1) Protocol Title

a) Safety and feasibility of using low frequency deep brain stimulation of the subthalamic nucleus to improve cognitive performance in patients with Parkinson's disease

b) Version: December, 14, 2015

2) Author of Protocol

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Researcher from other institution
Private Sponsor
Cooperative Group
Other: _____

3) IRB Review History

NA

4) Objectives

Our objective is to examine the safety and feasibility of using low frequency deep brain stimulation (DBS) to improve cognition in patients with Parkinson's Disease (PD). Although DBS of the subthalamic nucleus (STN) is a FDA-approved operation that is routinely performed in our patients with advanced PD, there is no clear standard for the stimulation frequency one should use to maximize benefits. There are few previously published studies that use low frequency stimulation (LFS) in PD, and furthermore, there are few studies that have examined the effect of DBS on cognition. Therefore, we propose a feasibility study that will provide safety and initial-efficacy data of low frequency DBS on cognition.

To do so, we plan to vary stimulation frequency in patients who are receiving DBS as part of their standard care. With regards to safety, we do not expect adverse outcomes of LFS. A previous group has utilized LFS for cognition in patients with PD and reported no adverse events (Wojtecki et al 2006). However, we will monitor potential safety issues through psychological, cognitive, and motor testing in cohorts of four patients. In that way, any unexpected safety issues or negative effects on performance will be detected prior to testing additional patients.

We propose to test the executive task performance of 20 patients with PD at baseline and following bilateral STN deep brain stimulator placement under no frequency, high frequency, and low frequency conditions. We further propose to

examine cognitive function under a variable duration of LFS. We hypothesize that there will be a trend towards improvement in task performance under the LFS setting, measured through reaction time and error rates, and that this improvement will be stable or enhanced with sustained LFS. We hope to utilize these results to inform the design of a larger phase 2 efficacy study. Our specific aims are as follows:

1) To monitor the safety of LFS in the STN of patients with PD by examining the psychological, cognitive, and motor consequences of LFS

2) To determine the feasibility of utilizing low frequency DBS to improve cognition in patients with PD by examining if there is a trend toward improved executive function with LFS over high frequency stimulation (HFS) and no stimulation settings.

3) To further examine feasibility by determining if the differential effects of LFS versus HFS of the STN are long lasting in a small patient group.

At present, DBS stimulators are set at varying stimulation frequencies based on the acute effects of DBS on motor performance, with limited understanding of cognitive consequences. Understanding the effects of different stimulation frequencies on non- motor tasks will help elucidate the mechanism behind cognitive impairment in PD. If our hypotheses are correct it could lead to the development of new treatment plans that involve alternating between low and high frequency stimulator settings to optimize both motor and cognitive domains. Ultimately, focused treatment for cognition may slow the progression from mild cognitive impairment to dementia, improving real world functioning and quality of life.

5) Background

PD affects over 4 million adults over the age of 50 with some estimates predicting this rate will double over the next 2 decades (Dorsey et al 2007). It is a disease characterized by the death of dopamine neurons in part of the basal ganglia (BGn) called the substantia nigra (SN). Because the BGn projects heavily to the motor cortical regions of the brain, the hallmark symptoms of the disease are predominantly motor. More recently, the resting BGn has been shown to have tight connections with many other areas of the brain, leading to the recognition of non-motor symptoms (NMS) as a major part of PD (Zgaljardic et al 2003). Cognitive impairment is one NMS that leads to increased disability, reduced quality of life, and may be the predominant source of disability at long term follow-up (Goldman & Litvan 2011). Some studies report that 80% of patients have Parkinson's disease with dementia (PDD) at later stages of the disease (Hely et al 2008). The cognitive impairments most often observed in PD are deficits in executive functioning, which rely on circuitry that connects the BGn with prefrontal areas of the brain. Patients have difficulty with mental planning, attention, and both establishing and adjusting task rules. They also show difficulties in visuospatial abilities and at later stages of the disease, exhibit explicit memory impairments (Owen 2004).

Treatment for cognitive impairment remains limited. Only rivastigmine has received approval from the FDA for PDD but is only modestly effective (Emre et al 2004). The conventional Dopa Replacement Therapy (DRT) improves motor symptoms but shows mixed effects on cognitive symptoms, improving some, and worsening others, largely due to nonspecific increases in dopamine (Poletti & Bonuccelli 2013). Deep Brain Stimulation (DBS) allows for targeted treatment to specific areas of the BGn. Currently, high frequency stimulation (HFS) is performed in the STN or globus pallidus interna (GPi) and has proved very effective in reducing motor symptoms when DRT has lost efficacy (Volkmann 2004), but like its oral counterpart, does not show substantial improvements in cognitive functioning (Halpern et al 2009). Some studies even show worsening function in verbal fluency and some executive function domains (Heo et al 2008). Unlike oral therapy, our understanding of how DBS works to improve BGn functioning remains in its infancy. There are great potentials for adjusting contact locations, stimulation frequency, and other stimulator settings in increasingly complex ways to optimize both motor and non-motor symptoms of PD. For example, the dorsal STN is thought to be more motor related and some propose that spread of current to non- motor regions of the STN may be responsible for cognitive impairments associated with STN DBS. In fact, controlling spread by computational modeling techniques to minimize ventral stimulation prevented some of the cognitive deficits observed with STN stimulation (Frankemolle et al 2010).

Clinical trials using DBS to improve cognition are underway with exciting preliminary reports. HFS of part of the hypothalamus improved cognition in 6 patients with mild Alzheimer's disease, increased activity in downstream circuitry involved in memory, and slowed cognitive decline (Laxton et al 2013, Laxton et al 2010).

While HFS has traditionally been used, there is new evidence suggesting low frequency stimulation (LFS) may be particularly important for cognitive functioning (Lisman 2005, McNaughton et al 2006). Research now suggests that neurons code information not only in their firing rate, but also in their firing frequency. The synchrony of neuronal firing within a brain area and the coherence of oscillations across brain areas within a network may be crucial for influencing and generating behavior across space and time (Engel et al 2001, Mann & Paulsen 2005, Niebur et al 2002). Low frequency oscillation in the theta range has been shown throughout many brain areas, including the hippocampus, temporal cortex, entorhinal, olfactory, somatosensory cortex, cingulate cortex, thalamus, across species (Lisman 2005). Animal studies have shown the importance of this rhythm for spatial navigation, learning and memory (Colgin 2013, Nyhus & Curran 2010). The theta rhythm is thought to be involved in learning by enhancing encoding of relevant incoming stimuli and thereby facilitating long term potentiation. Thus, too much or too little synchronization through disease processes that affect neurons and their networks would be expected to disrupt function. This has been demonstrated directly in traumatic brain injury (TBI) studies in rats by Dr. Shahlaie and co-workers. TBI rats exhibit impaired learning in water maze tasks. DBS in the theta range improves their performance, presumably returning the oscillatory frequency required for working memory and spatial learning (Lee et al 2013).

There are many exciting potentials for expanding this animal research into human populations to directly improve health and disease. One group of researchers

investigated the effects of LFS on cognitive impairments of PDD in humans (Freund et al 2009). They performed bilateral nucleus basalis of Maynert (NBM) DBS and bilateral STN DBS on one patient with PD. Using HFS in the STN and LFS in the NBM they showed improvement across a wide battery of neuropsychological tests measuring executive functioning, visuospatial skills, attention, concentration, language and memory.

As described above, the cognitive deficits in PD are thought to be due to network disruption in fronto-striatal circuits. Thus, targeting the executive dysfunction in PD may require stimulation of the BGn itself. Wojtechi and collegues demonstrated that low frequency STN stimulation improved verbal fluency when compared to HFS in 12 PD patients (Wojtecki et al 2006).

DBS of the STN is a FDA-approved operation that is routinely performed in our patients with advanced PD, and is considered to have a favorable safety and efficacy profile. However, stimulation of this brain region at standard stimulation frequencies has been linked to affective side effects in some patients receiving HFS (Smeding et al 2006, Strutt et al 2012). These effects are hypothesized to be due to ventral stimulation contacts as the ventral STN has connections with limbic regions of the brain, in combination with the reduction of DRT that can normally be achieved following DBS placement (Strutt et al 2012). The ventral region is also thought to be most likely to affect cognition. The safety of LFS in the STN is unknown but presumed to be minimal. Wojtechi et al reported that LFS in the ventral STN region did not cause any adverse events (Wojtechi et al 2006). Furthermore, lower frequencies are anticipated to have a reduced effect on the neural circuitry than high frequencies, and thus be safer than the standard high frequency stimulation.

Our goal is to build on this early work to further examine the safety and efficacy of theta frequency stimulation on cognition in PD. We propose that low frequency theta range stimulation in the STN is safe and may improve executive function in patients with PD. The trial we propose is not a surgical implant study as the patients are scheduled to undergo implantation of the deep brain stimulator as part of their routine clinical care, and will receive this surgery irrespective of our study. The implant is FDA approved for implantation into the STN of the brain in PD and patients are typically treated at a range of frequencies. The focus of our study is to determine whether theta frequency stimulation is safe and shows a trend toward improving cognitive performance, which could inform a larger efficacy study. Understanding the effects of different stimulation frequencies will help elucidate the mechanism behind cognitive impairment in PD and help develop advanced treatment programs.

6) Inclusion and Exclusion Criteria

Inclusion Criteria:

(1) Adult men and woman with a diagnosis of PD.
(2) Patients who are candidates for bilateral STN DBS placement surgery and who will receive this treatment as part of their routine care.
(3) Willingness to undergo temporary changes in STN DBS generator settings.

(4) Patients who have a caregiver who is willing to answer psychological screening questions on behalf of the patient.

Exclusion criteria:

(1) Patients less than 18 years of age.
(2) Patients who are not candidates for bilateral STN DBS placement surgery.
(3) Adults unable to consent
(4) Pregnant woman
(5) Prisoners
(6) Patients who score over 20 on the BDI indicating moderate depression

7) Number of Subjects

The target sample size is 22 subjects. The study design is a phase 1 safety and feasibility study. While results may show a trend towards efficacy, we will not be able to power the study toward efficacy. Two of these subjects will be used to evaluate the ease of use of the computerized cognitive test, but will not participate in any other study procedures and data will not become part of the study record. All subjects are to be enrolled locally at UC Davis medical center.

8) Recruitment Methods

a) Study-Wide:

NA

b) Local:

As part of our routine clinical practice at UC Davis, all patients that undergo STN DBS surgery are discussed in detail at the multidisciplinary Deep Brain Stimulation Case Conference, which includes representatives from Neurology, Psychiatry, Speech/Cognitive Therapy, and Neurosurgery. If patients are a candidate for the operation and score less than 20 on the baseline routine BDI, they are candidates for this study. Therefore, at the pre-operative visit with the patient they will be informed that, independent of their eligibility for DBS surgery, they may be eligible for a study investigating DBS frequency on cognitive performance in Parkinson's disease. If patients are interested in participating, they will be offered the opportunity to meet with a member of the study personnel that can provide them additional, detailed information regarding the study. The study personnel will be different from the treating neurosurgeon so that potential participants do not feel pressured to participate in the study. Consent forms will be provided with written information about the study goals, risks, and benefits.

Patients that plan to undergo STN DBS surgery at Sutter Medical Center and Kaiser Permanente in Sacramento may also be able to participate in this study. 'Dear Doctor' letters will be distributed to the Sutter and Kaiser DBS groups. Patients will be provided with a contact number to call if they are interested in learning more about the study. The

study will briefly be described on the phone. Patients interested in participating will be invited to UC Davis to meet with study personnel to review the study goals, risks and benefits in more detail. Consent forms will be provided at this visit and baseline cognitive testing will be performed if the patient decides to participate.

The dates of contact and written consent or refusal will be recorded. Participants will be advised that they have the right to say "Refuse to answer" to any questions that they find uncomfortable. They will be assured that participation is on a voluntary basis and they reserve the right to withdraw participation in the study at any point of time, and that declining to participate in the study will not have any effect on their medical care. Participants will be notified that with their consent, the research team will share any data collected from the screening and the study with their doctors at the end of their participation in the study.

An advertisement will be posted in the newspaper to recruit patients for the study. This advertisement will give a brief description of the study and instruct interested individuals to contact study personnel at the number provided to learn more about the study.

c) HIPAA:

As described in Question 8b above, the main eligibility criterion for this study is eligibility for STN DBS surgery. Therefore, the DBS Case Conference team will review individuals' medical records during evaluation for DBS surgery, per routine clinical practice at our institution. If the patient is a candidate for STN DBS and scores less than 20 on the BDI on routine screening tests, then a review of medical records may be performed to determine eligibility based on the inclusion/exclusion criteria above. Since medical records will be accessed prior to signing the consent form or HIPAA authorization, we request a waiver of HIPAA for recruitment purposes only. The use or disclosure of the PHI involves no more than a minimal risk to the privacy of individuals. All identifiers will be password-protected and access to data files will be given only to IRB- approved research personnel as listed in the research personnel list. Identifiers will be destroyed at the earliest opportunity consistent with the conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.

The protected health information will not be reused or disclosed to any other person or entity, expect as required by law, for authorized oversight of the research study, or for other research for which the use of disclosure of PHI for which an authorization or opportunity to agree or object is not required by 45 CFR 164.512. The research could not be practicably conducted without the waiver, and without access and use of the PHI for recruitment.

9) Compensation to the Subjects

Subjects will be compensated $10 per session. If the patient decides not to participate in further sessions, they will still receive the compensation for the completed sessions. Travel expenses up to $30 per patient will be provided if needed. The compensation will be in the form of a gift card and will be given at the time of the visit.

10) Study Timelines

The duration of the study from subject enrollment of the first patient to final data analysis will be approximately two years. Each individual subject will participate in the study for a maximum of 2 months for a total of 3 on-site experimental sessions and one telephone call. The first on-site visit will occur within the month prior to their planned DBS placement surgery, following the pre-operative visit. The second and third on-site visits will occur within the fourth week after the DBS electrode placement surgery, 3-4 days apart. A telephone call will be made 24 hours prior to the third on-site session to obtain additional safety information (Figure 1). Each participant will remain in the study for approximately 2 months from the time of consent. Participation is on a voluntary basis and subjects will reserve the right to withdraw participation in the study at any point of time.
We expect the duration to enroll all study subjects will be approximately 2 years based on the number of patients who meet the inclusion and exclusion criteria.

We expect to complete the study by July 2017. The data will be analyzed as individual patients complete the study with further analyses after data collection is complete.

11) Study Endpoints

1. Safety: Safety endpoints will be measured by neuropsychiatric, motor, and cognitive testing:

a) Neuropsychiatric tests. We will perform the BDI and NPI at baseline, at the first experimental session, once by telephone call after 24 hours of LFS, and a fourth time at the final experimental session. The score of the BDI will be compared across sessions and a score that rises above 20 will be considered positive for the development of moderate depression. The NPI assesses frequency, change in severity, and caregiver distress over 12 neuropsychiatric domains and we will look for caregiver reports of significant change across these domains.

b) Motor tests. The Unified Parkinson's Disease Rating Scale (UPDRS) will be performed prior to patient's surgery as part of the patient's routine care. We will repeat the scale at the final experimental session to assess changes in motor symptoms after sustained LFS.

c) Changes in cognitive function will also be assessed as described below.

2. Feasibility. Improvement in cognitive function will be measured by three cognitive tests: the Stroop test, the N-Back test, and the verbal fluency test. We will measure reaction time and error rates and look for significant changes across stimulator frequencies. The results from 20 patients will help us determine if a large-scale study of effectiveness is warranted and feasible.

Describe any primary or secondary safety endpoints.

See above.

12) Procedures Involved

a) Describe and explain the study design.

The study design is a safety and feasibility study. We aim to identify 20 PD patients who will receive bilateral STN DBS as part of their standard care. We plan to measure the safety of LFS in the STN as measured through psychological, cognitive, and motor scales, and compare cognitive performance with low and high frequency STN DBS. We propose that LFS in the theta range will not negatively affect psychiatric symptoms or alter motor symptoms, and will improve performance on tests of executive functioning.

This study will not affect whether PD patients receive a stimulator as all subjects are scheduled to undergo stimulation placement as part of their routine care. It also will not disrupt the standard procedure for implantation or initiation of treatment. The study will be conducted only in the brief period prior to the time when the stimulator is typically turned on. FDA approval for PD treatment in not limited to a specific stimulation frequency, and stimulator parameters are typically adjusted as symptoms evolve over time. The effect of participating in this study will therefore be minimal.

Patient's stimulators are typically turned on 4 weeks following electrode placement surgery at UC Davis. We plan to perform frequency manipulation and cognitive testing 3 weeks following electrode placement surgery, and 2 weeks following the surgery for the Implantable Pulse Generator (IPG). The study will therefore be completed prior to the standard time for the initiation of treatment stimulation. Patients' treatment stimulation will not be delayed by participating in the study. Patients' medications will not be adjusted during the study. The study timeline is shown in Figure 1. Times are based on when surgery can be expected based on the decisions of the patient's surgeon and neurologist.

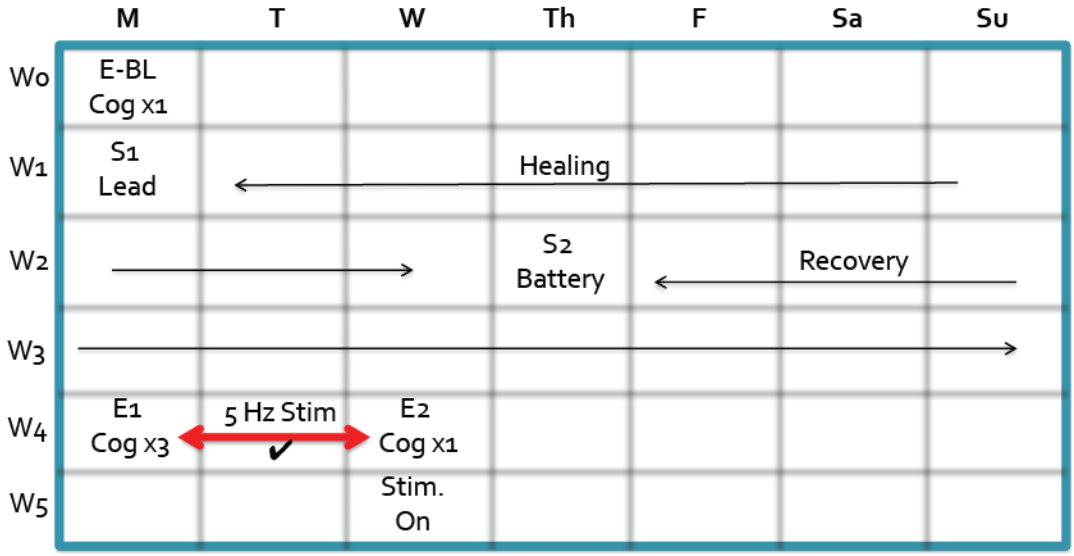

Figure 1: Week 0 (W0): Pre-op visit, Baseline experimental cognitive testing (E-BL Cog) (may occur 1-2 wks prior to lead placement surgery), Week 1 (W1): Surgery 1: DBS lead placement surgery (S1 Lead) as scheduled by patients' doctors, Week 2 (W2): Surgery 2: IPG surgery (S2 Battery) as scheduled by patients' doctors, Week 3 (W3): Recovery, Week 4 (W4): Experimental testing sessions 1 (E1 Cog) and 2 (E2 Cog) with frequency modulation, check mark indicates telephone contact, Week 5 (W5): Treatment Stimulation typically turned on as part of routine care.

Upon informed consent and enrollment, information regarding participants' age, gender, medications, medical history, surgical history, disease duration and imaging (magnetic resonance imaging, computed tomography) will be collected. As part of the standard assessment prior to DBS electrode placement, all patients undergo evaluation with the Unified Parkinson's Disease Rating Scale (UPDRS), Beck depression inventory (BDI) (Beck et al 1961), IQ testing, and a battery of neurocognitive tests. These tests are routinely repeated about 6 months to 1 year after DBS placement as part of patients' routine care. These tests will not be a direct part of the study but may be utilized as part of the patient's history.

As part of our experimental design, we will include a baseline experimental session prior to the patient's planned surgery that will consist of approximately 30 minutes of cognitive testing and baseline screening for neuropsychiatric symptoms using the BDI and NPI (Cummings et al 1994). Cognitive testing will consist of computerized and non-computerized tests. The NPI requires that a caregiver answer questions about the mental state and behaviors of the patient. The caregiver will be informed of the study at the pre- op visit if the patient consents and will be asked if they are willing to participate in the study procedure.

After patients' treatment team has performed their DBS surgeries, there will be two on- site experimental testing sessions with frequency manipulation and a telephone psychological screening session. The first will occur 22-24 days following the DBS lead placement surgery. During the session, each patient will repeat baseline cognitive testing

without stimulation and will complete the BDI. Informers will complete the NPI. Subsequently, the stimulators will be turned on, and each patient will repeat cognitive testing under gamma frequency (~130 Hz) and theta frequency stimulation (~5 Hz). The order of stimulation will be randomized. Stimulation will occur for 5 minutes prior to and continuously throughout each task. Amplitude and pulse width will be set to 3 V and 120 microseconds accordingly (Laxton & Lozano 2013) or as tolerated by the patient, and will remain constant across sessions. We will wait 20 minutes between testing conditions to elicit about 75% of DBS effects (Temperli et al 2003). At the end of the experimental testing session, the stimulator will be turned off or set to LFS in preparation for the second experimental session.

The second on-site experimental testing session will assess the effects of continuous theta stimulation on cognitive function. Patients will repeat cognitive testing after 48 hours of continuous theta stimulation. This second on-site testing session will occur 3-5 days following the first experimental session. Two days prior to the testing session, patients' stimulators will be turned on to the theta frequency stimulation setting and patients will return home and engage in normal activities. After 48 hours they will return to the clinic and repeat cognitive testing with continuous theta frequency stimulation. The UPDRS, NPI, and BDI will also be performed at this time. At the end of the session, their stimulators will be turned off.

We will screen for psychological changes by telephone once during the 2 day stimulation period. The patient will complete the BDI and a relative or caregiver will complete the NPI over the phone.

The structure of the experimental sessions is shown in Figure 2 and Figure 3.

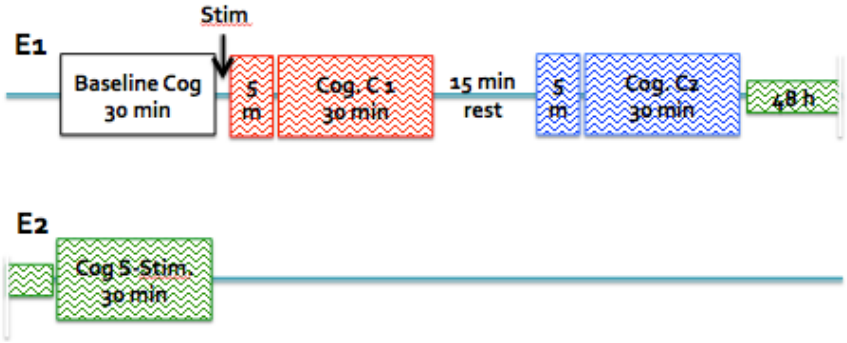

Figure 2: Stimulation schedule. The first experimental session (E1) will include 30 minutes of baseline cognitive testing. Stimulation will then be turned on (Stim) for 5 minutes prior to cognitive testing under the first frequency condition (either HFS or LFS depending on randomization) (Cog C1). Stimulation will then be turned off and the patient will have a 15 minute rest period. Stimulation at the second testing frequency condition will then be turned on for 5 minutes and the cognitive testing will be repeated (Cog C2). At the completion of this session, LFS will be turned on for 48 hours. When the patient returns to clinic for the second experimental session (E2) they will repeat cognitive testing after sustained LFS (Cog S-Stim). The stimulation will be turned off and the patients will return home to continue standard care. Shaded boxes represent periods of stimulation.

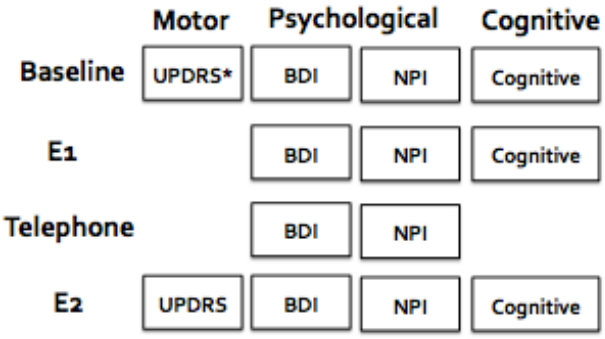

Figure 3: Safety Measures. Motor, psychological and cognitive tests present for each patient contact are indicated. *This motor test performed by neurologist as part of routine care and occurs at a clinic visit prior to the patient's anticipated surgery.

We will also identify and enroll two subjects that have PD in order to test the ease of use of the computerized cognitive test, prior to the enrollment of additional subjects. These subjects will perform the computerized cognitive test once and will not participate in any other study procedures. We will use this information to decide on optimal parameters within the computerized cognitive test such as stimulus presentation time and response time allowed.

Cognitive testing will include three cognitive tests. The first is the single-trial computerized version of the Stroop color-naming task. This task is an executive function task that measures attention and inhibition (MacLeod 1991). Performance on this task has been shown to be impaired in patients with PD. Patients make more errors, have a slower response times, and show increased Stroop interference relative to controls (Brown & Marsden 1988). Furthermore, performance may worsen following STN DBS placement, with further increases in error rates (Jahanshahi et al 2000, Witt et al 2004). Stimuli consist of three color words printed in one of the three colors such that there are congruent trials where the written color word and ink color match, and incongruent trials where the written color word and ink color do not match. Participants are instructed to ignore the written word, and perform one of three key presses corresponding to the color of the written word. They will first be trained to accuracy on the key presses using 100% congruent trials. Patients will be instructed to be both fast and accurate.

The second cognitive test is a computerized version of the N-back test, which has been shown to target working memory. Performance on this task has also been shown to be impaired in patients with PD (Beato et al 2008). Patients will perform 2 blocks of trials corresponding to 1-back, and 2-back. In this task, patients will be asked to make a key press when they see a matching spatial configuration one or two stimuli before the current stimuli.

The final test is the FAS phonemic fluency test. Patients will be asked to verbally name as many words as they can that start with the letters F, A, or S within a 1 minute time period. Patients will perform the verbal fluency test with each of the three letters once in random order after Stroop and N-back computer tasks have been completed. People with PD have been shown to have difficulty specifically with phonemic verbal fluency, which is thought

to rely on connections between the basal ganglia and the prefrontal cortex (Dadgar et al 2013, Jaywant et al 2014). Furthermore, DBS has been shown in some studies to impair phonemic verbal fluency, which may or may not recover over time (Ehlen et al 2014, Wojtecki et al 2006, Wu et al 2014). These specific letters were chosen based on the frequency of English language words that that begin with the letters (Borkowski et al 1967.)

Total testing time will be approximately 30 minutes per stimulation condition with 20 minutes between conditions, resulting in a total time of approximately 30 minutes for the baseline cognitive testing, 2 hours for the first experimental session and 30 minutes for the second experimental session. Additional time will be needed for setup and explanation of the task directions. Finally, 20 minutes of psychological screening will be performed at the baseline session, over the phone between experimental sessions 1 and 2, and following cognitive testing during experimental session 2.

Baseline Testing: 30 min cognitive testing, 20 minute psychological screening (Total Time: approximately 50 min)
Experimental Session 1: 20 minutes psychological screening, 2 hours cognitive testing (Total Time: approximately 2h 20 min)
Phone call between experimental session 1 and 2: 20 minutes psychological screening
Experimental Session 2: 30 min cognitive testing, 20 minute psychological screening, 20 min motor screening (Total Time: approximately 70 minutes)

b) Humanitarian Use Device (HUD)

NA

13) Data and Specimen Banking

No data or specimens will be retained longer than required by law or hospital policy.

14) Data Management and Confidentiality

The target sample size is 22 subjects. The study design is a safety and feasibility phase1 study. While results may show a trend towards efficacy, we will not be able to power the study toward efficacy.

Safety Data Analysis:
To examine possible effects on motor symptoms, we will screen for changes in the motor section of the UPDRS score after sustained LFS. After each patient is tested, we will calculate individual changes in UPDRS scoring. After the entire patient population is tested, we will use T-tests to determine if there is a significant change in the overall rating scale.

We will also examine changes in psychological symptoms. For each individual patient, we will measure the BDI and NPI at baseline, at the first experimental session, by phone call after 24 h LFS, and at the final experimental session. For the BDI, we will consider any score greater or equal to 20 as evidence of moderate depression and will terminate the study for any individual that shows evidence of depression. At the group level, we will calculate

the percentage of people that develop depression. For the NPI, we will calculate the total score. At the individual level we will look for the development of new symptoms in the 12 subsections. At the group level we will perform an ANOVA to look for significant changes across the 3 time points.

Cognitive Data Analysis:
The cognitive data analysis will examine the effect of theta frequency stimulation on cognitive task performance. Analyses for the Stroop task will include the examination of response time and error rates across stimulator settings. Two (trial type: congruent vs incongruent) by three (Setting: low, high, no stimulation) ANOVAs will be performed for both reaction time and accuracy. Post conflict and post error reaction time adjustments will also be examined across stimulator settings. For the N-back test, ANOVAs will also be performed to assess the effects of complexity (1,2-back) and stimulation frequency (none, high, low) on error rates. For the verbal fluency test, the average number of words generated across stimulation conditions and the change in word number on low and high frequency stimulation settings will be compared. Analyses will be performed using MATLAB and STATA.

Describe any procedures that will be used for quality control of collected data.
a.) Study-Wide:
NA

b.) Local

Describe the local procedures for maintenance of confidentiality.

This research is partly funded by a donation from the Chevo Foundation. The Chevo Foundation will not have access to any of the study documents including the data.

Data files to be stored include group assignment, background information, any head scans if performed, and results from neurocognitive and motor tests.

Data files will be stored on secured server through the assistance of the UC Davis Clinical and Translational Science Center, which will be password-protected and access to data files will be given only to IRB-approved research personnel as listed in the research personnel list. For data analysis, each subject will be assigned a unique identification number and there will be no reference to his/her name or any other personal identifier in any subsequent publication. All personal identifiers will be destroyed upon completion of the research and the required storage period. Protected Health Information (PHI) will not be reused or disclosed to any other persons or entity except if subject to an authorized oversight of the research project. Otherwise, the PHI will be protected to the fullest extent possible. Subjects will be given access to their results at the closure of the study. Data will be stored locally for no more than 5 years.

15) Provisions to Monitor the Data to Ensure the Safety of Subjects

Data from the first two subjects will be used only to determine the ease of use of the computerized cognitive test and will not be collected as part of the study. These participants will perform the cognitive test only and will not participate in any other study procedures. Data from the remaining subjects will be analyzed and evaluated in cohorts of 4 patients through the first 12 patients to determine whether subjects remain safe. This means we will evaluate the safety data from the first 4 patients before proceeding with subsequent subjects. We will evaluate data again after a total of 8 patients, 12 patients, and 20 patients. Data will be reviewed by a safety committee. The committee will include the PI, Dr. Kiarash Shahlaie in addition to Dr. Lin Zhang, Dr. Sarah Farias, and Dr. Katherine Scangos. Dr. Lin Zhang is a neurologist, co-director of the DBS group, and has participated in multiple clinical trials involving the Parkinson's disease population. Dr. Farias is an expert in neurocognitive assessment in Parkinson's disease and has experience in identifying study related neurocognitive effects in clinical trials in dementia.

Safety data will include performance on psychological screening tests, cognitive tests, and motor tests. Efficacy data will include performance on cognitive tests. All data will be reviewed by a safety committee as described above. If any patient develops motor effects that are uncomfortable, the study will be halted for that particular subject. Furthermore, if the patient develops worsening psychological effects as measured through psychological screening tools, the study will be halted and the patient will be referred for appropriate care through the departments of Psychiatry and Neurology at UC Davis.

Safety information will be collected at study visits and with a telephone call. It will be saved in the database established for this study.

Safety data for motor effects will be collected prior to the patient's surgery and at the final study visit. Psychological data will be collected prior to DBS placement, at the first study visit, by phone call during the sustained frequency stimulation period, and at the final clinic visit.

The principal investigator and study members will review the data after each clinic visit and telephone contact with the patient. A safety committee will review the data after the first 4 patients, 8 patients, 12 patients, and 20 patients. The committee will include the PI, Dr. Kiarash Shahlaie in addition to Dr. Lin Zhang, Dr. Sarah Farias, and Dr. Katherine Scangos. Dr. Lin Zhang is a neurologist, co-director of the DBS group, and has participated in multiple clinical trials involving the Parkinson's disease population. Dr. Farias is an expert in neurocognitive assessment
in Parkinson's disease and has experience in identifying study related neurocognitive effects in clinical trials in dementia.

Data will be analyzed and evaluated in cohorts of 4 patients through the first 12 patients to determine whether subjects remain safe. This means we will evaluate the safety data from the first 4 patients before proceeding with subsequent subjects. We will evaluate data again after a total of 8 patients, 12 patients, and 20 patients.

Safety Data Analysis: To examine possible effects on motor symptoms, we will screen for significant changes in the motor section of the UPDRS score after sustained LFS. After each patient is tested, we will calculate individual changes in UPDRS scoring. After the entire patient population is tested, we will use a T-test to determine if there is a significant change the motor section.

We will also examine changes in psychological symptoms using the BDI and NPI. We will examine percentage of people who convert to moderate depression as indicated by a BDI score 20 or higher. We will also look for significant changes in the BDI and NPI across time using ANOVAs.

Changes in cognition will also be analyzed by looking at reaction time and error rates on different cognitive tests as described previously.

- Any conditions that trigger an immediate suspension of the research.

None.

16) Withdrawal of Subjects

Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent.

Patients unable to perform cognitive tests due to effort or altered mental status.

Patients who experience any change in psychological symptoms that is concerning to the patient, caregiver, or test administrator as assessed through psychological screening tools.

Describe any procedures for orderly termination.

The patient is not undergoing any additional procedures, except for stimulation and cognitive testing.

Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.

Patients' data will be recorded, unless specifically asked to be withdrawn

Patients will continue to be followed for medical management

17) Risks to Subjects

Physical Risk:

- There is minimal to no physical risk. Once the patient's stimulation is turned off, the patient's pre-stimulation symptoms will likely return (Temperli et al 2003).
- There is a small chance that changes in affective symptoms including dysphoria, depression, mania, or psychosis may occur (Smeding et al 2006, Strutt et al 2012). Patients will be carefully screened using standardized assessment tools.
- All cognitive and memory tests are designed to be minimally difficult and pose minimal

risk to the subject. Patients may experience boredom or uncertainty by the cognitive testing.

Neurological Risk:

- There are no risks associated with activating the DBS system on post- operative day 22-24 for participating in this study. There is significant variability in timing of DBS therapy across institutions, with some groups activating the DBS on post-operative day 1 and other groups activating the device on/after post-operative day 30. There are no documented risks associated with the delay between DBS implantation and initiation of therapy.
- Although we expect LFS in the STN to improve cognition based on previous literature, we cannot rule out the possibility that prolonged ventral STN stimulation may temporarily worsen cognition in some patients.

Confidentiality Risk: There is also minimal risk of breach of confidentiality.

18) Potential Benefits to Subjects

There is no direct long lasting benefit to individual subjects. Patients may potentially experience sustained cognitive improvement over a period of time with low frequency stimulation but the duration is currently unknown. Patients may benefit from contributing to our understanding of the neural mechanism underlying cognitive impairment in PD. The information gained in the study will be used to direct treatment plans to improve cognitive impairment in PD and slow the progression of mild cognitive impairment to dementia.

19) Vulnerable Populations

If the research involves individuals who are vulnerable to coercion or undue influence, describe additional safeguards included to protect their rights and welfare.

NA

20) Multi-Site Research

If this is a multi-site study where you are the lead investigator, describe the processes to ensure communication among sites, such as:

NA

21) Community-Based Participatory Research

NA

22) Sharing of Results with Subjects

Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared.

Subjects will be given access to their results at the closure of the study. If patients desire, the results of the study will be shared verbally with their treatment team at the Parkinson's clinic. The information will not be shared with any other health care providers.

23) Setting

Describe the sites or locations where your research team will conduct the research.

- *Identify where your research team will identify and recruit potential subjects.*

Specific locations for recruitment will be in the UC Davis Department of Neurosurgery, Department of Neurology and the Ellison Ambulatory Care Center. We will be seeking patients who plan to obtain subthalamic nucleus depth electrodes for Parkinson's disease. We will also recruit patients from Sutter Medical Center and Kaiser Permanente in Sacramento that plan to undergo STN DBS surgery. A newspaper advertisement will allow for recruitment outside of the UC Davis Health network as well.

- *Identify where research procedures will be performed.*

All research procedures and all study visits will take place at UC Davis. For this pilot study, we require the DBS generator adjustment equipment and a quiet exam room for administration of cognitive and motor tests (i.e. ACC clinic exam room or testing room in UC Davis imaging center). The personnel required to consent the subject, administer the tests and analyze the data are sufficient and involve members of the Department of Neurosurgery, Department of Neurology, Department of Psychiatry, UC Davis Imaging Center, UC Davis Clinical and Translational Science
Center and the Center for Mind and Brain

- *Describe the composition and involvement of any community advisory board.*

NA

- *For research conducted outside of the organization and its affiliates describe:*

NA

24) Resources Available

Describe your staff and their roles. Describe the qualifications (e.g., training, experience, oversight) required to perform each role. When applicable describe their knowledge of the local study sites, culture, and

society. Provide enough information to convince the IRB that you have qualified staff for the proposed research.

If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify people by role (e.g., coordinator, research assistant, co-investigator, or pharmacist), a change to that person will not require prior approval by the IRB, provided that person meets the qualifications described above to fulfill their roles.

- Principal Investigator: review of past literature, administration of cognitive tasks, reprogramming DBS generator, analysis of data, recruitment of patients, undergo IRB course(s) for clinical research
- Co-Investigator: administration of cognitive tasks, analysis of data, recruitment of patients, undergo IRB course(s) for clinical research
- Research assistants: administration of cognitive tasks, analysis of data, undergo IRB course(s) for clinical research

Describe other resources available to conduct the research: For example, as appropriate:

- *Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?*

We have access to all patients referred to neurosurgery for implantation of electrodes for intracranial depth electrode seizure monitoring.

- *Describe the time that you will devote to conducting and completing the research.*

3 years

- *Describe your facilities.*

We require the ACC clinic exam rooms or cognitive testing rooms in the UC Davis imaging center for cognitive testing and electrical stimulation.

- *Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research.*

Patients will be provided the opportunity to discuss untoward events with the clinical team and any additional consultations medically indicated.

- *Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.*

Each member of the research team will undergo IRB course(s) for clinical research. Each member will be required to read the protocol.

25) Prior Approvals

Describe any approvals that will be obtained prior to commencing the research. (E.g., school, external site. funding agency, laboratory, radiation safety, or biosafety approval.)

NA

26) Provisions to Protect the Privacy Interests of Subjects

Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact or whom they provide personal information.

Each member of the team will introduce himself/ herself to the patient and identify his/her involvement in the study.

Describe what steps you will take to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures.

The patient will be told that he/she can refuse to participate at any point during the study.

Indicate how the research team is permitted to access any sources of information about the subjects.

The research team will have access to the secured database via password protection.

27) Compensation for Research-Related Injury

The subject should promptly tell the person in charge of the research if they believe that they have been injured because of taking part in this study. If a subject is injured as a result of being in this study, the University of California will provide necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by University or the study sponsor or may be billed to your

insurance company just like other medical costs. The University and the study sponsor do not normally provide any other form of compensation for injury.

28) Economic Burden to Subjects

Describe any costs that subjects may be responsible for because of participation in the research.

NA

29) Consent Process

Indicate whether you will you be obtaining consent, and if so describe:

- *Where will the consent process take place:*

Consent will be obtained in the preoperative clinic for UC Davis participants. For Sutter or Kaiser patients, consent will take place at their initial visit to UC Davis.

- *Any waiting period available between informing the prospective subject and obtaining the consent.*

No

- *Any process to ensure ongoing consent.*

Each experimental session will be described to the patient prior to its start, and the patient will be asked permission to proceed with the study.

- *Whether you will be following "SOP: Informed Consent Process for Research (HRP-090) (attach SOP with submission)."*

We will be following HRP-090, Informed Consent Process for Research.

HIPAA Authorization for Research

If the research procedures include accessing personal health information, via the medical records, it is required that subjects sign a HIPAA Authorization for Research form at the time of consent, unless a waiver of informed consent has been granted by the IRB.

For more information on HIPAA Authorization for Research visit the Compliance Program website.

We will obtain HIPAA authorization. Data files to be stored include group assignment, background information, any head scans if performed, and results from neurocognitive and motor tests. Data files will be stored on secured server through the assistance of the UC Davis Clinical and Translational Science Center, which will be password-protected and access to data files will be given only to IRB-approved research personnel as listed in the research personnel list. For data analysis, each subject will be assigned a unique identification number and there will be no reference to his/her name or any other personal identifier in any subsequent publication. All personal identifiers will be destroyed upon completion of the research and the required storage period. Protected Health Information (PHI) will not be reused or disclosed to any other persons or entity except if subject to an authorized oversight of the research project. Otherwise, the PHI will be protected to the fullest extent possible. Subjects will be given access to their results at the closure of the study. The data and/or specimens will be labeled with a code that the research team can link to personal identifying information when acquired. The code sheet will be secured and kept separate from the dataset.

Non-English Speaking Subjects:

The Consent Short Form will be used for non-English speaking subjects and all UC Davis IRB procedures and policies will be followed.

Waiver or Alteration of the Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

NA

Subjects who are not yet adults (infants, children, teenagers):

NA

Cognitively Impaired Adults:

NA

Adults Unable to Consent:

NA

Adults Unable to Consent:

NA

30) Process to Document Consent in Writing

We will be following the "SOP: Written Documentation of Consent (HRP-091)" and have attached the form with submission. We have used the "TEMPLATE CONSENT DOCUMENT (HRP-502)"to create the consent document. We have created written consent forms for both patients and their caregivers.

31) Drugs or Devices: N/A

The deep brain stimulation device is a FDA-approved surgical implant that is normally stored in the Implant Storage Room in the Pavilion Main OR. This storage room is locked. Operating room staff that normally retrieve this device for DBS surgery have keycard access to this room, as do many of the administrative managers in the Pavilion Main OR. The person in charge of ordering and stocking this device for surgical implantation is Peter Tham, CNIII.

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