

Bilateral Closed Loop Deep Brain Stimulation for Freezing of Gait Using Neural and
Kinematic Feedback

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3. INVESTIGATIONAL PLAN

3.1. Purpose

3.1.1 Background and significance

PD affects over 10 million people worldwide, with gait impairment and FOG affecting close to 75% as the disease progresses⁴⁴. Gait impairment is characterized by the loss of regular, rhythmic alternating stepping associated with normal forward locomotion and FOG is an intermittent, involuntary, and often sudden inability to perform alternating stepping: the feet appear ‘glued’ to the ground while the upper body continues its original trajectory. Both lead to falls, injury (even death), and a loss of independent living, but are difficult to measure and/or treat.

Deep Brain Stimulation of the subthalamic nucleus (STN), internal segment of the globus pallidus (GPi), and/or thalamus has become a standard of care, FDA-approved treatment for Parkinson's disease, tremor and dystonia. The DBS procedure implants chronic stimulating electrodes (leads; Medtronic models 3387 or 3389, or SenSight™ leads) into the nucleus of choice. The DBS leads are then connected to a subcutaneously implanted neurostimulator, (traditionally the Activa PC™ and more recently the Percept™, both FDA-approved) and stimulation is delivered at a constant amplitude and frequency, in an open-loop fashion. Although gait deficits and FOG may initially respond to continuous open-loop deep brain stimulation (olDBS) and medication, the symptoms often recur over time.

The episodic and predictable nature of FOG makes it well suited for aDBS and a device that overcomes the limitations of traditional high frequency olDBS and is capable of adapting therapy either in the frequency or intensity domain transiently to treat FOG while also treating other PD signs such as tremor and bradykinesia. Gait impairment and FOG were given the highest research priority from the 2014 NINDS PD conference⁴⁵. Both have unpredictable responses to dopaminergic medication and/or continuous high frequency olDBS^{46,47}. Although they may improve on low frequency (60 Hz) STN DBS, PD tremor may worsen, and most patients do not tolerate 60 Hz DBS for extended periods of time^{48–50}. Parameters of DBS used to treat motor signs of PD like FOG, may not be optimal for tremor and vice versa. Adaptive deep brain stimulation (aDBS) that responds to patient-specific neural and kinematic variables with customized DBS parameters could be an effective treatment for FOG to restore normal gait to PD freezers, while also treating other PD motor signs. aDBS, responding to markers of gait impairment and intermittent FOG may prevent FOG, falls and their consequences and would likely reduce adverse side effects associated with the traditionally used treatments.

The Activa® PC+S–NexusD/D3 system enabled the first STN aDBS experiments using a fully implanted neurostimulator, via bi-directional communication of information between the Activa® PC+S system and an external computer, which could also receive synchronized kinematic data via a wireless wearable sensor. Recent technology using wearable sensors made kinematic signals logical and feasible as behavioral control variables for kinematic aDBS. The data we and others acquired using the Activa® PC+S-

NexusD/D3/E aDBS systems provided feasibility data and design inputs for a fully embedded, rechargeable adaptive neurostimulator (Summit® RC+S, Medtronic Inc.), which is capable of performing bilateral aDBS, using lateralized independently controlled algorithms. The Summit® RC+S, a second-generation, sensing implantable DBS system adds functionality to the Acliva® PC+S system; it has the capability to adjust both frequency and intensity of neurostimulation and can respond to dynamic neural and behavioral features seen in the motor symptoms of PD.

The neural and/or behavioral markers of gait impairment and FOG were previously unknown, due to the lack of availability of technology for measuring synchronized neural and behavioral signals in freely moving people. Through over 4 years of research and regulatory experience in an academic-industry collaboration with Medtronic Inc., we have provided design inputs for the next generation aDBS devices^{9-11,51}. We have discovered neural and behavioral markers of gait impairment and FOG in the largest freely-moving PD cohort implanted with a Medtronic investigative neurostimulation/sensing system (Acliva® PC+S-Nexus D/D3/E), using synchronized neural and kinematic recordings during gait tasks that elicit FOG^{10,52}. Our research findings and the technological advances embedded in the Medtronic Summit® RC+S-system now enable the next step: the first clinical studies of lateralized, independent, bilateral STN aDBS for gait impairment and FOG in PD, driven by subject-specific neural or behavioral control variables. PD subjects will be implanted with the Summit® RC+S system, which can respond to neural and/or behavioral markers of FOG (LFP beta burst power and duration, and/or leg (shank) angular velocity and gait cycle (stride) time, respectively) by adapting DBS intensity or frequency, or will have already been implanted with the Percept™ PC or Percept™ RC, which can respond to neural markers of FOG (beta power) by adapting DBS intensity. This study will provide the design inputs to continue advancing aDBS device development and therapy, and will provide critical feasibility data for in-home trials of gait-driven aDBS in PD.

3.1.2 Study Objectives

1. Feasibility of bilateral STN Neural aDBS (NaDBS), driven by neural markers of gait impairment and FOG, and using control policy algorithms that adapt DBS intensity. We will test safety, tolerability and feasibility of bilateral NaDBS using laterally independent control policy algorithms based on STN-specific beta burst power and durations or beta power measured during gait tasks that elicit FOG.

2: Feasibility of Kinematic aDBS (KaDBS), driven by behavioral markers of gait impairment and FOG, and using control policy algorithms that adapt DBS intensity or frequency. We will test the safety, tolerability, and feasibility of STN KaDBS driven by subject specific shank angular velocity and gait cycle time during tasks established to elicit FOG. Inertial measurement unit (IMU) sensors worn on each shank to measure angular velocity during tasks.

Two different control policies will be tested using neural or behavioral markers of gait

impairment or FOG:

- (A) Modulating DBS intensity between subject-specific safe limits
- (B) Modulating DBS frequency from 140 Hz to 60 Hz during intermittent FOG.

3: Safety and tolerability of adding subject specific dose(s) of dopaminergic medication during NaDBS and KaDBS for gait impairment and FOG, using control policy algorithms that adapt DBS intensity or frequency. Subjects will be tested on NaDBS or KaDBS before and during normal morning medication doses. Safety, tolerability and any adverse effects will be measured as aDBS responds to medication-induced changes in neural or kinematic control variables.

3.2. Protocol

The experimental design of our study involves testing the feasibility of using certain neural and kinematic control variables to drive aDBS during two different gait tasks: stepping in place (SIP) and the turning and barrier course (TBC). The neural control variables that we have identified based on our preliminary work include movement band beta burst power and movement band beta burst duration. The kinematic control variable identified will be gait-cycle time, derived from shank angular velocity. We will test aDBS across different conditions which include:

- Current intensity based neural aDBS (NaDBS) off and on medication (at stimulation frequencies of 140 Hz or equivalent sense-friendly frequencies if implanted with the Percept™ PC/RC)
- Current intensity based kinematic aDBS (KaDBS) off and on medication (at stimulation frequency of 140 Hz)
- Stimulation frequency based KaDBS off and on medication (switching between stimulation frequencies of 140 Hz/ 60 Hz)

The experimental design will proceed in a bench-to-bedside manner such that both NaDBS and KaDBS will be tested during SIP first, wherein the patient is harnessed, followed by aDBS during the TBC, both in the clinic, paving the way for in-home testing. Starting with the SIP task helps to ensure patient safety and the subsequent use of the TBC mimics environments known to trigger FOG in the real world. Participants can then elect to participate in at-home testing of NaDBS if implanted with the Percept™ PC/RC.

The primary endpoint for the protocol will include the safe and tolerable delivery of NaDBS and KaDBS during the stepping in place task. Safe and tolerable in this context means that aDBS does not cause adverse effects that result in the subject being unable to tolerate the experiment. Side effects may include paresthesias (pins and needles), muscle twitching, dyskinesias, worsening of gait symptoms, mood or cognitive impairment, or any sense of malaise.

If the primary endpoints related to aDBS during SIP are successfully accomplished, implying safe and tolerable delivery of adaptive neurostimulation during the SIP task, we

will test safety and tolerability of adaptive neurostimulation in a task where the subjects can freely move, mimicking the in-home environment through a turning and barrier course (TBC). The secondary endpoint for the study protocol includes successful safe and tolerable delivery of adaptive neurostimulation during TBC.

Improvement with respect to the primary and secondary outcomes (see Study Outcomes, Section 3.2.4 or Outcome Measures, Section 3.2.7.) will facilitate in-home testing. Finer neural and kinematic control variables, and more intricate control policy algorithms will be designed for in-home testing of adaptive neurostimulation for FOG. Integrated neural and kinematic control policy algorithms will be designed such that a combination of the features enhances therapeutic benefit to subjects.

3.2.1 Study Design, Setting/location

This is an open label pilot study of fifteen people with Parkinson's disease. In-clinic experiments will be performed in the Stanford Human Motor Control and Balance Laboratory in the Department of Neurology and Neurological Sciences at the Stanford University Medical Center. The Stanford Human Motor Control and Balance Laboratory is unique aspect of the Stanford Movement Disorders Center, in which we have developed several quantitative measures of motor control and a parallel line of research in human motor control in Movement Disorders. These measures have been validated with the clinical scale most widely used in PD research, the Unified Parkinson's Disease Rating Scale-III (UPDRS-III).

3.2.2 Study Population

The study will be carried out in fifteen subjects with moderate to advanced PD, who will have either been evaluated and approved to have or already have subthalamic deep brain stimulation to treat their motor signs.

Subgroups: We aim to recruit an equal number of tremor dominant and tremor absent people and people with documented freezing episodes and those without. Some with tremor may or may not freeze and vice versa.

The initial cohort will be implanted with the Summit® RC+S system, and a secondary cohort will already have been implanted with the Percept™ PC/RC system.

3.2.3 Eligibility criteria

Inclusion criteria:

- Clinically-established PD
- Meets criteria for STN DBS eligibility as part of patient's standard medical care or already implanted in the STN with Percept™ PC/RC.
- The presence of complications of medication such as wearing off signs, fluctuating responses and/or dyskinesias, and/or medication refractory tremor, and/or impairment in the quality of life on or off medication due to these factors.
- Ability and willingness to return for study visits, at the initial programming and

after three, six and twelve months of DBS.

- Age > 18
- Freezing of gait questionnaire⁵⁴ (FOG-Q) or New Freezing of gait questionnaire⁵⁷ (NFOG-Q) score ≥ 1 and/or gait sub-score (Item 3.10) of MDS- UPDRS III ≥ 1
- $\geq 1.2 \mu Vp$ between 8-35 Hz on either the LSTN or RSTN (Percept™ PC/RC cohort only)*

Exclusion criteria:

- Dementia
- Untreated psychiatric disease
- Hoehn and Yahr stage 5 on or off medication (non-ambulatory)
- Age > 80
- Major surgical morbidities such as severe hypertension, coagulopathy and certain metabolic conditions that might increase the risk of hemorrhage or other surgical complications
- Presence of a cardiac pacemaker/defibrillator
- Inability to understand/sign consent
- Requires rTMS, ECT, MRI (Summit® RC+S cohort only), or diathermy**
- Are pregnant or lactating
- Has a cranial metallic implant
- History of seizures or epilepsy

*Since the NaDBS algorithm adjusts stimulation based on beta power, there needs to be enough signal or power present in that band for it to serve as a biomarker. Although it has been previously found that majority of PD patients exhibit significant power within beta band in the STN (Shreve et al., 2017 Clin Neurophysiol), some individuals may not display significant beta power either due to individual variability, poor electrode placement, or lack of signal quality due to the equipment malfunctions (e.g., fluid intrusion, poor impedances, etc.). The Summit cohort was recruited prior to implantation of the device and therefore there was no way to investigate the signal quality until after the investigational Summit RC+S device had already been implanted. Additionally, if it was found that a participant with the Summit RC+S device did not have enough signal in the beta band, they could still participate in the KaDBS portions of the protocol which do not rely on neural signals, but instead on peripheral sensors worn on the ankles.

Meanwhile, the Percept PC/RC cohort is being recruited after they have already been implanted with the device, as it is a commercially available neurostimulator. Since the Percept PC/RC cohort does not participate in the KaDBS portions of the protocol due to technical limitations of the device that do not allow stimulation to be adjusted from peripheral sensors, they then must have sufficient signal with beta in order to use the proposed NaDBS algorithm. This can be confirmed prior to consent through the FDA-approved BrainSense™ capabilities of the Percept PC/RC device.

** The Percept PC/RC device is MRI compatible, whereas the Summit RC+S device is not. rTMS, ECT, and diathermy are contraindications for both devices.

3.2.4 Study outcomes

Primary outcome: Measures of subject safety and tolerability of aDBS during gait

Secondary outcomes:

- Gait parameters: arrhythmicity, gait speed, mean shank angular velocity and gait cycle time
- Number and duration of freezing episodes (measured as percent of time spent freezing during the task)
- PD motor signs (UPDRS-III).

Controls for aDBS: continuous oDBS, intermittent (i)oDBS, aDBS during intentional stops, and during arm swinging while standing will provide necessary safety and tolerability information prior to in-home testing.

3.2.5 Study procedures

3.2.5.1 Experimental Protocol

There will be 4 visits per subject, spanning 1 – 2 years, each visit occurring every 3-4 months. Each subject will have their first study visit after therapy has been optimized and any necessary technical checks for safety have been completed. The experiments for Objectives 1 and 3 will include 2 visits with each visit spanning 3 days. The experiments for Objectives 2 and 3 will include 2 visits, with each visit spanning 4 days. The different aDBS stimulation conditions will be randomized across patients. The SIP visit associated with each condition will always occur before the TBC visit for that same condition. At the start of all visits, subject will arrive in the off/ON state (off medication, ON optimized clinical oDBS settings).

After consent but prior to any research testing, the subject will complete a short, pre-operative protocol if part of the Summit RC+S cohort. This includes the MDS-UPDRS parts I, II and IV, the C-SSRS, and the NFOG-Q. The ON/OFF UPDRS III completed by the subject's clinician as part of the standard DBS evaluation protocol will also be included in this data set. The Percept PC/RC cohort will also complete the MDS-UPDRS parts I, II and IV, the C-SSRS, and the NFOG-Q prior to the beginning of the testing protocol. The ON/OFF UPDRS III from the subject's standard DBS evaluation protocol will also be included in this data set.

In the time period between Initial Programming and a subject's first study visit, they will return to the clinic for visits with the study neurologist to optimize their therapy as part of standard clinical practice. In this time same period between Initial Programming and the first study visit, the research team will perform short technical checks for safety purposes and additionally, to inform the development of the subject-specific research protocols. These technical checks may include tests such as adverse event testing for intensity limits, ramp rate testing, voltage titration with short resting state sensing recordings, and short periods of sensing during movement. These technical checks will

provide an additional timepoint during the study to ensure patient safety as well as aid in the collection of artifact free data in future research visits.

In addition to clinical optimization and on-site technical checks, subjects may also complete supervised in-home technical checks and provide in-home neural and behavioral recordings. In-home technical checks will occur with the researchers via a secure video conferencing platform or home visits. Researchers will be able to remotely control the RC+S via a tablet computer and will monitor the patient for safety. Clinical stimulation settings can be restored at any time by the researcher or subject.

Subjects will be instructed how to stream data to a tablet computer. These recordings may be used to inform biomarker development for the neural and kinematic controllers used in the study visits. Subjects may be asked to provide more recordings during the rest of the study to further inform the control algorithms. Data are streamed to the tablet computer via Bluetooth through a clinical telemetry module (CTM) which can be kept in their pocket. Subjects may initiate streaming for brief recordings when they typically experience symptoms such as FOG episodes. They may also record video of these symptom episodes to the tablet computer. They will also have the option to wear the tablet and CTM in a backpack for continuous streaming of data up to 16 hours. Subjects also might wear peripheral monitors, such as an inertial measurement unit, that will synchronize with the data recorded on the RC+S stored on the tablet computer. All data stored on the tablet computer will be uploaded to HIPAA-compliant secured cloud storage by the investigators. With permission, investigators may make home visits or consult via a secure video conferencing platform to assist with trouble shooting as needed.

A clinic visit will occur during one of the days of each study visit.

Day 1 of each visit: The Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered, per FDA mandate for all device related studies (see Additional methodology details, Section 3.2.5.5). Baseline testing will then be administered (see below, Section 3.2.5.5). Safety and tolerability calibration tests will then be performed to determine (or confirm, if determined during a technical check) optimal parameters for the rate of DBS intensity increases and decreases (ramp rates) and for switching stimulation frequency. During the calibration tests, a questionnaire will be administered to determine which ramp rates are optimally safe and tolerable. We will investigate the tolerability specific to different current amplitudes as the tolerable ramp rate at low current intensities may not be the same as the tolerable ramp rate at higher current intensities (see Additional methodology details, Section 3.2.5.5). DBS intensity titration curves will be determined (see Fig. 4, Section 2) and a maximum tolerable current amplitude ($I_{\max}$) related to adverse effects (Aes) will be determined by the clinician. The aDBS experiments will never exceed this $I_{\max}$ as to avoid Aes. The $I_{\min}$ will be set as the lowest intensity at which there is tolerable gait improvement from DBS. The current intensity will not go under $I_{\min}$ during aDBS to maintain a safe therapy level at all times.

Subject-specific thresholds for neural and kinematic control variables (beta burst duration/power or beta power and shank angular velocity/gait cycle time) and classifier algorithms will be determined from the DBS intensity titrations (see Additional methodology details, Section 3.2.5.5) during SIP and TBC. These neural and kinematic thresholds will be used in the subsequent aDBS experiments.

Baseline testing by blinded rater consists of the speech intelligibility test (SIT), quantitative measures of bradykinesia and tremor during repetitive wrist flexion extension (rWFE) and/or a repetitive alternating finger tapping (RAFT) task, the UPDRS-(I-IV), NFOG-Q, and custom AE questionnaires (see Additional methodology details, Section 3.2.5.5).

During all visits and sessions, the subject will be blinded to the specific stimulation setting but will be able to give feedback throughout. If, during any intervention, the subject is unable to tolerate the therapy, that session will be stopped. The aDBS settings will form a separate group on the neurostimulator, so that the subject can be immediately returned to their clinical oDBS settings at any time. Subjects will be instrumented with eleven inertial measurement unit sensors (IMUs) to capture full-body kinematics (chest, lumbar (L5), left and right shanks, wrists, thighs, feet, and head). All experiments will have synchronized neural, kinematic and video recordings.

Visit days are outlined below. For patient comfort and/or convenience, visits may be spread out over more days or consolidated into fewer days. Patients may also elect to complete the visit over nonconsecutive days.

Visit 1: NaDBS with variable DBS current intensity, fixed frequency (140 Hz or equivalent sense-friendly frequency for Percept PC/RC cohort) during SIP task:

Day 1:

- SIP and Full baseline testing in the off/OFF state (off meds, OFF DBS) (see Additional methodology details, Section 3.2.5.5)
- Determine/confirm $I_{\max}$
- Determine/confirm safe and tolerable ramp rates of DBS intensity
- Current titration (see Additional methodology details, Section 3.2.5.5)
- Determine neural control policy thresholds for subsequent NaDBS (see Control Policy Algorithms, Section 3.2.5.2)
- Determine parameters to be used during ioDBS and oDBS (see Control Policy Algorithms, Section 3.2.5.2)
- Controls for aDBS: SIP interspersed with periods of intentional stopping during a short session of NaDBS (see Additional methodology details, Section 3.2.5.5)
- Controls for aDBS: Stand in place and swing both arms for 30 seconds during NaDBS (see Additional methodology details, Section 3.2.5.5)

Day 2:

- Randomized 20-minute sessions of oDBS, ioDBS, and NaDBS with SIP. The subjects will perform SIP after 20 minutes of stimulation wash-in in each

condition. At the end of each 20-minute session, the subject will perform SIP baseline testing (see Additional methodology details, Section 3.2.5.5).

Day 3:

- Take morning dose of medication and perform NaDBS run for 120 minutes. After 60 and 120 minutes, subject will perform the SIP task and SIP baseline testing (see Additional methodology details, Section 3.2.5.5).

Visit 2: NaDBS with variable current intensity, fixed frequency (140 Hz or equivalent sense-friendly frequency for Percept PC/RC cohort) with TBC task

Day 1:

- TBC and Full baseline testing in the off/OFF state (see Additional methodology details, Section 3.2.5.5)
- Determine/confirm $I_{\max}$
- Determine/confirm safe and tolerable ramp rates of DBS intensity
- Current titration (see Additional methodology details, Section 3.2.5.5)
- Determine neural control policy thresholds for subsequent NaDBS (see Control Policy Algorithms, Section 3.2.5.2)
- Determine parameters to be used during iolDBS and olDBS (see Control Policy Algorithms, Section 3.2.5.2)
- TBC interspersed with periods of intentional stopping during a short session of NaDBS (see Additional methodology details, Section 3.2.5.5)
- Stand in place and swing both arms for 30 seconds during NaDBS (see Additional methodology details, Section 3.2.5.5)

Day 2:

- Two sessions of randomized 120-minute sessions of olDBS, iolDBS, and NaDBS with TBC. During each of the 120-minute sessions, the subjects will perform TBC and TBC baseline testing after 60 and 120 minutes. (see Additional methodology details, Section 3.2.5.5).

Day 3:

- Third 120-minute session that was not completed on Day 2
- TBC off meds during NaDBS and perform TBC baseline testing to assess tolerability
- Take morning dose of medication and perform NaDBS run for 120 minutes with TBC. After 60 and 120 minutes, subject will perform the TBC task and TBC baseline testing. (see Additional methodology details, Section 3.2.5.5)

Visit 3 (Summit RC+S Cohort Only): KaDBS with variable current intensity, fixed frequency (140 Hz) as well as variable frequency (60/140 Hz), fixed current intensity with SIP task

Day 1:

- SIP and Full baseline testing in the off/OFF state

- Determine/confirm $I_{\max}$
- Determine/confirm safe and tolerable ramp rates of DBS intensity
- Determine/confirm safe and tolerable intensity for switching DBS frequency
- Current titration (see Additional methodology details, Section 3.2.5.5)
- Determine kinematic control policy thresholds for subsequent KaDBS (see Control Policy Algorithms, Section 3.2.5.2)
- Determine parameters to be used during iolDBS and olDBS (see Control Policy Algorithms, Section 3.2.5.2)
- Controls for aDBS: SIP interspersed with periods of intentional stopping during a short session of KaDBS (see Additional methodology details, Section 3.2.5.5)
- Controls for aDBS: Stand in place and swing both arms for 30 seconds during KaDBS (see Additional methodology details, Section 3.2.5.5)

Day 2:

- Two sets of SIP (randomized) during randomized KaDBS, olDBS and iolDBS will be tested. SIP baseline testing will be performed before and after each set of trials.
 - In one SIP set (3 total trials):
 - SIP during KaDBS modulating DBS current intensity responsively at 140 Hz
 - SIP during iolDBS at 140 Hz
 - SIP during olDBS at 140 Hz
 - In another SIP set (4 total trials):
 - SIP during KaDBS modulating (switching) frequency between 140 Hz and 60 Hz responsively
 - SIP during olDBS at 140 Hz
 - SIP during olDBS at 60 Hz
 - SIP during iolDBS switching frequency between 140 Hz and 60 Hz

Day 3:

Two variations of KaDBS will be randomized between Day 3 and Day 4: KaDBS modulating either current intensity or stimulation frequency before and after the administration of medication. Take morning dose of medication and perform SIP and SIP baseline testing with KaDBS after approximately 60 and 120 minutes.

Day 4:

Same protocol as Day 3 but with the KaDBS variation not completed in the prior day: KaDBS modulating either current intensity or stimulation frequency before and after the administration of medication.

Both variations may be tested on the same day or may be split across the two days.

Visit 4 (Summit RC+S Cohort Only): Same 4-day protocol as Visit 3 (SIP) will be followed except the task will be TBC with TBC baseline testing. On Days 3 and 4, the

TBC and TBC baseline testing will also be completed on each KaDBS variation off medication, prior to taking morning dose of medication.

Single-Blind Long-Term NaDBS Protocol

Following safe and tolerable completion of an aDBS in-clinic visit, participants from the Percept™ PC/RC cohort can elect to participate in the long-term phase of testing which involves a single-blind assessment of NaDBS. During this testing, participants will spend four weeks on either NaDBS or oIDBS (randomized order). Following four weeks, they will then switch to the other DBS condition for an additional four weeks.

Participants will complete a baseline, 2-week, and 4-week assessment in the lab. The in-clinic assessment will include:

- MDS-UPDRS III
- SIP
- TBC
- QDG
- WFE
- Speech
- Questionnaires

All tasks will be done in the on medication/ON DBS state.

Following completion of the four-week single-blind period, the participant will be given the choice, in conjunction with their clinician, to continue on NaDBS if NaDBS is found to be of comparable or better efficacy as open loop. If elected by the participant, they will continue on this mode with appropriate clinical follow-up for the duration of the study or once aDBS is approved by the FDA. The standard clinical practice at Stanford is for patients with Parkinson's Disease and DBS to have appointments with their neurologist every 3-6 months to assess whether any changes to therapy need to be made. If a patient elects to continue on NaDBS following the four-week single-blind protocol, they will continue to see their neurologist once every 3 months for the first year on NaDBS and then every 3-6 months after the first year to assess overall treatment of their disease and make any adjustments to NaDBS, if necessary. The same formal research assessment protocol from the 1-month single-blind period will be used every 3 months in the first year and 3 to 6 months following the first year to follow symptom progression on NaDBS. This will test overall motor symptoms (MDS-UPDRS III), gait (SIP and TBC), bradykinesia and upper extremity symptoms (WFE and QDG), and speech alongside feedback questionnaires.

Blinding: For the single-blind long-term NaDBS protocol for the Percept PC/RC cohort, participants will be blinded to whether they are on NaDBS or oIDBS for a given 4-week period. In order to carry out this blinding, we will utilize the functionality of the Percept PC/RC that allows setting up multiple groups. We will set up one group with the oIDBS settings and another group with the NaDBS setting that will each be tested in the 4-week

protocol. These groups will be labeled ‘Group A’ and ‘Group B’ so the participant will not be able to discern which group is which. Additionally, we will set up a third group that will have amplitude range settings from 0 to a clinically therapeutic level determined by the clinician. This will serve as the ‘fall-back’ group that the patient can switch to if they find their current group to be intolerable or sub-therapeutic. This third group will have a range from 0 to a clinically therapeutic level so that, if needed, the patient can manually change stimulation amplitude up or down with their patient programmer. There is also a ‘Suspend Therapy’ button that the patients can access on their programmer that will cause stimulation to stay at a pre-determined (by the clinician) stimulation amplitude. If a patient finds their stimulation group to be intolerable, they will have either of these options to return to tolerable stimulation amplitude. They then can work with the research and clinical team to set up an appointment to adjust stimulation settings of the groups if necessary. Note, a double-blind paradigm is not being used as it may not be feasible to keep the research team blinded when doing the formal in-lab evaluations at the 2- and 4-week mark as these sessions require interacting with the programming tablet.

Reason for Limiting Long-Term NaDBS Protocol to Percept PC/RC Cohort:

The Percept PC and RC devices are both commercially available FDA-approved devices and were designed with the capability to carry out long-term NaDBS at-home (although this capability is not currently FDA-approved). We are introducing the long-term NaDBS testing cohort specifically with the Percept PC and RC devices since these devices are well suited for at-home testing. The Percept PC and RC allow the setup of multiple groups, including aDBS, and the patient can switch between them with their patient programmer. This is a benefit for risk mitigation in the case that NaDBS is found to be intolerable or sub-therapeutic, as the participant can switch back to their original clinical settings at any time (See above for more details). We have used a similar protocol in 8 patients as part of the ADAPT study which involves sending patients home on NaDBS for prolonged periods of time on the Percept PC. Meanwhile, the patient programmer for the Summit RC+S device does not have the ability to switch back and forth between aDBS group and standard clinic groups. Although the Summit RC+S is also capable of running embedded NaDBS at-home, we are proposing to initially start with the Percept PC/RC cohort for at-home testing.

Additional testing: Once a subject completes the clinical protocol, they may optionally come in to complete additional, repeated testing. Each participant can return for up to 4 additional visits that occur every three months, per year. This testing will use only interventions already in use for the primary clinical protocol. This data would be used to further understand the safety and feasibility of closed loop deep brain stimulation systems. As these visits are optional, the length of the visits will be determined by the subject. These visits could be shorter or the same length as the full research visits and follow a similar procedure of finding safe and tolerable controller settings before the subject continues to kinematic testing.

3.2.5.2 Control Policy Algorithms

Neural aDBS:

Summit RC+S Cohort:

The neural adaptive deep brain stimulation (NaDBS) will be performed using beta band burst duration as the primary input variable. For the neural control policy algorithm, real-time local field potentials (LFPs) sensed and streamed by the RC+S system (Medtronic, Inc.) will be used to determine beta bursts. If the burst amplitude exceeds a pre-defined physiological threshold (Fig. 5, Section 2) and stays above the threshold for a pre-determined amount of time, the current amplitude will rise towards $I_{\max}$ at a pre-defined, safe ramp rate. If the burst amplitude goes below the threshold and stays there for a pre-determined amount of time (called the ‘termination delay’), the current amplitude will decrease towards $I_{\min}$ at a pre-defined, safe ramp rate. If the burst duration is temporally shorter than the termination delay, stimulation will not change. The minimum burst duration and termination delays will be determined on a subject-specific basis by analyzing their neural signals from the calibration periods.

Percept PC/RC Cohort:

The neural adaptive deep brain stimulation (NaDBS) will be performed using beta band power as the primary input variable. For the neural control policy algorithm, real-time power in a pre-defined beta band will be sensed by the Percept PC/RC system. Either a dual- or single-threshold algorithm will be used. In the dual-threshold algorithm, if beta power exceeds a pre-defined physiological upper threshold and stays above it for a pre-determined amount of time, the current amplitude will rise towards $I_{\max}$ at a pre-defined safe ramp rate. If the beta power goes below a lower threshold and stays there for a pre-determined amount of time, the current amplitude will decrease towards $I_{\min}$ at a pre-defined safe ramp rate. If beta power is between these two thresholds, stimulation amplitude will not change. Meanwhile, for the single-threshold algorithm, stimulation will increase if beta power is above the threshold and decrease if below the threshold. The thresholds for beta power will be determined on a subject-specific basis by analyzing their neural signals from the calibration periods. Short runs of NaDBS are performed during the calibration testing on the first day of a given visit. Both the single and dual-threshold algorithm will be testing during short runs of NaDBS. We will then compare patient feedback from our aDBS custom questionnaire and kinematic performance to decide on which threshold to use for the formal testing.

Reasons for differences in algorithms between cohorts:

Both single threshold (Little et al., 2013 Ann Neurol) and dual threshold (Velisar et al., 2019 Brain Stim; Gilron et al., 2021 Nat Biotechnol) have successfully been used to adapt stimulation based on beta. A single threshold algorithm is used with the Summit RC+S since the system is responding to beta burst durations on a rapid timescale (hundreds of milliseconds) in a similar manner as was done in Little et al., 2013. However, the Percept PC/RC device is unable to compute beta burst durations and is

only able to track beta power (or power within a frequency band of your choice) using an online FFT. Therefore, the signal is inherently more smoothed compared to burst durations. This signal may be better suited for a dual threshold algorithm as it operates on a slightly longer timescale (hundreds of milliseconds to seconds).

Kinematic aDBS (Summit RC+S Cohort Only):

Due to technical limitations of the Percept™ PC/RC device which does not feature a distributed mode in which a peripheral sensor can be used to adjust stimulation, Kinematic aDBS will be limited to only the Summit® RC+S cohort. The kinematic adaptive deep brain stimulation (KaDBS) will be performed using a “freezing model” to determine if the patient is exhibiting freezing behavior (freezing and/or impaired “abnormal” walking). We will determine parameters for the freezing model using values from signals recorded from two inertial measurement unit sensors (IMUs) worn on the shank of each leg and/or the RC+S® built-in accelerometer. We will use the shank angular velocity about the axis perpendicular to the forward swing direction which captures the kinematics of forward swing, as well as gait-cycle time, which is defined as the time elapsed between two subsequent mid-swing peaks in this shank angular velocity signal (because this is robust even when heel strikes are absent). These and/or other relevant gait features, such as arrhythmicity (the mean stride time coefficient of variation (CV) of both legs), will be utilized in the aforementioned model. A single or multiple thresholds between which the model outputs (e.g., probability of freeze) are allowed to vary will be set and tuned during the calibration period. For example, an upper “freezing” threshold may represent the minimum probability that a patient is freezing, while a lower “normal” threshold may represent the probability under which a patient is not freezing.

If the real-time output of the freezing model exceeds the freezing threshold, the current amplitude will increase towards $I_{\max}$ at a pre-defined, safe ramp rate for the duration of a termination delay (Fig. 8 Section 2). If the output of the freezing model falls below the “normal” threshold, the current amplitude will decrease to $I_{\min}$ at a pre-defined, safe ramp rate. When the output of the freezing model falls between the freezing and “normal” thresholds, the stimulation state will hold at its current intensity. In the case of utilizing a single threshold, there will be no hold state.

For KaDBS related to frequency modulation, if the real-time output of the freezing model exceeds the freezing threshold, the stimulation frequency will switch from 140 Hz to 60 Hz for the duration of a termination delay (Fig. 8, Section 2). If the output of the freezing model falls below the “normal” threshold, the stimulation frequency will switch to 140 Hz from 60 Hz. When the output of the freezing model falls between the freezing and “normal” thresholds, the stimulation state will hold at its current frequency. In the case of utilizing a single threshold, there will be no hold state. The frequency based KaDBS will occur at the highest current intensity for which frequency switching is tolerated.

Intermittent oIDBS (ioIDBS) (Summit RC+S Cohort Only):

Due to technical limitations of the Percept™ PC/RC device which does not allow pre-configuration of stimulation states, the iolDBS condition will be limited to only the Summit® RC+S cohort. To determine the parameters for iolDBS related to frequency based aDBS, a short 5-minute frequency-based aDBS run on Day 1 will be performed. This short run will include rest and both SIP and TBC tasks. After the run, the number of frequency switches per unit time (per minute) will be determined offline. The number of switches can be termed ‘x’. For iolDBS on later days, ‘x’ number of frequency switches will happen uniformly and randomly throughout every 60 seconds algorithmically. This will mimic the frequency based aDBS but in an unresponsive manner.

To determine the parameters for iolDBS related to current intensity based aDBS, a short 5-minute current-based aDBS run on Day 1 will be performed. This short run will include rest and both SIP and TBC tasks. After the run, local minima and maxima will be determined offline for the current intensity waveform obtained from the aDBS run. A dictionary of those local minima and maxima will be compiled algorithmically. For iolDBS on later days, the current intensity will uniformly and randomly ramp to different elements of the dictionary algorithmically i.e., the current intensity will be modulated in an unresponsive manner. This will also mimic the total electrical energy delivered (TEED) through the responsive aDBS run.

Continuous oIDBS (olDBS):

The current amplitude during olDBS sessions will be equivalent to the average current intensity during the short 5-minute aDBS session on Day 1 of each visit.

3.2.5.3 Signals Acquired

The Summit® RC+S (Medtronic Inc.) system will use local field potentials (LFPs) to perform all the aDBS experiments in the Summit RC+S cohort. Adaptive stimulation 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 the RC+S according to a preprogrammed algorithm.

The distributed application will be designed to stream the LFP data from the implanted device onto the computer during regular sensing sessions. This new device is rechargeable and has better communication bandwidth than the previous Activa® PC+S system. Bilateral sensing from both subthalamic nuclei can be performed at a sampling rate of as high as 500 Hz. The RC+S system also has an improved noise floor as compared to the previous device. The device is smaller in size and has an improved service life of approximately nine years. Additionally, it enables distance telemetry which aids in the facilitation of gait experiments. The RC+S is a constant current device, and the aDBS experiments will vary current amplitude and not voltage. The device will have four time domain LFP sensing channels with sampling rates for unilateral recordings of ~1000 Hz. The new RC+S system has a packet rate of 100 ms, a rate four times faster than that of the PC+S. This will enable the implementation of more dynamic control policy

algorithms that can respond to neural dynamics on a shorter-time scale, which is perhaps necessary for avoiding freezing episodes.

Short neural recordings to figure out correct gains and center frequencies (optimal filtering and amplification parameters) will not be required in this new system which will save time for other recordings. The filtering and amplification parameters will not have to be changed across conditions for different variables. The device will also allow for increased number of distinct stimulation frequencies without introducing stimulation artifacts in the neural recordings.

The Medtronic Model 3389 lead (Medtronic, Inc.) has four active electrodes through which stimulation can be delivered. Bipolar LFP recordings will be acquired from the electrodes surrounding the one through which the stimulation is delivered when possible. Medtronic will provide the Application Programming Interface (API) for the custom application design. The custom application will be used for bilateral sensing and stimulation capabilities during aDBS and during regular sensing sessions. The custom application will also be used to test safe stimulation ramp rates and stimulation amplitudes before running actual experiments. The host computer or embedded detector will house the classifier and control policy algorithms for both NaDBS and KaDBS.

For NaDBS, beta burst durations will be computed using the custom algorithm running on the computer or the embedded detector, and based on pre-defined thresholds, the stimulation will respond to the real-time beta bursts (see Control Policy Algorithms, Section 3.2.5.2).

For KaDBS, the PC will receive kinematic data (sampling frequency of 128 Hz) from the IMU sensors worn by the subjects and compute gait-cycle time from the shank angular velocity traces. In response to real-time variation in these parameters based on pre-defined thresholds, the stimulation amplitude will be modulated (see Control Policy Algorithms, Section 3.2.5.2).

The Percept™ PC/RC system will use power extracted from LFPs to perform all the aDBS experiments in the Percept PC/RC cohort. Adaptive stimulation can only occur in the embedded mode, in which control is accomplished within the Percept according to a preprogrammed algorithm.

The embedded algorithm in Percept PC/RC system is designed to adjust stimulation in response to power within a specific frequency band. For non aDBS recordings, raw LFP data can be recorded using the BrainSense™ mode, which uses a sampling rate of 250 Hz and can be analyzed off-line. This will be used for calibration recordings either OFF stimulation or during amplitude titrations that will then be used to determine the parameters for the embedded aDBS. For more details, see the Calibration Procedures.

The ramp rates during aDBS will be set such that they are safe and tolerable, and also ensure minimum data packet loss. High and equal ramp rates (for ramp up and ramp down of stimulation) can sometimes increase the data packet loss and that will be avoided. The telemetry antenna will be sufficiently secured to avoid unnecessary packet loss during bilateral communication.

The primary data acquisition (DAQ) system is a CED Power 1401 system (Cambridge Electronic Design Ltd., Cambridge, England) with twenty-four 16-bit analog-to-digital converter input channels. The system is controlled by Spike software (Version 2.7) on a dedicated laptop computer, and also includes two 8-channel CyberAmp 380 Programmable Signal Conditioners (Axon Instruments Inc.) that provide analog pre-filtering for the acquired signals. The CED DAQ system is used to concurrently record signals from the tri-axial accelerometer (ADXL330, Analog Devices, Inc., Norwood, MA), the EEG electrodes used for data synchronization, and the digital pulses from the APDM system. The signals from the accelerometers and the EEG electrodes will be sampled at 1000 Hz with gains of x1 and x5 respectively. Ground reaction forces will be captured at 1000 Hz with two force plates during the SIP task (Bertec Corporation, Columbus, OH, USA). The force data will be synchronized offline with the CED DAQ system. Upper and lower extremity movement will be monitored using angular velocity sensors on all four limbs during the repetitive wrist flexion extension task (Motus Bioengineering, Inc., Benicia, CA). Motion and orientation of various body segments will be measured using wireless IMUs (Opal, APDM Inc., Portland, OR). Each IMU contains a 3-axis gyroscope, 3-axis accelerometer, 3-axis magnetometer, and a temperature sensor for offset compensation. The system consists of 12 sensors that are controlled by Mobility Lab software (APDM, Inc., Portland, OR) on a dedicated laptop computer. During KaDBS, the kinematic signals will be streamed through Bluetooth directly to the computer hosting the custom application and managing the real-time aDBS algorithms. This state-of-the-art system allows us to wirelessly collect motion and orientation data. The accelerometer and gyroscope signals, acceleration and angular velocity, will provide movement related kinematic data that will reflect a subject's gait performance. The orientation data will allow us to characterize with higher precision the rotational motion of the subject during the turns. Subjects will wear the sensors during all movement related tasks. Specifically, the subjects will be instrumented with 11 IMUs to capture full-body kinematics (chest, lumbar (L5), left and right shanks, wrists, thighs, feet, and head).

All experimental protocols will be captured with a digital audio/video recording that has a clear view of the subject and all subjects will be asked to sign video release forms. The video data is verbally annotated at the beginning of each test. The digital output stream of thirty frames/second from a C930E Webcam (Logitech, Newark, CA) is recorded on a USB port by the Spike software that is running the CED DAQ system. This provides a video record synchronized with the other data collected by the system. A 10.5-inch iPad Pro (Apple Inc.), is used to record the UPDRS-III evaluations and the overall experimental

protocol. Signal analysis will be performed in MATLAB (version 9.2, The Mathworks Inc., Natick, MA, USA).

To calculate the parameters for intermittent open-loop DBS (iolDBS), total electrical energy delivered (TEED) during aDBS sessions will be determined to facilitate the design of iolDBS parameters.

TEED is given by: $TEED = (current2 * impedance) * (pulse\ width * frequency) * time$
For the SIP and TBC tasks, the number and duration of freezing episodes, and gait arrhythmicity will be determined and compared across different conditions. Gait arrhythmicity is defined as the mean stride time coefficient of variation (CV) of both legs. A greater mean stride time CV is indicative of less rhythmic gait.

Synchronization: Neural, kinematic and video data streams will be synchronized offline. The data acquisition board (Cambridge Electronic Design Ltd.) connected to a computer will record physiological signals from various wired sensors such as a tri-axial accelerometer and the EEG electrodes, through Spike software. Different events will be triggered and co-registered through this Spike software. For synchronizing the neural local field potentials with the other streams of data, a short duration pulse at 20 Hz will be administered at the start of each experiment. The pulse will be registered in the neural LFP recordings and also in the Spike software through three EEG electrodes. The EEG electrodes will be placed on the forehead, on the chest above the sensing neurostimulator, and on the collarbone (to serve as the ground). The inertial measurement unit sensors or IMUs (APDM Inc., Portland, OR) will be synchronized using a digital pulse that comes from the sensors at the start of data streaming. This signal will be registered distinctly in the Spike software. A mechanical event (hammer strike) on the force plates before the SIP task will be registered in the Spike software using a tri-axial accelerometer. All of these events through the Spike software will be used to synchronize the streams of data offline. The video runs in synchronization with the Spike software.

3.2.5.4 Description of Interventions

Neural Adaptive Deep Brain Stimulation (NaDBS) (Type: Device/sham)

Neural adaptive deep brain stimulation contrasts with current continuous open-loop DBS in that the stimulator can sense and respond to neural activity. This study will use the subject-specific neural signals, specifically subthalamic movement beta band burst power and duration or beta power, to drive NaDBS. These neural signals will be tracked and computed in real-time using an external computer or the embedded detector through the Summit® RC+S or Percept™ PC/RC system (Medtronic Inc.), and the concurrent modulation of stimulation parameters will be based on a pre-defined control policy algorithm that provides optimal DBS therapy.

Kinematic Adaptive Deep Brain Stimulation (KaDBS) (Type: Device/sham)

Kinematic adaptive deep brain stimulation is another form of aDBS that modulates DBS

parameters in a responsive fashion, this time responding to physiological signals that identify specific behaviors, such as walking. Behavioral features are extracted in real-time during movement related tasks. In this study, shank angular velocity, gait-cycle time, and other gait features will be tracked in real-time during gait tasks from eleven inertial measurement unit sensors (IMUs) which are placed on the legs, arms and trunk. The change in these behavioral features will indicate gait impairment and freezing, at which time the DBS will be modulated using control policy algorithms that have been determined to improve gait and FOG. Similar to NaDBS the behavioral signals will be tracked and computed in real-time and the commands to the neurostimulator to modulate DBS parameters will use an external computer through the Summit® RC+S system (Medtronic, Inc). The Percept™ PC/RC cohort will not complete this intervention due to technical limitations of the device.

Open-loop Deep Brain Stimulation (olDBS) (Type: Device/sham)

Open-loop DBS simply refers to the traditional method of delivering stimulation. It is not responsive to changes in a patient's neural or kinematic signals and the stimulation parameters do not change over time. In the context of this study, aDBS runs will be compared with olDBS runs based on safety and tolerability metrics. The average of the stimulation parameters during the short aDBS trial performed on Day 1 of each visit will be used to calculate olDBS parameters.

Intermittent Open-loop Deep Brain Stimulation (iolDBS) (Type: Device/sham)

Intermittent is a control for aDBS, where DBS intensity or frequency changes in a manner that mimics aDBS but is pre-determined and open-loop rather than being responsive to neural or kinematic signals. The algorithm and calibrations for iolDBS will be determined during Day 1 of each visit, using a shorter run of aDBS to determine a template of how DBS intensity or frequency changed in response to neural or behavioral signals. For intensity based iolDBS, current intensity will uniformly and randomly ramp to different values algorithmically i.e., the current intensity will be modulated in an unresponsive manner, but mimicking the pattern seen for aDBS. For frequency based iolDBS, 'x' frequency switches will be programmed to happen uniformly and randomly throughout every minute algorithmically mimicking frequency based aDBS but in an unresponsive manner. Both will match the total energy delivered during aDBS. The Percept™ PC/RC cohort will not complete this intervention due to technical limitations of the device.

aDBS + medication (Type: Combination)

The experimental protocol for Objective 3 will introduce dopaminergic medication during NaDBS and/or KaDBS. The subjects will take medication during NaDBS and KaDBS trials and the medication wash-in effect will be observed. It has been shown that the beta band power (13-30 Hz) in PD decreases as dopaminergic medication takes effect and as such, medication intake might lead to a reduction in the intensity of beta signals (smaller beta burst amplitude/ shorter burst durations). NaDBS would likely respond by decreasing

its intensity, whereas in KaDBS, dopaminergic medication may change the behavioral signals such as shank angular velocity and gait cycle time, leading to fewer freezing episodes being detected and less impaired gait. KaDBS would be predicted to have fewer changes in frequency and/or fewer changes of intensity. The safety, tolerability and response of NaDBS and KaDBS as medication takes effect will be monitored, in addition to whether this reduces adverse effects seen with oLDBS + medication.

3.2.5.5 Additional methodology details

Testing will include clinical assessments and quantitative measures of the subject's motor ability. Recordings of the neural signals from the subject's STN and kinematic signals from their limbs and torso will be obtained. The feasibility of using these signals to inform neural and kinematic aDBS will be determined.

Calibration Procedures

Custom Calibration Safety and Tolerability Questionnaire: We have developed a customized questionnaire that assesses the safety and tolerability symptoms experienced during the different current intensity ramp rates as well as when switching between stimulation frequencies.

Current Titrations to determine $I_{\min}$ and $I_{\max}$: At the start of Day 1 of each visit, subject-specific DBS intensity ranges ($I_{\min}$ and $I_{\max}$) will be determined. The procedure will involve setting the subject on different current intensities and then recording the neural/kinematic signals to obtain good characterization of signals at different intensity settings. $I_{\max}$ will be determined at the clinical DBS programming by the study neurologist.

Current Titrations for SIP: The subject will be tested during different current amplitude settings, e.g. at 0, 25, 50, 75, and 100% of $I_{\max}$. At each current setting, the subject will stand for 10 seconds, followed by 30 seconds of SIP. This will be followed by the next current setting using a pre-determined safe and tolerable ramp rate. Both neural LFPs, normalized vertical force and IMU kinematic data will be recorded during this procedure. The improvement in SIP/gait metrics/FOG will be quantified (e.g., by calculating gait arrhythmicity and % time freezing at each current setting (see Signals Acquired, Section 3.2.5.3)). This will facilitate the NaDBS runs involving SIP. The minimum DBS intensity that results in tolerable SIP performance will be defined as $I_{\min}$.

Current Titrations for TBC: The same procedure as explained before for SIP will be employed here. The task performed at each current setting will be TBC. The subject will stand for 10 seconds, followed by one 'ellipse' and one 'figure 8' during TBC.

Determining patient-specific neural control variable: The subject-specific frequency range of the movement beta band will be determined using the PSD diagrams determined during SIP or TBC, as shown Figure 4 (Section 2), and developed during the titration calibrations. For the Summit RC+S cohort, the raw LFP is filtered using a zero-phase 8th

order Butterworth bandpass filter in this movement band, rectified, and then squared. An amplitude envelope is calculated by linearly connecting consecutive peaks of the filtered and squared LFP cycle to form an outline of the maximum power. Bursts are identified as periods, during which the envelope amplitude is greater than a defined baseline. The baseline is determined by finding all the troughs in the envelope and setting the threshold to a multiple of the median trough power. The troughs are the local minima of the envelope and represent the local smallest peak amplitudes of the filtered and squared signal. The duration of each burst is determined as the interval between successive crossings over the baseline of the amplitude envelope. The average power within each burst is calculated by integrating the area under the bandpass filtered and squared LFP over the duration of the burst. For the Percept PC/RC cohort, power will be calculated using a FFT for the pre-determined movement beta band. This data will be used to set the neural thresholds and delays for the neural classifier algorithms for subsequent NaDBS runs involving SIP and TBC.

Reasons for differences in between cohorts:

The Percept PC/RC offers the ability to stream LFP data, but only for offline post-hoc analysis and not during aDBS. Whereas with the Summit RC+S device, you are able to stream/extract LFP data off the device in real-time to a computer in-the-loop using the distributed mode, where it can then be further processed and used to make stimulation decisions for NaDBS, the Percept PC/RC device only offers an embedded mode for NaDBS. Within this embedded mode, stimulation decisions can only be made based off power within a specific band that you choose that is calculated from an FFT. You do not have access to the raw LFP data in real-time and cannot use it to make stimulation decisions as part of NaDBS. We will record raw LFP data using the BrainSense™ mode during OFF stimulation recordings or during open loop stimulation amplitude titrations (i.e., recordings at different stimulation levels) as part of the calibration process. This mode allows LFP data to be recorded for offline post-hoc analysis. We can use this raw LFP data to investigate offline the full frequency spectrum of the signal to investigate how different parts of the frequency spectrum are affected by stimulation and can also use it to ensure that there is no substantial artifact with stimulation affecting the signal. Analysis of this raw LFP data will be used to determine which sub-band within the beta frequency should be tracked for NaDBS. This is typically decided by finding the peak frequency band within beta and ensuring that it attenuates with increasing levels of stimulation. Once this frequency is identified, it is used to setup the embedded algorithm where you select the center frequency of the power band you would like to track for NaDBS, and then set up the frequency window around that peak frequency (typically a 5-6 Hz frequency window around your center frequency of interest) on which to calculate power. Finally, you then need to decide on the power thresholds to use for adjusting stimulation based on the real-time tracking of beta power. The combination of OFF recordings and stimulation titration ON recordings allow us to see what power is observed within the beta frequency of interest at these different levels of stimulation. This can then be used to inform what threshold to use for beta power for either single- or

dual-threshold algorithms.

Determining patient-specific kinematic control variable: The IMUs will be used to obtain gait features at each current setting for both SIP and TBC. As mentioned above, this data will be used to set the kinematic thresholds for the kinematic classifier algorithms for subsequent KaDBS runs involving both tasks.

Full Baseline Testing

Full baseline testing for SIP visits (1 and 3) include all tests described below, except Speech, Repetitive Wrist Flexion Extension, and Repetitive Alternating Finger Tapping. Full baseline testing for TBC visits (2 and 4) include all tests described below.

Speech Testing: Speech Intelligibility Test (SIT): Computer program that generates random sentences from a pool of 1,100 sentences (sentences range in length from five to 15 words). Subjects will be recorded using a microphone as they repeat the sentences generated. This task will quantitatively measure communication efficiency by taking into account accuracy, speaking rate, and volume⁵⁶. Tests of diadochokinetic rate and sustained phonation will also be conducted to further characterize speech. During these tests, participants will be asked to repeat several consonant sounds as quickly and crisply as possible (diadochokinetic rate, such as “puh-tuh-kuh”) and to hold the vowel sound “Ah” (sustained phonation) for as long as they can.

Repetitive Wrist Flexion Extension (rWFE) and/or Repetitive Alternating Finger Tapping (RAFT): For rWFE, using solid-state gyroscopic sensors (Motus Movement Monitor, Motus Bioengineering Inc, Benicia CA or Opal, APDM Inc., Portland, OR) that measure angular velocity, subjects will perform self-paced repetitive wrist flexion extension (rWFE) for 30 seconds. The elbow will be kept at a 90-degree angle. The subject will perform the rWFE movement continuously until a verbal “stop” command is given. After resting for 30 seconds, a verbal “go” cue will be given and the subject will begin to move the other hand for 30 seconds until they hear the verbal “stop” command again. The initial rest period will be used to record tremor (if present), and the rWFE will capture bradykinesia (if present). Quantitative measures: angular velocity, frequency, and tremor power, and the CV (variability) of velocity and frequency. RAFT is a computerized objective measure of fine motor control using an engineered quantitative digitography (QDG) keyboard. During this task, subjects will perform alternating finger tapping movements (trill) on adjacent keys on the keyboard for each hand for up to 90 seconds. The engineered keyboard outputs a calibrated analog signal that corresponds to the displacement of the keys. Metrics such as downstrike velocity, interval between strikes, and duration of keystrokes will be extracted from the recorded signal.

Unified Parkinson’s Disease Rating Scale (numeric):

Part I: Mentation, Behavior and Mood

Part II: Activities of Daily Living

Part III: Motor Examination

Part IV: Complications of Therapy (includes Dyskinesias)

New Freezing of gait questionnaire (NFOG-Q, numeric): Validated questionnaire used to assess freezing of gait severity unrelated to falls in patients with PD. The NFOG-Q will be used pre-operatively and in the different therapy conditions to assess for gait impairment⁵⁷.

Custom Adverse Effects Questionnaire: We have also developed a customized questionnaire that monitors patient feedback and will assess any adverse effects such as muscle twitches and paresthesias, and records the frequency these are reported. The questionnaire will be administered at throughout and the end of each session. It is supplemented by the aDBS Feedback Questionnaire that further aids in the monitoring of any adverse reaction to stimulation parameters and an examiner rating of dyskinesia.

Columbia-Suicide Severity Rating Scale (C-SSRS): A series of questions that help identify whether someone is at risk for suicide, assess the severity and immediacy of that risk, and gauge the level of support that the person needs. The C-SSRS will be done pre-operatively in addition to at every research visit⁵⁵.

SIP Baseline Testing

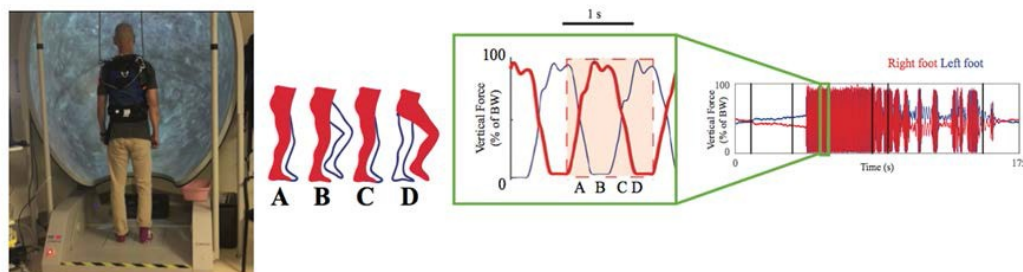
SIP baseline testing will include the aDBS Feedback Questionnaire, UPDRS III, and the Examiner Dyskinesia Rating, a custom examiner rating of the percentage of time dyskinesias were observed over a specified testing period.

TBC Baseline Testing

TBC baseline testing will include speech testing, rWFE and/or RAFT, UPDRS III, aDBS Feedback Questionnaire, and Examiner Dyskinesia Rating.

Per their tolerance, some subjects may be asked to complete additional testing, such as neural recordings at rest between various contact pairs (i.e., montage recordings), additional timepoints of speech, WFE, or RAFT, or additional oDBS trials on medication wash-in days.

Gait Tasks



choose during the task (“Subject Initiated Stop”), and (2) that the research staff will instruct the subject to stop stepping/walking at a random time point in the task (“Researcher Initiated Stop”). In the “Subject Initiated Stop” condition, when performing each stop, subject will say ‘stop’ out loud and will stand still for five seconds after stopping. They will then be given the ‘go’ command to start stepping/walking again. There will be a total of three subject-initiated stops performed by the subject during the gait task. In the “Researcher Initiated Stop” condition, the same protocol as above will be used, with the exception that the researcher will be the one instructing the stops at random intervals.

Standing in Place and Swinging Arms: Subject will stand in place still with arms to the side at rest for 30 seconds. They will then be given the ‘go’ command to which they will swing arms as they normally would while walking as they maintain a standing in place position for 30 seconds.

3.2.6 Clinical Assessments

Experiments by Year	Year 0	Visits 1-4													
Visit Number	Pre-Op ^b	1			2			3				4			
Day Number		1	2	3	1	2	3	1	2	3	4	1	2	3	4
ENROLLMENT:															
Informed Consent	X														
Clinical Evaluation*	X														
ASSESSMENTS:															
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X			X			X				X			
Calibration*		X			X			X				X			
Custom Safety and Tolerability Questionnaire		X			X			X				X			
Baseline Testing*	X ^a	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Stepping in Place (SIP)		X	X	X				X	X	X	X				
Turning and Barrier Course (TBC)					X	X	X					X	X	X	X
FOG Questionnaire	X	X			X			X				X			
Custom AE Questionnaire		X	X	X	X	X	X	X	X	X	X	X	X	X	X
INTERVENTION/ CONDITION:															
Off DBS		X			X			X				X			

Stimulation																
NaDBS 140 Hz		X	X		X	X										
olDBS 140 Hz			X			X			X					X		
iolDBS 140 Hz			X			X			X					X		
NaDBS 140 Hz + Medication				X			X									
olDBS 60 Hz									X					X		
iolDBS (changing frequency 140/60Hz)									X					X		
KaDBS (changing current)									X					X		
KaDBS (changing frequency 140/60Hz)									X					X		
KaDBS + Medication*										X	X			X	X	

*Subject to change

^aModified Baseline Testing: UPDRS I, II, and IV (research team), UPDRS III (clinical team), NFOG-Q, C-SSRS

^bPre-op events only occur in the Summit RC+S cohort.

Note: The Percept PC/RC cohort will not have pre-op assessments as they will already have been implanted with the device. They will also not complete Visits 3 and 4 or perform the iolDBS therapy condition. The Percept PC/RC cohort will use the equivalent 140 Hz sense-friendly frequency.

Single-Blind Long-Term NaDBS Protocol (*Percept PC/RC Cohort only)						
Experiments by Year	Year 2	Single-Blind NaDBS Follow-Up				
Visit Number	Baseline	Condition 1		Condition 2		Long-Term NaDBS
Week Number	0	2-week	4-week	2-week	4-week	3-6 months
ASSESSMENTS:						
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X
Calibration	X					
Custom Safety and Tolerability Questionnaire	X	X	X	X	X	X
Baseline Testing	X	X	X	X	X	X
Stepping in Place	X					

(SIP)		X	X	X	X	X
Turning and Barrier Course (TBC)	X	X	X	X	X	X
FOG Questionnaire	X	X	X	X	X	X
Custom AE Questionnaire	X	X	X	X	X	X
INTERVENTION/ CONDITION:						
NaDBS		X	X			X
olDBS	X			X	X	

Note: Percept PC/RC Cohort Only

3.2.7 Outcomes Measures

Name	Type	Time Frame	Brief Description
Safety and tolerability	Primary	Every visit	The New Freezing of Gait Questionnaire (NFOG-Q) and the Unified Parkinson's Disease Rating Scale (UPDRS, Section 3, Items 10 and 11) will be used to record worsening of gait. Changes in speech will be measured through the Unified Parkinson's Disease Rating Scale (UPDRS, Section 3, Item 1) as well as the speech intelligibility test (SIT) and measures of diadochokinetic rate and sustained phonation. UPDRS Sections 1, 2 and 4 will also be used as measures of safety and tolerability. Section 1 evaluates mentation, behavior and mood, Section 2 is a self-evaluation of patients' daily lives including speech, swallowing, handwriting, dressing, hygiene, failing, salivating, turning in bed, and walking, and Section 4 evaluates complications of therapy through questions about dyskinesia and clinical fluctuations. Finally, custom questionnaires will record patient's response after each intervention including the presence of paresthesias (pins and needles) and muscle twitching and an examiner

			rating of dyskinesia.
% Time Freezing	Secondary	Every visit	Number and duration of freezing episodes during the gait tasks (SIP and TBC) will be measured using the inertial measurement unit sensors (IMUs) and identified offline using a validated algorithm. All freezing episodes will be confirmed by a neurologist's blinded rating of the tasks' video recordings.
Gait Arrhythmicity	Secondary	Every visit	Stride (gait cycle) time will be measured using the dual force plates during the SIP task and inertial measurement sensors placed on subject's legs. Gait arrhythmicity is defined as the mean stride time coefficient of variation (CV) of both legs. A greater stride time CV is indicative of a less rhythmic gait or stepping.
Shank Angular Velocity	Secondary	Every visit	Shank Angular Velocity will be measured from inertial measurement units worn subject's leg. Reductions in this value are indicative of FOG and gait impairment.
UPDRS Section 3 Motor Score	Secondary	Every visit	PD symptoms will be measured by Unified Parkinson's Disease Rating Scale (UPDRS) Section 3. This is a motor examination to evaluate speech, facial expression, tremor at rest, action or postural tremor of hands, rigidity, finger taps, hand movements, rapid alternating movement of hands, leg agility, arising from chair, posture, gait, postural stability, and body bradykinesia and hypokinesia. Each item is scored on a scale from 0 (normal) to 4 (severe), with the total possible score ranging from 0 to 108.
Quantitative measures of Bradykinesia/Tremor	Secondary	Every visit	The angular velocity, frequency, and tremor power during a repetitive wrist flexion-extension (rWFE) will be measured using a wearable sensor and will be used to quantify bradykinesia and tremor. Metrics

			such as downstrike velocity, interval between strikes, and duration of keystrokes during the RAFT task may be measured using a quantitative digitography (QDG) keyboard to quantify fine motor control, bradykinesia, tremor, and rigidity.
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3.3. Risk Analysis

3.3.1 Justification

There is currently no cure for PD and no treatment that can stop the disease from progressing. STN DBS has greatly improved the care of people with PD but is continuously on and cannot respond to the patient's state of activity or fluctuation of motor symptoms. Changes to stimulation parameters may only occur at discrete intervals, during clinical appointments with the neurologist. In addition, DBS has been shown to sometimes elicit unwanted side effects such as speech difficulties, dyskinesia, mood changes, and cognitive impairment. These symptoms become increasingly apparent as the disease progresses. The knowledge gained from these experiments will determine, for the first time in human subjects, the technical limitations, safety, and tolerability of aDBS for gait impairment and FOG in PD. These experiments will be carried out by a team with extensive experience and success in the accurate placement of STN DBS leads and one of the only teams in the world to have extensive experience recording synchronous neural and quantitative kinematic data in freely moving human subjects, using the first and subsequent generations of closed-loop neurostimulators. In addition, the knowledge gained, specific state and motor behavior control variables and DBS parameters will provide the field at large the necessary design inputs and design validation to develop smarter neurostimulators capable of realizing even more precise aDBS for PD. This will be the prototype for similar datasets that can be collected from other disorders as DBS becomes an established therapy for a wider range of neuropsychiatric diseases.

3.3.2 Human Subjects Involvement, Characteristics and Design

The subject population will consist of adults diagnosed with Parkinson's disease, who have been evaluated on and off medication, have undergone detailed neuropsychological evaluation and have been approved by the interdisciplinary surgical review board for the implantation of subthalamic nucleus deep brain stimulation. As part of the review process, patients and/or caregivers will be evaluated to ensure they understand the demands of a rechargeable system and are suited for this particular device. The involvement of these human subjects is necessary to determine the feasibility of using adaptive DBS to improve gait impairment and FOG in freely moving people with Parkinson's disease. The involvement of human subjects in this study includes sitting and standing quietly at rest, stepping in place on a force plate while wearing a harness and

walking freely in forward direction at a comfortable speed. Subjects may walk in an open or closed environment in the lab while electrical signals are recorded from their brains and kinematic signals are recorded from the limbs and torso. Periods of neurostimulation will be performed as part of the research and this will be the same type of stimulation that is performed routinely during the clinical placement of STN DBS leads and/or the programming of the DBS system. A total of 15 subjects will be recruited and consent to be implanted with the Summit® RC+S system or have been implanted with the Percept™ PC/RC system. Subjects will be identified as having gait impairment by the clinical history of a subject's symptoms, and/or from their score on the Freezing of Gait Questionnaire (FOG-Q). Subjects will range in age from 18 to 80 years.

Stanford University Medical Center is a 600-bed tertiary care hospital, which provides advanced neurosurgical treatment for the full spectrum of neurological disease. All of the clinical and in-clinic quantitative motor testing, neural and kinematic recordings will be performed and obtained in the Stanford Human Motor Control and Balance Laboratory, which Dr. Bronte-Stewart started at Stanford nineteen years ago. The lab is immediately adjacent to the Movement Disorders clinic in the new Stanford Neuroscience Health Center, and clinicians are always available.

3.3.3 Risks

General risks of DBS surgery

To participate in this study, the PD patients will undergo DBS implantation surgery and they will be subjected to the risks associated with the standard surgical procedure that are listed in the surgical informed consent if receiving the Summit® RC+S. No modification of the standard DBS implantation surgery is necessary for this protocol. The Percept PC/RC cohort will have already undergone DBS implantation surgery prior to consent.

Risks specific to this protocol

Risk related with tasks performance:

The tools used for kinematic analysis are non-invasive (do not enter your body). Physical sensors are applied to the surface of your body. The tests are not physically painful (other than in the removal of adhesive tape holding the sensors on the skin).

The subject may become fatigued while performing the kinematic tasks due to changes in their stimulation settings. Any test of gait includes the potential of falling, for which protections are discussed below.

Risks related to stimulation:

DBS close to the STN may cause transient electrical sensations in the body and/or muscle twitching and these are expected during testing of the placement of the DBS lead clinically. These are transient and reversible. Subject feedback regarding the tolerability of different DBS parameter values and rates on increase of parameters will be an important part of the discovery; however, once the tolerable limit has been reached no further increases or rate of increases will be performed. Despite determining safety and

tolerability of aDBS during the calibration day, the subject may not tolerate the testing of aDBS, see protections below.

Risk related to the device usage:

There may be risks associated with the unapproved Summit® RC+S components. Please reference Medtronic MAF 2978 - Summit System and PMA P960009 - Medtronic Deep Brain Stimulation Systems.

The Percept™ PC device is a primary cell non-rechargeable device. As part of each study visit, calibration tasks will require streaming of raw LFP data either OFF or ON DBS.

Streaming LFP data puts additional demands on the device which accelerates battery depletion of the device. The expected additional depletion of the device's battery above its usual clinical use is expected to be 1 day of lost battery life per 1 hour of streaming. Each of the two neural visits are expected to require 1-4 hours of calibration tasks streaming raw LFP data.

The Percept™ RC device is a rechargeable device and therefore does not suffer from the same battery depletion issues as the Percept™ PC. Streaming of LFP data will temporarily deplete battery of the device faster for an individual charge compared to not streaming LFP data, and therefore may require more frequent recharging, but it does not alter the longevity of the device. Therefore there is no need to limit the amount of streaming of raw LFP data as there is for the Percept™ PC.

3.3.4 Risk Management and mitigation

Mitigation of risks of DBS surgery in general:

All DBS implantation surgeries will be performed at Stanford University Medical Center which provides advanced neurosurgical treatment for the full spectrum of neurological disease. The Stanford neurosurgical team that performs the DBS implantation surgeries is highly experienced with more than 750 cases performed. The operating room (OR) suite provides 21 state-of-the-art operating rooms including two dedicated neurosurgery rooms with 3 Stealth Neuro-navigational systems. The deep brain stimulation (DBS) lead implantations are performed in the functional neurosurgery OR (700 sq. ft.). Movement disorders neuromodulation program has developed efficient strategies to mitigate risks of DBS surgery which are outlined in the consent form.

Mitigation of risks specific to this protocol:

The project will be monitored to ensure the rights and well-being of the enrolled patients; to ensure that the technical aspects of the study are carried out in a safe, accurate, and consistent manner; and to ensure that the data is collected and stored in a secure manner. Prior to the initiation of the experiments, the DSMB will review the protocol, inspect the laboratory and the equipment to be used, ensure that the data will be collected and stored in a secure and reliable manner, and that the investigators are trained according to the protocol. They will participate in practice trials of the experiments with the investigators to document readiness before the study commences.

The overall timeline of the projects steps in a 'bench to bedside' fashion to test aDBS:

- First in the most controlled condition, stepping in place (SIP) on dual force plates, when the patient is in a harness
- Second, when they are freely moving in the lab or doing the turning and barrier course (TBC), which mimics environments that trigger FOG in the outside world
- Third, how the aDBS adapts when they take medication while freely moving.
- Lastly, for the Percept PC/RC cohort, how aDBS performs long-term in a home setting.
- *Fall risk: during the SIP the patient is in a harness and cannot fall; during the TBC the team is monitoring the task within arm's reach to stabilize the patient if necessary. Patients will only be sent home on aDBS following safe and tolerable completion of an aDBS in-clinic visit, and with their clinician's approval. Limits used for stimulation will provide therapeutic benefit. Therefore, the expected fall risk is not expected to be significantly higher on aDBS than clinical open loop DBS. Additionally, the at-home testing involves visiting the lab every 2 weeks initially which will allow frequent updates on how the participant is doing at-home. Patients will also have the ability to switch back to their clinical stimulation settings at any time using their patient programmer.

Patients will practice the gait tasks and the clinician will be present to assess the patient's neurological status. The aDBS settings will be made a separate group on the neurostimulator, so that the patient (or investigator) can return the patient to their clinical oldBS settings at any time.

Patients' mental and physical health will be taken into account when they become fatigued. We intend to perform some protocols over the course of several days so as to minimize excessive patient fatigue on any particular day. We have allocated in our budget funds to aid accommodations to make transport to and from the testing site more convenient for subjects. When spreading out the experimental protocol is not possible, we will shorten the research protocol to include essential experiments, which will leave time for the clinical portions of those visits. This will be determined on an ad hoc basis as each patient varies in terms of his/her ability to withstand extended periods of time off clinical therapy. We have invested in a comfortable reclining chair based on patient feedback, on which they can rest during the resting portions of longer experiments and downtime portions of the research.

Regarding the risk of additional battery depletion for the Percept PC cohort, we will minimize streaming of raw LFP data to only the necessary calibration periods. This will only be 1-4 hours per visit, therefore only reducing the battery life of the device by ~2 weeks or less. This will also be explicitly stated in the informed consent. This is not an issue for individuals implanted with the Percept RC.

There will be no custom software for working with the Percept PC/RC device. Unlike the Summit RC+S which had an available API to build off to interact with the device, the

Percept PC/RC device can only be interacted with through the Medtronic hardware and software described in MAF 3551 (Adaptive DBS for the Percept PC and RC) and PMA 960009 (Neurostimulation Systems for Deep Brain Stimulation). This will minimize potential risk of programming and running aDBS with Percept PC/RC.

Dr. Bronte-Stewart will be responsible for the subject during the entirety of the clinical and research components of the study. She will monitor the subject's neurological status and comfort during every study visit with help from a DBS programming nurse.

Long term plan for patients

The Summit® RC+S systems provide long-term therapy, equivalent to non-research versions of the devices. They are chronic implants and provide continuous standard clinical STN DBS even when patients are not on site for protocol visits. The rechargeable feature of these devices requires a comprehensive understanding of device function to avoid loss of therapy. Patients who receive this device will participate in an established educational program to teach them how to keep their device adequately charged. Upon completion of the study, patients will continue to receive therapy from these research devices and will be cared for by Dr. Bronte-Stewart at Stanford, in addition to care from their local primary neurologist if they live far away. Subjects will continue to have a clinical visit with Dr. Bronte-Stewart every three months primarily to manage DBS programming for the 9-year lifetime of the device. If the subject moves to another city or needs to receive care from another facility during this time period, they will be guided by the Stanford Neuroscience Health Center care team to find other groups that have the resources to continue programming for the Summit® RC+S device. After the Summit® RC+S runs out of its extended battery life, patients can choose to be re-implanted with the same device (pending availability) or any of the other commercial neurostimulators such as Medtronic's Activa® PC. When the proposed protocol is complete, we will likely ask current subjects to participate in future studies, as there are a limited number of research devices available and each patient is therefore an important component of our future ability to investigate the neural correlates of Parkinson's disease outside of the operating room. Each patient becomes even more important with regard to the ability to monitor neural data over time; as Parkinson's disease is known to be progressive, these chronic recordings will be invaluable in the understanding of underlying changes in neural signals that may be due to disease progression. Any patients participating in additional research protocols will return for research visits under the guidelines of the future Stanford IRB-approved protocol governing their participation.

The Percept™ PC and RC system are FDA-approved devices for STN DBS for PD. Therefore, following completion of the study, participants implanted with this device will continue to receive therapy from the device and their usual care.