Human Behaviors Related to the Expectation of Pain

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Physiological Studies in Healthy Subjects, Chronic Pain Patients and in Patients undergoing Neurosurgical Procedures of Human Forebrain Mechanisms mediating Somatic Sensation, Motor Control and Neurological Disorders.

1. Abstract

Many questions related to human somatic sensation and motor control cannot be assessed by research in non-human primates. Our preliminary studies point to the normal and pathologic mechanisms of sensory and motor function. We now propose, in patients undergoing stereotactic surgery for movement disorders and pain, to record the activity of single neurons, multiple neurons (local field potentials - LFP), electrocorticography (ECoG), and EEG.

The first hypothesis of this proposal is that thalamus, ventral striatum (deep structures), and thalamo-cortical ensembles are involved in signaling acute pain, and that abnormal activity in these structures is responsible for many of the symptoms found in neuropathic pain. This activity may also be related to pain-related attention and learning tasks.

The first hypothesis of this proposal will be approached by recording thalamo-cortical activity in response to painful and nonpainful peripheral stimuli, during awake stereotactic procedures for movement disorders and pain. We will also study the effect of attention, cognitive and learning tasks upon the recorded and behavioral response to painful and nonpainful somatic stimuli. The recording data will be analyzed for evidence of activation, evoked potentials, and functional connectivity between different forebrain structures. These results will be interpreted as evidence of networks subserving both pain and psychological processes influencing pain. Significance of the responses to these stimuli will also be assessed by the response to stimulation in the same structures. These studies will provide important direct evidence of the networks and patterns of forebrain activity associated with acute and chronic pain, and will complement the results of animal studies.

Attempts to understand many movement disorders such as Parkinson's disease (PD), dystonia, or essential tremor are limited by the lack of convincing primate models of these conditions. In this proposal, our second hypothesis is that many hyperkinetic disorders are the result of abnormal processes which distort signals between the basal ganglia and the thalamus (deep structures) and the cortex. Interpretation of the results will focus upon networks as revealed by activation and functional connectivity between these forebrain structures. Further evidence of these networks will be assessed by the effects of electrical stimulation carried out during surgery for treatment of movement disorders and pain, including subcortical stimulation, direct motor cortex stimulation with electrical pulses (direct pulsed cortical stimulation), and scalp-applied transcranial direct current stimulation (tDCS).

Recent demonstrations that the mechanisms of action of deep brain stimulation take place partly in motor cortex (Gradinaru V et al., 2009, Payoux P et al., 2004) and the fact that cortical stimulation can modulate neural activity at the basal ganglia level (Strafella AP et al., 2004 , Q Li et

al., 2012), imply that noninvasive brain stimulation and direct pulsed cortical stimulation could be used to demonstration cortical and subcortical network functional connectivity. Additional uses include the possibility of integrating cortical and subcortical brain stimulation (de Hemptinne et al., 2013). These studies have the potential to clarify the etiology of movement disorders and to map avenues for their treatment.

The speech production system which is disrupted in Parkinson's Disease and other movement disorders, might provide a unique possibility for investigating the neurophysiology of motor control in the human brain. Hypophonia and hypokinetic dysarthria are prevalent in patients with Parkinson's disease (PD). Deep brain stimulation of the subthalamic nucleus does not result in consistent improvement in speech and can negatively impact language function. These observations indicate an important role for the basal ganglia in the speech production system. However, due to the limited knowledge about the role of the basal ganglia in speech production and control, the neurophysiology of the speech related symptoms of the Parkinson's disease are poorly understood and the clinical treatments are very limited. Investigation of the structural organization and function of basal ganglia in the speech motor system will provide significant opportunities for understanding the neurophysiology of the basal ganglia and the pathophysiology of PD and might facilitate the pathway for more efficient treatment of PD symptoms, particularly speech related disorders.

2. Objectives

Objective I:

Objective I is to assess the hypotheses that the cortex and deep nuclei of the brain (e.g. thalamus, ventral striatum) are involved in signaling acute pain, and that abnormalities of this region are responsible for many of the symptoms found in neuropathic pain.

The primary outcome is to assess the effect of painful and nonpainful somatic stimuli upon ongoing and evoked spike, local field potential, and EEG activity recorded from cortical and deep nuclei in response to painful stimuli. Non-invasive EEG will be used in healthy subjects and chronic pain patients. Analysis of these results for functional connectivity will allow us to characterize networks subserving pain processing and their disruption or augmentation in chronic pain.

The secondary outcome is to determine the effect of attention, along with cognitive and learning tasks involving somatic stimuli upon ongoing and evoked activity, local field potential and EEG activity recorded from cortical and deep nuclei. Non-invasive EEG will be used in healthy subjects and chronic pain patients. Analysis of these results for functional connectivity will allow us to characterize networks subserving pain related cognitive processes and their disruption or augmentation in chronic pain.

Objective II:

Objective II is to test the hypothesis that actual and imagined movements and movement disorders are the result of ongoing and movement related activity of single neurons, local field potentials and EEG activity recorded from cortical structures and deep nuclei (basal ganglia and thalamus).

The primary outcome is to establish the effect of ongoing and evoked spike, local field potential and EEG activity recorded from cortical and deep nuclei upon movement disorders such as tremor, Parkinson's disease, dystonia and dyskinesia. Analysis of these results for functional connectivity will allow us to characterize networks involved in movement disorders.

Secondary outcomes will include determination of the influence of actual and imagined movements upon ongoing and movement related spike, local field potential, and EEG activity recorded from cortical and deep nuclei.

We also will investigate the effects of direct cortical stimulation with electrical pulses on the motor cortex and other cortices by measuring electrophysiological signals, and will evaluate stimulation effects on disease symptoms.

Additionally, we will determine whether scalp-applied tDCS over the motor cortex also results in modulating single neuron spiking activities or changes in cortical phase –amplitude coupling.. This will be helpful in providing more understanding of the mechanisms of action of DBS and tDCS, and may indicate the usefulness of integrating the two different types of brain stimulation in the future.

Other secondary outcomes will determine whether motor learning or adaptation are the result of ongoing and movement related spike, local field potential and EEG activity recorded from cortical and deep nuclei.

Other secondary outcomes will also include the determination of the mechanisms of speech characteristics as coded in the basal ganglia-thalamocortical network during production and auditory processing of speech based on specific task related spike, local field potential, and EEG activity recorded from cortical and deep nuclei.

3. Background

This application proposes to measure CNS activity in healthy subjects, patients with chronic pain from knee osteoarthritis, patients with chronic pain from chronic widespread pain or fibromyalgia, and in patients undergoing micro- and macro electrode mapping during stereotactic surgery for the treatment of movement disorders or pain. Objective I will involve some form of sensory stimulation (e.g. somatic, visual, auditory, etc.) during recordings (EEG, local field potentials - LFP) from cortex, deep structures such as thalamus, and basal ganglia (ventral striatum, pallidum etc). For example, patients might rate a somatic stimulus while evoked potentials are measured to provide evidence that electrical events in the brain are related to psychophysical ratings of sensation. This result might be interpreted as evidence that the electrode site is involved in processing of somatic sensation.

Objective II will undertake studies of actual movement, imagined movement or movement disorders. During these types of movement recordings will be carried out through the same structures

as described above. Studies of actual and or imagined movement will be carried out by asking patients to carry out imagined movements or actual movements. Disordered movements will be studied by observing spontaneous movements or asking the subject to carry out maneuvers which provoke these movements. These maneuvers will include distraction tasks like mental arithmetic which provokes parkinsonian tremor. We now propose to analyze activation and functional connectivity between deep brain and cortical structures.

Activation by sensory stimuli or movements will be determined by examining changes in neuronal firing rates, ongoing EEG frequency and spectral power as recorded from the structures named above. Cortical or deep structures jointly processing sensory signals will be identified by calculation of correlation, coherence and causality between the EEGs or LFPs recorded from these structures in response to sensory stimuli. Coherence is a measure of synchrony (and functional connections) between signals from different electrodes, and causality is a measure of the extent to which signals at one electrode are causal of those at another electrode (Glaser and Ruchkin, 1976;Granger, 1969;Liu et al., 2011c). All regulatory aspects of this study will be the responsibility of the study coordinator (Ms P Lowe) and the PI.

Transcranial direct current stimulation (tDCS) is a commonly used non-invasive form of brain stimulation for studying motor functions in health and disease. It involves the attachment of surface electrodes to the scalp through which very small electric currents (1 or 2mA) are applied via a current regulated device that is powered by a battery. The currents do not produce any sensation. Importantly, when the electrode is placed over the region of the motor cortex, the small currents appear to affect the excitability of the neural tissue, as measured by the size of the motor evoked potential (MEP) induced by a single pulse of transcranial magnetic stimulation and recorded in hand muscles. tDCS will be used intraoperatively to demonstrate the functional connectivity between primary motor cortex and the subthalamic nucleus. We wish to characterize the mechanisms of action of tDCS as a noninvasive cortical stimulation for motor symptom control in PD patients (Benninger et al., 2010).

Recently, research into the impact of tDCS in Parkinson's patients has been growing. Early studies indicated motor function improvement as a result of the anodal stimulation of M1 (Fregni et al., 2006). Other investigations into the effects of tDCS on motor symptoms have demonstrated improvements in gait and bradykinesia (Benninger et al., 2010) and improvements in tapping and pointing movements (Grüner et al., 2010). More recent motor symptom studies have shown significant improvements in gait with reductions in freezing-of-gait episodes (Valentino et al., 2014; Von Papen et al., 2014) as well as increases in trunk velocity and average sway (Kaski et al., 2014). Additionally, tDCS prompted prolonged improvements in tests to measure executive function (Doruk et al.,2014) and time up and go task performance (Manenti, R. et al. 2014). tDCS will be used intraoperatively to demonstrate the functional connectivity between primary motor cortex and the subthalamic nucleus. We wish to characterize the mechanisms of action of tDCS as a noninvasive cortical stimulation for motor symptom control in PD patients.

Synchronous, rhythmic changes in the membrane polarization of neurons form oscillations in local field potentials. It is hypothesized that high-frequency brain activity reflects local cortical information processing, and low-frequency brain rhythms project information flow across larger

cortical networks (Zheng and Colgin, 2015). This provides for a complex form of information transmission due to interactions between oscillations at different frequency bands, which can be displayed using cross-frequency coupling (CFC) metrics. Phase-amplitude coupling (PAC) is one of the most common representations of the CFC. PAC reflects the coupling of the phase of oscillations in a specific frequency band to the amplitude of oscillations in another frequency band. In a normal brain, multi-item working memory is accompanied by PAC in the hippocampus, and changes in PAC have been associated with diseases such as schizophrenia (Allen et al., 2011), Alzheimer disease, (Goutagny et al., 2013) and Parkinson's disease (de Hemptinne et al., 2013). The results of recent studies of Parkinson's patients during deep brain stimulation lead placement surgery demonstrate that the mechanisms of action of deep brain stimulation in movement disorders in general and Parkinson's disease specifically might be related to the modulation of PAC in motor cortex (de Hemptinne et al., 2015). In this study, we also wish to investigate the effects of direct cortical pulsed stimulation over motor cortex on the PAC signal and its correlation with the motor symptoms of the disease. This type of stimulation might provide a unique opportunity to investigate the mechanisms of action of cortical stimulation in Parkinson's disease and other movement disorders, along with possible therapeutic effects.

There is evidence that the basal ganglia may play some role in language. For example, recent studies of ischemic lesions and Parkinson's disease suggest that the basal ganglia play a role in the controlled processes supporting lexical–semantic processing (Copland et al. 2000a , b; Copland 2003). In that regard, speech irregularity such as soft speech (hypophonia) and reduced vocal loudness, monopitch, disruptions of voice quality, and abnormally fast rate of speech (hypokinetic dysarthria) are common speech related symptoms in Parkinson's disease and other movement disorders (Canter, 1963; Carter 1965; Ho et al. 1998). Such interruptions most commonly take place in the basal ganglia, where insufficiency of the level of dopamine causes slowed (bradykinesia) or failure to respond (akinesia) in speech production organs. The lips and tongue incompletely shape the appropriate formations for making the sounds of words; the vocal cords do not adjust for the quality of sound the words require; breathing may be inadequate to produce the volume of air necessary to produce adequate sound through the vocal cords (Coates et al. 1997; Pinto et al. 2004). Although deep brain stimulation of the subthalamic nucleus (STN) improves most of the motor symptoms in eligible PD patients but often does not result in consistent improvements in speech and in some cases may negatively impact language function (Lorinda et al. 2011). Here, we intend to use the unique opportunity of DBS lead placement surgery to provide access to the deep structures in the human brain and investigate the functional role of the basal ganglia in the speech production system.

Objective I: Sensory Processes.

Our preliminary studies have demonstrated the presence of human thalamic and cortical pain pathways and networks. Thalamic neurons and cortical EEG or local field potentials demonstrate that these structures respond either differentially or selectively to thermal and painful stimuli. Cortical structures also show electrical activation or directed functional connectivity with each other during painful stimuli. Attention and learning tasks can have an effect upon activation or directed functional connectivity within and between cortical structures.

The activity of these deep brain and cortical structures may be the result of connectivity between them. We now propose to examine joint activation of, and functional connectivity between, these deep brain and cortical structures. We also plan to complete studies of the responses of these structures to somatic stimuli, activation and synchrony. Therefore, these studies seek to demonstrate the presence of pathways and networks which produce transmission of somatic signals through the thalamus. These networks might be disrupted by stimulation of the brain electrically or through transcranial magnetic stimulation (TMS).

Stress related to pain or performance of tasks, perhaps including the CPTpain, can induce increases in cortisol levels (Zimmer et al., 2003; Hansen et al., 2008). Individuals with high chronic daily stress levels have greater levels of baseline cortisol and possibly circulating proinflammatory markers (e.g. IL-1β and IL-6); they are also more likely to develop persistent pain syndromes (Vachon-Presseau et al., 2013a, 2013b; Potier et al., 2017; Siegrist and Li, 2017).

We also aim to explore the influence of single nucleotide polymorphisms (SNPs) upon sustained attention to pain and the magnitude of the vigilance decrement. We will first evaluate the effects of common SNPs known to influence pain perception, fear of pain, error processing during performance of a cognitive tasks (Witte AV and Floel A 2012; Bonenberger, et al 2015; Gurvich C and Russell SL 2015; Forsberg JT, et al 2018). Pain related SNPs will also be examined including: catechol-O-methyltransferase (COMT) Val158Met, the serotonin transporter promoter long or short tail mutation (5-HTTLPR), and mu opioid receptor gene (OPRM1) Asn40Asp. These predictions will be carried out on baseline genotype measurements and used for DNA extraction and analysis.

Objective II: Motor Control:

Preliminary data in patients with movement disorders have demonstrated that activity in deep and cortical structures is related to the disordered movement. This includes studies of tremor, dystonia, dyskinesias, and hemiballismus. Preliminary data also suggest that dyskinesias, such as dystonia, demonstrate that inhibition related burst firing is correlated with changes in pallidal and subthalamic activity. All these data suggest that a decrease in inhibitory input from the pallidum to the thalamus and then to the cortex may explain dystonia and other hyperkinetic disorders. The proposed studies will examine movement related activation of, and functional connectivity between, these deep brain and cortical structures.

In studies of imagined movement, patients will be asked to carry out imagined movements or actual movements. Preliminary studies have demonstrated that activity in deep nuclei is related to imagined movements or phantom movements in an amputee. We now propose to examine joint activation of, and functional connectivity between, these deep brain and cortical structures.

Motor learning or adaptation will be carried out during planar arm movements which are perturbed by of forces which will change the trajectory of the movement. Subjects will learn to adapt so as to compensate for the perturbation. For these studies, as

in the past, we will employ a robot, which is a sophisticated device for measuring and perturbing upper extremity movement.

An approach that has been attempted recently for PD symptom control is transcranial direct current stimulation (tDCS). tDCS is a non-invasive procedure in which direct current (typically 1-2mA) is passed through anode and cathode electrodes that are placed on the head and localized using MRI, transcranial magnetic stimulation (TMS), or EEG. tDCS was first used by Fregni et al. on PD patients. They examined patients in the moderate stage who were off medication for 12 hours and found that application of anodal tDCS over the left primary motor cortex (M1) produced 20% improvement of clinical motor scores (as compared to sham stimulation). In this proposal, we will investigate the effects of tDCS on neuronal activity of the deep nuclear structures and also changes in phase –amplitude coupling at the cortical level (de Hemptinne et al., 2015) to seek possible explanations for the mechanism of action of DC stimulation.

Tonic pulsed motor cortex stimulation was introduced in early 1990 for the relief of chronic facial pain (Tsubokawa et al., 1991a, b) and recently, its use has been extended to exploration in patients with movement disorders. There is some evidence that direct cortical stimulation of the motor cortex through strip electrode contacts may relieve the motor symptoms of patients with PD (Canavero et al., 2002, 2003; Pagni et al., 2005, 2005). It may also provide some benefit for patients with PD during concurrent STN-DBS after chronic implantation and in long-term follow-up (Cioni, 2007, Meglio and Cioni, 2009). Motor cortex stimulation is highly influenced by DBS technology and in some studies uses a similar pulse generator. The stimulation pulse trains are similar to DBS systems, with similar adjustable parameters (Canavero et al. 2002, 2003; Cilia et al. 2007, 2008; Fasano et al. 2008; Gutierrez et al. 2009; Pagni et al. 2005; Strafella et al. 2007; Tani et al. 2007).

In order to investigate the neurophysiological role of the basal ganglia in speech production and control, subjects will perform speech production tasks intraoperatively. For each recording site, this will generate the data needed to characterize the scale and level of encoding and gain effects within single neurons, their surrounding local field potential (LFP), and their synchrony with sensorimotor cortex electrocorticography (ECoG).

4. Study Procedures

Study Population:

Subjects include patients with a neurologic disease such as movement disorders (Parkinson's disease, tremor, dystonia) and chronic pain which may be treated by awake stereotactic procedures. These subjects may be studied during the operation, in both intra-operative and extra-operative settings. In addition, healthy subjects will be studied by the extra-operative setting before or after surgery. In addition healthy subjects, subjects with chronic pain from knee osteoarthritis and subjects with chronic pain from chronic widespread pain or fibromyalgia, or chronic pain as a comorbidity with PTSD will be studied in the Lenz Functional Neuroscience lab.

Recruitment:

Patient Populations**:** Patients will be recruited from new, prior, and current patients of the PI in the Johns Hopkins Outpatient Center or through posted advertisements. Patients attending surgeries will be consented for surgery at the visit before the preoperative visit. The research protocol will be discussed at the preoperative visit.

Chronic Pain Patients: Knee OA patients will primarily be referred to the study from a study at Hopkins Bayview (Co-I: Claudia Campbell), while patients with PTSD and comorbid chronic pain will be referred from the Hopkins Anxiety disorder clinic (Co-I Joe Bienvenu) the Hopkins Followup Clinic for the Medical ICU (CoI, Ann Parker). They will call the study team and the study team will describe the study, answer questions, screen the patient and schedule a time for them to come in to the lab to obtain consent if they elect to proceed. All chronic pain patient groups will be recruited from pain clinics in the greater Baltimore area, including those at Johns Hopkins and University of Maryland, by flyers and brochures. Flyers and brochures will also be given to patient advocacy and support groups.

Healthy Participants:

Healthy participants will be recruited for psychophysical and EEG studies and will include spouses and/or other relatives of patients involved in these studies; these participants will be recruited in the Johns Hopkins Outpatient Center. Healthy participants may also be recruited from employees and students at the Johns Hopkins Medical Institutions and University, East Baltimore Campus. Subjects will be recruited in the Johns Hopkins Hospital. Employees and students will be recruited by posting IRB-approved flyers. The confidentiality of the subject's data will be maintained by strict adherence to the requirements for Data confidentiality. Employees and students who report directly to the PI may be recruited for these studies, but will only participate in the portions of the study involving minimal risk.

Consenting:

Patient Populations Undergoing Surgery: Written consent for operative research testing will be taken in JHOC by a study team member other than the PI at a preoperative visit after the patient has decided to have surgery and has signed the operative consent form. Therefore, the operative consent will be distinct from the research consent by differences in timing, and personnel. Extra-operative research testing will be carried out after the preoperative visit with the patient. Participants with a language or hearing impairment and non-English speakers will be excluded.

Healthy subjects **OR** Chronic Pain Patients **OR** Patients not undergoing surgery **OR** Patients who have already had surgery: For new, current or prior patients of the PI not having surgery, consent will be taken at a regular clinical visit with the PI. If the patient asks to take the consent home to review, then another visit may be scheduled for the consenting, or it be done on the day the research procedures are performed, prior to these procedures.

Consenting Procedures: Issues of privacy will be discussed when the research consent is taken, by explanation to the section of the consent dealing with privacy. The PI will be responsible for the consenting process. Confidentiality of the consenting process will be assured by taking consent during a private interview between the subject and the individual obtaining the consent, as stated

above: 1. Thirty minutes will be allotted to obtain consent. To assess the patient's understanding of the study, the patient will answer questions on the protocol regarding the inclusion criteria and the nature of the research testing, and risks. Participants may receive the consent form in advance. To assess the subject's understanding of the protocol, the subject will answer questions regarding the inclusion criteria and the nature of the research testing, including risks. Participants may receive the consent form in advance. Participants with a language or hearing impairment and non-English speakers will be excluded.

Timeline/Timing of Procedures Participants:

All the testing procedures will be carried out in both intra- and extra-operative sessions; these procedures are described below in the section title '*Research Testing Procedures for both -- and Extra-operative Sessions'*. Healthy controls will be studied during extra-operative session, i.e. outside the operating room.

Patients who have chosen to have surgery may participate in up to three testing sessions. These testing sessions may include a session performed during the surgery; in the operating room (intra-operative session). Some patients will undergo one session prior to surgery, and/or another session after the surgery; these studies will be performed outside the operating room (extra-operative session).

Physiological monitoring of the central nervous system (CNS) will be carried out during both intra- or extra-operative sessions. CNS monitoring in the intraoperative sessions will include recordings of single neuron activity, local field potentials from microelectrode and surface electrodes, and the EEG. CNS monitoring in the extra-operative sessions will include EEG alone. Any intra- or extraoperative session may include monitoring through EKG electrodes, EMG electrodes, accelerometers, eye position sensors, and skin conductance monitors.

Surgical Standard of Care Procedures:

The target for the procedure is first estimated radiologically and then confirmed by recording physiological signals in the brain. As a part of the radiologic localization, the stereotactic frame is applied and the location of the lesion or implant site for the stimulator is determined by imaging in either the magnetic resonance imaging (MRI) or the computerized tomography (CT) suite. Physiological confirmation of the optimal target site is determined during the procedure in the operating room. Placement of the electrode in the brain is carried out through a scalp incision and a dime sized hole in the skull. The radiologic prediction of the target is then confirmed using Standard physiological recording includes recordings of electroencephalography (EEG), field potentials and neuronal action potentials, as well as electromyography (EMG), and accelerometry. The surgical procedures target the Ventral intermediate nucleus of the Thalamus (Vim), the Subthalamic nucleus, and the Globus Pallidus in patients being treated for tremor, Parkinson's disease, and dystonia, respectively.

The procedure is completed by implanting a stimulator at the target which has been estimated radiologically and confirmed electrophysiologically. The standard physiological procedure involves

different maneuvers to characterize the neuronal activity including: a detailed sensory examination, performance of different voluntary movements (making a fist, pointing with the arm unrestrained, etc.), and performance of simple behavioral tests. Sensory and motor activity will be assessed by standard techniques including recordings from EMG and EEG electrodes, and accelerometers. Electrical stimulation of the brain is carried out at 1.5 milli-amp currents to evoke somatic, visual and auditory sensations, and to influence the disordered movements.

For implanting the ECoG strip, the preoperative MRI study will be used to plan the surgical target and trajectory. We will identify a point on the primary motor cortex (M1), 3 cm from the midline, based on anatomical identification of the central sulcus. The goal is to target the arm-related area of M1, slightly medial to the 'hand knob' (Yousry et al., 1997), in the same parasagittal plane as the typical entry site for placement of the subthalamic nucleus or thalamic deep brain stimulator electrodes. The location on the scalp will have a radio-opaque marker stereotactically placed on it. After drilling the frontal burr holes and opening the dura mater an eight-contact subdural electrocorticography strip (2.3 mm contacts, 1 cm spacing) will be placed on the brain surface and directed posteriorly in a parasagittal plane to provide contacts covering M1 and the primary sensory cortex (S1). In some cases, one subdural strip may be placed through both burr holes. The location of the burr holes will be determined by the selection of the safest entry point for the intended deep brain stimulator trajectory with no additional skull or scalp exposure needed for electrocorticography strip placement. The burr hole will then be sealed with a fibrin sealant after placement of the electrocorticography strip (and guide tube for microelectrode recording/deep brain stimulator lead placement).

Research Testing Procedures for both Intra- and Extra-operative Sessions:

The section below includes research tests which may be used during intra- or extra-operative testing in patients with movement disorders or pain, and in extra-operative testing in healthy subjects. The tests, or combinations of tests, listed below in this section, and in the section on Risks, are numbered using the same system as is used in the Consent.

Physiological monitoring may be carried out in any of these situations. The intra-operative recordings are carried out at sites in the brain to localize function for the operative procedure. During the research tests below, somatic sensory and motor activity will be assessed during recordings which employ techniques to monitor CNS and peripheral nervous system activity (see above section *Timeline/Timing of Procedures*).

Objective I: Sensory Processes

In these studies the patient is presented with a sensory stimulus (pain, visual, auditory, tactile) and the response is recorded. In most cases the sensory stimulus will be applied during a cognitive tasks engaging attention or learning. All experimental protocols and variables will be under computer control and will be carried out in healthy subjects or patients undergoing functional stereotactic procedures for movement disorders or pain.

The intra-operative studies will be carried out over multiple sessions; each session will include recordings from a single neuron. In many of these sessions, painful or nonpainful somatic stimuli, and other stimuli will be presented in a single train. The painful somatic stimulus will be a cutaneous laser stimulus (Themis, Starmed Tec, Starnberg, Germany) and the non-painful stimulus will be a cutaneous electrical stimulus (DS7A, Digitimer, Hertfordshire, UK). The length of the sessions will be less than one hour and twenty minutes in total.

Analysis of the response to these stimuli will include source modeling, and is carried out to estimate the location of the cortical generator for the evoked potential, and activation resulting from that stimulus. Subsequent studies will examine sites activated in a coherent fashion during the processing of the sensory stimulus. Analysis of single neuron and LFP recordings will look for evidence of desynchronization, coherence and directed functional connectivity between different structures. The results will be interpreted as evidence of connectivity within sensory networks. All experimental protocols and variables will be under computer control.

During the testing sessions, we will also measure the salivary cortisol levels. Cortisol levels are responsive to acute stress and acute tonic pain (Zimmer et al., 2003; Dedovic et al., 2009). Subjects will be informed to not engage in moderate exercise or consume food or drink two hours before the testing sessions (Hansen et al., 2008).

To determine the effect of the behavioral protocols on the cortisol response to stress, we will collect saliva before, immediately after, and 30 minutes after completion of the task (Zimmer et al., 2003). Saliva samples will be expressed from the salivettes using syringes into cryovials. Further, blood samples will be draw before and after the CPTpain vigilance protocol by Lenz lab laboratory staff who have completed online training and an in-person practical assessment by the Johns Hopkins Institute for Clinical and Translational Research. During each blood draw staff will collect two 8.5 ml samples of blood; one in an acid citrate dextrose (ACD) tube and one in a serum separator tube (SST).

The samples will be processed and stored by the JHMI Genome Core Resources Facility (GCRF). After receiving the blood samples, GCRF staff will aliquot the whole blood samples from the ACD tubes into 2 to 4 cryovials of about 1 ml each (excess blood will be disposed of properly). For the SST, GCRF staff will invert the tube 10 times, and allow clot to form for 10 to 20 minutes. Once clot has formed, GCRF staff will centrifuge the SST at room temperature at 1100 1300 G for 10 minutes. After centrifugation, GCRF staff will aliquot the serum (located above the polymer barrier) in 500 to 1000 µl aliquots in 2 to 4 cryovials. Samples will be stored at the GCRF at no more than -80 °C until further assays for cytokines or SNPs, for example.

Objective II: Sensory Processes: Sensory Stimulation

During sensory testing, somatosensory stimulators will be used to deliver cold, heat or a mechanical (pressure) stimulus to the participant's skin. Somatic sensory testing will include determination of mechanical and heat thresholds and description of these stimuli. These psychophysical tests will be included with the use of a questionnaire of ideal type pain descriptors and a verbal descriptor visual analog scale (VAS), which rates the intensity and unpleasantness of the pain evoked by these stimuli. The VAS will be anchored by verbal descriptors of the intensity of pain appropriately spaced along the scale. Behavioral tasks will be employed such as conditioning or

attentional paradigms (see below). Seventy patients will be studied with one or more of these tests, most commonly the laser.

These Test Stimuli will include:

1) Ice Water Immersion: The patient's forearm to the mid-shaft, appropriate to the side of the exploration or the psychophysical testing, will be placed in ice water (4 degrees centigrade). The subject will be asked to leave the arm in the water for as long as he/she can tolerate.

2) Thulium YAG laser Stimulator: A painful heat laser stimulus (Themis, Starmed Tec, Starnberg, Germany) of 15 msec duration will be applied to the participant's forearm or face while the patient wears protective glasses. The stimulus is delivered by skin will be precisely timed heat pain stimulus, which facilitates temporal analysis of forebrain neuronal activity related to pain.

3) Contact Thermal Stimuli: Both heat and cold stimuli will be applied to the participant's forearm using a computer-controlled Peltier-based thermode connected to a feedback-based system (Pathway Thermal Sensory Analyzer, MEDOC). This system provides for precisely specified warming and cooling temperature changes, allowing for the determination of threshold detection of warm, cool, heat pain and cold pain sensations, and precise stimulation during sensory behavioral studies.

4) Mechanical Stimulation of the Skin: The somatic sensory testing will include the following mechanical stimuli: i) brushing the skin with a camel-hair brush, ii) von Frey hairs, iii) large, medium, or small arterial clips to a fold of skin, and iv) punctate probes. Mechanical stimulation of the skin will also include a non-penetrating towel clip (110–121, Jarit Surgical Instruments, New York, NY) with two parallel 4 by 5 mm serrated surfaces that could be approximated in 10 reproducible steps by using a ratchet. Approximation of the surfaces of the towel clip has been described in terms the number of steps on the ratchet.

5) Mechanical Stimulation of the Muscle: This will include a blunt pressure stimuli applied over bone ligaments, tendons and muscle with a pressure algometer (Wagner Instruments or SBMedic). These four tissues could be stimulated by structures around the wrist such as the boney radial head, the lateral collateral ligament, tendons of the long and short flexors at the volar aspect of the wrist, and muscles of the thenar eminence.

6) Muscle Contraction (Ischemia) Test: The blood supply to the participant's arm appropriate to the side of the procedure or the side of psychophysical testing will be cut off by placing a standard blood pressure cuff on the participant's arm and inflating the cuff to 220 mm/Hg. Then, the participant will be asked to grip a handle repeatedly while the cuff is inflated. Finally, the participant will be asked to relax his/her hand while the cuff remains inflated for another one to two minutes.

7) Electrical stimulation of the Skin: an FDA approved constant current stimulator (DS7A, Digitimer, Hertfordshire, UK) or a constant current stimulator (S12, Grass, Warwick, RI , U.S.A.) will be applied to the hand to produce a non-painful tingling sensation. The electric stimulus will be delivered through a pair of Ag/AgCl electrodes filled with isotonic paste (9-mm diameter, Docxs Biomedical Products,

Ukiah, CA) placed on the wrist. The subject will be free to remove the electrodes from her/his hands at any time.

8) tDCS Stimulation: The tDCS portion of the experiment will begin with DC current (maximum of 2 mA) stimulation delivered through surface electrodes (TransQE from IOMED®, surface area: 25 cm^2) using a Phoresor® II Auto (Model No. PM850, IOMED®, Salt Lake City, Utah 84120, USA). In some experiments, one electrode will be positioned above the primary motor cortex of an affected side, the other electrode will be placed over the forehead. In other experiments, one will be positioned over the primary motor cortex of an affected side and the other one above the contralateral motor cortex. Anodal or cathodal tDCS will be delivered for 20 min. The current will be increased in a ramp-like fashion to reduce the appearance of transient phosphenes usually present with rapid on-off applications. Previous studies have demonstrated that these parameters of tDCS modulate motor cortical function for up to 90 minutes following the end of stimulation and in a study in stroke patients this stimulation elicited motor performance improvements that outlasted the stimulation period.

   For sham stimulation the electrodes will be placed in the same way as for real tDCS in the absence of real stimulation, this means stimulation will be increased to a current strength near the perception threshold and will be decreased afterwards and set to 0 mA output for a period of 20 min. With this procedure participants are usually unable to differentiate between tDCS and sham stimulation.

   After prepping and draping the subject's scalp for the surgical procedure, the tDCS electrode arrays will be positioned approximately over the hand region of the motor cortex following the guidelines of (Edwards et al., 2013; Kou et al., 2012; Villamar MF et al., 2013). We employ surface electrodes (TransQE from IOMED®, surface area: 25 cm^2) connected to a conventional tDCS device using a Phoresor® II Auto (Model No. PM850, IOMED®, Salt Lake City, Utah 84120, USA) to deliver DC to the scalp via electrodes. The central active electrode is placed above the representational area of the ADM muscles (approximately over C3 or C4 based on the International 10/20 EEG System corresponding to the laterality of Parkinson symptoms) and the reference electrode is located in contralateral motor cortex. The microelectrode will be positioned in the target of interest (subthalamic nucleus or globus pallidus interna), and recordings of multiunit and field potential activity as a baseline will take place for 5 minutes. Application of tDCS will then be performed at a set current of 2 mA for 10 minutes. Recordings of multiunit and field potential activity will take place during the application of tDCS and for a period of 5 minutes after the cessation of the tDCS.

9) Direct Cortical Stimulation: The contacts from the subdural strip electrode, which is placed on the hand motor area, are utilized in either a unipolar or a bipolar configuration to deliver the stimulation current. The stimulation parameters will roughly fall into the ranges (amplitudes from 2 mAmp to 6 mAmp, rates from 10 Hz to 130 Hz, and pulse widths from 60 μsec to 450 μsec) (Canavero et al., 2003; Canavero et al., 2002; Cilia et al., 2007; Cilia et al., 2008; Fasano et al., 2008; Gutierrez et al., 2009; Pagni et al., 2005; Strafella et al., 2007; Tani et al., 2007). Direct cortical stimulation will be delivered by either the Alpha Omega NeuroOmega data acquisition system (Nazareth, Israel), or the Blackrock Microsystems NeuroPort data acquisition system incorporating the CereStim applicance (Salt Lake City, UT).

10) Auditory Stimulation and Speech Testing: A conventional speaker including earphones will be used to produce auditory stimulation and a high quality microphone will be used to record the sound of the subjects in the speech production task. In some tasks, participants will repeatedly read aloud syllable triplets, in which each triplet will be composed of items drawn from a pool of 16 syllables. The subject's voice may be recorded, and also played back to them using an earphone. Stimuli: The "basis set" for many experiments will be 4 consonants and 4 vowel phonemes, chosen such that they comprise different combinations of 5 articulator features, and 8 major phonetic state spaces (4 C and 4 V; lower portion of grid) described in human motor cortex. These will be combined to create 16 unique CV syllables, which vary in the frequency of occurrence and lexical status. The composition of this stimulus set will allow us to probe for multiple levels of encoding in the context of a single speech production task and acquired datasets. Other stimuli will also be used consisting of speech segments and tone sequences with similar outcome measures of correlation with the neural recordings.

    In order to increase the accuracy of speech production timing measures, an external noninvasive piezoelectric sensor will used for quantitatively monitoring the respiratory effort during the speech production task. The sensors are attached to a strap that is placed around the subject's chest and abdomen. The resulting signal will provide an indirect representation of respiratory effort, based on chest and abdominal movement.

    Data collected from subjects enrolled in the auditory stimulation and speech testing are entered to the Research Electronic Data Capture (REDCap) database system. REDCap is a secure, HIPAA-compliant, web-based system for building and managing research projects, and to facilitate data analysis and transfers between investigators. The REDCap system provides functionality and features to enable researchers to rapidly develop analysis tools for databases. For each subject, a record will be created in REDCap and will include: subject age and sex, diagnosis code and a brief clinical history including age of disease onset, DBS target, pre-op UPDRS III motor examination results, pre-op neuropsychological examination results, pre-op speech analysis measures, pre-op medications, 6 month post-op UPDRS III motor examination results, 6 month post-op neuropsychological examination results, 6 month post-op speech measures, 6 month post-op medications, and medical imaging (CT, MRI, fluoroscopy) results will be recorded in the database.

    The baseline neuropsychological testing obtained clinically at Johns Hopkins (as part of routine clinical care within the context of the preoperative multidisciplinary treatment committee evaluation) includes the testing listed in Table 1. Occasionally, additional testing is performed at the discretion of the neuropsychology team.

    Table 1.

Dementia Rating Scale	Multi-component screening of cognitive functions
Speed and Capacity of Language-Processing Test	Word knowledge, speed of reading comprehension
Boston Naming Test (short form)	Visual confrontation naming
Word List Generation	Guided by initial letter Guided by meaning

Hopkins Verbal Learning Test-Revised	Learning, recall, and recognition of a word list
Brief Visuospatial Memory Test-Revised	Learning, recall, and recognition of geometric designs
Brixton Spatial Anticipation Test	Non-verbal problem solving
D-KEFS Tower Test	Nonverbal planning and problem-solving
Trail Making Test	Visual scanning, mental tracking, and graphomotor speed
Grooved Pegboard Test	Manual speed and dexterity
Sniffin' Sticks Odor Identification Test	Olfactory perception
Geriatric Depression Scale	Self-rated symptoms of depression
Frontal Systems Behavior Scale (self-rating)	Change in major behavioral domains associated with frontal lobe functioning

Objective III: Sensory Processes: Behavioral Tasks

These tasks will include attention tasks and a learning task which involves the painful and nonpainful stimuli, as described above under *Sensory Processes: Sensory stimulation,* including Heat Stimuli (Laser -2 and Thermode-3), and Electrical Stimuli-7. Attentional protocols will be carried out in one session, often with presentation of a painful (laser, thermode, or electrical), and a nonpainful (electrical or thermode) stimulus presented in a single train in random order. The subject is instructed to either: i) count or ii) push buttons in response to the painful stimulus (attention to pain), or the non-painful stimulus (distraction from pain) or both, as presented in random order and counterbalanced across patients. In three other tasks, a single train will consist of: i) only nonpainful stimuli which the patient counts, ii) only painful stimuli which the patient counts and iii) only painful stimuli while the patient performs a cognitive task, e.g. reading for comprehension.

Some subjects in both categories will be involved in protocols for classical conditioning or learning, which occurs when a neutral conditioned stimulus (CS+, a light or sound) is paired with an unconditioned aversive or appetitive (reward) stimulus (US). In the case of aversive conditioning, the US might be the painful cutaneous laser, thermode, or electrical stimulus, while in appetitive conditioning it might be a reward of one dollar. As measures of psychological variables, we propose to administer psychological questionnaires including depression, anxiety and PTSD scales.

Under Objective I extra-operative studies will often be carried out over a two hour session during which painful and nonpainful stimuli will be presented in a single train. During the extra-operative conditioning protocol, two or three sessions may be carried out on different days. Within each session there will be rest periods and between two and six separate trials with either attentional or conditioning tasks. The length of the intraoperative sessions will be less than one hour in length.

In this protocol the conditioning phase (one session) will be followed by the extinction phase (one session) during which the CS will be presented repeatedly without the US. Thereafter, the reversal of extinction phase will occur (one session) in which the return of the CR will occur spontaneously, or by reinstatement or by renewal. As a measure of autonomic activation we will record the skin conductance throughout all phases of conditioning by use of a Skin Conductance Coupler (V71-23, Colbourn Instruments, Boston MA).

In summary, under this cognitive protocol separate trials will include sessions of the habituation phase which is involves unpaired presentation of stimuli, the acquisition phase which involves the

paired presentation of stimuli, and extinction of conditioning and reversal of extinction phases. Decreased extinction or increased reversal of extinction may characterize pathologic fear or anxiety traits. Each of these phases may comprise a separate session or trial of the conditioning protocol as described above. Intraoperative studies will involve only attention testing or the conditioning and extinction phases of conditioning protocols.

Some healthy subjects, chronic pain patients, and the patients described above with epilepsy will be involved in attentional and learning protocols as described above. Stimuli are listed above (Objective II: Sensory Processes: Sensory Stimulation) and include laser (item 2), Thermode (item 3) and electric (item 7) in a single train, or two levels of stimulus intensity of one modality in a single train, e.g. low and high levels of the electric modality. Either modality may be nonpainful, or painful with a pain level of less than 6 out of 10 on a scale in which 0 is no pain and 10 is the worst pain imaginable. Often one of the two modalities of stimulation will often be painful while the other is nonpainful. The two modalities or intensities of stimuli will be applied at random interstimulus intervals and in random order, so that one stimulus may be less frequent (e.g. 5 to 25% of total stimuli) than the other (e.g. 95 to 75%). The subject will be asked to count the stimuli or signal the occurrence of one or both stimuli by key presses, which indicatets detection of that stimulus.

Prior to using the laser in any participant, a calibration and verification procedure will be followed. Specifically both beam diameter and energy output will be measured.

"1. Energy output

a. Measure energy with thermopile and energy meter. The routine will be a series of energies such that the settings are 11 J, 12 J, 13 J, 14 J, 13 J, 12 J, 11 J, 12 J, 13 J, 14 J, 13 J, 12 J, 11 J, 12 J, 13 J, 14 J, 13 J, 12 J, 11 J. This series of up-and-down continuous staircase covers the range of stimuli used in our protocol and accounts for laser energy output hysteresis.

b. Save the results. Make sure the average of each energy output as measured is no more than 10% more than the expected value.

c. Record the results in participant binder.

2. Beam diameter

a. Save and date back of zap-it paper. Measure beam diameter at 11 J, 12 J, 13 J, and 14 J on zap-it paper to ensure the 10 mm diameter setting. Measure each energy output measure three times with Zap-it Grid paper. Confirm that the maximum spot on the zap it paper is not more than 10.9 mm, while the smallest spot is no less than 9.1 mm. Record the results in participant binder."

Extraoperative studies will be carried out in healthy subjects and the patient population described above. Sessions of attention will involve one session while those of conditioning will involve two or three sessions. The intra-operative studies will be carried out over multiple sessions, each session for recordings from a single neuron. In many of these sessions painful (laser) or nonpainful (electric) somatic stimuli, and other stimuli will be presented in a single train. The length of the combined sessions will be less than one hour in total.

Motor Control:

These tests are will be used to study movements of the upper extremity. One or more of these tests, commonly involving imagined movements, will be carried out at up to 7 recording sites and will take 5 to 10 minutes at each site. All experimental protocols and variables will be under computer

control and will be carried out in healthy subjects, patients not going to surgery, or patients undergoing functional stereotactic procedures. In patients undergoing extra-operative testing and recordings of electrical signals, basic sensory and motor testing will be part of routine care. The proposed studies represent more involved sensory and motor protocols, and these protocols will not be part of standard care.

1) Subjects will be studied while performing actual upper extremity movements in response to a light cue. The nature of the cued movement will be indicated by verbal commands such as 'make a fist' at the start of a trial consisting of several presentations of the cue. Imaginary movements will be carried out at each joint in the upper extremity contralateral to the recording on a verbal command such as 'imagine that you are making a fist without moving'. EMG recording and movement sensors such accelerometers will be employ.

2) Torque motor: In the motor testing, torque motors and an articulated handle will be used to measure arm movements to visual targets in a planar work space in front of the chest. The patient's arm will be supported in a sling throughout trials, which will last less than 10 minutes. This device will allow us to examine neuronal signals related to the motor learning and error detection during arm movements.

3) Motor Tracing: Subjects will be instructed to use finger to trace targets shown on a touch display. This task may be done before, during or after the operation to evaluate the controllability and stability of patient's motor function. Healthy participants serving as controls may also perform this task.

Sensory Processes and Motor Control: Psychological Testing:

Neuropsychological and Psychological Tests:

Many patients with movement disorders involved in these protocols will undergo extra-operative pencil and paper psychological tests or structured interviews, in addition to those which are required for clinical assessment. In total, the extra-operative testing of these patients may include a standard neuropsychological battery of tests of intelligence, language, motor function, learning, memory, and attention. Patients may also be tested with a psychological battery including measures of personality, depression/mood, fear/ anxiety, and avoidance behaviors. Many of these same tests will be carried out in healthy subjects.

Patients with movement disorders will be assessed by quality of life and disability indices specific to their condition, as part of standard clinical assessment. In addition, they may undergo intra-operative studies using validated, abbreviated protocols for some of these extraoperative tests. These will include tests of attention, learning, memory, fear/anxiety, and avoidance behaviors.

Patients Undergoing Surgery:
For patients involved in extra-operative studies there may be one preoperative and one postoperative testing session, each lasting approximately 2 hours. The intraoperative procedures will last approximately 1 hour and twenty minutes during the time that the patient is in surgery.

Patients Not Eligible for Surgery, choosing not to have surgery, or already having had surgery:
After consent is obtained, there will be at least one visit lasting approximately 4 hours.

Healthy Participants and Chronic Pain Patients with Knee Osteoarthritis and Chronic Pain Patients with Chronic Widespread Pain, Fibromyalgia, and with PTSD:
These participants will have one visit for consenting and education to determine eligibility. Then, there will just one additional visit lasting approximately 2 hours.
During one laboratory session we will ask healthy participants to provide three saliva samples; one at the beginning of the session, one immediately after completing the behavioral task, and one 30 minutes after the behavioral task. At the beginning and end of this same session, we will ask subjects to provide blood samples, which will be obtained by ICTR-trained staff of the Lenz lab by venipuncture. Each sample will be one 8.5 ml volume acid citrate dextrose tube and one serum separator tube of blood. Saliva and blood samples will be stored at no more than-80 °C by the Johns Hopkins Genetic Core Resources Facility for later analysis of cortisol, cytokines and SNPs. All data relating to genetic information, including saliva and blood tube sample containers will be deidentified at origin and assigned a subject code corresponding to the subject's behavioral and imaging data. This will minimize the likelihood of discovery of personally identifiable information.

5. Inclusion/Exclusion Criteria

Patient Inclusion/Exclusion Criteria:
Intra-operative studies may be carried out in patients undergoing functional stereotactic procedures for the treatment of movement disorders or pain. All these subjects must meet standard medical and anesthetic criteria to be a candidate for these surgical procedures. If the subjects do not meet these criteria then they are not a candidate for surgery and so will not be a candidate for these intraoperative studies.

Extra-operative studies may be carried out in healthy subjects and patients not candidates for surgeries. They may also be carried out pre- and post-operatively in subjects undergoing functional stereotactic procedures.

Exclusions for intra- and extra-operative research tests will include patients with significant language, hearing, or cognitive impairment, and non-English speakers.

The tDCS and direct cortical stimulation testing procedures will not be performed on patients with seizure disorders, or a history of having a seizure. However, some studies suggest that cathodal tDCS may be a potential therapeutic tool in epileptic disorders, particularly in drug-resistant patients (Fregni et al., 2006; Yook et al., 2011).

Healthy Participant Inclusion/Exclusion Criteria: All healthy individuals between 18 and 80 years of age will be eligible to serve as healthy participants. Patients with a history of significant neurological or non-neurological illnesses will be excluded. Gender or age matching will not be used to

counterbalance the population of healthy controls. Participants will be asked to submit to urine drug analysis, those who subsequently test positive for illegal drugs or refuse testing will be excluded.

Patients with chronic pain from knee osteoarthritis: All individuals between 18 and 80 years of age with chronic pain (pain ≥45 of the past 90 days and pain intensity ≥ 3/10 for the past 24 hours) from knee osteoarthritis will be eligible for this portion of the study. Patients with a history of significant neurological illnesses will be excluded. Participants will be asked to submit to urine drug analysis, those who subsequently test positive for illegal drugs or refuse testing will be excluded.

Patients with chronic pain from chronic widespread pain or fibromyalgia: All individuals between 18 and 80 years of age with chronic pain (pain ≥45 of the past 90 days and pain intensity ≥ 3/10 for the past 24 hours) from chronic widespread pain or fibromyalgia (defined as pain present in 4 of 5 areas of the body (right leg; left leg; right arm; left arm; neck, upper and lower back) and present in at least 7 painful sites) will be eligible for this portion of the study. Patients with a history of significant neurological illnesses will be excluded. Participants will be asked to submit to urine drug analysis, those who subsequently test positive for illegal drugs or refuse testing will be excluded.

6. Devices

The rationale for choosing the torque motor and laser for these studies rests on our long, safe experience with both these devices. In addition, there are practical advantages to these exact devices versus similar devices. Both devices were classified as non-significant risk devices, as described below. In the case of the non-painful somatic stimulation, an electric stimulator was chosen which is FDA-approved. The skin conductance coupler was chosen because of its widespread use to measure autonomic activation, and its classification as a non-significant risk device (see Application Section 23).

Torque Motor

The robot is used to examine the adaptive control of reaching in force fields. Briefly, the subject holds onto the handle of a robotic arm and reaches to targets that are displayed on a video monitor. A sling was used to support the subject's arm and restrict movements to the horizontal plane. The subject reaches to targets which appear 10 cm from the center of the monitor at 1 of 4 angles. At the start of each trial, the subject holds the cursor at a crosshair which indicates the beginning of a trial. The crosshair then disappears and a square box target is displayed which the patient reaches to. A precision (torque) motor is used to produce a force to impede or assist the reaching movement. The subject's response to the force is measured as an indicator of the subject's ability to adapt his movement to changing conditions. At the end of each reach, the subject receives color and sound feedback on the speed and duration of his/her reach.

The mechanical design of the robot places its area of operation so it is impossible for the machine to hit the subject's torso, head, or legs. The only area where the robot could potentially impact the volunteer is in the hand or arm area. To prevent this, multiple procedures have been set in place. 1) The volunteer has a panic button that upon pressing will disable power to the actuators.

This disables the robot and makes it a passive system. 2) The experimenter also has a panic button that duplicates the action of the volunteer's panic button. 3) The robot is under computer control. Software continuously monitors the position of the robot's handle. If the robot leaves a small operating workspace, power is shut down to the robot's actuators.

Because of these characteristics this device does not meet the definition for a significant risk device which is a device having the 'potential for serious risk to the health, safety, or welfare of a subject' (Website of the JHM Office of Human Subjects Research - IRB: Investigational Medical Devices). 'Such devices do not have to comply with FDA premarket approval and performance standards prior to use in research studies', like the present research study.

Laser

Cutaneous heat stimulation will be delivered by a portable semiconductor laser (see Application Section 23). The stimulus intensity will be adjusted to elicit a sensation similar to a pinprick and a visual analog scale of intensity reading of 3-4/10 (usually 10-13 Watts/mm2). At these parameters, a component of mechanical, warm or heat sensation is not reported spontaneously or in response to direct questioning. In order to avoid sensitization, the laser beam will be moved at random to a slightly different position for each stimulus. During the entire recording session continuous white noise will be delivered to each ear through earphones (Click-tone module - Grass Instruments, Co., Quincy, Mass. U.S.A.).

The risks of this portion of the protocol are minimal. The use of the laser to produce a pain stimulus is associated with a risk of burning the skin. The characteristics of the short duration laser pulses to be used in this study are well known. There have been no unintentional burns in our extensive experience over the past thirteen to thirty-two years in research studies of patients in the epilepsy monitoring unit and the laboratory of Drs. Ringkamp and Meyer. However, reddening of the skin (Grade 1 Burn or Sunburn) may occur at sites where the laser is applied (freckling). These have always resolved within a few days in our experience. Additionally, the laser poses a risk to vision if laser light enters the eye. During these studies, as in the past, all persons in the room will wear glasses and the signs will be posted on the door warning that the laser is in use and that entry is forbidden.

Because of these characteristics this device does not meet the definition for a significant risk device which is a device having the 'potential for serious risk to the health, safety, or welfare of a subject' (Website of the JHM Office of Human Subjects Research - IRB: Investigational Medical Devices). 'Such devices do not have to comply with FDA premarket approval and performance standards prior to use in research studies', like the present study.

Electrical Stimulator

In this protocol, a primary outcome is to assess the effect of painful and non-painful somatic stimuli upon ongoing and evoked activity recorded from the cortex and the thalamus. We have now decided on electrical stimulation of the skin as the non-painful somatic stimulus. This stimulation will be applied to the wrist in order to produce a non-painful tingling sensation. For this purpose, we propose

to use a constant current stimulator (DS7A, Digitimer, Hertfordshire, UK) which is FDA approved with a 510(k) letter (Application Section - Devices). The electric stimulus will be delivered through a pair of Ag/AgCl electrodes filled with isotonic paste (9mm diameter, Docxs Biomedical Products, Ukiah, CA) placed at the wrist. The PI has long experience with devices of this type. Another electric stimulator (S12, Grass, Warwick, RI, U.S.A.) will also be used. This S12 stimulator has been used to stimulate on human cortices in UCLA (Schrader LM et al. 2006).

The risks of this stimulus are minimal. The subject will be free to remove the electrodes from his/her wrist at any time. Electrical stimulation of the skin and peripheral nerves has been carried out routinely with this and similar devices in Clinical and Research Neurophysiology laboratories around the world for many years. Finally, the electric stimulator for this study has recently been calibrated and certified for use in this protocol by the Clinical Engineering Service (CES) at the Johns Hopkins Hospital. The approval letter from the JHH CES can be found in Section 23 of the application.

As a local example of the safe use of these devices, the Department of Neurology at NINDS-NIH, under the direction of Dr. Mark Hallett, has four decades of experience with the use of this and similar devices. These devices have been safely used by Dr. Hallett to produce electrical stimulation of skin and peripheral nerves to investigate a wide range of research questions.

Contact Thermal Stimulator

Quantitative sensory testing is carried out with the Medoc System, which delivers thermal stimuli through a thermode (inch square) placed on the skin. This sensory testing system will be used to determine warm/cold detection thresholds and heat/cold pain threshold. These tests will take about 10 minutes for one set of thresholds. As soon as the subject presses the button to indicate the detection or the pain threshold the temperature will return to 32°C baseline temperature. In addition, the thermode will be computer controlled and has built-in controls to prevent injury. The subject can remove the hand from the device at any time.

The risks of the protocol are minimal. The characteristics of this device are well known since it has been used around the world for decades without reports of injury. However, reddening of the skin may occur at sites where the thermode was applied. These have always resolved within a matter of hours.

Because of these characteristics this device does not meet the definition for a significant risk device which is a device having the 'potential for serious risk to the health, safety, or welfare of a subject' (Website of the JHM Office of Human Subjects Research - IRB: Investigational Medical Devices). 'Such devices do not have to comply with FDA premarket approval and performance standards prior to use in research studies', like the present study.

Medoc devices have been used safely to produce controlled thermal and painful stimuli over a twenty year period at numerous centers worldwide. Specifically, these devices have been used safely over to be a sixteen year period in the laboratory of Dr Greenspan (Dentistry, U Maryland). He has safely used several versions of this same device as in this protocol over that period. This protocol has been reviewed yearly and approved by the IRB in University of Maryland (Chairperson: Robert Rosenthal).

Transcranial Direct Current Stimulation (tDCS) Device

We employ surface electrodes (TransQE from IOMED®, surface area: 25 cm2) connected to a conventional tDCS device Phoresor® II Auto (Model No. PM850, IOMED®, Salt Lake City, Utah 84120, USA) to deliver DC current to the scalp via surface electrodes.

tDCS will be administered with a current strength of 2 mA for maximum of 10 min by a constant current stimulator. Based on subject restrictions two types of electrode configuration will be applied:

1. Conventional rectangular sponge pad: we will use a pair of saline-soaked surface sponge electrodes (anode: 7×5 cm^2; cathode: 7×5 cm^2). The anode electrode will be positioned over the motor cortex representational area of the hand region on an affected side, and the return electrode will be placed above the contralateral motor cortex area.

2. 4×1 ring: The central active electrode will be placed above the representational area of the unaffected side hand (coinciding with the center of the anodal pad used for regular-pad stimulation) and surrounded by four return electrodes (each at a ring center to ring center distance of 3.5 cm from the active electrode) which will be connected to a four-to-one wire adaptor for the DC stimulator. Altogether five sintered Ag/AgCl ring electrodes (outer radius: 12 mm, inner radius: 6 mm) will be stabilized with plastic holders filled with EEG conducting gel (H + H Medical Devices, Germany and with gel-skin contact area $\sim 25 \pm 2.5$ mm^2). Since the sensation to tDCS could differ with electrode and gel type (Minhas P, et al. 2010), here we will apply the suggested Ag/AgCl sintered ring electrodes (Minhas P, et al. 2010), and the conducting gel for less skin sensation as reported by the subjects.

Numerous methods utilize external landmarks to locate the motor strip(pre central gyrus). The motor strip typically lies anywhere from 4 to 5.4 cm behind the coronal suture. Based on the International 10/20 EEG system the C3 and C4 locations correspond to the left and right motor cortex (Edwards et al., 2013; Kido et al., 1980; Sarmento et al., 2008; Ebeling et al., 1987).

Skin Conductance Coupler

In this protocol, we describe psychological measures of cognitive or affective processes during conditioning. We now seek to assess Skin Conductance as a physiological indicator of the autonomic activation throughout all conditioning trials in this protocol. The skin conductance response will be assessed by use of a device which applies a small constant voltage between two electrodes and measures current to estimate conductance of the skin between the electrodes. This Skin Conductance Coupler (V71-23, Coulbourn Instruments, Boston MA) applies a constant 0.5 Volt potential through Ag/AgCl electrodes filled with isotonic paste (9mm diameter, Docxs Biomedical Products, Ukiah, CA). These electrodes are placed on the hypothenar surface of the subject's hand. To further assure that the electrical leakage current is within safe limits, a medical grade isolation transformer will be used between the wall plug and the device (Dale Technology Medical-Grade Isolation Transformers, NY, USA). Finally, the Skin Conductance device in this study has been calibrated and certified by the Clinical Engineering Service (CES) at the Johns Hopkins Hospital.

Because of these characteristics, this device does not meet the definition for a significant risk device which is a device having the 'potential for serious risk to the health, safety, or welfare of a subject' (Website of the JHM Office of Human Subjects Research - IRB: Investigational Medical Devices). Such (non-significant risk) devices do not have to comply with FDA premarket approval and performance standards prior to use in research studies', like the present study.

Auditory Equipment Description

Speech recording is carried out with the Zoom System (Zoom H6 - 6 simultaneous track recording, 4 balanced inputs) and a high quality microphone is employed during recording (Preosonus PRM1 Precision Flat Frequency Microphone). Also, in order to increase the quality of the recorded speech signal a high quality audio cable is used (High-quality, braid shield XLR, Monster Performer 600 Mic Cable).

Respiratory Effort Sensor

The SleepSense Piezo Crystal respiration sensor (respiratory effort sensor based on piezoelectric crystal technology) is used to measure the temporal pattern of speech production including the initiation of speech. The Piezo Crystal respiration effort sensor is made from a piezoelectric crystal that generates a small electric potential in response to stress and movement and converts chest or abdominal respiration motions to an analog voltage that provides an indication of respiration waveform. The SleepSense Piezo Crystal respiration sensor is designed with an electrically isolated piezo element to increase immunity to environmental artifacts and provide improved signal stability if the sensor shifts spatially throughout the respiratory displacement. The sensor bands are strapped around the patient's abdomen or chest, and do not make contact directly with the patient's skin.

Direct Cortical Stimulation Equipment

a) The Alpha Omega Neuro Omega clinical data acquisition system (Bethlehem, Israel) is a physiological navigation system intended for different neurosurgery and neurophysiological clinical applications, including recording from and stimulating brain motor and sensory neurons to accurately navigate for neurosurgery target localization during the treatment of movement disorders and to aid in the placement of deep brain stimulation leads. The system is capable of recording from and stimulating various areas of the brain (deep structures and cortex). The system is FDA approved for these purposes, and in this protocol will be used for performing single unit recordings from subcortical structures, macrostimulation (via the guard-ring element of an implanted microelectrode) of subcortical structures, cortical electrocorticography recordings, and cortical direct current stimulation.

b) The Blackrock Microsystems CereStim R96 is a fully programmable neurostimulator designed for the Blackrock Microsystems data acquisition system (Neural Signal Processor) with 96 output channels and the capability of producing up to 16 simultaneous electrical stimuli. The biphasic current pulses generated by the CereStim R96 are intended to stimulate neurons through surface contacting macro-electrodes. The CereStim 96 comes with the Stim Manager Software and both Matlab SDK and C++ SDK. Stim Manager operates in two modes: Manual and Program. Control of the stimulator through C++ or Matlab APIs provides a simple path for integration of the stimulation system directly

into experimental control systems. The user first selects an electrode from the Electrode Array Panel (1-96) and then creates a custom stimulus in the Waveform Panel. The latter allows the user to specify single-stimulation parameters by defining individual phases including polarity, number of pulses, inter-phase delay, amplitudes, phase width and frequency. The CereStim R96 is an additional utility to the existing Blackrock data acquisition system. It is currently approved by the Johns Hopkins Medicine IRB under protocol IRB00040308 for direct cortical stimulation applications during invasive epilepsy monitoring.

7. Study Statistics

This is a single institution, long-term exploratory study to understand forebrain networks of human sensory processing and motor control. Specifically Objective I will address cortical and subcortical networks of sensory signaling and processing, while Objective II will address the cortical and subcortical networks involved in motor control.

Due to the exploratory nature of the study, all outcome data will be collected regardless of data type such as electrophysiological responses, or timing, or the questionnaries related psychological function. In general, data will be summarized using descriptive statistics and graphical techniques. Within and between-subjects comparsions will use paired and unpaired analysis, respectively. Longitudinal outcomes or repeated measures will be considered and possibly be analyzed using generalized linear model. Correlation coefficient or concordance correlation coefficient will be used to estimate correlation between two outcomes.
The outcome measures for the three objectives are indicated below:

Primary and secondary outcome variables:

Objective I:

Under Objective I we will determine functional connectivity between structures at which single neuron and LFP responses occur in response to painful laser stimuli. Secondary outcome variables will address cognitive processes related to sensory stimuli and the networks which subserve them. These networks will be defined by measures of functional connectivity between electrode sites such as correlation, coherence, and causal (directed) interactions.

Network characteristics will be estimated by measures of connectivity at the time of laser stimuli between sites such as correlation, coherence, functional connectivity, and causal interactions.

Objective II and III:

Our primary outcome variables will identify the functional connectivity within networks of cortical and subcortical structures which subserve movement. We will determine functional connectivity between structures activated during actual and imagined movement. Recordings will be made of single neuron and LFP activity in the basal ganglia, thalamus and cortex during actual and imagined movements.

Our secondary outcome variables will identify the functional connectivity within networks of cortical and subcortical structures which subserve movement disorders. We

will determine functional connectivity between structures activated during disordered movement. We will also determine the effects of tDCS on single and multiunit activity in the recorded subcortical structures. Recording and analysis techniques will be similar to those under the primary outcome of this of this objective.

Data Sharing

Specifically for the Auditory Stimulation and Speech Testing intraoperative studies described above, we wish to share a subject specific descriptive and electrophysiology data set with the University of Pittsburgh Medical Center (Dept. of Neurosurgery) as part of an NIH Brain Initiative funded study (U01 NS098969 - Subthalamic and corticosubthalamic coding of speech production, PI – Mark Richardson). This study is additionally administered under the University of Pittsburgh IRB # PRO13110420 (Intraoperative Brain Recordings in Movement Disorders Patients).

The data transfer will utilize the REDCap research database system in a shared study database. Subject records will include: subject age and sex, diagnosis code and a brief clinical history including age of disease onset, DBS target, pre-op UPDRS III motor examination results, pre-op neuropsychological examination results (as per the summary above), pre-op speech analysis measures, pre-op medications, 6 month post-op UPDRS III motor examination results, 6 month post-op neuropsychological examination results, 6 month post-op speech measures, 6 month post-op medications, and medical imaging (CT, MRI, fluoroscopy) results will be recorded in the database.

Additionally, deidentified cortical strip ECoG, audio voice responses, and subcortical single and multi-unit activity and LFP will be shared for these select subjects derived from the approximate 30 minute intraoperative auditory and speech testing protocol. The encrypted, HIPAA compliant data base for this transfer will utilize the Pitt-Box (University of Pittsburgh sponsored) application.

8. Risks

As in previous studies, the main risk of intra-operative tests is identified as the fatigue associated with additional testing at several recording sites during the localization procedure. Therefore, the main risks of the operation are associated not with the research tests, but with the standard surgical procedure.

In addition, the somatic sensory, motor, and psychological tests may be applied during extra-operative testing in all patients and healthy subjects. These tests are associated with relatively minor risks during both intra-and extra-operative testing. These risks are listed below by the category of testing. The tests, or combinations of tests, below in this section, and in the section above on '*Research testing procedures ...*'., are numbered using the same system as is used in the Consent.

None of these risks has resulted in a patient injury in the many years in which these research procedures have been performed for prior studies. All subjects will have the option to withdraw from the protocol at any time without penalty.

Risks for Research Testing Procedures for both Intra- and Extra-operative Sessions:

Somatic sensory research testing:

Sensory stimuli, such as the laser, mechanical, nonpainful electrical stimulation, and ice water (see above section on '*Research Testing Procedures …* '), are applied so that the patient can remove themselves from the stimulus at any time. In addition, the thermal stimulators (laser and contact thermode) are computer controlled, with built in controls to prevent injury. The laser stimuli may lead to a grade 1 burn (sunburn) manifest by skin freckling lasting for a few days.

The ischemia test lasts for about three minutes. In the ischemia test, the investigator will stand at the patient's side and will be prepared to deflate the cuff at any time.

Biological Specimen Sampling:

There is a low risk of infection or bruising from the blood sampling. We reduce this risk by using sterile needles, alcohol scrub, applying pressure to your arm after removing the needle, and using state certified phlebotomists experienced in conducting blood draws. An additional low risk possibility is that a participant might experience light-headedness associated with the needle stick.

There are no known risks to providing a saliva sample.

Motor Research Testing:

During Torque motor testing the patient will be able to release the manipulandum of the Torque Motor at any time. Unexpected movements of the torque motor will be aborted by an accessible switch which will disable the machine and which may be pushed by anyone in the room.

Psychological Research Testing:

These are minimal risk procedures. In conditioning studies, the CR will be extinguished by presenting the CS+ without the US (extinction) to normalize the CR. Numerous imaging studies of classical aversive conditioning and psychological interviews and questionnaires have been carried out safely at universities across the United States in psychiatric patients and in healthy controls (reviewed in (Rauch et al., 2006;Phelps, 2006)).

The psychiatric-structured interviews and questionnaires pose a small time burden and a minimal emotional burden or risk to participants. Participants may be uncomfortable answering some questions. They will be instructed that they may choose not to answer questions they do not want to. The seriousness of any risk would be minimal, particularly since any emotional burden would occur in the context of an interview with a practicing psychiatrist or a clinical psychologist, who could

intervene if there were any symptoms during the interviews. There is a small risk of breach of confidentiality if data security measures were compromised.

Transcranial direct current stimulation:

Weak direct currents can be applied non-invasively, transcranially and painlessly. Such application leads to transient changes in corticomotor excitability that is fully reversible. There are no known risks of percutaneous, transcranial DC stimulation of the brain, other than mild local discomfort at the electrode sites. In the current published studies on humans, the following objective safety data were reported:

No significant elevations in temperature of the electrodes.

No demonstrable changes in the skin underlying electrode placement after a stimulation period similar to the one proposed in this protocol.

Mild itching sensation in the absence of pain. This never led to stopping a study in any of the previous reports.

No change in serum neuron-specific enolase (NSE, marker for neuronal damage) in 5 subjects immediately and 1 hour after exposure to 13 min of 1 mA anodal DC to motor cortex.

No changes in diffusion weighted or contrast-enhanced MRI and in EEG after exposure to tDCS.

Nitsche et al. have studied several hundred subjects so far without reporting any side effects apart from a slight itching under the electrode and a short phosphene if the stimulation was switched on or off abruptly. In his own work and in his review of the modern literature, Priori found no evidence or mention of adverse effects using this technique. Additionally, several months' use of this technique at NIH in approximately 30 subjects (Drs. Wassermann and Lomarev) was performed in the absence of any deleterious side effects. All of these reports are in accordance with our experiences in a recently performed study by Dr. Pablo Celnik in elderly healthy volunteers and chronic stroke patients. Furthermore, the NINDS IRB approved recently a protocol of Drs M. Hallett and Lomarev (03-N-0116) to apply tDCS repetitively (8 sessions) in Parkinson patients. Both anodal and cathodal tDCS have been successfully applied during 20 minutes in 12 stroke patients, including 2 patients with cortical stroke, without any adverse effects

Finally, a review paper discussed the safety of tDCS in humans. tDCS application over motor and non-cortical areas in 102 subjects (in healthy individuals, migraine patients, post-stroke patients, and tinnitus patients) revealed the most common adverse effect after tDCS was a mild tingling sensation, followed by fatigue, then a light itching sensation under the stimulation electrodes. Not as common, but mentioned, were headache, nausea, and insomnia. Poreisz et al. concluded that tDCS is associated with very minor adverse effects in healthy humans and patients with varying neurological disorders

In addition, other recent publications have shown that it is also possible to use 2mA intensities without significant risk or complications (current density of 0.095 mA/cm2 and delivered a total charge of 0.086 C/cm^2.) over the cerebellum or prefrontal cortex for 15 minutes without any

complications. Finally, in an editorial by Bikson, unpublished data is reported using current densities of 25.46 A/m2 for 20 minutes with minimal sensation and no skin damage.

An animal study (rat) (Liebetanz et al., 2009), investigated the safety limits of extended transcranial direct current stimulation. Fifty-eight rats received single cathodal stimulation at 1–1000 μA for up to 270 min through an epicranial electrode. Histological evaluation was performed 48 h later. A threshold estimate was calculated from volumes of DC-induced lesions. Brain lesions occurred at a current density of 142.9 A/m^2 for durations greater than 10 min. For current densities between 142.9 and 285.7 A/m^2, lesion size increased linearly with charge density; with a calculated zero lesion size intercept of 52400 C/m^2. Brains stimulated below either this current density or charge density threshold, including stimulations over five consecutive days, appeared the same as nonstimulated controls. The results of these systematic animal studies provide an estimate of a safety threshold for deleterious DC effects. With respect to the charge density, the upper limit used for these proposed human intraoperative studies is lower by two orders of magnitude.

One perceived limitation for the use of tDCS intraoperatively in subjects undergoing DBS lead placement is the resulting modification of current flow by the presence of surgical burr holes. Modeling studies can provide insight into how skull defects would affect current flow through the brain. Based on modeling results modifying the stimulation current intensity and changing the electrode location or electrode type can compensate for the effects (Datta et al., 2010). In the case of a craniotomy, there is a relatively highly conductive fluid pathway for current entering the brain, but it is highly dependent on the craniotomy position relative to the electrode montage used with tDCS. A small defect under the anode electrode leads to current flow in the cortex restricted to locations directly under the defect. A similar sized defect placed between the electrodes does not significantly alter current the flow pattern in comparison with a healthy head with no defect (Datta et al., 2010).

The tDCS electrodes in this study will be placed at least 3 cm from the closest burr hole.

The psychological and neuropsychological tests are administered by pencil and paper or by a structured interview with a practicing psychiatrist or clinical psychologist.

Implanted EEG electrodes:

Subdural strip electrodes consist of a series of metallic electrodes mounted in thin plastic in such a way that it can lie smoothly on the surface of the cortex. They provide high amplitude ECoG signals, and are widely used for monitoring, seizure mapping and stimulation for functional mapping. Subdural strip electrode implantation, mostly used for identifying the epileptogenic focus in epilepsy patients, is a relatively safe procedure (Wyler et al., 1984). The application of strip electrodes is not restricted to epilepsy patients. In movement disorder patients, positive effects of chronic motor cortex stimulation via epidurally implanted electrodes have been first reported by Canavero and Paolotti (2000) and Canavero et al., 2002 and Canavero et al., 2003, by implanting the strip electrodes extradurally over M1 via a small craniotomy. The results of recent studies on Parkinson's patient during deep brain stimulation surgery demonstrate that subdural strip electrode implantation over human motor cortex is safe (de Hemptinne et al., 2013, de Hemptinne et al., 2015). These recordings provide a unique opportunity to investigate the mechanisms of action of deep brain stimulation in

movement disorders in general and Parkinson's Disease specifically (Crowell et al., 2012, de Hemptinne et al., 2013, de Hemptinne et al., 2015).

In traditional subdural electrode strip placement procedures, the associated risk of infection is greatest when there are more than 100 electrode contacts implanted, an excess of 10 exiting electrode cables, or if the electrodes remain for 14 days or more (Fountas , 2011). Infection is not a major risk in the procedure as proposed because the electrode is left in place for a much shorter time span (4 hours) than typical strip placement procedures (7-14 days). Additionally, the cables pertaining to the electrodes remain within the sterile field for the duration of the procedure, further decreasing the risk of infection. Another risk of electrode placement is hemorrhage. Significant intracerebral hemorrhage has been reported, with an incidence of 2.5% from 1,582 patients assessed with depth electrodes from a literature review (Pilcher et al., 1993, 2004), and 1% or less incidence in a more recent study (Blume, 1997).

Fountas (Fountas, 2011) found hemorrhages to be limited and scattered. Postimplantation edema has been reported, with occurrences varying between 0.5% and 14% (Fountas , 2011; Van Gompel et al., 2008; Hamer, et al., 2002). Although the exact pathophysiologic mechanism of edema associated with subdural electrode placement remains unclear, it is hypothesized that edema development is a result of compression of large cortical veins by large subdural grids. Edema may be reduced by systematic administration of steroids (Fountas, 2011), or the use of smaller strip electrode arrays. Postimplantation edema poses the greatest risk in young patients, previously damaged cortical areas, or involving electrode grids with large surface areas and thus is unlikely to affect our proposed subjects.

Direct Pulsed Cortical Stimulation:

Intraoperative application of electrical current to the cortex in patients with tumors or epilepsy has become a standard technique during brain surgery for inferring the function of brain areas. While the patient performs motor, language or cognitive tasks under controlled conditions, the cortical surface is stimulated with a strip or grid electrode to provoke reproducible, transient changes in behavior (Borchers et al., 2012). For example, the representation of language functions was mapped to the human left hemisphere (Ojemann et al., 1989, 1991; Duffau et al., 2003,2005; Sanai et al., 2008) whereas spatial processing of visual objects (Thiebaut De Schotten, M. et al.2005) and spatial orienting and exploration (Gharabaghi et al., 2006; Kleinman et al., 2007) were mapped to the human right hemisphere.

Studies of Cortical Stimulation in Parkinson's Disease

Cortical stimulation for the treatment of Parkinson's disease has been investigated recently (Lefaucheur, 2009). Here, cortical stimulation is mostly performed after chronic implantation of strip electrodes over the motor cortex. Following closure of the craniotomy, the electrode cable(s) are connected to a trial stimulator. Based on over 3–14 days of test stimulation, the best stimulation parameters and electrodes are decided in terms of improvement in Parkinson's symptoms. Among the total number of 37 Parkinson's disease patients that enrolled in a motor cortex stimulation study, the occurrence of epileptic seizures has been reported during test stimulation in a minority of patients N=1, Arle et al., 2008).

In this group of studies, most neurosurgeons attempted intraoperative test stimulation by using subdural grid electrodes. Test bipolar stimulation (210-1000 μs –generally 400-500-μs, 1-5 Hz up to 100Hz, with intensities up to 50 mA, anodally, and also cathodally) was applied by means of the contacts situated over the primary motor or sensory cortex. There were no other complications caused by the device or the implant procedure, and all patients tolerated the implantation procedure well. (De Rose et al., 2012; Canavero, 2015; Tani, and Saitoh, 2016). In contrast to these tonic stimulation studies, our proposed phase-dependent stimulation techniques represent a much narrower (reduced number of pulses) and much more transient (active only during specific bandpass power changes) (Chen et al., 2011, 2013) form of cortical pulsed stimulation, and we feel the chance of seizure production will be reduced for these reasons. The application of cortical stimulation is performed solely for research reasons as outlined here, to assess changes in subthalamic nucleus activity (Kim et al.,2008; Magill et al.,2001), and to assess possible clinical benefits for phase-dependent stimulation modalities. Since there is a risk of seizure with cortical stimulation, an IV antiepileptic (usually levetiracetam) (Zachenhofer et al.,2011; Bahr et al., 2012; Kirmani et al.,2014; Jin et al., 2012)will be administered at the start of the surgical procedure. This is performed routinely for DBS lead placement procedures at Johns Hopkins due to the already present risk of seizures with the surgery.

Studies of Cortical Stimulation in Patients with Epilepsy

Rates of stimulation induced seizures have been measured in patient groups with and without symptomatic epilepsy concomitant with a brain tumor. Szelényi et al. used stimulation currents up to 40 mA, and found that 1/63 (1.6%) patients in the symptomatic epilepsy group suffered a stimulation induced seizure (Szelényi et al., 2007). In the nonsymptomatic group, similarly, 1/66 (1.5%) suffered a stimulation induced seizure. The range of reported seizure induction for intraoperative stimulation is from 1.2% (for a train of five stimulation technique) up to 9.5% for continuous 60 Hz stimulation (Szelényi et al., 2007). Zangaladze et al. also studied a series of invasively monitored patients undergoing cortical stimulation for mapping and used stimulation currents up to 17.5 mA at several stimulation frequencies (5-50Hz) (Zangaladze et al.,2008). These authors found that the production of neighboring electrode after discharges (which herald the onset of a seizure) are greatly reduced with lower stimulation frequencies while the actual cortical mapping is just as sensitive (Zangaladze et al.,2008). To further clarify, these stimulation induced seizure estimates occur in patients with known seizures or epilepsy. Subjects considered for this study do not have seizure disorders, and will be excluded from stimulation studies if there is a history of any seizure episode. Of note, a similar stimulation protocol involving phase dependent stimulation in epilepsy patients has been approved by the Johns Hopkins IRB under Protocol # IRB00040308.

The use of stimulation in the protocol described in this grant is much less intense than stimulation paradigms typically used for mapping. Phase-dependent stimulation techniques use subthreshold stimulation current levels timed to transiently measured periods of rhythmic activity generally lasting for only a few seconds. Monitoring for after discharges in neighboring electrodes will be used as a stopping point for further stimulation. After discharge monitoring is used routinely in the epilepsy community as a sign to abort cortical stimulation at a particular electrode (Lesser et al., 1999; Motamedi et al.,2002 ; Ojemann et al., 1989, 1991). Stimulation testing will be aborted and no further testing will be performed on subjects exhibiting after discharges.

Because of the additional subdural strip cabling present on the sterile field, there is a theoretical increased risk of postoperative infection. The strip itself is sterilized as well as the associated cabling preoperatively. Subjects undergo postoperative staple removal and wound check appointments with the surgeon involved in these procedures, and oral antibiotics are started at the sign of any stitch abscess or localized skin infection. Infections can necessitate the explantation of the DBS system. Psychosocial risks should be no higher than that already associated with awake intraoperative testing using microelectrode recording. There are no additional radiation risks associated with this protocol. The patients undergo a preoperative head CT examination for targeting and trajectory planning (when fused with the preoperative high resolution MRI), intraoperative imaging including fluoroscopy and O-arm modalities for lead localization, and an immediate postoperative head CT and later brain MRI examination after the surgery to assess lead placement.

Auditory Stimulation and Speech Recording

Auditory stimulation and speech production recordings are completely noninvasive and there are minimal to no risks associated with this kind of testing. Auditory stimulation is kept at a normal conversation level (<60 dB) to protect the ears (Way et al.,2013; Liu et al., 2000).

a. Steps taken to minimize the risks.

i) Risks related to computer-controlled sensory tests (laser and contact thermode) are controlled by software limits, and by limitation of the power delivered by any stimulator. With these tests (number 1 above section 'Medical risks listing … ') and with the ice water test, the patient will have the ability to remove his hand from the water at any time.

ii) Risks related to the ischemia test (number 2 above) will be minimized by having the investigator at the patients side throughout the test, prepared to deflate the cuff at any time.

iii) The risks of motor testing (number 3 above) are controlled by limits of the torque motor excursion and by the patients' ability to release the manipulandum at any time; any member of the research team will be able to disable the stimulator if they observe unexpected movements of the motor. All subjects will have the option to withdraw from any protocol without penalty.

iv) For the tDCS system, we will use either Conventional rectangular sponge pad: we will use a pair of saline-soaked surface sponge electrodes (anode: 7 × 5 cm^2; cathode: 7× 5 cm^2). The anode electrode will be positioned over the motor cortex representational area of the hand region on an affected side, and the return electrode will be placed above the contralateral motor cortex area or 4×1 Ag/AgCl ring electrodes: with plastic holders filled with EEG conducting gel. This will reduce the total applied current and increase the stability of stimulation. The 4 × 1 ring configuration will increase the flexibility of electrode placement with respect to the burr holes and also will allow focal stimulation of the motor cortex (Datta et al., 2010). This allows for a very low intensity current stimulation level. Even in the worst case, the current density generated by transcranial direct current stimulation on healthy head with a two electrode montage (two 5x5 cm

electrode pads) using 2 mA on the bilateral primary motor cortex (C3 anodal an C4 cathodal), is about 0.95 A/m^2 which is far below the tissue damage threshold . Brain tissue damage generally occurs at a current density of 142.9 A/m^2 or greater (Liebetanz et al., 2009).

v) With regard to the potential for patient fatigue or frustration while performing the speech production task, patients will be closely monitored for signs of stress, and patients will be asked if they would like to take a break or to stop participation in the task altogether.

vi) The risks for direct pulsed cortical stimulation are similar to the risks already present during awake deep brain stimulation lead placement procedures, with the exception of the addition of the phase-dependent selective pulse stimulation using the cortical strip. In that regard, we will exclude patients with underlying seizure disorders, history of epilepsy and under treatment with medications that can provoke seizures. Both the techniques of ECoG recording and stimulation while monitoring for after discharges represent established techniques for recording ictal and interictal periods and for brain mapping in the invasively monitored epilepsy population. Monitoring for after discharges will be performed during this transient application of stimulation pulses. Stimulation currents will be kept ≤ 6 mA. Keppra (2,000 mg for the typical range of patient weights) will be administered in IV form prior to skin incision. All testing will be aborted if afterdischarges are observed at any time.

b. Plan for reporting unanticipated problems or study deviations.

Any unanticipated problems or study deviations will be reported by notification of both the Neurosurgery Quality Assurance Office and the IRB via the in accordance with the current IRB guidelines for event reporting.

9. Benefits

The data collected under this protocol may improve our understanding of the location of recording or stimulation sites in the brain of the patient under study. This data may improve the safety and efficacy of the patient's procedure, although this is not a common event. The benefits for society include demonstration of techniques and physiological landmarks that will inform our understanding of the function and diseases of the human forebrain.

10. Payment and Remuneration

Twenty-five dollars per hour and parking expenses will be paid for research procedures performed outside the operating room.

11. Costs

Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

Participants will not have to pay for any research study procedures. The standard of care

surgical procedures will be paid for by the patient or their insurance