Chronic effects of deep brain stimulation on cortical local field potentials in Parkinson's disease and primary dystonia Study

(Activa PC+S)

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Protocol Synopsis

Title	Chronic effects of deep brain stimulation on cortical local field potentials in Parkinson's disease and primary dystonia
Study Phase	Phase I
Device(s)	**Device Information:** Devices to be used in this study are grouped below according to FDA approval. All are Medtronic Devices. Investigational • Activa PC+S implantable pulse generator, Model 37604 • Sensing Programmer Model 8181 for Activa PC+S • Sensing Programmer Software Model 8180 for Activa PC+S • Lead extension Model 37087 • Nexus-D System • Nexus-D Application Programming Interface (API) Intercept Patient Programmer, model 37441Approved for other indications • Medtronic Lead Model 3391 • Medtronic Resume II paddle electrode model 3587A Approved for the intended indication • N'Vision Clinical Programmer Model 8840 • Clinician Programmer Software Model 8870 • Patient Programmer Model 37642 • Lead Model 3389 • External Neurostimulator 37022 • Lead extension model 37086 • Activa SC 37603 single channel pulse generator
Indication	Adults with Parkinson's disease (PD) or primary generalized or segmental dystonia, who experience inadequate symptom relief in the setting of optimal medical therapy by a movement disorders neurologist, and who have been offered implantation of a deep brain stimulator system.
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Medical Safety Monitor	The medical safety monitor board (MSMB) consists of a neurologist and neurosurgeon outside of our home institution, who have no direct involvement in this study but who have expertise in implantable devices. The neurologist is Dr. Michael Okun at the University of Florida, Gainesville, and the neurosurgeon is Dr. Jeff Ojemann at the University of Washington, Seattle. Treatment related adverse events assessed as definitely, probably, or possibly related to study procedures and either serious or unexpected, noted by any study personnel will be reported within 10 working days of their knowledge of the event to the MSMB. The MSMB will then advise the PI on potential changes in procedures to improve safety, or, in the event of multiple serious adverse events, may invoke stopping rules.
Treatment	Long-term stimulation of the basal ganglia for Parkinson's disease or primary dystonia
Study Site	University of California, San Francisco 779 Moffitt, 505 Parnassus Ave San Francisco, CA 94143
Study Design	This is a single-center study of the neurophysiology of human movement disorders with two goals: 1) Assess the feasibility of chronic brain recording using a novel fully implantable pulse generator (Medtronic Activa PC+S), which has the capability of sensing and storing local field potentials (LFPs) recorded from implanted electrodes, in addition to providing therapeutic deep brain stimulation (DBS). 2) Study acute and chronic effects of therapeutic DBS on cortical LFPs. Participants will also have the opportunity to participate in an add-on study to test practical applications of this device, such as "closed loop" stimulation, in which neural feedback is used to program optimal DBS settings. These additional studies will utilize the Nexus-D (Medtronic), which streams data noninvasively from Activa PC+S to an external computer in near real time. Study subjects will have implanted, in addition to their standard DBS electrode(s), a unilateral flexible 4-contact electrode (Medtronic 3391 lead or 3587A lead). This lead will be advanced through the same burr hole used for the DBS lead implants. This electrode array does not penetrate the brain surface, but rests on the surface of the motor cortex. The cortical electrode, as well as the standard therapeutic DBS electrode implanted on that side, will be attached to a Medtronic Activa PC+S pulse generator placed in the ipsilateral pectoral area. On the contralateral side, for patients scheduled for bilateral DBS implantation, a standard therapeutic DBS electrode will be connected to a standard Medtronic single channel pulse generator (Activa SC). At multiple time points up to 24 months post implantation, subjects will have outpatient visits to collect data, download cortical LFPs, and, in the add-on Nexus-D study, test applications of closed loop DBS. Some subjects who have signed consent for the Nexus-D2 substudy will have the option for data downloading and

	operant conditioning at home. The goal of the operant conditioning is to evaluate whether PD patient practice in modulating brain activity may lead to clinical improvement of PD symptoms
Objectives	In fifteen patients undergoing DBS implantation for PD or primary dystonia (10 PD; 5 dystonia), we will implant a unilateral subdural cortical electrode in addition to the DBS electrode, and connect these to a novel implantable pulse generator that can store field potential data (Medtronic Activa PC+S). At multiple time points post-implantation in our clinic, we will record and download cortical and basal ganglia LFPs on and off of DBS therapy in the following behavioral conditions: a.) rest b.) during a computer controlled binary choice arm reaching task c.) walking up and down a hallway *Hypotheses*: *1)* Long term recording of cortical LFPS is technically feasible with stable signals over 1 year, without adverse events *2)* Chronic (6 and 12 months) basal ganglia DBS alters the spectral characteristics of the M1 LFP (spectral power in beta and gamma bands), the magnitude of movement related M1 beta band change, and the coupling between beta rhythms and broadband gamma activity. We expect that in PD, DBS-induced changes will appear in early recordings (immediately after starting DBS), whereas in primary dystonia, cortical changes will be seen only after long-term DBS. *3)* DBS-induced changes in abnormal cortical oscillatory activity may predict the degree of DBS-induced improvement in motor function *4)* Markers of abnormal cortical or basal ganglia oscillatory activity can help determine clinically effective stimulation settings.
Patient Population	Study subjects will be adults with Parkinson's disease (PD) or primary dystonia, recruited from a clinic population of patients scheduled to undergo unilateral or bilateral DBS implantation for amelioration of their movement disorder symptoms.
Sample Size	15 subjects
Efficacy Assessments	<u>Clinical rating scales of motor function</u>: For PD patients: Unified Parkinson's Disease Rating Scale (UPDRS) parts I-IV and dyskinesia rating scales. UPDRS part III will be scored on and off of antiparkinsonian medications. For dystonia patients: Burke-Fahn Marsden Dystonia Rating Scale (BFMDRS) and Toronto Western Spasmodic Torticollis rating scale (TWSTRS). <u>Other rating scales (all patients)</u>: Clinician Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C).
Safety Assessments	1)Physical examination at all study visits 2) Check of pulse generator stimulation parameters, impedance measurements, and battery voltage at all study visits 3) Surgical or nonsurgical protocol-defined adverse events as recorded on adverse events case report forms 4) Assessment of suicidality using the Columbia Suicide Severity Rating Scale, at all protocol-defined outpatient visits

	5) In visits where the Nexus will be used for closed loop stimulation, all possible stimulation settings are preselected by clinicians to avoid the possibility of producing major stimulation-induced adverse effects

Statistical Methods and Data Analysis

ECoG and LFP data will be analyzed in the frequency domain for mean log power in the beta and gamma bands, movement related changes in beta and gamma band power, and coupling between low frequency rhythms and broadband gamma power (12, 20, 21). Using a repeated measures ANOVA statistical analysis, summary statistics for power in relevant frequency bands, movement related power changes, and indices of phase-amplitude coupling will be compared at different time points, different DBS conditions (on and off), and different disease states (PD or primary dystonia).

Although the sample size is small, in each disease group we will assess the correlation between these brain physiology measures, and clinical instruments used to measure the motor benefit produced by DBS. In particular we will ask: 1) Did the degree of cortical synchronization, as assessed by a quantitative index of phase-amplitude coupling (PAC) prior to starting stimulation therapy, correlate with the degree of benefit produced by DBS (difference between clinical ratings at 12 months on stimulation and baseline pre-implantation, off medication). 2) Did the magnitude of DBS-induced suppression of cortical synchronization (difference between PAC on-stimulation at 12 months, versus prior to starting stimulation therapy) correlate with the degree of benefit produced by DBS (difference between clinical ratings at 12 months on stimulation and baseline pre-implantation, off medication) 3) For the add-on study examining potential therapeutic uses of Activa PC+S: 1) Did the DBS stimulation settings which minimized metrics of cortical synchronization or basal ganglia synchronization, produce a therapeutic benefit compared with the off stimulation and off medication state; and 2) Did operant control of cortical or basal ganglia rhythms produce a therapeutic benefit compared with the off stimulation and off medication state prior to learning operant control.

Since this is a pilot study of chronic cortical recording, the sample size is likely to be too small to provide definitive answers to all research questions. Based on this exploratory analysis, it is anticipated that the next phase of the study will focus on a subset of the research aims, with 10-15 subjects per group.

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