC+S placed in the ipsilateral pectoral area, via two lead extenders (Medtronic Model 37087) recommended by the manufacturer for use with PC+S. The lead extenders are tunnelled subcutaneously between the parietal incision and a 5 cm incision over the pectoralis muscle, where a pocket is bluntly dissected for the Activa PC+S. The contralateral DBS lead will constitute a separate system that is attached to a standard Activa SC primary cell generator in the contralateral pectoral area (via a standard model 37086 lead extender), and will not be used for neurophysiology data collection. If the patient were not participating in research,

he/she would receive either one Activa PC dual channel generator, or two Activa SC single channel generators (one on each side).

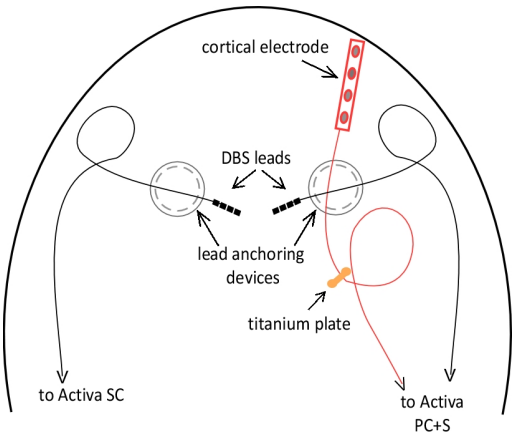

Figure 3. Schematic of implanted hardware as seen from top of head. The cortical electrode (red) passes through same burr hole as the ipsilateral DBS lead, covers the prefrontal cortex and is anchored with a titanium mini-plate.

Activa PC+S Data collection sessions: Detailed in **Table 2**. During data collection we will record up to four bipolar channels, from the cortical and/or subcortical electrodes, for up to 30 minutes prior to a data download. Data download will then performed non-invasively using the Medtronic model 8181 sensing programmer provided by Medtronic Inc., via a wand resting on the skin over the Activa PC+S device, while the patient seated comfortably in a chair.

Behavioral states for Activa PC+S brain data collection: For each recording session, data will be collected in two behavioral conditions: at rest seated in a chair and during computer-controlled tasks that gage mood, anxiety, or impulsivity.

Medication state for Activa PC+S brain data collection: At most study visits occurring between surgery and 3 months after surgery, Activa PC+S brain data will be collected in the on and off medication states. For study visits 2 through 6 recordings will be done in the medication on and off states, in either order depending on patients' symptoms and comfort.

The off medication state is defined as 12 hours off all anti-Parkinsonian medications at baseline (prior surgery) then will be tailor to capture patient's low mood state. The on medication state is defined as 30-60 minutes after normal or "suprathreshold" dose of anti-parkinsonian medication (dose greater than that required to induce an on-state). At all visits after that, data will be collected on or off medication depending on patient's symptoms in each medication state.

Stimulation states for Activa PC+S brain data collection: At all visits, brain data will be collected without therapeutic subcortical stimulation that is used to control motor symptoms. Therefore, DBS might be turned off before starting the Activa PC+S recordings. At visits between 4 months and 10 months, the effect of open-loop PFC stimulation on non-motor symptom severity will be tested and used to develop closed-loop paradigms. Therefore, for each visit between 4 and 10 months, data will be recorded with and without open-loop PFC stimulation.

Once stimulation settings potentially beneficial at improving non-motor symptoms without inducing side effect have been identified, patients might be offered to participate in a blind study of the effect of chronic cortical stimulation. This 2-week clinical trial of sham versus active cortical stimulation is done in a blinded fashion in order to prevent experimental biases arising from a participants' expectations. Two stimulation conditions, active and sham, will be activated for 1h each day for 14 days in a pseudorandom fashion, while assessing symptoms with momentary questionnaires and recording brain signals. These 2 modes will be programmed in the Activa PC+S, in which up to 4 groups with different stimulation settings can be set. The 'active' mode will be set with the stimulation settings proven to be potentially therapeutic in clinic while the other ('sham') will be set with the cortical stimulation at 0V or 0mA. Every morning, for 2 weeks, participant will be asked to activate one of these 2 groups for 1h in a pseudorandom fashion, using the patient programmer. After 1h, non-motor symptoms will be assessed with tablet-based VAS and/or performance of tablet-based cognitive/emotion tasks. In addition, brain signals will be simultaneously recorded, downloaded at a subsequent visit and analyze off-line to determine the effect of stimulation on the biomarker identified in the early phase of this study. During this test, patient and the researchers interacting with the patient, will be blinded of the stimulation condition. In both group STN/GPi stimulation will be kept on and patient will be on regular PD medication to avoid potential confounding effect of DBS/medication control on motor signs. For safety, patient will be instructed to stop this test and go back to their clinical stimulation settings (with their patient programmer) if any side effects were to happen. However, our preliminary data show that chronic stimulation (>=24h) did not induced side effects. A similar protocol will then be used to determine whether adaptive cortical stimulation can better control mood symptoms than continuous cortical stimulation.

Patient activation of the brain recording function: All data collection in the formal study visits described above will be initiated by the study staff. In addition to these data collections, the patient will be given the Intercept Patient Programmer, model 37441, and allowed to "mark" distinctive or more severe phases of non-motor symptoms at home on their own. For example, a patient with fluctuating anxiety will be instructed in the outpatient clinic how to mark the anxiety onset at home, and initiate a brief brain recording. Any brain data collected during these visits may be downloaded in the next clinic visit or by patient him or herself at home. If the patient is not comfortable downloading the data at home, with the patient's permission, arrangements can be made for the study staff to visit the patient's home for data downloads. Study staff may also arrange with patients to visit their homes to help with initiating data collection. Such visits will ensure that data collection is initiated correctly, and by completing downloading at home, will reduce time spent during formal study visits to the clinic. In PD, non-motor symptoms often occur at predictable times during the day that coincide with medication state, allowing study staff to schedule recordings or a home visit likely to coincide with these symptoms. Patients can, for example, initiate a recording before medication during acute anxiety or depression episodes, or after medication, when these symptoms have improved. The intercept patient programmer does not enable stimulation of the electrodes; it only enables recordings of the data and is thus safe for patients to use at-home after initial training with research staff.

***Nexus-D and E System Study*:** Patients who have had the Activa PC+S device implanted for 12 months (Phase 1 of the study) will start Phase 2 of the study that utilizes the Nexus-D and E interface, which is capable of

implementing closed-loop paradigms and neurofeedback cognitive training. Patients will participate in phase 2 of the trial, between 13 and 24 months post implantation, involving five visits.

Closed-loop stimulation will test a strategy for automated control of DBS settings using the aberrant neuronal signal underlying non-motor symptoms identified in phase 1 to trigger stimulation. To test stimulation strategies, at the start of a session in phase 2, Activa PC+S brain data will be collected while the patient is experiencing non-motor and/or behavioral symptoms. These data will be streamed using the Nexus-D System in conjunction with software from the Nexus-D programming interface. The Nexus System provides a conduit between Activa PC+S and a computer and can transfer stimulation update commands to Activa PC+S. Nexus data streaming will occur while the patient is seated at rest. During the streaming procedure, stimulation settings may be automatically, iteratively, adjusted based on biomarkers of non-motor symptoms. These adjustments will always remain within allowable settings pre-programmed by a clinician using standard procedures (i.e. using the Medtronic 8840 programmer). In addition, some closed loop algorithms may be implemented within PC+S without the need to stream data to an external computer using Nexus-E. The identification of non-motor symptom biomarkers will inform development of a closed-loop stimulation paradigm. The final algorithm can be uploaded on to the PC+S device using Nexus E. This allows for automated, biomarker detection-based stimulation that is completely functioning within the patient, without the need to stream to an external computer.

In addition, Nexus-D and E will be used to train subjects to voluntarily modulate the abnormal activity, in a manner that may improve these symptoms. Operant control of motor cortical oscillatory activity has been demonstrated in normal nonhuman primates (21). The Nexus-D and E will be used to represent the amplitude of the abnormal signal in the one dimensional position of a cursor on a computer screen in front of the patient. Subjects will be asked to voluntarily minimize the aberrant signals as represented by the cursor, while their non-motor symptoms are assessed.

Summit RC+S Data collection sessions, in clinic: During in-clinic data collection we will sample up to four time series channels at 500-1000 Hz, to include at least one bipolar motor cortex channel and one bipolar basal ganglia. Data are streamed wirelessly at a distance up to 2 meters, to a windows based laptop running the application programming interface (Researcher Development Kit) provided by the manufacturer, via the clinician telemetry module (CTM). For data collection during walking, a small tablet computer may be used so that patients can wear the tablet and CTM in a small backpack, or neural signals can be stored on the RC+S for subsequent download. As for data collected with the PC+S, in order to identify markers of mood, or confirm those found with the PC+S, and study the effect of PFC stimulation, patients might be off medication and/or off DBS during for the duration of these visits, while patients are resting or engaged in tasks.

Summit RC+S data collections at home: In addition to these data collections, patients will be instructed how to stream neural data to an external tablet computer in their home in order to identify markers of mood and study the effect of PFC stimulation. Data are streamed to an external tablet via the clinician telemetry module (CTM), a small peripheral unit the patient can keep in their pocket. Whenever the CTM is paired with RC+S it can stream data over Bluetooth to the tablet computer. Patients initiate data streaming using a command that investigators set up on their home tablet computer. To facilitate biomarker identification, patients will be asked to make “snapshots”, brief recordings when they are in low and high mood states.

Patients may also wear the tablet and CTM in a backpack, for continuous data streaming for up to 16 hours, to follow the evolution of putative mood state biomarkers over time. During data streaming, patients may wear peripheral monitors, such as inertial monitoring units that will input to the same computer receiving neural data. Data that are streamed at home to the tablet computer, will be uploaded to a HIPAA-secure cloud site for rapid access by investigators. With patients' permission, investigators will make home visits to assist with or troubleshoot data streaming and wearable monitors or to do study visits if that is preferred by the patient compared with coming to clinic.

Adaptive stimulation Mode: We will perform in-clinic or at home testing of adaptive stimulation wherein brain signals, such as theta, alpha or beta power, will be used to titrate stimulation parameters (stimulation current) in a pre-specified range. RC+S allows two possible biphasic waveforms, passive recharge and active recharge. We plan to use the active recharge mode for adaptive sensing, as this will facilitate sensing by reducing stimulation artifact. Adaptive stimulation with RC+S can occur in one of two modes: Distributed, in which the control algorithm resides on the researchers' external computer, or embedded, in which control is accomplished within RC+S according to a preprogrammed algorithm. For in-clinic testing we will primarily use the distributed mode unless the embedded mode is more efficient and accurate in terms of control algorithm time control. During in clinic testing, ECoG and basal ganglia LFP data will be streamed to the researcher computer to verify that therapeutic adjustments are appropriate to the detected neural signals. Patient's symptoms will be assessed with VAS at settings previously identified as potentially therapeutic at improving mood. At the end of the in-clinic or at home adaptive stimulation testing sessions, the PFC stimulation will be turned off. Data collected during these brief in-clinic adaptive simulation tests will be used subsequently to design an optimal personalized adaptive stimulation strategy for home testing. The adaptive control algorithm developed will then be embedded in RC+S and tested at home. Prior to home use of adaptive stimulation, patients will be given and instructed on how to use the Clinician Therapy Module (CTM) and a tablet computer provided by the lab to interface with the CTM device which in turn communicates with the Summit RC+S. These devices allow them to switch off adaptive DBS and turn off cortical stimulation. During study visits patients will be asked to complete a case report form listing common adverse events that may relate to changes in stimulation levels.

Possible adaptive control algorithms: We will develop adaptive control algorithms using the Medtronic Research Development Kit. Since control algorithms will be based on each subjects' personalized neural signatures of mood states, we cannot specify exact algorithms prior to obtaining recordings from RC+S. In general, we expect the controller to utilize spectral power from one or more frequency bands extracted from cortical and/or basal ganglia recordings. Our preliminary data suggest that theta (5-8hz), alpha (8-10 Hz) and beta (12-30 Hz) as possible biomarker of mood. The controller will be based on threshold crossings in one or more of these frequency ranges and will change stimulation current between a low-therapeutic level and a high-therapeutic level. For each proposed control algorithm, we will test the performance of the algorithm using an external RC+S and the RDK prior to implementing adaptive control in the patient.

Safety of adaptive stimulation: During adaptive stimulation, several safety features protect patients from the potential from uncomfortably high stimulation settings or from prolonged periods with clinically inadequate settings. Stimulation parameters that can be implemented by the control algorithm are preselected with clinicians to avoid the possibility of producing major stimulation-induced adverse effects. No possible combination of stimulation settings will exceed the upper charge density limit of 30 microcoulombs per centimeter squared per phase. Prior to home testing, patients will be instructed on how to exit adaptive mode at any time and turn off cortical stimulation should excessive discomfort occur if needed.

Conclusion of study: Formal data collection will be completed at 5 years post implantation. However, it is expected that patients will be followed for life in our clinic, as is the case for patients implanted with DBS devices that are unrelated to research. The cortical electrode would not be utilized after the formal data collection phase is complete, unless further studies are conceived and approved based on the data collected in the present study.

At study completion, should adaptive PFC stimulation mode prove efficacy for individual patients, and the patient requests use of adaptive mode; they may be set to adaptive mode either on a "compassionate use" basis, with appropriate clinical follow up, or they may be offered participation in further research protocols that may be developed

Should a serious adverse event occur that is thought to be related to the presence of the cortical electrode, such as focal seizure or motor weakness congruent with device localization, the cortical lead will be removed. Removal will be accomplished by re-opening the original frontal incision and grasping the lead at or just posterior to the burr hole originally used for placement, taking care not to dislodge the therapeutic DBS electrode. The end of battery life for Activa PC+S is expected to occur 2-4 years after placement, depending on the chronic therapeutic stimulation parameters (similar to the non-research sister device Activa PC that does not have a sensing function). When its battery approaches end of life, it is expected that the Activa PC+S device will be replaced, via the original chest incision, with the Medtronic Summit RC+S device or a standard Medtronic pulse generator. The Summit RC+S IPG may be recharged for up to 9 years after placement, depending on the chronic therapeutic stimulation parameters (similar to the non-research sister device Summit RC that does not have a sensing function). Following this period – the RCS will be replaced with a commercially available DBS device.

7.0 Clinical Measurements

Primary

Physiological measurements related to neural oscillatory activity will include: power-spectral analysis studying multiple frequency bands (i.e. in the delta, theta, alpha, beta, gamma bands), cross-frequency coupling (22-24) and coherence between electrodes.

Secondary

Clinical ratings of non-motor symptoms will be measured by multiple scales such as BDI-II, BAI, PAS, HADS, QUIP, YBOCS, VAS. Clinical rating scales of motor function will include NEW MDS UPDRS I-IV and dyskinesia rating scales. UPDRS part III will be scored on and off of antiparkinsonian medications. Additional measures will include Clinician Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C). Baseline comprehensive neuropsychological testing will be performed including: Montreal Cognitive Assessment (MoCA), the Columbia Suicide Severity Rating Scale (C-SSRS), Symbol-Digit Modality Test (SDMT, written and oral versions); Delis Kaplan Executive Function System (DKEFS Trail making test, Design Fluency), Neuropsychological Assessment Battery (NAB Digit Span, Memory, Visual Discrimination);

Rey-Osterreith Complex Figure (ROCF Copy & Immediate Trials); Controlled Oral Word Association (COWA, FAS & Animal Fluency), Boston Naming Test. Several of these tests (MoCA and Neuropsychological Assessment Battery) have alternative forms available which will be used to avoid practice effects.

All motor scales will be performed or administered by a movement disorders neurologist at baseline, 12 months and 24 months of DBS therapy. For all other visits a subset of these scales will be used based on patients symptoms and will be collected by members of the research and clinical teams.

8.0 Data Management

All physiological data will be stored in password protected computers in the PI's laboratory that is always locked with a keyless card-access entry system. Data will be backed up on UCSF's HIPAA-compliant server. In publications or presentations of the data, data will be grouped by case number in chronological order with all patient identifiers removed. All DBS patients at our center routinely undergo videotaping and sign a separate consent to be videotaped. When presenting videotape data at scientific conferences, we will utilize only videos from patients who have consented to have their videos shown. With patient's permission, de-identified electrophysiological data may be shared with Medtronic or other researchers at other institutions, in accordance with HIPAA regulations.

Clinical data (baseline and follow up rating scales) will be entered into a customized, password-protected encrypted web-based database. This resides on a server at UCSF and is managed by the Department of Neurology, with backup support by the information technology service at UCSF. The database can be accessed by a licensed user from a secure internet server at UCSF but is protected by firewalls from networks outside of our institution.

9.0 Statistical Methods and Data Analysis

LFP data will be analyzed using wide power-spectral analysis as well as analysis of specific frequency domains (i.e. in the delta, theta, alpha, beta, gamma bands). We will also examine region-specific coherence and cross-frequency coupling in addition to coherence between cortical and subcortical brain areas. Using a repeated measures ANOVA statistical analysis, summary statistics for power in relevant frequency bands, power changes, and magnitude of coupling and coherence will be compared at different time points, different DBS conditions (on and off), different medication states (on and off), in a repeated measures (within subjects) design. The small number of subjects is mitigated by the ability to study varying mood states longitudinally within each subject. We will assess the correlation between the severity of non-motor symptoms and brain physiology measures. Additionally, bootstrapping statistical applications (i.e. a Monte Carlo algorithm) and general linear mixed models can be utilized to investigate potential statistical effects, given the small sample size).

Since this is a pilot study of chronic cortical recording, the sample size is likely to be too small to provide definitive answers to all research questions. Based on this exploratory analysis, it is anticipated that the next phase of the study will focus on a subset of the research aims, with 10 subjects per group.

Sample size calculation: This is a pilot study of a novel chronic brain recording technique. The goals are to assess technique feasibility, to collect pilot data that will be used to frame more detailed hypothesis about DBS mechanisms, and (in the add-on study using Nexus-D and E) to explore potential strategies for therapeutic use of the Activa PC+S and Summit RC+S neural interface. Thus, there is no formal sample size calculation.

Criteria for study success that would justify a larger subsequent trial: This study will be considered to justify a larger subsequent trial if we can demonstrate:

1) Chronic LFP recording from the cortex, of adequate quality to assess signatures of non-motor symptoms
2) No permanent serious adverse events occur
3) Therapeutic benefit in non-motor symptoms produced by cortical stimulation (open loop or closed loop) or neurofeedback training.

Data and safety monitoring plan

Treatment-emergent adverse events that are assessed by the principal investigator as possibly, probably, or definitely related to surgical implantation or chronic cortical recording AND are unexpected or meet seriousness criteria (death, immediately life threatening, hospitalization >24 hours, persistent or significant disability, or significant intervention required to prevent one of the previously-stated outcomes) will be reported to the IRB, device manufacturer and the FDA via the MedWatch online voluntary reporting form within 10 working days of the study team's knowledge of the event.

All such events will also be reported to the medical safety monitor (MSM), which consists of a neurologist, Dr. Michael Okun (University of Florida, Gainesville), outside of our home institution, who has no direct involvement in this study but who has expertise in implantable devices. Treatment-related adverse events assessed as definitely, probably, or possibly related to study procedures and either serious or unexpected, noted by any study personnel will be reported within 10 working days of their knowledge of the event to the MSM. The MSM will then advise the PI on potential changes in procedures to improve safety, or, in the event of multiple serious adverse events, may invoke stopping rules.

10.0 Regulatory Requirements

Prior to the start of the study, the following documents will be collected and filed:

- Signed protocol signature page
- Curriculum vitae of the PI and Sub-investigators, updated within 2 years
- Current medical licenses for the PI and all Sub-investigators
- Financial disclosure form signed by the PI and all Sub-investigators listed on the
- Copy of the IRB approval letter for the study and approved and the IRB Membership List.
- Investigator Agreement

Investigator Obligations

Dr. Starr will be responsible for ensuring that all study site personnel, adhere to all FDA regulations and guidelines regarding clinical trials, including guidelines for GCP (including the archiving of essential documents), both during and after study completion. Additionally, he is responsible for the subjects' compliance to the study protocol.

All information obtained during the conduct of the study with respect to the subjects' states of health will be regarded as confidential. This is detailed in the written information provided to the subject. An agreement for disclosure of any such information will be obtained in writing and will be signed by the subject.

Informed Consent

The investigator will obtain and document informed consent for each subject screened for this study. All subjects will be informed in writing of the nature of the protocol and investigational therapy, its possible hazards, and their right to withdraw at any time, and will sign a form indicating their consent to participate prior to the initiation of study procedures.

Institutional Review Board

This protocol and relevant supporting data are to be submitted to the appropriate IRB for review and approval before the study can be initiated. Amendments to the protocol will also be submitted to the IRB prior to implementation of the change. The PI is responsible for informing the IRB of the progress of the study and for obtaining annual IRB renewal. The IRB must be informed at the time of completion of the study and should be provided with a summary of the results of the study by the PI. The PI must notify the IRB in writing of any SAE or any unexpected AE according to ICH guidelines.

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Appendix A –
CV
See attachment

Appendix B –

Patient Informed Consent Form

See attachment

Appendix C –
Case Report Form

See attachment

Appendix D –

Risk Assessment

Appendix E –

Medtronic Device Descriptions

Investigational

- Activa PC+S implantable pulse generator, Model 37604
- Sensing Programmer Model 8181 for Activa PC+S
- Sensing Programmer Software Model 8180 for Activa PC+S
- Intercept Patient Programmer, model 37441
- Activa PC+S lead extension model 37087
- Nexus-D System
- Nexus-D Application Programming Interface (API)
- Nexus-E firmware and Activator
- Summit RC+S implantable pulse generator (IPG), Model B35300R
- Research Lab Programmer (RLP), Model 4NR010
- Clinician Telemetry Module (CTM), Model 4NR011
- Research Software Development Kit (RDK), Model 4NR013
- Patient Therapy Manager(PTM), Model 4NR009
- Recharge Therapy Manager (RTM), Model 97755

Approved for other indications

- Medtronic Resume II paddle electrode model 3587A

Approved for the intended indication

- N'Vision Clinical Programmer Model 8840
- Clinician Programmer Software Model 8870
- Patient Programmer Model 37642
- Lead Model 3389
- External Neurostimulator 37022
- Lead extension model 37086
- Activa SC 37603 single channel pulse generator

Appendix F –
Explanations of acronyms frequently used in the protocol

DBS – deep brain stimulation

ECoG – electrocorticography

LFPs – local field potentials

Nexus D2 – Interface created by Medtronic which allows streaming of Activa PC+S data to a computer and for the computer to make updates to stimulation (within a pre-specified safe range). This allows testing of closed-loop algorithms in clinic and also the streaming necessary for the operant conditioning paradigm.

Nexus D3 – Firmware update to Nexus D2 that allows 1) Streaming of higher quality (uncompressed) Activa PC+S data to a computer and 2) use of the fully embedded Nexus E system, necessary for closed loop DBS out of the clinic.

Nexus D2/3 – General term which encompasses Nexus D2 and D3.

Nexus E – Refers to the embedded Nexus E system where data automatically updates stimulation parameters without streaming to a computer. Allows testing of closed loop paradigm outside of the clinic.

Nexus E Activator – Patient device that works with Nexus E to allow patients to switch out of closed loop mode and into standard mode whenever they choose.

PD – Parkinson's Disease

STN – subthalamic nucleus

PFC – prefrontal cortex