Scalar Closed-Loop STN / GPi DBS Based on Evoked and Spontaneous Potentials (Intraoperative Studies)

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Purpose of the Study

The purpose of this study is to measure neural activity during deep brain stimulation (DBS). There are two types of neural activity that we will record from DBS electrodes during this study: DBS local evoked potentials (DLEPs) and spontaneous, local field potentials (LFPs). We will measure the effects of varying stimulation parameters on both the neural activity and changes in motor symptoms -- bradykinesia and tremor -- in subjects with Parkinson's disease (PD). Correlating neural activity characteristics with changes in symptoms will improve our understanding of the mechanisms of action of DBS. This intraoperative study will specifically compare our ability to record neural activity using circuitry developed at Duke for this purpose [Kent et al, 2015] to a new, implanted pulse generator (IPG; RC+S) developed by Medtronic. These intraoperative studies will specifically test a preliminary version of the RC+S (that is not designed for implantation), and will lead to a clinical trial assessing the efficacy of the implantable RC+S IPG in PD patients once this device is available and approved for this trial.

Background and Significance

Deep brain stimulation (DBS) is a surgical intervention that is effective in treating movement disorders, particularly Parkinson's disease (PD). A battery-powered IPG, placed in the patient's chest, delivers electrical stimulation to a connected brain electrode typically implanted in the subthalamic nucleus (STN) or globus pallidus internus (GPi). Despite the clinical effectiveness of DBS, the underlying physiological mechanisms of action remain unclear and there is no capability for device self-adjustment or responsiveness to patient symptoms, limiting the full optimization of this treatment.

Stimulation parameters (amplitude, frequency, and pulse width) are programmed after surgery and at follow-up intervals, and the efficacy of DBS depends on finding parameters that reduce symptoms without causing side effects. However, there are over 42,000 available combinations of amplitude, frequency, and pulse width in the IPG, and few data describing the relationships between stimulation parameters and clinical outcomes. As a result, the selection of stimulation parameters is an ad hoc process, with associated difficulties of time, expense, and patient discomfort. Further, the patient is often deprived of the optimal benefits of stimulation until this time consuming process leads to efficacy.

Application of each DBS pulse results in activation of a population of neurons around the electrode. This evoked neuronal activity creates a signal -- the DBS local evoked field potential (DLEP) -- that can be recorded with two of the four contacts on either the clinical DBS electrode or a second electrode. Thus, this intraoperative recording approach does not require implantation of any electrical hardware. The magnitude and character of the DLEP response will reveal the type and spatial extent of neuronal element activation during stimulation, including between brain regions, such as between subthalamic nucleus (STN) and globus pallidus externa (GPe). Our previous work exploring the mechanisms of action of DBS revealed a very strong correlation between the number and type of activated neurons and clinical efficacy during variation in stimulation intensity [Kuncel et al, 2007; Kent et al, 2015]. Therefore, we expect a strong correlation between the recorded DLEP and the changes in symptoms during DBS. Spontaneous, local field potentials (LFPs) are also recorded using the same methods described above. LFPs are signals measured with electrode contacts that are continuously generated by ongoing neural activity, whereas DLEPs are short-duration signals evoked immediately following stimulation pulses. Together, DLEPs and LFPs are a potential biomarker for disease state and severity in PD, which we will

test initially intraoperatively and long-term using the RC+S IPG for scalar closed-loop control of the DBS parameters.

The shape and magnitude of DLEPs and LFP activity may also be sensitive to DBS electrode location, and this dependence suggests that they may assist with targeting brain structures during DBS implant surgery as well as post-operative selection of stimulation contacts and dynamic adjustment of stimulation parameters [Kent et al., 2015; Chen et al., 2006]. We therefore expect that DLEP and/or LFP characteristics will vary with the placement of DBS electrode relative to the brain regions targeted for stimulation.

Study Design and Procedures

We will measure DBS local evoked potentials (DLEPs) and/or local field potentials (LFPs) together with motor symptoms (tremor and/or bradykinesia) in response to deep brain stimulation (DBS). The study will be conducted in the operating room at Duke University Medical Center. Additional operating room costs will be covered by institutional resources at Duke. The study will be performed on subjects who are undergoing implantation of the DBS system during an awake, stereotactic procedure for PD.

The subject group will only include patients undergoing a DBS implant procedure for PD. The surgical procedure will proceed as needed for treatment of Parkinson's disease (PD), including implantation of the DBS electrode (one into STN or dual electrodes into STN and GPi/GPe) into the targeted regions of the brain. For this research, subjects will receive temporary (~45 min) percutaneous extensions to the DBS electrode(s) and DBS lead cannula after implantation. These temporary extensions will connect to both our Duke stimulation and recording system or the Medtronic RC+S test recording system, alternating as needed, to allow recording and direct comparison of neural DLEP responses and/or LFPs using the two different stimulation/recording systems. Details of the stimulation and recording system are provided in the Study Interventions section. After the study is completed, the second DBS electrode (if placed) and the temporary percutaneous extensions will be removed. Then, the ordinary clinical conduct of the procedure will continue for treatment of the patient’s movement disorder.

We will measure tremor and/or bradykinesia in persons with PD during DBS. Subjects will be familiarized with and able to practice the evaluation tasks before preparation for surgery. Further, they will be asked to discontinue use of dopaminergic and/or anti-tremor medications overnight prior to the study (as is the clinical routine for this procedure), to reduce variability of motor symptoms due to the time course of medications. We will conduct evaluations using unilateral stimulation, with the limb contralateral to the side of stimulation used for measurement of motor symptoms. Subjects may also be asked to rate any side effects that they experience on a 0 - 10 scale.

Contacts on the subject's DBS electrode will be used for stimulation and recording, with a second electrode in either STN or GPi/GPe used for recording. The four DBS contacts are designated as 0-1-2-3 in the ventral-dorsal direction. For monopolar stimulation, a single contact will be used for cathodic stimulation (1- or 2-) and a conductive pad will be placed on the subject's skin, outside of the sterile field, to serve as the return electrode. The recording contacts will be two other contacts on the DBS lead. For bipolar stimulation, DBS pulses will be applied between two electrode contacts, and the recording contacts will be the two remaining free contacts. The stimulus waveform will be a charge-balanced biphasic pulse, with charge restricted to values below the limit set by the manufacturer, 30 µC/cm2. Another conductive pad will be placed on the subject to serve as the recording reference. The

DBS lead cannula or a surgical retractor normally placed at the cranial incision site may also be used as the recording reference or return electrode.

In subjects with tremor-dominant PD, we will record both the tremor and DLEP and/or LFP responses from the DBS electrode(s). Several trials will be conducted with different stimulation amplitudes, frequencies (≤185 Hz), temporal patterns, and contact configurations. The stimulation amplitude will be less than that identified to be uncomfortable to the subject or that generates side effects, as determined by a neurologist and/or neurosurgeon during the initial testing phase following implantation. The different stimulation parameters will be delivered in randomized order, and the subject will be blinded to the parameters. Measurements will be made during 2-minute trials, in which stimulation will be off for the first minute of the trial, and on for the remaining minute. At 30 s into both the off (baseline) and on phases of the trial, tremor will be measured for 20 s. The neural activity will also be measured from the electrode during both the off and on phases. The total amount of time necessary for data collection will be about 45 minutes.

Tremor will be measured using an accelerometer taped to the back of the subject's hand, and with the wrist extended such that the hand is parallel to the forearm. The elbow may either be supported or unsupported, depending on which induces greater tremor (determined prior to any trials in each subject). Tremor as measured by an accelerometer correlates well with clinical tremor rating scales [Elble et al, 2006].

In subjects with Parkinson's disease who do not have dominant tremor symptoms, we will record both bradykinesia testing responses and DLEP and/or LFP potentials. Several trials will be conducted with different stimulation amplitudes, mean frequencies (≤185 Hz), temporal patterns, and contact configurations. The maximum amplitude delivered will be determined as described as above. The different stimulation parameters will be delivered in randomized order, and the subject will be blinded to the parameters. Measurements will be made in 10-minute trials, in which stimulation will be off for the first five minutes of the trial, and on for the remaining five minutes. At approximately 90, 210 and 250 s into both the off (baseline) and on phases of the trial, bradykinesia will be measured for 20 s. The neural activity will also be measured from the electrode during both the off and on phases of the trial. The total amount of time necessary for data collection will be about 45 minutes.

For bradykinesia measurements, the subject will be instructed to press alternately the right and left buttons of a computer mouse with the index and middle finger of their hand as rapidly and regularly as possible. Bradykinesia will be measured as the timing of alternating finger presses, a validated test of bradykinesia [Taylor-Tavares et al., 2005].

Before DBS surgery, the subject's baseline pathological motor symptoms may be assessed in the pre-operative setting, to familiarize the patient with the task ahead of the implant procedure. Tremor or bradykinesia will be measured using the previously-described accelerometer measurement or the mouse click task, respectively. This task will take about 5 minutes, and will be performed in the DBS-off condition. No sedation will be administered until after this has been completed.

Following DBS surgery, the subject’s pre-operative MRI and post-operative high-resolution CT scans may be used to determine the location of DBS electrode contacts within the brain. Placement of the electrode during DBS implant surgery will not be altered by the research study.

Study Interventions

The stimulation and recording system applies deep brain stimulation (DBS) and simultaneously measures the DBS local evoked potential (DLEP) and/or local field potential (LFP) responses from either the same or a second DBS electrode. Stimulation will be delivered through either an optically isolated stimulator (bp isolator, FHC Inc.) and pulses controlled by a high-speed digital-to-analog converter via MATLAB (Mathworks, Inc.), or the Medtronic RC+S test device. Both of these stimulation/recording devices are nonsterile and outside of the sterile field and will be connected to the DBS electrode using sterile connecting wires. The DBS lead cannula or a surgical retractor normally placed at the cranial incision site may be used as a return electrode. The locations used for the return electrode and recording reference will be recorded on the case report form.

For recording DLEP and/or LFP signals, the Duke system combines commercial amplifiers -- either SR560 low-noise voltage preamplifiers (Stanford Research Systems) in a custom serial configuration or a single g.USBamp amplifier (g.tec Medical Engineering) -- to limit the amplitude of the DBS stimulation artifact in the recording. Differential recordings are made from two DBS contacts, with each recording contact serving as an input to the preamplifier. A circuit employing solid-state relays and anti-parallel diodes is utilized at the inputs of the amplifiers to limit the size of the artifact signal at high amplification and prevent saturation of the recording amplifiers. The DBS lead cannula may be used as a recording reference. The Medtronic RC+S test system includes the full stimulation and recording circuitry embedded in the RC+S IPG/PC+S IPG but in a non-implantable form that can be directly connected to the DBS electrode through a sterile extension.

Study subjects may undergo standard of care imaging procedures required for their surgery, including pre-operative MRI and/or post-operative high-resolution CT scans. The research protocol will not modify these procedures, but the images collected may be used to determine the location of DBS electrode contacts in the brain.

The electrical safety of the study apparatus will be tested and certified annually for electrical safety.

Perioperative staff responsible for preparing subjects for surgery will be given a flyer that explains how perioperative patient care will be affected by requirements of the research study. This form will require all monitoring equipment (IV line, blood pressure cuff, pulse oximeter, etc.) to be placed contralateral to the limb used for measurement of motor symptoms. Additionally, instructions for sedation and intraoperative sterile drape setup will be listed. Contact information for the study coordinator, attending surgeon, and principal investigator will also be provided.

Selection of Subjects

It is anticipated that a total (maximum) of 32 individuals will be studied over four years. Subjects will be recruited from the Movement Disorders Programs at Duke University after having been referred for DBS surgery and have agreed to undergo the clinical procedure. Patients will only be asked about research participation after being scheduled for the procedure. They will participate on a volunteer basis with informed consent as approved by Duke University. Apart from Parkinson's disease (PD) these individuals will be in good health, as determined by their ability to undergo the DBS procedure. Inclusion criteria (separate from the criteria to undergo the DBS implant procedure for Parkinson’s disease) are that the patient is able to understand the study and consent form, and is interested in proceeding with research

during the invasive brain surgery to receive a DBS system for treatment of PD. Exclusion criteria are an inability to execute the motor tasks during the study and pregnancy. The age range will be 18 to 80. Since all patients will be undergoing an elective surgical procedure for a chronic movement disorder then the possibility of pregnancy is determined during standard pre-operative screening, and if the patient is determined to be pregnant (using a pregnancy test obtained along with the other needed blood tests per standard of care) then the elective procedure will be canceled and delayed until after the pregnancy is concluded and the patient has recovered. This is standard practice for any elective surgical procedure since there is a possibility of unintended harm with anesthesia to the pregnancy.

Subject Recruitment and Compensation

We expect to enroll a total of 32 subjects maximum in this intraoperative study at Duke University. Subjects will be recruited and enrolled from individuals who have Parkinson's disease (PD) and who are scheduled to already undergo the planned deep brain electrode placement for treatment of their movement disorder. The surgical operation and research study will occur at Duke University Medical Center. Initial contact concerning the research study will be made by the patient's neurosurgeon (Dr. Dennis Turner or Dr. Shivanand (Nandan) Lad), who will be performing the stereotactic surgery (either frame-based or frameless), during the patient's pre-operative appointment. Patients receiving either type of electrode implantation will be recruited for the study. Duke patients that cannot be contacted in the Duke Clinic prior to surgery will be screened by the study staff using a telephone script. Consent will then be performed by Dr. Turner, Dr. Lad, or the study staff.

If the subject agrees to be enrolled, the Study Coordinator will contact the PI or his staff to indicate the patient's enrollment in the research during the planned procedure. If the subject does not sign the informed consent or does not qualify for the study, any recorded information will be destroyed.

Subject selection will not discriminate on the basis of gender, race, or ethnicity, but the eligible population is limited, since only patients already scheduled for DBS procedures for their Parkinson's disease will be candidates. The incidence of Parkinson's disease (PD) is higher in men (~65%) than women (~35%), and so we expect to enroll more male PD subjects than female subjects. The incidence of patients who undergo deep brain stimulation (DBS) for PD and are minorities is low (~5%), so we expect to enroll fewer subjects that are minorities than subjects who are not minorities. The percentage of the population undergoing DBS for PD and are children is very small, and so we do not expect to enroll any children. The age range will be 18 to 80.

Subjects will be identified by assignment of an identification code consisting of the year the study was conducted and the order of subject enrollment.

Subjects will be compensated $50 for their participation in this study. There will be no costs to the subject as a result of participation in the study.

Consent Process

The consent process will typically be conducted by the Study Coordinator, but may also be conducted by the PI and Collaborators included in the Key Personnel. Dr. Grill will not obtain consent due to a conflict of interest.

The consent process will occur at the Duke Clinic, in a preoperative holding consult room, or in the personal offices of the study staff. The consent process will take approximately 10 minutes, but will continue until all participant questions are answered. During the consenting process, a member of the study staff will meet with the participant to answer any questions. Participants are then given the personal contact information of the study's PI, neurologists, and neurosurgeons, as well as the Duke University Institutional Review Board. Each subject will be allowed as much time as desired to make their decision.

All potential subjects will be informed that participation in the research study is completely optional and that declining to participate will not affect their medical care. Study related risks will be conveyed through a review of the consent form led by a member of the study staff.

Since the study procedures require communication between the subject and investigators, subjects that do not speak English will be excluded from the study.

Subjects will be competent to give consent as they have already consented to undergo the DBS procedure. Competency will be determined by the research team.

Risk / Benefit Analysis

Subjects who participate in this clinical study will derive no direct benefits to themselves. However, the data gathered in this study will be used to understand the mechanisms of action of deep brain stimulation (DBS) and provide a means for the rational selection of stimulation parameters based on recorded neural activity.

This proposed clinical research study has certain risks, though these are similar to the risks associated with DBS electrode implantation surgery or replacement of the implantable pulse generator (IPG) and clinical selection of stimulation parameters (routinely performed after DBS implantation). In some patients (and in the eventual clinical trial with the implantable RC+S IPG) we will place dual STN and GPi/GPe DBS electrodes. This is similar to the clinical practice of replacing the DBS electrode clinically (up to 5 times in different brain regions) as needed for optimization of the electrode stimulation results and the risks are within the ordinary risks of the DBS surgical procedure.

There are risks associated with having subjects refrain from taking their dopaminergic and/or anti-tremor medication overnight prior to the study, but this is the clinical standard of practice implemented for new DBS implants in PD patients. This will create risks associated with the symptoms a subject experiences in the unmedicated state, and will be reviewed with the subject at the time of consent.

There is a risk of infection at the incision site where the extension wire is externalized for connection to our stimulating and recording system. To minimize the risk of infection, the surgery to place the percutaneous extension is done under sterile conditions and the incision site will remain in a sterile field through the clinical study.

There is a slight risk of inadvertent electrical shock due to connection to the external stimulating and recording equipment required to conduct the study. All electrical equipment will undergo routine and periodic biomedical safety checks. Further, all electromechanical equipment used during the clinical study will be tested and certified annually for electrical safety. Surgical retractors and cannulae used to

deliver electrical stimulation will be protected against corrosion, and will therefore not increase electrical safety risks.

There is a risk of subject discomfort as stimulation may cause transient side effects, reduce the benefit of DBS, or even transiently worsen symptoms. Subjects may experience slight discomfort due to side effects experienced with certain stimulation parameters. Side effects include muscle contractions, dysarthria, ocular deviations, tremor, and paresthesias. However, side effects are reversible and will cease once the stimulation is turned off. In addition, some stimulation parameters may cause symptoms to worsen, but these symptoms will return to pre-stimulation levels soon after stimulation is turned off. Subjects will be asked to report any sensations they feel as a result of stimulation, and will be observed for any effects of the stimulation on tremor or bradykinesia.

There is a slight risk of tissue damage resulting from the electrode-tissue interaction during stimulation. To minimize this risk, we will apply charge-balanced biphasic pulses. This stimulation waveform is similar to that used in the clinically implanted stimulator (Medtronic), and charge densities will be below the manufacturer's established limit of 30 μC/cm2. Thus, the risk of tissue damage will be similar to the risks associated with everyday use of the implanted DBS system.

No general anesthesia will be given to subjects during surgery, and the procedure will be performed under local anesthesia to allow subjects to perform the tasks required in this study. Subjects will receive monitored anesthesia care (MAC), in which sedation will be administered as needed, such that subjects are still responsive and pathological motor symptoms (tremor or bradykinesia) are present.

There are risks associated with undergoing brain imaging procedures (MRI and/or CT) required for conduct of DBS surgeries and post-operative follow-up. The research study does not modify these procedures or their associated risks.

If an individual chooses not to participate in the study, he or she will still have surgery to implant the DBS electrode.

Data Analysis and Statistical Considerations

The data set will consist of recordings of neural and/or LFP recordings, and either mouse click timing data for measurement of bradykinesia in Parkinson's disease subjects or tremor accelerometry data for patients with Parkinson’s disease. The DLEP recordings will be serially averaged with stimulus-triggering to remove random noise while preserving the evoked response. The signal-to-noise ratios of DLEP recordings will be compared across data sets to determine which combination of stimulation and recording sites maximize recording quality. We will quantify performance on the mouse click timing task by the delay between key presses and the time each key is held. Tremor will be quantified by calculating the total power within a window of the power spectrum of the time series of the tremor. We will perform ANOVA and post-hoc statistical analysis, in which the amplitude, frequency, and contact configuration used for stimulation will be the independent variables, and with dependent variables describing bradykinesia, tremor, and DLEP characteristics. We will also calculate correlation coefficients between tremor or bradykinesia and DLEP characteristics. Data and statistical analyses will be conducted by the study team, including the study statistician, Donna Niedzwiecki (Associate Professor of Biostatistics and Bioinformatics).

Additionally, clinical study staff may use pre- and post-operative brain imaging to determine the location of implanted DBS electrode contacts. The only data generated from this analysis will be a determination of the location of the contacts used to record neural activity (DLEPs and/or LFPs) relative to the brain region targeted for stimulation. Other study staff will analyze DLEP and/or LFP recordings obtained during surgery to generate a prediction of recording contact location prior to imaging analysis for each subject, and clinical study staff will be blinded to these predictions during imaging analysis.

Subjects will be included in data analysis if DBS is clinically effective at reducing motor symptoms for particular stimulation parameters, and DLEP and/or LFP data are observed during at least one trial.

Dr. Dennis Turner and Dr. Shivanand (Nandan) Lad conduct a total of 4-6 new DBS implants for PD per month. We have recruited approximately 1 subject per month at Duke over the past 18 months to participate in other intraoperative studies. Thus, we expect to recruit a maximum of 32 subjects during the course of this study at Duke University.

Data and Safety Monitoring

Safety concerns in this study include risks of worsening motor symptoms experienced by subjects in the non-medicated state, hemorrhage or infection at the incision site where the extension wire is externalized, inadvertent electrical shock by the stimulation and recording system, DBS-induced side effects or worsening of symptoms, and tissue damage at the electrode-tissue interface. Research subjects will be monitored by their physician during the study and in post-operative follow-up appointments. Further, subjects' medical records will be reviewed by study staff to monitor for study-related complications. The PI will review adverse events as needed to determine if there are any unexpected risks or if events are occurring at a higher than expected frequency. Any complication will be reported to the Duke University Medical Center Institutional Review Boards as a safety adverse event.