Protocol with Statistical Analysis

Plan Included

Project Title: The Human Thalamocortical Network in Tourette Syndrome

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IRB Protocol

1) Project Title: The Human Thalamocortical Network in Tourette Syndrome

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3) Abstract: Deep brain stimulation (DBS) has emerged as a highly efficacious treatment for addressing basal ganglia disorders[14-16, 61] such as Parkinson disease, essential tremor, and dystonia. Recently, groups including the UF Center for Movement Disorders and Neurorestoration have applied DBS for the treatment of OCD and TS[10-12, 59]. Although three brain targets have been tested in open-label series, one, the centromedian (CM) thalamus-parafascicular complex, has to date the greatest number of documented cases revealing significant improvements in motor tics). The globus pallidus interna (GPi) and the anterior limb of the internal capsule (ALIC)/nucleus accumbens have also emerged as potentially effective areas for amelioration of medication refractory tics, however they have been less studied[24, 49]. The CM target was chosen for this study as we believe it will have the greatest chance to yield positive efficacy and safety data (specific aim 1), and will also provide a target where physiological changes related to motor tics are likely to be discovered (specific aim 2)[59]. The University of Florida uses the CM thalamic region target for Tourette DBS. The reason that this target was chosen for this protocol was that our center has used the target and developed preliminary safety and efficacy data. This target also is the most commonly used worldwide, and we track all side effects of all global implants in the International Tourette Deep Brain

Stimulation public database at our institution and this is recently published in JAMA Neurology. We have shown CM has the physiological signals that differentiate tic from voluntary movement and this makes it an ideal target. Side effects depend on the contact chosen for programming and we can adjust the stimulation to avoid all side effects. The side effects we encounter include paresthesia, dysarthria, dizziness, pulling (capsule) and blurry vision. These are reversible with programming changes.

We will assess the effectiveness of chronic (continuous) stimulation of the CM thalamic region for suppressing motor tics in TS (specific aim 1). The Medtronic Summit RC+S device and cortical ECOG strips (Model 09130) can record local field potentials (LFPs), and can be programmed to detect specific electrographic patterns. The device allows physiology to be recorded even after internalization of the hardware. The physiology underlying TS will be examined in specific aim 2. Additionally, in specific aim 2 we will be able to record from electrocorticography (ECOG) leads (Medtronic Model 09130 cortical strip) which will be placed over the pre-motor and motor cerebral cortex. These studies will enhance our understanding of the pathophysiology of the disease and will help in developing better rationales for future studies. The experimental design will facilitate stimulation in the CM region, and recording from the ECOG. The presence of a detectable physiological change in CM or from the ECOG (specific aim 2) will allow for the experimental use of a closed loop DBS system, where a tic is detected on the ECOG, and a stimulation pulse is delivered in the CM region (specific aim 3).

4) Background: Tourette syndrome (TS) is a chronic neurodevelopmental disorder

characterized by motor and phonic tics, typically occurring with childhood onset[1-5]. The syndrome is commonly associated with other neuropsychiatric comorbidities (e.g. attention deficit hyperactivity disorder (ADHD), obsessive compulsive features (OCD), and other behavioral manifestations). In the majority of TS cases the motor manifestations can be managed using a combination of TS education, comprehensive behavioral intervention for tics (CBIT), and/or a variety of medications, and behavioral therapy[5, 6]. The natural history of TS has revealed that most patients will experience significant improvement of tics in late adolescence or early adulthood[5, 6]. However, experts now recognize that there is a subset of patients who will continue to experience disabling tics despite optimal medication and behavioral management. For these severely affected patients, deep brain stimulation (DBS) has the potential to improve refractory and disabling tics[7].

DBS has been well established as a treatment for Parkinson's disease, essential tremor, dystonia, and OCD, and has achieved full approval, or a humanitarian device exemption for each of these indications.[8-18] There have been many DBS studies and position papers detailing careful and meticulous techniques for screening patients[19-21].

DBS, though a minimally invasive therapy, still has associated risks, and DBS failure can result in medical complications and this endpoint can have economic consequences[22]. Patient selection and management can likely improve the risk-benefit ratio for individual sufferers and this will likely apply to TS DBS[23]. The importance of pre-operative assessment, patient selection, DBS team expertise, DBS team experience, and post-operative management has been shown to be important,

especially when groups have studied cohorts of patients that have been DBS failures[22, 23]. Since TS is a childhood onset disorder, often with complex clinical features, a waxing and waning course, and frequent neuropsychiatric comorbidities[5], the evaluation of patients has a level of complexity greater than many of the other current DBS indications[23]. During the evaluation period there is also a risk that tics may be falsely under- or over-quantified due to frequent changes in tic manifestations, and effects of social context. The first attempted surgeries for TS were ablations (i.e. lesions) placed in the thalamus and these were performed by Hassler and Dieckmann[24]. In 1999, Visser-Vandewalle reported the first case of thalamic DBS for TS[25]. Since this report, multiple groups have observed improvement with DBS despite utilizing many brain targets and many approaches[25-43].

Most early TS DBS studies consisted of either single case reports or small case series (Level of Evidence IV), and these reports had widely variable methodological and outcome reporting[23]. Since the initial reports and guidelines there has been an explosion in the field of international publications reporting both DBS successes and failures.. In 2005, the TSA hosted a meeting of internationally recognized experts to develop recommendations to guide research and early use of DBS in TS[44]. Additionally, a collaborative international network of investigators was established, and in 2010-11 the TSA commissioned an International Database of Deep Brain Stimulation Studies in Tourette Syndrome (TSA DBS Registry, http://tsa-usa.org/dbs/), which has been recently launched. The major update since 2006 has been the relaxing of the recommendation that all patients be 25 years of age or older.

Tourette, has now followed all of the other DBS indications which use age as a relative factor in the decision by a multidisciplinary team. There is no standard accepted age for DBS surgery, and there have been many reported successful cases below the age of 25[37, 42].

5) Purpose: The purpose of this research study is to evaluate the effectiveness and safety of a possible new treatment for TS. The Medtronic Summit RC+S device and cortical ECOG strips (Medtronic Model 09130 cortical strip) can be programmed to record physiology and to provide chronic (continuous stimulation), or alternatively responsive stimulation to deep brain structures.

Specifically, this investigation will:

(1) Test the hypothesis that centromedian (CM) continuous brain stimulation will be an effective and safe method for the treatment of tics in medication refractory TS. There is now a growing body of evidence supporting the use of DBS for tic suppression. Implantable brain stimulators provide a reversible and programmable solution to neuromodulation which are safer (no tissue destruction) and potentially more effective than ablative techniques such as thalamotomy, capsulotomy, and cingulotomy, especially because they can be performed bilaterally[62]. There are however important issues that may limit standard DBS effectiveness in this population including specific problems unique to this group of patients including the paroxysmal nature of the disorder. It would be desirable to design a therapy such as the one proposed in this grant application to neuromodulate only when needed (closed loop or responsive therapy). We plan to implant CM

thalamus and cortical ECOG bilaterally in 10 medication refractory TS subjects. We will employ a prospective blinded staggered onset design. We hypothesize that by using a chronic (continuous) stimulation strategy we will be able to achieve a greater than 40% reduction (over 6 months) in total tics (motor and phonic on the YGTSS) in more than ½ of our subjects (6/10). We will in this study assess safety and also employ stopping rules to ensure subject safety.

(2) Define the intra-operative and post-operative physiological changes seen in TS. We hypothesize that there will be rate and pattern changes in the physiology that will correlate with the clinical manifestation of motor and phonic tics. Following implantation and internalization of hardware, the device used in this study will be able to record physiology (i.e. the LFP). This unique feature is not currently available for other FDA approved brain stimulation devices (Medtronic PC and SC, Minneapolis, Minn), and the option will allow our team to document physiology, and to measure, using videotape analysis, electromyogram, and position sensors placed on muscles and areas of the body that exhibit tics, and we will attempt physiological correlation using LPS's from the CM region and from ECOGs. We have recently discovered band specific frequencies[59] in thalamic LFPs, and these frequencies emerged after therapeutic DBS in a small cohort of human TS subjects. We quantified increases in gamma oscillations and their correlations with improvement of TS symptomatology, and found that those subjects obtaining the best clinical outcome from thalamic DBS exhibited the greatest gamma power changes[59]. Thus, the correlation between gamma band activity and clinical tic scores supports the theory that thalamic gamma band dynamics[59] are correlated with improved

symptomatology in TS. Because synchronized gamma oscillations are a fundamental property of thalamocortical communication and DBS therapy, we will perform a comprehensive study of the modulations to define the relationship between gamma oscillations and tic expression in cortical and subcortical targets. In order to accomplish this goal, we will use a DBS system that utilizes an implanted programmable neurostimulator that will allow for synchronized recording of cortical and subcortical LFPs, and consequently enable the investigation of tic-related brain oscillation dynamics. This avenue of research is the first critical step in neurosensing and responsive neuromodulation. The neurostimulator (Medtronic Summit RC+S device and cortical ECOG strips (Model 09130) is novel in that it can be can be programmed to provide continuous or responsive stimulation. Both deep brain and cortical ECOG strips will be placed as part of this system. We will collect real time, local field potentials (LFPs) that are time synchronized with clinical behavior, and we will collect these from both the CM region and from pre-motor and motor cortex in order to study thalamocortical interactions in the context of human TS. The collection of these potentials will allow us to better understand the fundamental neural activity important to tic generation (specific aim 2), and to attempt responsive stimulation approach (specific aim 3). Our proposal will uncover the neuronal activity inherent to CM and from cerebral cortex, and will reveal how DBS affects this activity in the human TS patient.

(3) Test the hypothesis that responsive brain stimulation will provide an alternative to chronic deep brain stimulation in TS. We hypothesize that we will be able to use physiological changes collected in Specific Aim 2 to tailor a responsive

therapy for TS patients. This paradigm is preferable to chronic stimulation for its potential to reduce stimulation-related side effects. Outcomes will be measured by comparing the results of chronic continuous stimulation (Specific Aim 1) to an acute test of responsive stimulation (Specific Aim 3). Responsive stimulation parameters will be identical to chronic continuous stimulation parameters and will strictly be within safety ranges. If acute responsive stimulation leads to low side effects and comparable clinical outcomes for a patient, we will test chronic responsive stimulation for one week at a time, up to four weeks in total. This procedure will be performed at an appropriate time point (approved by the Principal Investigator) after the 6 month primary endpoint is reached but prior to Month 36 (study completion) (see visits 6.1-6.4 in schedule of events). The patient programmer will allow patients to turn off responsive stimulation and switch back to standard continuous therapy. A firmware update from Medtronic will allow the Summit RC+S internal signal sensing and processing units to communicate with the stimulation unit. Outcomes for chronic responsive stimulation will also be measured by comparing the results of chronic continuous stimulation.

Duration of the Investigation: We expect the duration of this investigation will be five years. In the first year we plan to implant and follow the first two subjects. In Year 2 we will plan to implant and follow the third, fourth, and fifth subjects while we continue to follow the first two subjects. In Year 3 we plan to implant and follow the sixth and seventh, and eighth subjects while we continue to follow the first five subjects. In Year 4 we plan to implant and follow the ninth and tenth subject, but also to continue to follow the other eight subjects. In Year 5 we will complete follow-up

and data analysis and submit publications for peer review. These time estimations are plans that could be subject to change based on a number of external factors that may be out of our control. We plan to follow each subject clinically for a minimum of 24 months following implant, and to follow them for 12 more months for a minimum of 2 and a maximum of 4 research visits, and then clinically each year as long as they wish to remain implanted, and to assess needs for battery replacement. We plan to apply to CMS and Medicare for insurance coverage of the device implantation and battery replacement costs, and to apply to Medtronic for device donation (Medtronic has already reviewed this proposal in their scientific grants committee and approved donation of the devices and replacement devices).

6) Protocol: Methodology to be used - The study will be a prospective blinded design. Subjects will include ten individuals with medication refractory and severely disabling TS. We expect to consent and screen 50 individuals in order to enroll ten. A total of 6/10 subjects (60%) will need to be "responders" as a result of the intervention (YGTSS motor tic subscale reduction of $\geq$40%) for this study to reach effectiveness criteria.

Inclusion Criteria

- The diagnosis of TS must be made by both a fellowship-trained movement disorders neurologist and a psychiatrist and must meet Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria for a diagnosis of TS.
- Yale Global Tic Severity Scale (YGTSS; 100) must be $\geq$35/50 for at least 12 months and the motor tic subscore $\geq$15. The TS must be causing incapacitation with severe distress, self-injurious behavior, and/or quality of life disruption.

OCD, Depression, and ADHD are not exclusionary[63-65] provided tics are the major difficulty requiring surgical intervention.

- There are no gender criteria for this study.
- The subject's TS symptoms must be medication refractory. To meet the medication refractory criteria, subjects must have been treated by a psychiatrist or neurologist experienced in TS with therapeutic doses (doses adapted from Scahill's recommendations of at least three dopamine blocking drugs) either 1-4 mg/day of haloperidol or 2-8 mg/day of pimozide, risperidone (1-3 mg/day), and aripiprazole (2.5-5 mg/day)]. There must be at a minimum[66] single trial with an alpha-2 adrenergic agonist (0.1-0.3 mg/day). In summary, we will use exact criteria stated by Mink et. al. TSA DBS Guidelines published in 2006, to determine if subjects are medication refractory.
- Clinically relevant depression must be pharmacologically treated and deemed stable (by the study psychiatrist).
- Must have been stabilized for one month on TS medication without a dose change prior to surgical intervention. If medication trials resulted in discontinuation of TS medications the subject must be stabilized for three months off TS medicines.
- Must be willing to keep TS related medications stable and unchanged throughout the trial.
- Must have been offered habit reversal therapy/cognitive behavioral intervention therapy (HRT) if a subject did not have it prior to enrollment. Subjects are not required to participate in HRT but it will be highly encouraged, and must be completed prior to the start of the protocol. Those who improve significantly with

HRT will be excluded from receiving surgery.

- If the tic is focal or addressable by botulinum toxin treatment, the study neurologist will offer to administer a trial of botulinum toxin prior to consideration of surgical therapy. If the subject chooses not to have the treatment, they cannot participate in the study. If the patient responds satisfactorily to botulinum toxin, and their quality of life significantly improves, they will be excluded.
- Must be 21 years of age or older (noting that the TSA recommendations for DBS have been revised and now remove the strict age criteria[49] (TSA DBS Working Group and International Database on TS DBS, Chair is the PI of this FDA IDE, Dr. Okun).
- Patient and/ or caregiver should be able to recharge the system as needed. Patients should be cognitively able to understand battery charging and status.

Exclusion Criteria

- Any previous neurosurgical intervention including DBS or ablative brain lesions, any metal in the head and any type of implanted stimulator.
- Untreated or unstable anxiety, depression, bipolar disorder or other Axis I psychiatric disorder.
- Presence of psychotic features.
- Significant psychosocial factors that can cause increased risk.
- The presence of only simple motor tics, a movement disorder other than TS, or medication related movement disorders from TS medications.
- The presence of drug-induced tics (potentially associated with the use of stimulant

medications, anticonvulsant drugs, etc).

- Severe medical co-morbidity including cardiovascular disorder, lung disorder, kidney disease, chronic neurological disease, hematological disease, or frailty that impact tolerability of the surgery as judged by the screening physicians.
- Abnormal brain magnetic resonance imaging (MRI) scan including hydrocephalus, stroke, structural lesions, demyelinating lesions, or infectious lesions that would potentially confound the outcome or safety of the surgery as judged by the study neurosurgeon. Also excluded if severe atrophy is present.
- Dementia or cognitive dysfunction that will place the subject at risk for worsening cognition, and/or may impact the ability to cooperate with tasks involved in the study.
- Any attempt or intent of suicide in the last six months.
- Significant substance abuse or dependence (e.g., stimulants, alcohol, opiates, benzodiazepines) within the past six months.
- Multiple failed medication treatments of inadequate dose or duration.
- History of noncompliance with previous medical and psychosocial treatment efforts.
- Severe head banging tics (any tics which have the potential to result in damage to the DBS).
- Women of child-bearing potential who are pregnant or who wish to become pregnant during the study (a urine pregnancy screen required).
- A positive urine drug screen for illicit substances (a urine drug screen is required), not to include marijuana/cannabinoid use.

- History of multiple surgical procedures with poor outcomes.
- Unexplained gaps in medical history.
- Pending lawsuits or other legal action.
- Patients who expect or are likely to require a future MRI.
- Patients who do not have access to a site that can program the device if they cannot come to UF for clinical re-programming followup.

Recruitment: There are approximately 600 TS patients actively followed with yearly appointments at the UF Psychiatry and Movement Disorders clinics. An average of three new TS patients are evaluated each week for diagnosis and treatment options, and many are now referred to our institution for DBS based on our experiences with OCD and movement disorders. It is unknown how many TS patients are medication-refractory. However, if we conservatively assume that 2.5-5% of existing patients will be eligible for the study, that will result in a pool of approximately 20-40 patients, plus an additional 4-6 patients a year from referrals of new patients during the life of the grant. From this pool, we anticipate being able to recruit 10 patients (2-3 per year) over 5 years to complete this study. Subjects will be paid a $200 stipend, to be paid after each visit is complete, per visit (with exception of the post-implant visits, as it does not require a separate trip to our center) to help compensate for time and travel. Unscheduled visits will be compensated if requested by the study team. One unscheduled visit per calendar year will be compensated for patient-requested unscheduled visits, though there is no limit to how many they may request. Additionally, the PI of this protocol is also the PI for the International Tourette Syndrome DBS database project, and receives TS DBS referrals from all over the

world, which will also aid in study recruitment.

Subjects will be recruited in one of three ways: 1) the neurology clinic, 2) the psychiatry clinic, or 3) through referral by the Tourette Syndrome Association and their TSA DBS database project. We will also utilize an IRB (Institutional Review Board) approved database to recruit eligible patients from the TS population who are followed in the Movement Disorders Clinic at UF.

Obtaining Informed Consent: Prior to any intervention, the principal investigator (PI), along with the neuropsychiatric study coordinator, will explain the protocol and study procedures as well as the risks and benefits of the surgical procedure, device related complications, medical related complications, and the risk of not obtaining the "perceived benefit" from surgery. The PI will explain what choices the subject will have at the conclusion of the study (if the subject consents and is implanted), including the alternatives of 1) continuing active stimulation at current settings, 2) continuing active stimulation but searching for new settings, 3) discontinuing stimulation, and 4) discontinuing stimulation and removing the device. If a subject continues to receive active stimulation at the conclusion of the study, the subject will be followed clinically by the PI and seen at yearly intervals until the device receives FDA approval, or alternatively until the device is no longer available. The Summit programmer is unique to the device under study. Commercially available programmers do not support the Summit system. Therefore, at the conclusion of the subject's participation, he or she will be limited in clinical programming follow-up to institutions (such as UF) who have the Summit programmer. The PI will follow each patient enrolled for the entire battery life of the RC+S, due to the limited availability

of the research programmer. These visits beyond the study duration will be standard yearly routine DBS programming checks. The PI will explain the time commitments for each study visit, as well as potential time commitments for any study related adverse events. Finally, the PI will discuss alternatives to participating in the study including 1) continuing medical therapy, 2) entering a TS drug trial, 3) seeking behavioral interventions (HRT, etc.), and 4) entering other device related studies for TS that may be available such as for transcranial magnetic stimulation (TMS).

7) Research Plan: This study will assess the safety and effectiveness of bilateral simultaneous implantation of CM DBS and ECOG for medication refractory TS. The primary effectiveness outcome variable for each subject will be a YGTSS total tic subscale reduction of ≥40%, and the primary safety outcome will be defined as the serious adverse event (SAE) rate using historical data published from Parkinson's disease randomized trials[13, 67-71]. The study will also examine the physiology associated with TS and tics, as well as explore the possibility of the effectiveness of responsive stimulation.

The study will follow a prospective blinded design. Effectiveness, tolerability, and safety will be assessed and the study will allow for exploration of appropriate programming parameters and physiology.

Multidisciplinary Pre-Operative Screening and Evaluation: The multidisciplinary pre-operative screening and evaluation will include four specialties: 1) movement disorders neurology, 2) psychiatry, 3) neurosurgery, and 4) neuropsychology. Details of the steps in the multidisciplinary pre-operative screening and evaluation are provided below.

The potential study subject will be evaluated by a neurologist and a psychiatrist, and each will perform a complete medical history. The subject will be asked to provide medical records as applicable from previous medical providers, and complete a medical history form. The subject will be asked to "sign off" that this medical history form is accurate and complete, to the best of his/her knowledge, so that the study team can ensure that medical history-related eligibility criteria have been assessed. The PI and study coordinator will perform urine pregnancy screening, and physical examination. The diagnosis of TS will be made based on strict DSM-V criteria, and will be confirmed by the study neurologist and psychiatrist. A psychiatrist will perform a psychiatric history and will be assisted by the study coordinator in collection of scales and questionnaires. The data and measures collected are listed below.

General Demographics Sheet: Each subject will be assigned an independent ID number (assigned by the study coordinator). The following information will be collected: age, disease duration, all medical comorbidities, all medications and dosages, family history, smoking history, alcohol history and substance abuse history.

Mini International Neuropsychiatric Interview (MINI): The MINI will be used to provide DSM-V diagnoses. This is a clinician-administered comprehensive psychiatric assessment based on DSM-V criteria. This tool will provide a pre-operative diagnosis of DSM-V Axis I disorders. The MINI is a brief structured diagnostive interview for the major psychiatric disorders that will typically last 20 to 30 minutes. The MINI will be used for screening purposes to ensure that all patients have met inclusion criteria (i.e., all psychiatric co-morbidities identified and treated

prior to DBS surgery), and will be used to assess whether pre-operative psychiatric diagnoses impart risk for post-operative mood changes.

Columbia Suicide Severity Rating Scale (C-SSRS): The C-SSRS is a questionnaire that uses a rating scale assessment to determine if there is a risk of or presence of suicidal ideation or behavior.

Quality of Life Assessment Scale (QOLAS): The QOLAS is a 10-item interview designed to assess quality of life in 5 domains: physical, psychological, social/family, work, and cognitive. The participant is asked to rate quality of life in each domain at the beginning of the study, and these ratings are compared to those later in the study to measure change in quality of life.

Yale Global Tic Severity Scale (YGTSS): The YGTSS is a semi-structured interview designed to assess tic presence and severity. Current motor and phonic tics are then rated separately according to number, frequency, intensity, complexity and interference on a 6-point ordinal scale. The YGTSS has excellent inter-rater agreement, good psychometric properties, and is recommended for use in the Tourette Syndrome Association (TSA) DBS guidelines.

Modified Rush Tic Rating Scale (MRTRS): The MRTRS is a validated measure that examines five domains of impairment in TS. The scale allows for a videotape protocol, in which an independent blinded reviewer assesses tics by video when the examiner has left the room. Ratings of 0-4 can be assigned on five disability categories: number of body areas, frequency of motor tics, frequency of phonic tics, severity of motor tics, and severity of phonic tics. The sum of these ratings yields a total score of overall tic disability (0-20). The videotapes for this study will be rated

by an independent, blinded movement disorders neurologist.

SF-36: The SF-36 is a validated 36 question quality of life measure. The results will give an 8-scale profile of functional health and well-being. The SF-36 is a generic measure that does not target a specific disease.

Hamilton Depression Rating Scale (HAM-D): The HAM-D is a semi-structured clinician administered interview designed to measure a range of symptoms. The HAM-D consists of a 17-item questionnaire designed to evaluate depressed mood, the cognitive symptoms of depression, as well as the co-morbid symptoms of anxiety.

Yale-Brown Obsessive Compulsive Scale (Y-BOCS): The Y-BOCS provides a quantitative measure of the symptoms of OCD. The Y-BOCS is a widely used and psychometrically sound clinician-rated, semi-structured interview assessing the OCD symptom severity. The Y-BOCS rates the severity of obsessions and compulsions across five items and provides a total severity score. We will be using the 10-item version which uses 5 items each for obsessive thoughts and compulsive behavior. This scale provides a quantitative measure of the severity of OCD on a scale of 0 to 40.

Young Mania Rating Scale (YMRS): The YMRS is one of the most frequently utilized rating scales to assess manic symptoms. The scale has 11 items and is based on the patient's subjective report of his or her clinical condition over the previous 48 hours. Additional information is based upon clinical observations made during the course of the clinical interview. Items specifically assess the following symptoms: elevated mood, elevated energy, increased sexuality, decrease in sleep, irritable and aggressive behavior, increased rate and amount of speech, language and thought

disorders, appearance, and grandiose or paranoid ideation. This scale will provide a quantitative measure of the symptoms of mania on a scale of 0 to 60.

Conner's Short Version ADHD Scale Adults (CAARS) short form: This is a multimodal assessment of the ADHD behaviors and problems in adults. This is a short form survey that will take 10 minutes to administer and it will provide a baseline of ADHD symptoms including Inattention/Memory Problems, Impulsivity/Emotional Lability, Hyperactivity/Restlessness and Problems with Self-Concept.

Premonitory Urge for Tics Scale (PUTS): This is a ten-item questionnaire to assess how much a Tourette patient feels an urge to tic and the intensity of the urge. It takes about 7 minutes to administer. Scores range from nine to thirty-six (item ten is not scored), with higher scores indicating higher intensity of urge.

***Multidisciplinary Evaluation: Evaluation by Neurosurgeon*:** A DBS fellowship-trained neurosurgeon (Dr. Kelly Foote) will perform a complete history and a physical examination, evaluate medical co-morbidities, obtain or examine a recent brain MRI scan, and clinically assess all medical co-morbidities and potential risks of TS surgery.

***Evaluation by Neuropsychologist*:** All potential participants will undergo a neuropsychological evaluation in order to screen for potential attention, memory, and/or other cognitive deficits that might potentially interfere with their participation in this protocol. The specific measures will provide broad-based coverage of the major cognitive domains and include validated measures routinely given to our DBS patients (pre and post-surgery), as well as those recommended by the TSA in their

general guidelines[44].

Table 1. Neuropsychological Measures

Cognitive Construct & Estimated Time	**Measures** - The neuropsychological measures have been chosen for sensitivity, resistance to practice effects and/or availability of equivalent parallel forms. * Denotes that parallel forms will be used.
General Intellect (Total Time=30')	**Weschler Abbreviated Scale of Intelligence** (WASI-II) - A quick, reliable measure of intellect yielding verbal, performance and full scale IQ estimate. The 4 WASI-II subscales include Vocabulary, Similarities, Block Design, and Matrix Reasoning. It is nationally standardized. Individuals who score below the 5th percentile will not be enrolled in this study. Administered only during the initial screening.
Attention & Working Memory (Total time = 10')	***Digit span and Spatial Span** from Weschler Memory Scale-IV - both span measures involve immediate retention of sequences, both forwards and backwards. One is verbal (digit span) and the other is visual (spatial span).
Episodic Memory (Total time=45')	***California Verbal Learning Test-2** - A sensitive verbal memory test that involves immediate and delayed recall of a list of words. Cued recall and recognition is also tested. There are 2 different forms with strong consistency and agreement. **Story (Logical Memory) and Face Memory (Visual Reproductions) subtests** from the Weschler Memory Scale-IV - Involves learning and remembering meaningful information, including stories and unfamiliar faces
Visuospatial (Total time=15')	***Judgment of Line Orientation**. Consists of 30 items, each showing pairs of angled lines to be matched to the display cards. Two equivalent forms are available.
Executive & Mental Efficiency (Total time = 12')	**Trail Making Test** - A timed measure of set shifting, visual search, and flexibility. Scores will be based on time to completion. ***Stroop Interference Procedure** - A reliable measure assessing the ability to inhibit prepotent response; sensitive to fronto-striatal dysfunction. ***Word Fluency** (phonemic and category) – involves speeded generation of words beginning with target letters (i.e., F, A, S) or from designated semantic categories.
Motor (Total time=10')	**Grooved Pegboard** - A measure of fine motor coordination and processing speed. Each hand is tested separately.
Mood Measures	**Beck Depression Inventory-2** (BDI-II) - A brief self-report scale of depression. **State Trait Anxiety Inventory** (STAI; 124) - A 40 item scale assessing state & trait anxiety.

Following the multidisciplinary screening, the neurologist, psychiatrist, neurosurgeon, and neuropsychologist will meet to discuss the findings and confirm inclusion/exclusion criteria are all adequate. The multidisciplinary team must be convinced that there are no significant cognitive deficits in any potential study subjects, and they must agree that the risk-benefit ratio is appropriate to proceed with DBS surgery.

8) Schedule of Assessments:

In addition to screening measures, assessments will be made throughout the course of

VISIT*	MINI	YGTSS	MRTRS	SF-36	HAM-D	Y-BOCS	QOLAS	YMRS/ CAARS	Neuro-psychology Battery	C-SSRS
Pre-operative	X	X	X	X	X	X	X	X	X	X
Month 1 (day 30)		X	X	X						X
Month 2 (day 60)		X	X	X						X
Month 3 (day 90)		X	X	X						X
Month 4 (day 120)		X	X	X						X
Month 5 (day 150)		X	X	X						X
Month 6 (day 180)		X	X	X	X	X	X	X		X
Month 12		X	X	X	X	X	X	X	X	X
Month 18		X	X	X	X	X	X	X		X
Month 24		X	X	X	X	X	X	X		X
Followup visits (2-4 visits within a 12 month period)		X	X							X
Visits 6.1-6.4**		X	X							X

the study. Data on complications and possible side effects of surgery will be collected in an on-going manner by the study coordinator. The following schedule of assessments is a summary of the assessments that will occur during the study.

Schedule of Assessments **(Pre-operative includes screening and baseline.)***

*visits will occur +/- 14 days from target date, except for the Month 1 visit which will occur +/- 7 days from target date

** Visits 6.1-6.4 will be up to one month at a time (+/- 14 days), for up to 4 months, at a time point approved by the Principal Investigator between Month 6 and Month 36, based on the individual's response to acute responsive stimulation. If they occur beyond month 24, they make take the place of the follow up visits.

This schedule is a guideline for which questionnaires/ assessments will be administered during the study. The principal investigator may decide all items

listed in the schedule of assessments are not necessary at every visit, with the exception of the C-SSRS. Subjects will be interviewed using the YGTSS at screening and one day prior to implantation we will recheck YGTSS to be sure they continue to meet eligibility criteria. The MRTRS will be videotaped, and blinded review will be performed by two movement disorders neurologists at baseline and at 6 months. The blinded reviewers will examine videotapes from baseline and six months in chronic continuous stimulation, OFF DBS, and responsive conditions. Additionally the study psychiatrist, assisted by the study coordinator, will perform baseline, Month 6, Month 12, Month 18 and Month 24 follow-up visits including the HAM-D, Y-BOCS, YMRS, QOLAS, SF-36, C-SSRS and CAARS (as necessary) (follow-ups to be performed +/- 14 days). The neuropsychology battery will also be obtained by the study neuropsychologist pre-surgery and approximately one year post-surgery. The C-SSRS will be administered at each study visit by the study neurologist or psychiatrist to monitor for suicidal ideation and/or intent. Along with these assessments, there will be careful documentation of all adverse events and concomitant medications therapy (reporting any medications the patients may have taken that were not allowed by protocol). At any time, participants may request to be seen for an "unscheduled visit," for example, to assess programming parameters or address an adverse event. It will be up to the principal investigator's discretion which assessments to perform at unscheduled visits. For an overview of the study procedures and timepoints, the Schedule of Events is included below.

Schedule of Events

Study Events per ICF and Protocol (monthly visits to occur +/- 14 days, except month 1, which will occur +/- 7 days) **	Screening	Baseline	Bilateral Lead Implants***	IPG Implant ***	Thresholds	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Visits 6.1 - 6.4*	Month 12	Month 18	Month 24	Follow up visits
Informed Consent	X															
Medical History (included in each consult as applicable)	X	X****														
Neurology Exam	X															
Physical Exam ((included in each consult as applicable)	X	X****											X		X	
Vital Signs	X	X		X	X	X	X	X	X	X	X		X	X	X	
Collection of Urine Samples	X															
Urine Pregnancy Test	X	X****														
Drug Test	X	X****														
Psychiatric Exam	X															
Neuropsychologist Exam	X												X			
Demographics (age, disease duration, family history, smoking history, alcohol history and substance abuse history)	X															
Structured Clinical Interview for DSM-V (MINI)	X															
Yale Global Tic Rating Scale (YGTSS)	X	X				X	X	X	X	X	X	X	X	X	X	X
Blinded Yale Global Tic Rating Scale (YGTSS)	X										X					
Pre-Implant Modified Rush Tic Rating Scale (MRTS)	X															
Modified Rush Tic Rating Scale (MRTS) with device turned on, off, and "responsive" setting						X	X	X	X	X	X	X	X	X	X	X
Blinded Rating Modified Rush Tic Rating Scale (MRTS)	X										X					
SF-36® Health Survey	X					X	X	X	X	X	X		X	X	X	
Hamilton Rating Scale for Depression (HAM-D)	X										X		X	X	X	
Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)	X										X		X	X	X	
Young Mania Rating Scale (YMRS)	X										X		X	X	X	
The Conner's Attention Deficit Questionnaire (CAARS)	X										X		X	X	X	

Neuropsychological Battery (Weschler abbreviated scale of intelligence, digit span and spatial span, California Verbal Learning Subtest, Story and Face Memory Subtest of WMS-III, Judgement of Line Orientation, Stroop Test, Trailmaking Test, Word Fluency Test, Grooved Pegboard, State Trait Anxiety Inventory, Beck Depression Inventory II)	X												X			
Premonitory Urge for Tics Scale (PUTS)	X	X				X	X	X	X	X	X	X	X	X	X	X
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X				X	X	X	X	X	X	X	X	X	X	X
Physiology Collection		-			X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessment Schedule (QOLAS)	X										X		X	X	X	
Review of Inclusion/Exclusion Criteria	X	X														
Review by multi-disciplinary DBS panel	X															
Neurosurgical Exam, including co-morbidities, risk assessment	X															
MRI brain w/dye			X													
CT scan for localization				X												
Anesthesia				X												
Hospitalization			X													
Device Activation					X											
Device Programming					X	X	X	X	X	X	X	X	X	X	X	X
Explant																X
Replacement procedure (either new battery or non-IDE DBS)																X
Concomitant Medication Log	X	X		X	X	X	X	X	X	X	X		X	X	X	
Adverse Event Log		X		X	X	X	X	X	X	X	X		X	X	X	

* Visits 6.1-6.4 will be up to one month at a time (+/- 14 days), for up to 4 months, at a time point approved by the Principal Investigator between Month 6 and Month 36, based on the individual's response to acute responsive stimulation. If they occur beyond month 24, they make take the place of the follow up visits.
** Patients will receive a $200 stipend per visit to help compensate for time and travel, with the exception of "post implant," as it is typically done during the same trip as the IPG implant visit.
*** Lead and IPG implant will be completed within 30 days
**** Only done at baseline if screening visit assessment is over 30 days before surgery

9) Surgical Procedure: A high resolution, volumetric, three tesla MRI scan will be obtained prior to the surgical procedure. On the morning of the procedure, a Cosman-Roberts-Wells (CRW) head ring will be applied under local anesthesia and a high-resolution stereotactic head Computed Tomography (CT) scan will be obtained. Using software developed at UF, the CT and MRI images will be fused and stereotactic targeting will be carried out using the high quality MRI images. Only imaging procedures that adhere to the DBS manufacturer's guidelines will be used in this study. This software facilitates navigation in "AC-PC space" (a computationally reformatted MRI with a three-dimensional, orthogonal Cartesian coordinate system centered on the patient's mid-commissural point), which is readily defined by identifying the anterior and posterior commissures and a non-colinear midline point in the patient's brain. The initial target and trajectory will be selected in AC-PC space and the corresponding CRW coordinates will be automatically generated and used to set the stereotactic frame. Detailed microelectrode recording will confirm the location of CM prior to implantation.

CM Location: The stereotactic target of CM will be defined anatomically utilizing lateral, antero-posterior, and midline points of reference. The anterior commissure, posterior commissure, and midline points will be defined on our computer software. The antero-posterior coordinate will be defined relative to the midcommissural point. The CM target will be stereotactically targeted at 5 mm lateral, and 4 mm posterior to the midcommissural point. A trajectory will be chosen to avoid blood vessels and the base of sulci. A dime to nickel sized burr hole will be placed and a microelectrode recording apparatus set up on the head frame. The CM thalamus will be located by

recording cells in the dorsal thalamic tier using microelectrode recording, and by fusion to our 3-dimensional atlas which can be morphed to the subject's MRI and then the target located by superimposing microelectrode recordings (3 passes) on the morphed atlas. The physiological recordings will be utilized to define 10 mm above CM thalamus, delineate the dorsal border, and record through the length of the nucleus (approximately 10 mm), and into ventral thalamus (approximately 10 mm). Additionally, the ventral thalamic border will be delineated by the microelectrode recording. The study PI is experienced in microelectrode mapping (over 900 DBS cases) and will determine the correct location and depth of the final lead. The subject will have position sensors placed on the extremities with motor tics. Recording of cells and position sensors will be synchronously obtained, along with a videotape to correlate tics. Once the pattern of physiological signal has been verified, the final lead will be placed to cover both the dorsal and ventral extent of CM. Contacts 1 and 2 (of 0, 1, 2, 3 ventral to dorsal configuration) will be placed in the center of the target. The lead will be tested by macro-stimulation to obtain thresholds for benefit and side effects. A fluoroscopic X-ray will then be obtained and the lead secured using the plastic cap provided in the DBS kit (Medtronic, Minneapolis, Minn)

After placement of each CM DBS lead, a cortical ECOG strip on each side will be placed through a second small burr hole to reach the desired pre-motor and motor cortical strip region. A Medtronic Summit RC+S device which is a new neurostimulator that has the ability to acquire, process, and store neural activity from ECOG and deep brain LFP leads will be placed subclavicularly within 30 days of lead implant (and tunneled and connected by a lead extension as is standard in DBS

operations). The lead configuration is connected directly to the battery source which will be placed in a subclavicular pocket and will consist of the following: lead 1 – left CM depth electrode, lead 2 – left cortical ECoG strip for pre-motor and primary motor, lead 3 – right CM depth electrode, and lead 4 – right cortical ECoG strip for pre-motor and primary motor. Lead 1 and lead 2 will be connected via a Y-connector (Medtronic 37082) provided by Medtronic to form a single channel 8-contact connector because Summit RC+S only allows 2 8-contacts leads instead of 4 4-contact leads. The same will be done to lead 3 and lead 4. There will be one neurostimulator (Summit RC+S) implanted within the chest connected to all four leads.

The placement of the Medtronic Model 09130 cortical strip will target M1 at a point on M1 approximately 3 cm from the midline. This targeting will be based on the anatomic identification of the central sulcus and by using the method described by Shimamoto e.a.[72], we will use these authors' published procedure to place and verify the ECOG lead[72]. Once the new burr hole is drilled, the dura matter will be opened and the Medtronic Model 09130 cortical strip will be placed over pre-motor and motor hand/arm regions. The "hand bump" is an easily identifiable landmark on the stereotactic MRI. We will also check the "phase reversal" on somato-sensory evoked potential which will assist in confirming the electrode position is over the M1 hand/arm area. A small notch will be placed on the burr hole to help hold the cortical strip in place, and the burr hole will be sealed with a fibrin sealant. Post-implantation, subjects will be comprehensively evaluated for any untoward symptom and will receive the appropriate treatment as necessary. Subjects will continue to be evaluated

throughout the study for any significant health changes and referred accordingly for clinical care as needed.

10) Description of the Hardware: The system that will be used includes the neurostimulator itself; the implantable leads; a programmer that includes a wand and telemetry interface; a recharging coil and controller for recharging Summit RC+S neurostimulator; and a patient remote control to check battery status and whether the device is on or off. These devices are called the Recharge Therapy Manager (RTM, Model 97755) and Patient Therapy Manager (PTM, Model 4NR009), respectively. The patients will receive training from the research group, and will be given written instructions to take home. The Clinician Telemetry Module (CTM, Model 4NR011) is used to set up the device stimulation. The sensing parameters will be setup through the Summit RC+S Research Development Kits. The depth leads for CM have a flexible, isodiametric lead body that encloses four insulated wires, and have four cylindrical electrodes at the distal end. The proximal end has four contacts adapted for connecting to the neurostimulator device (Medtronic lead models 3387). The depth lead is implanted into the brain to provide an interface through which stimulation can be delivered, or the activity of the brain can be monitored by the device or observed by a clinician using a programmer. The model 3387 DBS lead has four electrodes with 1.5mm contacts and 1.5mm spacing. The RC+S stimulator is rated for 9 years and is rechargeable. Patients will be required to charge as needed to maintain device functionality.

The Medtronic Model 09130 cortical strip has a flexible, isodiametric lead body that encloses four insulated wires, and has four disk electrodes within a paddle at its distal

end. The proximal end has four contacts adapted for connecting to the neurostimulator device. The strip lead is implanted into the brain to provide an interface through which stimulation can be delivered or activity of the brain can be monitored by the device, or observed by a clinician using a programmer.

There will thus, in summary, be two CM thalamic leads (one in each brain hemisphere) and two ECOG strips (one in each brain hemisphere), and one neurostimulator (Summit RC+S) implanted in the chest.

Subjects will have a post-operative CT scan for lead location and to assess for intracranial air and hemorrhage. The CT scan will be fused back to the MRI. Each of the four contacts on each deep DBS lead will be measured, and localized on an atlas to confirm the correct lead position. In the future if an experimental fMRI or MRI is considered, FDA and IRB approval will be sought. The Summit system has not been evaluated for MR compatibility.

11) Specific Approaches for Specific Aim 1 Overview: The study will follow a prospective blinded design (see Figure 1 below). Effectiveness, tolerability, and safety will be assessed, and the study will allow for exploration of appropriate programming parameters.

12) Study Summary: Once subjects have been consented, baseline measures must be collected within two weeks of the surgery. Subjects will be followed with standardized measures for a minimum of 24 months (+/- 14 days) post-DBS implantation and a maximum of 36 months (+/- 14 days) post-DBS implantation for the research study. The main outcomes will be measured at 6 months post-DBS (+/-

14 days). There will then be three additional days of data collection where subjects will be either "on" DBS, "off DBS" or "on DBS responsive mode (Figure 1 and 2)." MRTRS scales will be collected in each mode for an independent video review. Stimulators will be blindly set to the "mode" for the day and left in that mode for one hour prior to data collection which will include MRTS and also physiology as recorded by the neurostimulator.

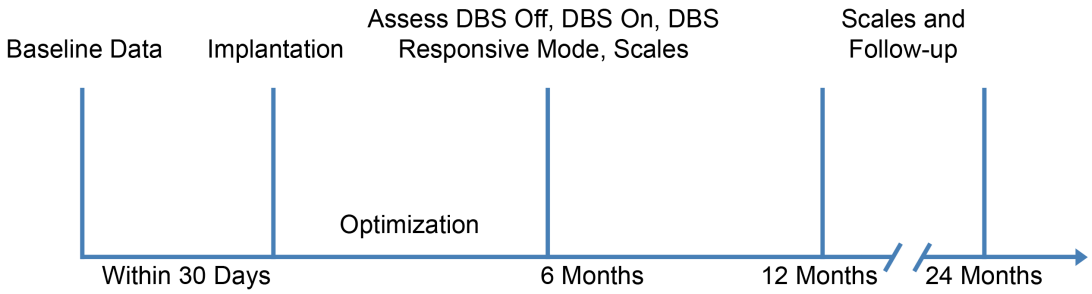


Figure 1. Study design

- Following recruitment and multidisciplinary screening, candidates will receive bilateral CM DBS plus bilateral ECOG strips, and bilateral chest implanted neurostimulators.
- Prior to implantation, primary outcome and secondary outcome variables will be assessed. A blinded videotape will be obtained of the MRTRS. The blinded videotapes will be evaluated by two blinded movement disorders neurologists who will score the MRTRS's at baseline and 6 months (+/- 14 days).
- Implantation will be accomplished by a neurosurgeon and neurologist, both of whom will not participate in the blinded evaluations of subjects.
- The primary effectiveness outcome for the study will be ≥40% reduction on

the blindly rated YGTSS total motor/phonic tic sub-scale at six months on DBS as compared to pre-op baseline. The secondary effectiveness variable will be assessed by the MRTRS blinded ratings.

- The primary safety outcome will be defined as the serious adverse event (SAE) rate in patients compared to the SAE rate in patients implanted with the Medtronic DBS device for treatment of Parkinson's disease as drawn from published randomized studies[13, 67-71]. The intent is to show that the serious adverse event rate will not exceed the 95th percent confidence interval for the historical experience with the Medtronic DBS for Parkinson's disease. A 95% confidence interval for the SAE rate will be utilized for an analysis of data for 10 subjects at their three month visits due to the small sample size.
- The secondary outcome measure will consist of a review of the types, duration and frequency of non-serious adverse events. Therefore, all adverse events will be used as an additional measure in determining safety outcomes.
- The safety experience will be reviewed approximately every 6 months by the Data Safety Monitoring Board (DSMB). The DSMB will be informed of all serious adverse events and all mild adverse events which are potentially device related. The DSMB will designate each AE as mild or severe; as device related, uncertain to be device related or not device related; and as anticipated or unanticipated. The DSMB may employ a stopping rule for greater than 1 device related death or completed suicide.

Details of the Protocol:

- Following consent, subjects will be screened by the multidisciplinary team

and ethics panel to be certain all inclusion and exclusion criteria are met.

- Following approval by the multidisciplinary and ethics panel, subjects will undergo baseline studies and within four weeks will receive bilateral CM devices and bilateral ECOG devices.
- Stimulation will be turned on within one week (+/- 7 days) after the implant completion which will be approximately one month post lead implantation.
- All subjects will undergo once a month programming visits for months 1-6 (+/- 14 days, with the exception of Month 1, which has a +/- 7 day window). Additional visits may be needed to obtain optimization of settings. Physiological data will be collected from both the CM thalamus and the ECOG strips during all protocol visits, and responsive parameters will also be tested. Subjects may also choose to come to the clinic for "unscheduled visits" as they deem necessary. The activities done at these visits will be at the discretion of the principal investigator.
- Physiology data beyond month 12, and the chronic stimulation titration (visits 6.1-6.4), may be performed at the participant's home as necessary rather than at the University of Florida. The equipment used are all mobile as shown in the RC+S system configuration as explained in Section 18 (refer to Figure 3).
- Details of physiology collection procedure: The subject will be asked to put on EMG sensors and signals from this device will stream into the research host computer (RHC). The signals from the Summit RC+S device will also be downloaded onto the RHC, which will have the Summit Research

Development Kit (RDK) installed (refer to Section 19). Stimulation and brain activity data since the previous visit can then be reviewed and analyzed on an individual basis.

- The CM neurostimulators will be programmed in an outpatient setting to deliver only chronic continuous stimulation in all patients. Stimulation parameters will be adjusted as necessary to provide maximal tic reduction. The cortical strips will be chronically set to record mode for data collection only, until the acute Aim 3 responsive trial.
- The neurologist and DBS programmer will be allowed to adjust stimulation parameters during months 1-5 to achieve maximal tic suppression and minimal to no side effects. The programming that will be employed will be identical to that used for Parkinson's disease randomized trials[13, 67-71].
- At day 180 (6 months +/- 14 days), the primary and secondary outcome variables will collected, as will all scales. If optimization is not achieved at Month 6, Month 6 data collection may be postponed as deemed necessary by the Principal Investigator (with the exception of the C-SSRS), up to 12 months (+/- 14 days) past the first programming visit (Month 1). However, there must be a 30 period of stable stimulation settings before primary outcomes are assessed.
- Primary and secondary outcomes and physiology collection will be assessed over approximately 3 outpatient days. The "on" DBS condition will be used and compared to the pre-operative baseline for the primary outcome (specific aim 1). The other conditions will be used for secondary analyses, and the on

responsive stimulation response will be compared to the pre-operative baseline (specific aim 3).

- Beyond the 36 month study period, the Principal will continue to follow and provide standard of care visits to subject throughout the duration of battery life (labeled to last 9 years). These visits will be treated and billed as routine DBS checks.

Algorithm for CM Thalamus Device Programming: Programming to be performed for this study by the device programmer under the supervision of the PI.

Prior to programming sessions each month, there will be a one to two hour physiology data collection session (specific aim 2). Fifteen minutes of real time physiological baseline monitoring will be recorded from the device (this will be videotaped and motion sensors will be applied to capture tics and correlate with physiology). Responsive settings will be checked each month and any improvement in tics noted.

- Each of the four thalamic contacts on the DBS lead will be checked for benefits and side effects of stimulation using the identical paradigm employed by our clinic for subjects receiving best clinical care with Parkinson's disease DBS[73]. The initial programming paradigm is designed to help the clinician choose the best stimulation contact by first identifying thresholds and side effects for each lead while holding frequency and pulse width constant.
- A baseline MRTRS will be recorded prior to each programming session.
- Electrical impedances and battery life will be checked to ensure the integrity of the device. Any anomalies will require immediate referral to the implanting

neurosurgeon for evaluation and potential correction.

- High frequency stimulation will be held constant at 130Hz, and pulse width held constant at 90μs during the duration of the initial programming session.
- Each lead contact (0, 1, 2, 3) will be independently tested on each of the two CM leads. The voltage will be increased by .1-.5 volts until a side effect is encountered or alternatively until 7 volts is reached. Any side effect lasting >30 seconds or that is uncomfortable for the subject will be immediately acted upon by the programmer by decreasing the current to a tolerable level or turning the device to an off position. The current setting evoking a side effect will be documented so that it will not be used for future programming at that contact. We will record data during the different stimulation settings to investigate the induced changes in the brain signals that may provide signatures of optimal stimulation settings.
- The benefits on visible tic suppression will be subjectively assessed at each contact and each setting; the contact providing the most improvement will be chosen for chronic monopolar stimulation.
- A concluding MRTRS will be recorded at the conclusion of this initial programming session, following a 20 minute period at the chronically chosen settings.
- Each month the programmer will have the latitude to change the contact, frequency, or pulse width of stimulation liberally, and as often as needed until optimal settings are discovered for visible tic suppression.

- There must be a 30 day period where no changes are made to the final DBS parameters prior to the examination of the primary outcome measure.
- All scales and a blinded videotape will be obtained of the MRTRS at 6 months in the on, off and at responsive stimulation settings will be performed.
- The MRTRS videotapes will be scrambled by the statistician for all conditions and time intervals so the videotape review will not be biased.

A summary of Month 6 data collection is provided below (Figure 2), note these conditions will be presented blindly to the patient, and then performed over 3 separate days of testing. The order of the three conditions will be set by the statistician and counterbalanced across all 10 patients (figure 2 below):

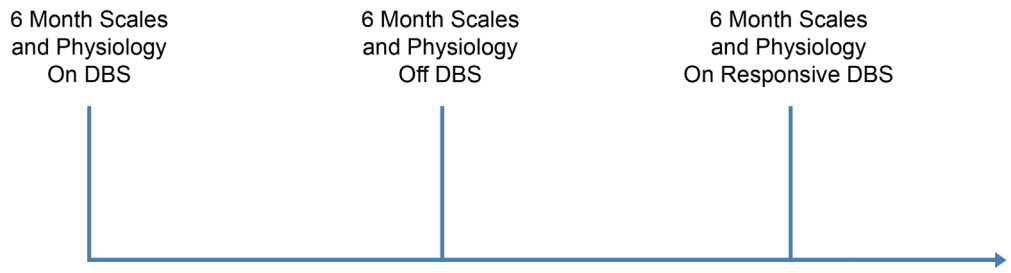


Figure 2. Timeline of clinical scales for reporting study outcomes.

Specific Approaches for Specific Aim 2: The information obtained in specific aim 1 during each data collection session will be sorted, and correlations between physiology and tics, urge to tic, or behavioral abnormality will be sought. The signal-processing tools that will be utilized for this task will include established spectral analysis methods, namely:

- Power changes in the time and frequency domains

- Changes in inter-channel coherence and/or cross-correlation
- Fractal dimension and line length
- Presence of phase amplitude coupling between gamma band activity and other oscillations

The combination of these analysis techniques in multiple brain regions (cortical and thalamic) allows for detection of thalamocortical interaction. Endogenous modulation of thalamocortical rhythmicity occurs during specific cognitive processes, several of which (e.g. sensorimotor gating, and focused motor action) have been implicated in the pathophysiology of TS[57]. This analysis will be performed for two reasons. First, these analyses may yield triggers detectable by the device by utilizing detection and signal analysis tools (i.e. spectral power estimation). This analysis will be performed for two reasons. First, these analyses may yield predictors detectable by the device by utilizing detection and signal analysis tools: line length trending, area-under-the-curve trending, and half-wave detection, applied in various logical combinations on single or multiple channels. Second, using an *a priori* limit on the multiple analysis methods will aid in assigning significance to any changes observed. This analysis will also allow us to conclude the total number of subjects in our cohort with gamma or other band oscillations. The analysis will allow us to examine whether there is an ECOG motor or pre-motor signal that can be used for responsive stimulation (detect in the ECOG and respond with DBS from the CM).

Specific Approaches for Aim 3: If an electrophysiological change or set of changes from baseline can be observed to preferentially accompany motor tics, across a given subject's data, with significance $p < 0.1$, it will be defined as a *predictor* for that

subject. Note that we do not require a high level of significance here; nor do we require the predictor to be entirely absent from baseline data. We assume that the consequences of a false positive (i.e., detection of the predictor without accompanying tics) are negligible. This is justified since the amount of stimulation that will be delivered responsively will in any case be less than that which would be delivered by their regular continuous stimulation. We will utilize available analysis tools to examine outcomes, but we will also report to the FDA on any new responsive stimulation detection and programming tools that may become available during the course of this protocol, and request permission to use them if appropriate.

Subjects for whom predictors can be identified during acute physiological data collections in Months 1-5, as described above, will have a responsive DBS setting programmed for their six-month outcome testing. In responsive mode, the device may titrate the amplitude of stimulation within previously set comfort and safety levels, if tic signatures are not suppressed (i.e., until non-symptomatic brain signals are attained). If patients respond favorably during acute responsive testing, we will test chronic responsive stimulation for one month at a time (+/- 14 days), at some time point approved by the Principal Investigator between Month 6 and Month 36 (see visits 6.1-6.4 in schedule of events). The stimulation amplitude will be set to its optimal setting for chronic stimulation. The new patient programmer will allow patients to turn off responsive stimulation and switch back to standard continuous therapy. Subjects without a predictor will not have a chronic responsive setting.

Options for the Subject Once Specific Aims are Complete: Subjects may at any time during the study opt to terminate their participation and may also opt for

hardware removal. The investigator may continue to empirically adjust stimulation settings based on patient tolerance, and both short-term and long-term response. As long as the RC+ S batteries are implanted, all subjects implanted will have the option for chronic or responsive stimulation depending on their individual preference and effectiveness of each technique. For subjects not under optimal control following 6 months of DBS therapy, we will offer open-label programming to search for the best parameters. Subjects who continue to receive active stimulation, will be followed by the PI and seen at yearly intervals. Patients will be able to be implanted with the standard Medtronic device after the study period once the RC+S is depleted. However, only the RC+S allow closed loop stimulation. As long as the subject is implanted with the RC+S device, the Principal Investigator will continue to follow and provide standard of care visits to subject throughout the duration of its battery life (labeled to last 9 years). These annual visits will be treated and billed as routine DBS checks. We will discuss with the subject the option of explanting their devices and pursuing insurance authorization to implant a standard Medtronic DBS device in CM for control of tic as needed.

13) Description of Power Analysis and Statistical Methods:

Power Analysis: We will determine the effectiveness of DBS by comparing total tic score (YGTSS) at the six month time point to the pre-operative value for each subject. A 40% or greater reduction will be considered a successful response. The power to detect a statistical significance between a null proportion of 0.10 (this assumes that the true proportion of successful responders is 10%). The power analysis revealed that for an alternative proportion of .60 (i.e., 6 of 10 patients will show a

40% or greater reduction in motor tics at six months) there is a statistical power of 0.80 at an alpha level of .05. Therefore, we anticipate ten participants will be required for this study. The *power* procedure in Statistical Analysis Software (SAS), version 9.1 was used to conduct the power analysis. Data collected from this study will provide additional and currently unavailable data to inform power analysis of subsequent studies in Table 2 below.

Table 2. Power Analysis for Sample Size Effects

Table Power Analysis	Sample Size					
	8 patients		*9 patients*		*10 patients*	
Alternative proportion	***Number of responders***	***Power***	***Number of responders***	***Power***	***Number of responders***	***Power***
.30	2	0.25	3	0.27	3	0.29
.40	3	0.39	4	0.43	4	0.46
.50	4	0.54	5	0.59	5	0.63
.60	5	0.70	5	0.75	6	0.80

General Analysis Approaches: The Wilcoxon signed rank test will be used to test for significant pre-post changes in numerical measures (e.g., YGTSS). Spearman correlations will be used to test relationships among numerical measures (e.g., neurocognitive measures, severity of tics and quality of life measures). Both the Wilcoxon signed rank and Spearman correlation tests are nonparametric procedures that are robust from data departures from normality and appropriate in the case of small sample sizes. All statistical tests will be two-sided and will be considered significant if p-values are less than 0.05. SAS software will be used to conduct all data analysis.

Specific Analysis Approach for Aim 1: We will determine the effectiveness of the "on condition" of DBS by comparing motor tic score (YGTSS) at the six month evaluation to the pre-operative value for each subject. A 40% or greater reduction will be considered a successful response. We will then test the hypothesis that the proportion of successful responders is greater or equal to (6/10) using the exact

binomial test. We will compare the baseline motor YGTSS to the on DBS condition at six months (primary outcome). We will also perform comparisons of baseline to on/off/responsive conditions, and also comparisons of on/off conditions at six months as secondary analyses. To compare on versus off condition, we will form paired difference scores of YGTSS (YGTSS on minus YGTSS off) at six months and test for significance using the Wilcoxon signed rank test.

Specific Analysis Approach for Aim 2: We will first investigate rate and pattern changes in physiology and the possible correlation with clinical manifestation of motor tics by using exploratory data analysis techniques that will be graphical in nature. These exploratory techniques will include spectrograms and event related potentials. We will then conduct a preliminary time series analysis estimating fractal dimension, line length, and area-under-the-curve of the raw signal. The data obtained from these analyses will inform subsequent analysis and guide the development of statistical methods to analyze these types of data streams. Subsequent analysis will be more comprehensive, and will include time-frequency analysis of specific frequency bands, measures of coherence between channels containing movement related activity, and quantification of phase-amplitude coupling between frequency bands of interest. Any of these techniques has the potential to identify candidate predictors of tic onset.

Specific Analysis Approach for Aim 3: This protocol calls for testing an acute responsive DBS condition in subjects who reveal physiological predictors that can be set to sense tic by ECOG, and to respond to tic on the CM implanted device. It may also be possible to both sense and deliver stimulation from the CM DBS lead. Data will be analyzed using the Wilcoxon signed rank test. **We will collect physiology**

data and analyze the data, and test chronic responsive stimulation settings one month at a time for those subjects that respond well to the acute testion after Month 3.

Risk Analysis: The Medtronic Activa RC+S device and Medtronic Model 09130 cortical strip system represents a new therapeutic approach to treating TS. As such, the probable risks and anticipated benefits of this treatment approach must be considered based on information from the literature of deep brain stimulation. This experience suggests that deep brain stimulation has an acceptable risk profile and that anticipated benefits outweigh the probable risks. Kimmelman and colleagues in a recent meta-analysis of deep brain surgery for Parkinson's disease revealed a favorable risk-benefit ratio with the estimated intracerebral hemorrhage rate of 1.57% (95% confidence interval, 1.26%-1.95%), and the proportion of trajectories associated with serious neurological deficits was only 0.41% (0.28%-0.60%)[74].

14) Safety Studies and Potential Risks with the Investigational Device:

Experience with the Medtronic RC+S device and Cortical Strips:

There are currently no human patients implanted with the Medtronic Activa RC+S along with the Medtronic Model 09130 cortical strip for TS.

Safety of Chronically Implanted Neurostimulators: Probable risks associated with chronically implanted neurostimulators and of devices implanted in the cranium include the risks of surgery-related adverse events such as hemorrhage and infection, chronic implantation adverse events such as infection, erosion and necrosis, stimulation-related side effects or discomfort, and stimulation associated brain injury. Experience from randomized DBS studies for Parkinson's disease suggest a low

overall risk[13, 67-71]. Additionally, a recent expert consensus led by Bronstein et al. reviewed DBS complications[75]. The rates of surgical complications depended on the team and experience and included intracranial hemorrhage, stroke, infection, lead erosion without infection, lead fracture, lead migration, and death. These were all rare complications and the most worrisome overall complication was the possibility of symptomatic intracerebral hemorrhage which was less than 2% at experienced medical centers. Hardware infection was the most commonly reported serious adverse effect and ranged from approximately 5% to 20% among reports in the literature[75].

Safety Experience with Medtronic Summit RC+S device and Cortical Strips in TS

There are no human cases published of the use of this device in TS DBS.

Perception of Neurostimulation: Stimulation of the brain has the potential to produce sensations that are noxious or disturbing. Any stimulation related side effects can be alleviated by re-programming or turning the device to an off position, which we plan to do during this study.

Other Medtronic Summit RC+S and Cortical Strip System Potential Risks:

The following adverse events have been reported with deep brain stimulation: dysaesthesias, speech disorders, headache, abnormal thinking, abnormal vision, double vision, abnormal dreams, difficulty swallowing, paresis/paralysis, pneumonia, CNS depression, hostility, personality disorder, confusion, paresthesia, anxiety, chest pain, hallucination, drowsiness, amnesia, nausea, vomiting, dizziness, walking difficulty, postural hypotension, increased salivation, agitation, delusions, difficult

breathing, fainting, sleep disorder, rapid heart rate and deep thrombophlebitis[74, 76-78].

If the patient is not satisfied with the programming stimulation options at home and would like them to be revised outside of the standard clinical study visits, reprogramming can only be performed at UF. This is because standard Medtronic stimulation programmers that can interface with standard Medtronic neurostimulators, which can be found at other institutions, do not interface with the Summit RC+S.

Summary of the Most Serious Medtronic Summit RC+S and Cortical Strip Risks:

There are no human cases published on this device in TS DBS and therefore there is no summary data available except what can be referenced in the Device Masterfile #2010.

Some medical procedures such as diathermy, electroconvulsive therapy, and transcranial magnetic stimulation are prohibited because the amount of energy coupled into the implanted lead system can result in heating and neural tissue damage. Any medical procedure that delivers energy to an implanted lead system has the potential to cause tissue damage by induced heating. Therapeutic radiation to the head should be avoided due to potential damage to the Medtronic Summit RC+S and Medtronic Model 09130 cortical strip system. This is included in the labeling appendix which we include in this IDE.

Treatment with therapeutic ultrasound to the head and neck should not be performed since energy may be sent thorough the leads resulting in brain damage. The effects of

therapeutic ultrasound treatment below the head and neck on the System are unknown and should be avoided unless the risk of not using the treatment outweigh the risks of using it. However, imaging with diagnostic ultrasound to any part of the body is safe and will not interfere with the System.

***Magnetic Resonance Imaging*: The Summit system has not been evaluated for MRI safety. Therefore, subjects will be asked to carefully consider whether they anticipate future MRI scans. This is a risk-benefit trade-off that will be discussed prior to study participation. If necessary, a CT scan will follow device implantation.** Images of the brain produced using ultrasound or magnetic resonance imaging (MRI), may be compromised by a cranially implanted medical device. In addition, there are risks associated with neuroimaging that require following safety guidelines; failure to do so may result in serious injury to the patient.

The high magnetic field associated with MR imaging may cause induced currents and/or mechanical forces on the pulse generator and/or lead(s); these may be perceived by the patient and could result in dislodgement of a pulse generator and/or the lead(s). In addition, the radio frequency (RF) fields used in MR imaging may cause induced currents and heating of the pulse generator and/or lead(s); these may cause damage to the surrounding tissue.

MR imaging of patients implanted with a neurostimulator device may be safe under certain conditions (see labeling appendix), however failure to follow MR safety guidelines may result in injury. While the number of incidences has been low, there have been two reported cases of severe injury resulting from MR imaging of patients implanted with deep brain stimulators. In one case, a patient who was implanted

bilaterally with DBS electrodes for treatment of PD experienced dystonia immediately following an MRI procedure. In this case, it is thought that the heating in the leads may have caused thermal tissue damage. In the second case, a patient with bilaterally implanted neurostimulation systems developed a neurologic deficit following an MR procedure. In both incidences the scans were performed using parameters that deviated from the manufacturer recommended safety guidelines[79, 80].

System Replacements, Lead Connection Changes, and Explants

***Battery Depletion*:** In the event of battery depletion (whether due to a pre-mature failure or following the labeled 9 year lifetime), an additional surgical procedure will be required to replace the Neurostimulator, assuming that the System functionality is still desired.

The risks posed by a Neurostimulator replacement or explant procedure are expected to be lower than those of the initial implant. During a replacement procedure, there is no need to create a new craniectomy, resulting in a much shorter procedure time. The previously implanted leads are attached to the new neurostimulators or are abandoned. Therefore, neurostimulator replacements does not require penetration of the dura.

When the RC+S battery is depleted, the patients will be given the option of replacement or explantation. For the former, the depleted device, will be replaced by either an RC+S (with 4 electrode array inputs) or one commercially available RC device (with 2 electrode array inputs). In the latter case, the cortical leads will be left in place, disconnected proximally, with the thin proximal end of the extension

exposed and buried deep to the IPG. This will avoid the risk of inadvertent delivery of unintended cortical stimulation as a potential programming error. Only continuous (conventional) DBS can be delivered from the RC devices. If the study doctor determines it is necessary to remove the device, or if the patients request that the device be removed, the cost of removal will be billed to the insurance company. The patients will be responsible for paying any deductible, co-insurance, or co-payments for these explant services, and for any non-covered or out-of-network services. Patients will be informed that DBS electrode removal involves substantial risk of reversible and irreversible harms, such as requiring additional brain interventions, further hospitalizations, long-term use of antibiotics or other medications, possible loss of the benefits of future stimulation and psychological distress.

Summary of Risks to Subjects: Though there is no safety data in humans specific to the devices used in this study, the safety experience of DBS systems in the literature has been reassuring[75]. Significant adverse events associated with implantation of the neurostimulator and leads, such as hemorrhage, CNS infection and poor wound healing can occur with DBS. Subjects have tolerated DBS devices well, both in terms of comfort with the cranial implant as well as with stimulation. And the common side effects encountered that are unique to TS CM DBS have been a subjective sensation of eye pulling/twitching, sensory phenomenon, nausea, and dizziness. All of these common side effects with CM DBS are reversible by changing the stimulation setting or turning the device off. [37, 38, 59, 75, 76, 78, 81-83].

Procedures for Protecting Against or Minimizing Risks: We plan to follow the

Tourette Syndrome Association's recommendations and only enroll adults with TS whose tics are severe and intractable to medical therapy[44]. Our investigation will use rigorous inclusion and exclusion criteria, pre- and post-operative assessments using standardized rating scales and comprehensive post-operative assessments including neurological, psychiatric, and neuropsychological evaluations. Study subjects will be assessed by a psychiatrist or neurologist using the C-SSRS at each study visit to monitor for suicidal ideation and/or intent. In addition, the UF Movement Disorders Center has expertise in diagnosing and treating TS in a multidisciplinary manner.

Effective screening and the neurological/psychiatric evaluation will rule out other conditions that may prevent subjects from participating in these studies. Once the subject enters the study, s/he will be closely followed by an experienced clinical research team. Careful monitoring of all subjects via phone contacts and clinical management throughout the study will help minimize risk. The clinical research team has developed considerable expertise in monitoring the safety of subjects participating in research studies. There is an experienced research neurologist/psychiatrist available 24 hours a day, seven days a week.

After the neurostimulator is programmed to provide stimulation, subjects can suspend stimulation by application of a remote device. The remote device can be held over the chest neurostimulator and used to turn the device off.

The protocol includes exit criteria for those who believe their condition is worsening during any particular phase of the study, and participants can withdraw at any time. Subjects may also wish to discontinue stimulation for any reason and we will support

this decision. Symptom worsening to the point that the subject becomes actively suicidal or requires hospitalization will prompt immediate assessment by an unblinded investigator of whether the subject should continue in their current study phase. Deterioration in symptoms, mood, anxiety, cognition, or in general level of functioning noted by the subject, family members, study physician or other research staff will also prompt assessment by an unblinded investigator of whether the subject should continue in their current study phase.

If determined by the investigators and/or the subject that it is in their best medical interest to have the device removed, it will be done expeditiously. In the event a problem develops after one month post-surgery, the neurostimulator can be removed leaving the leads in place. In the past, subjects that have the leads left in place have not experienced adverse advents except for the restriction on future MRI scans. This restriction may affect the participants' ability to thoroughly evaluate other conditions should they develop in the future. The procedure would not restrict the participant from future neurosurgical procedures.

Risks to privacy are negligible in this protocol, since subjects will not be identified by name or by any personal health information in any summary reports or publications.

Anticipated Benefits: The primary anticipated benefit to subjects receiving an implanted Medtronic Summit RC+S and Medtronic Model 09130 cortical strip is the potential for a significant reduction in the symptoms of TS that would not be reasonably possible with further trials of medications and other approved treatment options. Experience in deep brain stimulation for the treatment of psychiatric disorders reported in the literature suggest that deep brain stimulation can benefit

patients by reducing symptoms without significant stimulation-related adverse events[11, 26, 37, 84]. The subjects will also have the benefit of the RC+S's 9-year rated battery life, resulting in the likelihood of fewer battery replacement surgeries, thereby reducing medical risk and financial commitments. The RC+S is the only rechargeable system with closed loop capability.

15) Justification for the Investigation: This study will provide important safety, targeting, and effectiveness data for the treatment of medication refractory TS. The device and methodology are novel, and this study can provide potentially important experience for expanding stimulation options beyond standard chronic high frequency DBS. The study allows for "tailoring" of therapy to individual patient needs in a disorder that is known for its paroxysmal nature. Low duty cycle stimulation, particularly responsive stimulation, may have therapeutic advantages beyond what is currently available and this may allow further expansion to treatment of other neurological and neuropsychiatric disorders. This device may have added benefits in saving battery life, and preventing tolerance. Finally, this study will offer physiological data from deep brain thalamic structures in the human. Such information is conspicuously lacking from current literature, and has the potential to corroborate current models of TS pathophysiology. Furthermore, physiology may enhance our basic understanding of the circuitry involved in this disorder and help us to develop better, more focused hypothesis driven studies.

16) Patient Population, including number, age, sex and condition: A total of ten subjects, 21 years and older with TS. Subjects must not have an active diagnosis of DSM-V major depression or other active and disabling psychiatric disorders. There

are no restrictions on ethnicity, social background, or gender. Only subjects who are able to give full informed consent would be accepted. Subjects who currently meet DSM-V criteria for: Bipolar or Psychotic Depression, Organic Mental Disorder, Schizophrenia, Schizoaffective Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified will be excluded from this study.

17) Monitoring Procedures: This project entails substantial risk to subjects. Therefore, we have established the following monitoring procedures.

Multidisciplinary Pre-Operative Screening and Evaluation: The multidisciplinary pre-operative screening and evaluation will include four specialties: 1) movement disorders neurology, 2) psychiatry, 3) neurosurgery, and 4) neuropsychology.

Data Safety Monitoring Board (DSMB): This study will have a designated DSMB composed of three members (A neurologist, a psychiatrist, and a non-neurological physician) without ties to the current study or any conflicts of interest. The DSMB will be charged with the duty of meeting every 6 months to discuss all of the AE's for the study.

The safety experience will be frequently reviewed by the Data Safety Monitoring Board (DSMB). The DSMB will be informed of all serious adverse events and all mild adverse events which are potentially device related in the opinion of the investigator. The DSMB will designate each AE as mild or severe; as device related, uncertain to be device related or not device related; and as anticipated or unanticipated.

Once the first subject is enrolled, the DSMB will meet approximately every 6 months in person, via teleconference, or electronically until all subjects have completed the 6

month primary outcome. The DSMB has the authority to suspend further enrollment pending investigation of safety concerns raised by SAEs occurring in the trial. The DSMB has a stopping rule for more than one death or more than 1 suicide deemed to be device related. The DSMB stopping rule for an individual subject would be a suicide attempt deemed potentially device related.

Adverse Event Reporting: Once a subject is enrolled into the study, continuous close monitoring will be conducted by the Principal Investigator (PI) in conjunction with the neurosurgeon and other investigators as well as the University of Florida's Institutional Review Board (IRB), through annual reports of progress and by immediate notification of serious and unanticipated adverse events by the PI to the IRB.

Stopping rules for the study have been established: This study will be suspended by the DSMB only if an unexpected and severe psychiatric or neurological complication occurs and they deem suspending or stopping the study appropriate. Specific examples that would warrant suspending the study include the following, only in the event that they do not reverse with adjustment or discontinuation of the DBS device:

- Severe worsening of symptoms
- Induction of severe difficult to treat depression

Additionally, the DSMB has a firm stopping rule for more than a single death or suicide attempt in the cohort during the 6 month post-operative period.

18) Device Description Summary: The Summit RC+S system is a multiprogrammable device that both delivers electrical stimulation and records

bioelectric data through one or two leads implanted in the brain. Summit RC+S electrical stimulation is based on the RC neurostimulator but adds the functionality of bioelectrical data recording (sensing). There are no new tissue contacting materials in Summit RC+S.

Stimulation is provided by controlled delivery of current from a battery in an implantable neurostimulator (INS) to metal electrodes surgically implanted in the brain in the same manner as previous Activa RC. The INS is typically placed in the pectoral location. Current is conducted to the electrodes via electrical conduits, including extensions and leads, which are tunneled subdermally through the neck, travel through the skull, and terminate in a neural structure appropriate to the neurological disease being treated.

Like Activa RC, the Summit RC+S system is capable of providing stimulation to 2 leads, each with 4 electrode contacts. Stimulation parameters are adjusted to optimize therapy for the patient. They can be independently controlled and include the following: active electrode(s), electrode polarity, pulse width, amplitude, and frequency. The stimulation settings are stored in programs. A program is a specific combination of pulse width, rate, and amplitude settings acting on a specific electrode combination on a lead, or on a lead and the INS, in unipolar mode. Up to four programs can be combined into a group.

Pulse width, amplitude, and electrode polarity are independently programmed for each program within a group. Rate, rate limits and cycling for each program within a group must have the same values.

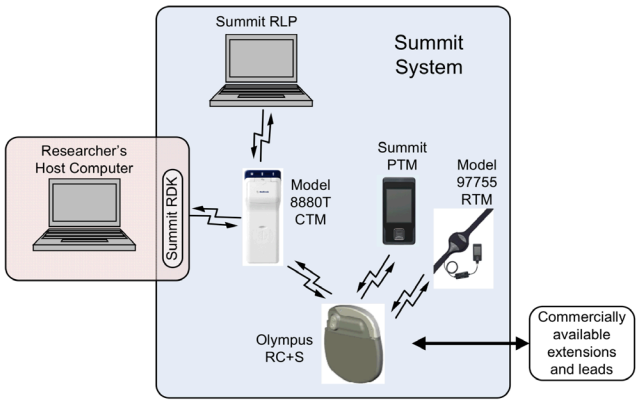
Stimulation is delivered to a maximum of two implanted leads (one lead per

hemisphere), with a maximum of 4 electrodes per lead. Rate is limited to 250 Hz, pulse width is limited to 450 μsec, amplitude is limited to 10.5 V (or 25.5 mA) and the charge density warning threshold is 30 $\mu C/cm^2$/phase. The RC+S is a rechargeable device. Patients must charge the device as often as needed to maintain its functionality. This could be as often as daily. Failure to properly recharge the stimulator will result in loss of stimulation. The patients will receive training from the research group on how to recharge the device, and will be given written instructions to take home. They can reach out to the research team whenever they encounter any issues.

Stimulation programs are controlled by the clinician via the unique Summit programmer and cannot be controlled by commercially available programmers.. Sensing functions, the recording of bioelectric data, is controlled by a separate sensing clinician programmer.

19) System Overview:

The system block diagram of the Summit RC+S is given below in Figure 3. This investigational system is being provided to investigator-clinicians as part of the NIH BRAIN Initiative Public-Private Partnership with institutional and FDA investigational device exemptions.



- Summit RC+S implantable pulse generator (IPG), Model B35300R
- Research Lab Programmer (RLP), Model 4NR010
- Clinician Telemetry Module (CTM), Model 4NR011
- Lead extension Model 37087
- Research Software Development Kit (RDK), Model 4NR013
- Patient Therapy Manager (PTM), Model 4NR009
- Recharge Therapy Manager (RTM), Model 97755

Figure 3. Block diagram the Summit RC+S.

RC+S communicates with peripheral devices via the Clinician Therapy Module (CTM), which must be within 2 meters of RC+S during communications. For clinical programming of the device, the research lab programmer (RLP) is linked to RC+S via the CTM. Most research related uses of RC+S are programmed on an investigator's windows-based host computer using the Research Development Kit (RDK). The RDK is an application programming interface (API) that can be programmed to establish a data and command conduit between a host computer and RC+S. This conduit can be utilized by researchers to receive sensing data and also send low-latency stimulation update commands back to the neurostimulator, via the CTM. The patient recharges the device using the Rechargeable Therapy Monitor (RTM), and can interrogate it to check its function using the Patient Therapy Manager (PTM). The patients will receive training from the research group on how to use these devices, and will be given written instructions to take home. They can reach out to the study group whenever they encounter issues.

The RDK is designed for rapid, automated closed-loop algorithm prototyping. This

programming interface provides for a low-latency bi-directional data port between an implantable device and an external computer that processes data and algorithms. The RDK includes software that resides on the host computer to enable a variety of software programs (e.g., Java programs, Matlab® scripts, and graphical Matlab Simulink® models) to communicate with RC+S. This architecture allows algorithms to be both flexible and safe: flexibility is enabled because algorithms on the host computer can be as complex as needed and also utilize data from sensors connected to the external computer (e.g, wearable accelerometers, gait and posture sensors, etc.); safety is ensured because updates to the implantable stimulator are limited to those permissible by the patient programmer and thereby constrained to ranges set by a clinician. With Summit RC+S demo units and the Summit RDK, we will first design toolboxes for the algorithms we currently use in our projects with the Activa PC+S. Since we have data collected with 6 TS patients, we will utilize these datasets and input them into the Summit RDK as if they are being received from the RC+S implant. This rich dataset will allow us to learn how to program the SDK for real-time analysis. Since the RC+S allows for data streaming of brain signals in real time without any signal degradation, next steps would be to implement more sophisticated machine learning and data mining algorithms on our computers. More importantly, we can connect a demo unit RC+S to external signal generators to program sensing algorithms and understand the ADC conversion processes within the RC+S. Finally, we can also connect the RC+S to oscilloscopes to study the stimulator outputs and stimulator output timings.

Prior to the Medtronic PC+S and RC+S devices there was only one FDA-approved, totally implantable neuromodulation device that has the capability of sensing brain activity and delivering therapeutic stimulation: The Responsive Neurostimulation (RNS) device from Neuropace Inc. RNS is FDA-approved for the treatment of epilepsy. It has the capability to deliver short stimulation trains in the presence of epileptic activity and is designed to deliver a few pulse trains a day (5 minutes of stimulation a day). The very short battery life of this device precludes the delivery of constant or near-constant stimulation, as is the contemporary standard for movement disorders. A second platform, from Medtronic Inc. that allows adaptive stimulation paradigms was also recently introduced. The first-generation device, the Activa PC+S, has been available under physician-sponsored investigational device exemptions since 2013 and was the device we used for the current FDA IDE G130253. Several groups worldwide have begun to utilize this device in a variety of brain disorders, for sensing subcortical LFPs or cortical ECoG potentials to advance understanding of disease pathophysiology. Our team at UF has extensive experience with PC+S in the context of our current study focusing on multi-site brain recordings during Tourette deep brain stimulation. Recently, several add-ons to the basic PC+S platform were developed to prototype promising adaptive control algorithms. Although we and others have learned much from this experience, some problems with the first-generation PC+S platform have limited full testing of adaptive control. Its signal-to-noise ratio may preclude detection of high frequency (>100 Hz) cortical activity, fully internalized adaptive control strategies are limited, and its lack of recharging capability has raised concern for battery drainage when testing adaptive algorithms. Additionally, since Medtronic is phasing out the PC+S there is a risk that their device supply will not be able to support the remaining implants in our IDE protocol and

therefore we will very likely need to switch to Summit RC+S eventually**;** this second-generation bidirectional (sense and stimulate) interface has a rechargeable battery, and an improved signal to noise ratio allowing detection of high frequency brain signals. It also has a greater flexibility in the implementation of adaptive algorithms. The RC+S can be considered an "upgrade" to the PC+S, as it still provides closed loop stimulation, but also is rechargeable, providing a much longer battery life (labeled as 9 years vs. approx. 2-3 years).

Adaptive stimulation with RC+S can occur in one of two modes: Distributed, in which the control algorithm resides on the researcher host computer (RHC), or embedded, in which control is accomplished within RC+S according to a preprogrammed algorithm. For in-clinic testing we will primarily use the distributed mode. During in clinic testing, ECoG and Cm-Pf LFP data will be streamed to the RHC to verify that neural correlates of tics can be detected. These detected events will then be used to responsively deliver DBS. We will also study markers of clinically optimized settings, by comparing signals to charge balanced stimulation settings that we know will not provide clinical benefit.

An adaptive control algorithm is embedded in RC+S. Prior to home use of adaptive stimulation, patients will be given and instructed on how to use the Clinician Therapy Module (CTM) and a tablet computer provided by the lab to interface with the CTM device which in turn communicates with the Summit RC+S. These devices allow switching off adaptive DBS and returning to open loop DBS.

Adaptive control algorithms: We will develop adaptive control algorithms using the Medtronic Research Development Kit. Since control algorithms will be based on each subjects' personalized neural signatures of tic symptomology, we cannot specify exact

algorithms prior to obtaining recordings from RC+S. In general, we expect the controller to utilize spectral power from one or more frequency bands extracted from cortical and/or thalamic recordings. Our initial data points to significant deviations from baseline data during tics in the Cm-Pf that is not present during voluntary movements (see Figure 4). These features can be captured using power bands of low frequencies up to 8Hz.

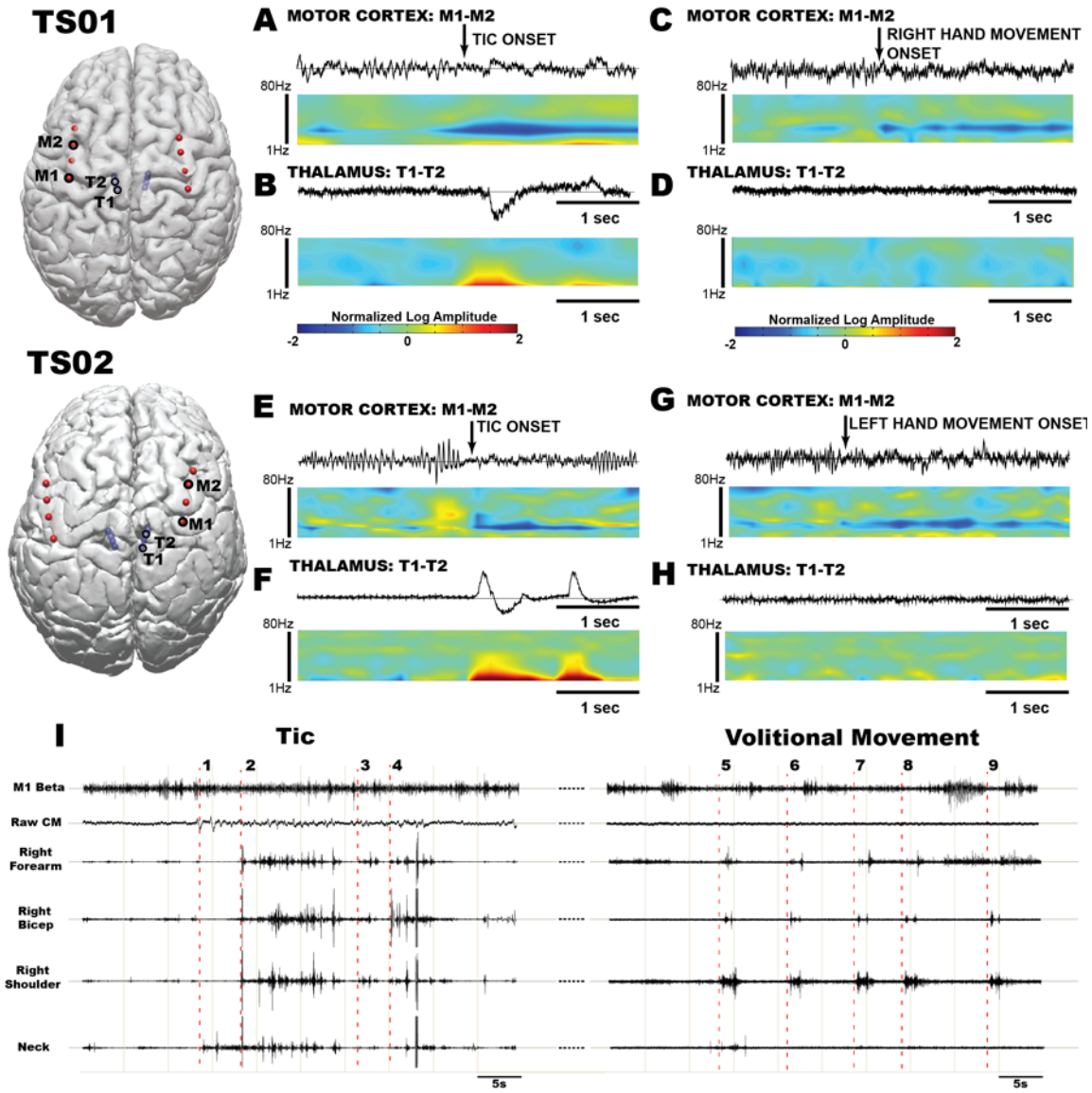


Figure 4. Differentiating tics and volitional movements. Shown is the time series and spectrogram for each condition. **(A,B,C,D)** correspond to TS01, Images **(E,F,G,H)** correspond to TS02. **(B,F)** Increases in CM low frequency LFP are concurrent with **(A,E)** motor cortex beta desynchronization LFP at the onset of tics. **(D,H)** No increases in low frequency CM LFP are

observed during volitional movements, such as grasping (shown), but **(C,G)** motor cortex beta desychronization is still observed. **(I)** Data from follow up visit month 2. Subject TS01 was instructed to tic freely. Tic onset denoted by red dotted line: **(1)** A neck wrenching tic (simple), **(2)** Rapid arm throwing tic (complex long), **(3)** Arm wrenching tic (complex), **(4)** Arm throwing and neck twisting tic (complex long). In a separate trial the subject was asked to perform a series of volitional movements. Movement onset denoted by red dotted line: **(5)** Talking and opening/closing hands rapidly, **(6,7)** Opening/closing hands, **(8,9)** Rapidly shaking hands. No tics were observed during the volitional movement condition.

The controller will be based on threshold crossings in this frequency range or possibly multiple frequency ranges, and will change stimulation current between a low-therapeutic level and a high-therapeutic level. For each proposed control algorithm, we will test the performance of the algorithm using an external RC+S and the RDK prior to implementing adaptive control in the patient. System integration will be checked by connecting the demo RC+S unit to signal generators to verify sensing algorithms, and by connecting the demo RC+S unit to oscilloscopes to verify stimulation delivery is consistent with algorithm outputs using previously collected neural data from PC+S devices. Testing and documentation of system integration for sensing and stimulation will comply with FDA CFR 820.30 on design controls for implanted devices.

***Safety of adaptive stimulation*:** During adaptive stimulation, several safety features protect patients from the potential from uncomfortably high stimulation settings or from prolonged periods with clinically inadequate settings. Stimulation parameters that can be implemented by the control algorithm are preselected by clinicians to avoid the possibility of producing major stimulation-induced adverse effects. No possible combination of stimulation stetting will exceed the upper charge density limit of 30 microcoulombs per centimeter squared per

phase. Prior to home testing, patients will be instructed on how to exit adaptive mode at any time and return to open-loop mode should excessive discomfort occur, but are encouraged to consult with study staff if possible prior to doing so.

***Summit RC+S sensing malfunction or premature battery drainage*:** Should the sensing capability of Summit RC+S fail, without failure of the therapeutic stimulation function, we will attempt to restore it by noninvasive restoration of the software (see design master file for Summit RC+S referenced in this application). Should the sensing function be permanently lost with no compromise of the therapeutic function, no specific treatment is needed, and the patient would exit from the study. Regarding the possibility of premature depletion of battery life due to use of the sensing function in addition to the neurostimulation function, this risk is mitigated by the fact that the sensing function utilizes relatively little energy (compared to therapeutic stimulation). Within its lifetime labeled for 9 years, RC+S has no known limit to the number of times it can be recharged.

Manufacturing Information: Please reference Medtronic MAF 2978, PMA P960009 and P840001 for information on these devices.

Device Charges: The Investigational Device, including the Summit RC+S system, will be provided by Medtronic.