Neural and Kinematic Features of Freezing of Gait for Adaptive Neurostimulation

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1. PURPOSE OF THE STUDY

a. Brief Summary

Continuous deep brain stimulation (cDBS) is an established therapy for the major motor signs in Parkinson's disease. Currently, cDBS is limited to "open-loop" stimulation, without real-time adjustment to the patient's state of activity, fluctuations and types of motor symptoms, medication dosages, or neural markers of the disease. The purpose of this study is to determine if an adaptive DBS system, responding to patient specific, clinically relevant neural or kinematic feedback, is more effective than continuous DBS on the motor Unified Parkinson's Disease Rating Scale (UPDRS III) and specific phenotypic measures in Parkinson's Disease.

b. Objectives

1). Determine the efficiency and effectiveness on PD signs of adaptive DBS (aDBS), triggered by patient-specific resting state neural activity, compared to continuous DBS (cDBS) using the UPDRS III and validated, high-resolution kinematic metrics of tremor, bradykinesia and freezing of gait (FOG).
2). Determine whether aDBS using a kinematic classifier pertinent to the patient specific phenotype is more efficient and/or effective on PD symptoms than aDBS using the using the patient's specific resting state neural classifier and/or cDBS.
3). Determine whether aDBS is more efficient and effective than cDBS in the optimized on medication state after six months of cDBS. We believe that the results of these experiments will make it possible for DBS to realize its full potential: a new generation of context-dependent, continuously adaptive DBS devices will have the ability to sense and modulate brain signals that are correlated to abnormal movement and will provide DBS therapy in different locations based on motor phenotype and state of activity.

c. Rationale for Research in Humans

The Nexus D and Nexus E systems are a newly developed technology allowing for bi-directional communication of information between the Activa® PC+S and a portable computer (PC). The PC will use real time neural and kinematic data to develop classifiers of the behavioral states of rest, tremor, and bradykinesia in PD. The investigator team will develop a series of algorithms (control policies) on the PC, which will inform the Activa® PC+S to turn ON or OFF (at a preset, safe and therapeutic setting) based on the kinematic or neural classifiers of PD. Using this established neural interface for the first time in human PD subjects, we will develop optimal patient-specific customized classifier and control policy algorithms. This will drive the future creation of closed-loop neuromodulation devices, embedding and automating sensing and stimulating platforms.

2. STUDY PROCEDURES

a. Procedures

For subjects not already enrolled in eprotocol 25916:
The patient will have a full physical and neurological examination to determine if it is appropriate for them to participate in this study. The clinical examination will include all the assessments used to evaluate if a patient with Parkinson's Disease is a good candidate for Deep Brain Stimulation surgery such as the Unified Parkinson's Disease Rating Scale. Additionally the patient will complete a Colombia Suicide Severity Scale Assessment at all study appointments to monitor for emergence of suicidal ideation or intent. After surgery, at the time of initial programming of the implanted neurostimulator. Patients will arrive in the off medication, OFF DBS state. Medication will be stopped 72 hours (extended release forms of dopamine agonists), 24 hours (regular form of dopamine agonists, controlled release forms of carbidopa/levodopa (CD/LD))and /or 12 hours (regular CD/LD, entacapone,rasagiline, selegiline,amantadine) before testing. The DBS system will not have been activated after the implantation.
The patient will undergo quantitative assessment of motor function in the Stanford Human Motor Control and Balance Laboratory. This will include quantitative digitography (QDG), quantitative range of motion analysis (Motus, LG G Watch, APDM System), tremorography, surface electromyography (EMG), and computerized dynamic posturography. Note: the subjects will be given practice trials in all of the quantitative tasks listed below, to ensure that the goal and the instructions of the task are understood before each assessment is performed.
1) repetitive wrist flexion-extension movement – rwFE; Using solid-state gyroscopes sensors (Motus Motion analysis system, LG Gwatch), that fit like a glove on the patient's hands and surface EMG sensors (Delsys Bagnoli 2 EMG System) placed on the skin above the wrist flexor and extensor muscles, the wrist movement and the muscle activation patterns will be quantified. Specifically, we will directly measure angular velocity and muscle activations. The patient's arm will be kept in a 90 degrees elbow flexion with forearm in a neutral position. The patient will perform a wrist flexion extension movement continuously from the "go" to the "stop" command. This test will assess the subject's bradykinesia state.
2) Tremorography; If the subject shows visible tremor of the hands, using the above mentioned angular velocity sensors, his/her resting or postural tremor behavior will be measured. Surface EMG sensors will be placed on the skin above the forearm muscles to capture the muscles activation pattern.
3) Repetitive alternating finger tapping (RAFT) keyboard task; RAFT is a computerized objective measure of movement velocity, speed of movement, and timing using an engineered keyboard (Quantitative DigitoGraphy) with two adjacent keys. The subject will alternatively finger tap (trill) on the keyboard. The test will be performed twice for each hand. The patient will be seated at a table on which the keyboard is placed with the hand that does not perform the task placed in his/her lap. The subject will be instructed to tap as fast as he/she can while maintaining the alternating movement. This test will quantify a set of movement abnormalities seen in Parkinson's Disease patients such as bradykinesia, freezing of movement, tremor or fatigue.
4) Stepping in place (SIP) task: the subject will be asked to step in place repetitively on two adjacent force plates (Smart EquiTest, Neurocom Inc) with each foot on each force plate. The subject will step at a speed similar with his/her normal walking. A baseline quiet stance will be acquired at the beginning and the end of the test. The subject will wear a harness to protect him/her from falling. The subject will wear sensors on their hands,arms,chest,trunk,feet and legs(APDM System). This test will quantify measures such as gait asymmetry, gait rhythmicity and left-right step coordination. These metrics may provide clues to underlying mechanisms involved in freezing of movement in PD. Our lab showed that the SIP metric has a high sensitivity (93%) and specificity (87%) for identifying freezers from non-freezers.
5) Unified Parkinson's Disease Rating Scale part III – Motor Examination (UPDRS III); The clinical motor assessment of the subject will be performed using the UPDRS III scale.
6) Gait Analysis: Subjects will wear sensors on their hands,arms,chest,trunk,feet and legs(APDM System). These tasks will quantify measures such as gait asymmetry, gait rhythmicity and left-right step coordination during subjects normal walking. Subjects may be asked to do regular forward walking as well as walking around obstacles (such as chairs, or small room dividers). These obstacles will be used in order to elicit freezing, which often occurs in constrained spaces. This type of freezing is frequently encountered in subjects' daily lives. Subjects will be monitored carefully by research team in order to ensure their safety and comfort.
7) Vibrotactile Stimulation: Patients will wear the gloves at rest or during kinematic movement analysis described above. If patients report pain or discomfort associated with the gloves, they will be taken off immediately. We do not anticipate this to occur.
The Local Field Potentials (LFP) from the DBS leads (electrodes) will be recorded during each kinematic test using the new sensing capabilities of the implanted neurostimulator (Activa PC+S). The LFP data will be retrieved from the neurostimulator during each kinematic test. The Nexus-D and Nexus E Systems will be used. Nexus-D and Nexus-E establishes a connection between the implanted neural electrodes and an external computer or their

implanted INS (the device in the patient's chest). This will allow for recording of neural activity in real time and adjustment of stimulation within clinically safe limits using prewritten algorithms that respond to real time neural and kinematic recordings. Real time STN LFP beta band power will be calculated both OFF DBS, and during “therapeutic” DBS. DBS will be applied through the electrode (1 or 2) that lies in between the electrode pair (0-2 or 1-3) with the greatest beta power. Therapeutic DBS: 100-190 Hz, 60 microsec at 3 volts OR the highest voltage <3V, that does not cause adverse effects. We will confirm that the therapeutic DBS will attenuate rest beta power by >= 50%5. Patients will be seated at rest, or while performing self- paced repetitive wrist flexion-extension (WFE) for periods of 10 seconds, after a “Go” signal with angular velocity sensors attached to the hand. They may also do other tasks outlined above during closed loop stimulation.

Specific Aim 1a and 2a (SA1a, SA2a): Determination of classifier thresholds:
SA1. Resting state neural: ON and OFF triggers when the beta band power > 50% and < 25% respectively of the resting state beta power differential (beta power OFF – ON therapeutic DBS). SA2. Kinematic, tremor/bradykinesia: ON and OFF triggers when rectified tremor amplitude/root mean square angular velocity (Vrms) of WFE > 50% or < 25% of tremor/Vrms differential (OFF – ON therapeutic DBS) respectively.
Specific Aim 1b and 2b (SA1b, SA2b): Outcomes will be measured after 30 minutes of aDBS or cDBS. For neural and tremor aDBS, the Activa® PC+S will be updated in real time. For bradykinesia aDBS, the Activa® PC+S will be updated with the Vrms from 10 second epochs of WFE that the PD subject will perform every 2 minutes during the 30 minute trial. At the six month visit the subject will come in on medication on stimulation and SA1 and SA2 will be repeated in the then optimized on medication state. The control policy algorithms will be adjusted as necessary to adapt to this state (Specific aim 3, SA3) At the 1, 3, 6, 9 and 12 month visits subjects will come in off medication and on stimulation and will repeat quantitative assessment of motor function. This may include quantitative digitography (QDG), quantitative range of motion analysis (Motus, LG G Watch, APDM System), tremorography, surface electromyography (EMG), and computerized dynamic posturography and UPDRS III. The subject will perform these assessments in the on clinical stimulation state and will repeat all or a subset of these tests in the off stimulation state. Subjects may continue these motor tests after the 12 month visit during their regularly scheduled clinic visits. Most often, this is every 3 months, however, patients may come in more or less often, depending on their clinical schedules.

For subjects already enrolled in eprotocol 25916:
Subjects who have been implanted with the Activa PC+S Neurostimulator system and who are enrolled or who have completed the Brain Radio initial study may be asked to consent to Nexus study. They will be asked to come in for additional visits (may be at follow-up if still enrolled or an additional study session.) These participants may complete the specific aims 1,2,3 listed in above protocol in addition to collecting data recordings with Nexus-D and Nexus-E systems.

These patients previously had a 'Nexus D' system, however, they will need a firmware update so that they are running Nexus-D in conjunction with Nexus-E. These patients will sign an updated consent before proceeding with the update. Nexus E Firmware Update: They will undergo a Nexus E Firmware update at their next study visit. The Nexus E firmware update will take approximately 30 minutes to perform. During the firmware update, the subject will not receive any therapeutic stimulation.

Battery life on the Activa PC + S (research device) and the Activa PC (non research device, used in standard DBS surgeries) is estimated to last for about 2-4 years. When the battery level reaches below 2.75, recording on the device is disabled in the ACtiva PC + S. Soon after this, the battery life will slow and the patient will need a replacement device. This is the same procedure as the standard DBS surgeries. If the patient chooses and is invited to continue in the study, they can choose to get the Activa PC + S as their replacement device, instead of a non research Activa PC device. This would allow the patient to continue in the research study with their new device.

b. Procedure Risks

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

c. Use of Deception in the Study

Deception will not be used.

d. Use of Audio and Video Recordings

Audio and video recording will occur for use during data analysis, and will be copied on an encrypted hard disk locked in a cabinet in a room that is locked when unoccupied. The video recording from the video camera will be erased.

e. Alternative Procedures or Courses of Treatment

The alternative is to get the standard DBS device implanted and not participate in the study.

f. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

Yes

g. Study Endpoint(s)

NA

3. BACKGROUND

a. Past Experimental and/or Clinical Findings

Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN), internal segment of the globus pallidus (GPi), and/or thalamus has become standard of care, FDA approved treatment for Parkinson's disease (PD), tremor and dystonia. DBS consists of the implantation of chronic stimulating electrodes (leads), Medtronic models 3387 or 3389, into the nucleus of choice. Currently the DBS is chronically on and does not use any feedback parameters from brain physiological signs, unlike standard cardiac "demand" pacemakers. Patients with tremor are the only group who may elect to turn off the DBS generator during sleep, when their tremor is absent, to prolong battery life.
In the sensorimotor regions of the target nuclei, neuronal firing rates and firing patterns become abnormal, along with widening of the somatosensory receptive fields during these movement disorders. It is now well known that there are prominent electrical rhythms in basal ganglia nuclei in PD, tremor and dystonia, which may contribute to the abnormal movements. However it is not known whether abnormal brain signals actually cause abnormal movement in PD and if so which signal may cause which motor sign in PD. Until this is understood it will be impossible to determine the parameters of electrical stimulation which are optimal for each motor sign. It is also not known if abnormal brain neurophysiological signals change after short or long-term neurostimulation.

Over the last 12 years we have developed quantitative measures of bradykinesia, freezing of gait (FOG) and tremor using an angular velocity sensor (Motus Movement Monitoring System, Motus Bioengineering Inc, Benicia, CA), a customized engineered keyboard, and dynamic force plates (Smart Equitest, Neurocom Inc Clackamas, OR). We use the sensors and keyboard in the operating room (OR). We have validated the sensors and the keyboard using repetitive limb and finger movements as measures of bradykinesia versus the standard clinical rating scale, the Unified Parkinson's Disease Rating Scale (UPDRS) motor scale (III) in PD, and we have demonstrated that there are improvements in quantitative measures of bradykinesia, from medication and chronic STN DBS, and during intra-operative DBS(1- 7). For 6 years we have been recording single unit and LFP signals, intra-operatively, in the brains of awake patients undergoing DBS(1, 8-11).

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b. Findings from Past Animal Experiments

NA

4. RADIOISOTOPES OR RADIATION MACHINES

a. Standard of Care (SOC) Procedures

Identify Week/Month of Study	Name of Exam	Identify if SOC or Research
NA	NA	NA

b. Radioisotopes

i. Radionuclide(s) and chemical form(s)

NA

ii. Total number of times the radioisotope and activity will be administered (mCi) and the route of administration for a typical study participant

NA

iii. If not FDA approved: dosimetry information and source documents (package insert, Medical Internal Radiation Dose [MIRD] calculation, and peer reviewed literature)

NA

c. Radiation Machines – Diagnostic Procedures

i. Examination description (well-established procedures)

NA

ii. Total number of times each procedure will be performed (typical study participant)

NA

iii. Setup and techniques to support dose modeling

NA

iv. FDA status of the machine and information on dose modeling (if procedure is not well-established)

NA

d. Radiation Machines – Therapeutic Procedures

i. Area treated, dose per fraction/number of fractions, performed as part of normal clinical management or due to research participation (well-established procedures)

NA

ii. FDA status of the machine, basis for dosimetry, area treated, dose per fraction and number of fractions (if procedure is not well-established)

NA

5. DEVICES USED IN THE STUDY

a. Investigational Devices (Including Commercial Devices Used Off-Label)

Investigational Device 1	
Name:	Activa PC +S
Description:	The Model 37604 Activa PC+S system is a multiprogrammable device that both delivers electrical stimulation and records bioelectric data through one or two leads implanted in the brain. Activa PC+S electrical stimulation is based on the Model 37601 Activa PC neurostimulator but adds the functionality of bioelectrical data recording (sensing). Activa PC and Activa PC+S share the same therapy and form factor. There are no new tissue contacting materials in Activa PC+S.
Significant Risk? (Y/N)	Y
Rationale for Non-Significant Risk	NA
Investigational Device 2	
Name:	Nexus-E Research Tool
Description:	The Nexus-E 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. Nexus E is the updated version of our previous tool, Nexus D.
Significant Risk? (Y/N)	Y
Rationale for Non-Significant Risk	NA
Investigational Device 3	
Name:	C-MF Tactor Simulator
Description:	Vibrational stimulation embedded into a glove that is attached to the fingertips.
Significant Risk? (Y/N)	N
Rationale for Non-Significant Risk	This is an external device, that is attached to the fingertips to provide light vibratory pressure. Although it is not expected to be uncomfortable, if it is, the subject can easily remove the device at any time. This device has been used in another research protocol (35238), and no patients have found the stimulation painful or had to remove it.

Investigational Device 4	
Name:	Google Glass
Description:	An optical head-mounted display designed in the shape of a pair of eyeglasses. Glasses will be worn during forward walking tasks as the display shows an individual walking to a specified cadence.
Significant Risk? (Y/N)	N
Rationale for Non-Significant Risk	Google glasses will be used in accordance with their intended commercial use. They will display video of an individual walking to various cadences with an audio metronome. Device will be used as subjects perform forward walking tasks. Device does not present serious risk to participants' health, safety, or welfare.

b. IDE-Exempt Devices

IND-Exempt Device 1	
Name:	Motus Movement Monitoring System
Description:	solid state gyroscope sensors to be used to measure rwFE and tremography
IND-Exempt Device 2	
Name:	Delsys Bagnoli 2 EMG System
Description:	Surface EMG sensors
IND-Exempt Device 3	
Name:	Smart EquiTest
Description:	Dynamic force plates
IND-Exempt Device 4	
Name:	QDG Keyboard
Description:	Keyboard for RAFT (repetitive alternating finger tapping)
IND-Exempt Device 5	
Name:	APDM System
Description:	APDM system (APDM, Inc., Portland OR) contains up to 12-Opal Movement Monitoring System and Laptop Lenovo ThinkPad is used to wirelessly monitor patients movements and gait.
IND-Exempt Device 6	
Name:	LG G Watch
Description:	LG G Watch with 9 axis accelerometer and gyroscope. (To be used in place of or in addition to Motus Movement System)

6. DRUGS, BIOLOGICS, REAGENTS, OR CHEMICALS USED IN THE STUDY

a. Investigational Drugs, Biologics, Reagents, or Chemicals

Investigational Product 1	
Name:	NA
Dosage:	NA
Administration Route:	NA
Investigational Product 2	
Name:	NA
Dosage:	NA
Administration Route:	NA
Investigational Product 3	
Name:	NA
Dosage:	NA
Administration Route:	NA

b. Commercial Drugs, Biologics, Reagents, or Chemicals

Commercial Product 1

Name:	NA
Dosage:	NA
Administration Route	NA
New and different use? (Y/N)	NA
Commercial Product 2	
Name:	NA
Dosage:	NA
Administration Route	NA
New and different use? (Y/N)	NA
Commercial Product 3	
Name:	NA
Dosage:	NA
Administration Route	NA
New and different use? (Y/N)	NA

7. DISINFECTION PROCEDURES FOR MEDICAL EQUIPMENT USED ON BOTH HUMANS AND ANIMALS

NA

8. PARTICIPANT POPULATION

a. Planned Enrollment

i)34 ii)34 iii)The study will be carried out in up to 34 people with moderate to advanced PD, who will have been evaluated and approved to have subthalamic deep brain stimulation to treat their motor signs.This includes up to 15 subjects who are also enrolled in eprotocol 25916.

b. Age, Gender, and Ethnic Background

The study will include male and female patients regardless of ethnic background. The age of the participants will be between 18 and 80.

c. Vulnerable Populations

No potentially vulnerable subjects will be enrolled in this study.

d. Rationale for Exclusion of Certain Populations

Idiopathic Parkinson’s disease does not occur in children.

e. Stanford Populations

None

f. Healthy Volunteers

None

g. Recruitment Details

The surgical team (Patient's Neurologist or Neurosurgeon) will identify potential participants from their patients who have chosen implantation of an Activa DBS system as their preferred treatment option. Physician will ask potential participant for permission to be contacted by a study team member. Participants will learn more about the study from members of the study team.

h. Eligibility Criteria

i. Inclusion Criteria

1.A diagnosis of idiopathic Parkinson's disease, with bilateral symptoms at Hoehn and Yahr Stage greater than or equal to II.
2.Documented improvement in motor signs on versus off dopaminergic medication, with a change in the Unified Parkinson's Disease Rating Scale motor (UPDRS III) score of >= 30% off to on medication.
3.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.
4.Subjects should be on stable doses of medications, which should remain unchanged until the DBS system is activated. After the DBS system is optimized (during which time the overall medication dose may be reduced to avoid discomfort and complications such as dyskinesias) the medication dose should remain unchanged, if possible, for the duration of the study.
5.Treatment with carbidopa/levodopa, and with a dopamine agonist at the maximal tolerated doses as determined by a movement disorders neurologist.
6.Ability and willingness to complete the tasks and return for study visits, at the initial programming and at their clinic follow up visits.
7.Age > 18

ii. Exclusion Criteria

1.Subjects with significant cognitive impairment and/or dementia as determined by a standardized neuropsychological battery.
2.Subjects with clinically active depression, defined according to the Diagnostic and Statistical manual of Mental Disorders, Fourth Edition (DSM-IV) criteria and as scored on a validated depression assessment scale.
3.Subjects with very advanced Parkinson's disease, Hoehn and Yahr stage 5 on medication (non-ambulatory).
4.Age > 80.
5.Subjects with an implanted electronic device such as a neurostimulator, cardiac pacemaker/defibrillator or medication pump.
6.Subjects, who are pregnant, are capable of becoming pregnant, or who are breast feeding.
7. Patients with cortical atrophy out of proportion to age or focal brain lesions that could indicate a non-idiopathic movement disorder as determined by MRI
8.Subjects having a major comorbidity increasing the risk of surgery (prior stroke, severe hypertension, severe diabetes, or need for chronic anticoagulation other than aspirin).
9.Subjects having any prior intracranial surgery.
10.Subjects with a history of seizures.
11.Subjects, who are immunocompromised.
12.Subjects with an active infection.
13.Subjects, who require diathermy, electroconvulsive therapy (ECT), or transcranial magnetic stimulation (TMS) to treat a chronic condition.
14.Subjects, who have an inability to comply with study follow-up visits.
15.Subjects, who are unable to understand or sign the informed consent

i. Screening Procedures

Subjects with Parkinson's disease who have been accepted for DBS implantation will be asked if they wish to participate in this study. All subjects will have undergone challenged on medication and practically defined off medication evaluations by a fellowship trained movement disorders neurologist and detailed neuropsychological testing by a neuropsychologist prior to being presented at the movement disorders surgical review board. The movement disorders surgical
review board consists of the neurosurgeons, movement disorders neurologists, psychiatrist, neuropsychologist, and nurse specialists, who evaluate each candidate's suitability for surgery and reach a consensus decision about each person. If they are accepted for DBS, they are scheduled to meet the neurosurgeon. At this visit they will be met in

person by the research coordinator, who will upon their permission sit down in person with them and their family and explain the study and review the informed consent.

j. Participation in Multiple Protocols

The investigators will ascertain whether the patient is participating in other investigational studies, and, if so, if the study will conflict with this protocol.

k. Payments to Participants

No payment will be provided for participation in this project.

l. Costs to Participants

The patient or the patient's insurance company will be responsible for all charges involved in the DBS implantation procedure and for follow-up examinations including hospital charges, neurologist's fee, and the device charge. The patient's insurance company will be billed for all treatment-related costs which include all tests required to follow the patient's disease and any side effects of the treatment. These are all standard costs that are not affected by the study. There are no additional charges for participation in the study.

m. Planned Duration of the Study

The entire study will take 5 years to complete. The device battery runs out within 2-5 years after implantation. Patients will participate throughout this time. Total time per participant for: (i)screening: 2 day evaluations taking about 2 hours each morning;(ii) active participation in study: 2-5 years;(iii) analysis of participant data; 2 years.

9. RISKS

a. Potential Risks

i. Investigational devices

The investigational DBS device (Activa PC+S model 37604) is based on the FDA approved commercial DBS device (Model 37601 Activa PC)but adds the functionality of bioelectrical data recording (sensing). Activa PC and Activa PC+S share the same therapy and form factor and there are no new tissue contacting materials in Activa PC+S. Therefore the risks of the Activa PC+S should be similar to Activa PC. We don't anticipate that there will be any additional risks associated with using this device.
The risks of implanting the FDA approved device(Activa PC) are minimal but include risks at surgery of local bleeding, skin contusion or infection, tenderness at the site of implantation, device failure, discomfort after device placement in subcutaneous tissue, or due to local current spread if there is a break in the lead or connections.

The Nexus-E investigational research tool is only FDA approved for use in studies such as this one and is not commercially available. The Nexus E-System will only be used during study visits and will only be able to make changes to stimulation within the preset safety constraints set by a clinician. The Nexus-E System does not allow the clinician or pre-written algorithms to change the stimulation configuration beyond those pre-set safety limits. Potential issues that could occur while using the Nexus-E system may include device malfunction or premature battery drainage of the DBS device.

The tactile stimulator, which uses C-MF Tactors, is being used for an off-label use as treatment for Parkinson's disease. The device gently vibrates the fingertips. We suggest that this is a non-significant risk device. No official statistics are available on its safety. The only theoretical anticipated risk might be worsening of Parkinson's symptoms. We will be vigilant for this unlikely possibility. We have tested this device in another protocol for safety and tolerability (35238), and we have not had any reported discomfort from the vibratory stimulation.

Risks associated with using Google Glasses during forward walking tasks are minimal but may include losing balance while watching videos on display.

ii. Investigational drugs

NA

iii. Commercially available drugs, biologics, reagents or chemicals

NA

iv. Procedures

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).

v. Radioisotopes/radiation-producing machines

NA

vi. Physical well-being

Low

vii. Psychological well-being

Low

viii. Economic well-being

Low

ix. Social well-being

Low

x. Overall evaluation of risk

Medium

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b. International Research Risk Procedures

NA

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c. Procedures to Minimize Risk

The planned procedures for protecting against and minimizing all potential risks will be the same as for the standard clinical DBS treatment delivered with the marketed version of the device. Additionally patients will be monitored for suicidal ideation and/ or intent using the Colombia Suicide Severity Scale assessment(C-SSRS). This is to evaluate and monitor risk associated with any DBS therapy and is not unique to particular use of this investigational device. Patients will undergo a baseline assessment at their first appointment and will complete the Since Last Visit version of the scale at each followup study appointment.

The C-SSRS will be reviewed and scored during each visit. If the participant has suicidal ideation and/or answers yes to any question on the Colombia suicide severity scale (questions 1-5)they will be referred by a physician to a psychiatrist immediately as per standard clinical practice.

Stimulation will be maintained at clinically recommended levels and never exceed 30 microcoulombs per square centimeter per phase.
The testing done in the laboratory brings minimal additional risks. A neurologist and a specialized nurse will be available when the testing is performed. A Monitoring Entity will verify that the investigators have adequate qualifications and resources and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

All PHI will be stored on encrypted and password protected computers kept in locked rooms.

d. Study Conclusion

The study will terminate when 30 patients have been enrolled and tested. Participants will no longer undergo testing when their device battery runs out, if they are not reimplanted with a new Activa PC + S.

e. Data Safety Monitoring Plan (DSMC)

i. Data and/or events subject to review

The project will be monitored to ensure the rights and well-being of the patients, who consent to it, 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, are accurate, complete and verifiable.Prior to the initiation of the experiments, the ME 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 in the protocol. They will participate in “dry runs” of the experiments with the investigators to document the above readiness before the study will commence.
The monitors will verify that the investigators have adequate qualifications and resources and remain adequate throughout the trial period, that which facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period. The monitors will have formal meetings with the protocol director, Dr. Bronte-Stewart and the investigative team semi-annually to review the numbers of patients recruited, to document that the data is being collected and stored correctly, to document any adverse events, equipment issues and or data concerns. Monitors will formalize these with a report which will be provided to the IRB annually. Monitors will agree to meet on an ad hoc basis if there are any concerns that need to be addressed immediately. They will have the authority to recommend that the study be terminated if they believe that this is in the best interest of the subjects enrolled.

ii. Person(s) responsible for Data and Safety Monitoring

The Monitoring Entity will be a Data Monitoring Committee consisted of three members.

Monitors

Selection and Qualifications
1). Anca Velisar MS, will oversee the technological and data aspects of the study. Anca Velisar has two Engineering Masters degrees (Biomedical and Electrical) Anca Velisar has been a member of the Stanford Human Motor Control Lab since 2011 and manages all the kinematic equipment in the Laboratory and all the computers used for data storage. Anca Velisar is knowledgeable about all aspects of the DBS surgical procedure and has experience managing all the electrophysiological equipment and assisting the neurosurgeon with quality assurance checks of the anatomical targeting and surgical procedure.
2). Dr. Lising is a Fellowship trained Movement Disorders neurologist and an Clinical Assistant Professor in the Department of Neurology and Neurological Sciences at Stanford University School of Medicine. Dr. Lising has special expertise in the management of patients with implanted DBS devices. Dr. Lising will monitor all the clinical aspects of the protocol and experiments.
3). Dr. Robert Fisher is the Maslah Saul Professor in the Department of Neurology and Professor, by courtesy, of Neurosurgery at the Stanford University Medical Center. He has extensive experience in conducting clinical trials including a stage III trial for DBS therapy treatment of Epilepsy.

iii. Frequency of DSMB meetings

Semi-annually and a written report will be provided

iv. Specific triggers or stopping rules

when a patient complains of adverse effects with the use of the device

v. DSMB Reporting

if no adverse effects the reports will be filed to the IRB annually. If adverse effects happen, then the ME reports will be send to IRB committee immediately.

vi. Will the Protocol Director be the only monitoring entity? (Y/N)

N

vii. Will a board, committee, or safety monitor be responsible for study monitoring? (Y/N)

Y

f. Risks to Special Populations

NA

10. BENEFITS

There is no personal benefit for the participants in the study. We believe that the results of this study will make it possible for DBS to realize its full potential: a new generation of context-dependent, continuously adaptive DBS devices will have the ability to sense and modulate brain signals that are correlated to abnormal movement and will provide DBS therapy in different locations based on motor phenotype and state of activity

11. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.