Defining Targets for Tic Detection and Suppression in Tourette Syndrome Deep Brain Stimulation

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IRB Protocol

1. Project Title

Defining Targets for Tic Detection and Suppression in Tourette Syndrome Deep Brain Stimulation

FDA IDE: "Tourette Syndrome Deep Brain Stimulation: Modulation of Oscillations for the Treatment of Tourette Syndrome"

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3. Abstract:

Tourette syndrome (TS) is a continuous lifelong disabling condition that is highly prevalent and socially embarrassing. Deep brain stimulation (DBS) has emerged as a promising treatment option for addressing uncontrollable tics in medically resistant and severe TS cases. We have undertaken a major informatics initiative by establishing the International TS DBS Registry and Database, a multi-country consortium that has captured long term outcomes of 340 TS DBS patients representing an estimated 50-75% of the worldwide population. The data has revealed strong evidence supporting two deep brain targets as potentially effective: the centromedian nucleus region (CM) of the thalamus, and the anterior globus pallidus internus (aGPi). Next generation sensing-enabled DBS systems can record brain activity in patients with TS and can identify the neurophysiological correlates of tics. We have demonstrated in a series of recent TS DBS projects the important building blocks paving the way for the current proposal. First, we demonstrated that tic suppression could be achieved with scheduled DBS, thus providing proof of concept that for TS DBS the device does not need to be continuously activated to suppress tics[1]. Next, we uncovered the neurophysiological changes underpinning tic, thus providing physiology-based markers for use in a future closed loop system[2]. We then built on this finding by defining a physiological signal, drawn from a single brain target (CM), to reliably separate voluntary movement from tic[3]. Our findings revealed that use of subcortical targets were more reliable for monitoring tic physiology (compared to the primary cortex) and that subcortical targets were also effective for delivering stimulation to suppress tics. The current project will bring all of our previous work together through a funded NIH UH3 Brain Initiative grant. We will implant and monitor 8 research subjects with a subcortical closed-loop system for detection and suppression of tics. The project will use the FDA-approved Medtronic Percept PC and/or RC devices.

4. Background:

Tourette syndrome (TS) is a neuropsychiatric disorder which can manifest in the form of medication refractory motor and/or vocal tics. Deep brain stimulation (DBS) is a therapy which can be applied in select TS cases following an appropriate multidisciplinary team-based screening. There is abundant and accumulating evidence available from the University of Florida Tourette Association of America International DBS Registry and Database that TS DBS can suppress both vocal and motor tics. We contributed to the understanding and advancements in Tourette DBS through a series of NIH funded grants. Now that our group has developed a technique to differentiate tics from voluntary movements and our group has recorded tics from human brain, we are in a strong position to refine the next generation of DBS technology. Instead of a solution where the DBS device remains continuously in an "on" position, we have developed an approach which may alleviate many of the adverse effects of DBS through the application of a technology called closed loop DBS. Using our approach, we can sense the brain signal underpinning the manifestation of a tic. We can then tap a different part of the tic relevant circuit to deliver a brief electrical stimulation to suppress the tic. This current project aims to take the next step in the refinement of the "closed loop" approach to TS DBS.

5. Specific Aims:

Specific Aim 1. Identify structural network projections from the centromedian nucleus region (CM) of the thalamus, and the anterior globus pallidus internus (aGPi) to guide pre-operative surgical planning and post-operative selection of stimulation parameters.
Our working hypothesis, based on our recent publications, is that a quantitative integration of each de novo subject using our continuously growing connectome of prior TS DBS subjects can be used to guide DBS lead placement and selection of stimulation parameters to achieve our primary outcome.

Specific Aim 2. Identify neurophysiologic markers of tic generation in CM and aGPi
Our working hypothesis is that physiological signatures can be identified in the CM and aGPi before and during the occurrence of tics, and these signals will be distinguishable from voluntary movement. This project will allow us to understand the neural activity that leads to tic generation, identify structural network connections, reveal how DBS affects this neural activity in humans, elucidate how activity changes overtime and better define DBS targets to reduce TS symptoms.

Specific Aim 3. Test feasibility, safety, and efficacy of closed-loop TS DBS guided by electrophysiology and network projections
We will test the safety, feasibility, and preliminary efficacy over a 6-month period (Months 4-9) of closed-loop DBS detected from one target (CM or aGPi) while stimulating the other target. The primary outcome threshold will be ≥30% improvement on the Yale Global Tic Severity Scale (YGTSS) from baseline for each subject. The secondary outcome of the study will assess safety by assessing the adverse events and comparing safety outcomes to historical data on closed-loop DBS.

6. Research Plan:

Project Overview:
We will implant and monitor 8 research subjects with a subcortical closed-loop system for detection and suppression of tics. The project will use the FDA-approved Medtronic Percept PC and/or RC devices, which is an implantable neurostimulator capable of recording neural signals. We will target the CM nucleus of the thalamus and the aGPi in each brain hemisphere from each subject and we will connect the two leads placed in each brain hemisphere to two devices.

We will, during **months 1-3 post-implantation**, perform detailed brain physiological recordings to determine which brain region in each hemisphere will provide an optimal physiological tic detection signal (i.e. a physiological signature for tic in the individual subject). The brain target (CM vs. aGPi) may differ in each subject, and in each brain hemisphere of each subject, as the selection of the "tic detector" will be guided by the quality of the physiology and will be agnostic to the location.

We will then, **during months 4-9 post-implantation**, optimize the DBS settings for tic suppression. During the 4 weeks between visits participants will complete one YGTSS assessment weekly via UF telemedicine with the study coordinator to track real time progress. At Month 9 programming should be optimized and unchanged for approximately one month. At which time the primary outcome variable of tic suppression, the YGTSS, will be measured. Subjects will then be followed long term for a total of 24 months.

Summary of the timeline for the study:
The duration of this investigation will be five years with a total of 8 subjects consented and implanted. We anticipate having to screen 24 medication refractory TS subjects to achieve 8 implants.

In the first year of the study, we plan to implant and to follow our first subject.

In Year 2, we plan to implant and follow 3 additional subjects while continuing to follow the first subject.

In Year 3, we plan to implant and follow the fifth and sixth subjects while continuing to follow the first four subjects.

In Year 4, we plan to implant and follow the seventh and eighth subjects while continuing to follow the other six subjects.

In year 5 we will complete all primary outcome variables, begin data analysis, and we will plan to submit publications for peer review and update clinicaltrials.org with outcome data.

These time estimates are plans that could be subject to modification, based on a number of external factors and we will update the IRB on any changes in real time.

We plan to follow each subject clinically for a minimum of 24 months following device implantation. At the end of the initial 24-month study period, subjects will have the choice of 1) continuing active stimulation at current settings, 2) discontinuing stimulation, and 3) discontinuing stimulation and removing the device.

We will then evaluate each subject annually as long as they wish to remain implanted. We will monitor for battery depletion and monitor for the potential necessity for neurostimulator battery replacement.

Specific steps for each subject in the study:

- Following consent, subjects will be screened by the multidisciplinary team including neurology, neuropsychology, psychiatry and neurosurgery (in person). A meeting between these specialists will generate a recommendation to proceed, table or reject potential inclusion in the study.

- During this Screening period the subject will undergo a brain MRI with contrast and meet with the Study Coordinator who will record information and perform assessments and questionnaires. Participants may be sedated or put under general anesthesia for MRI scans as movement within the scan is likely for patients with Tourette Syndrome. The use of anesthesia will be determined by study physicians and the anesthesiologist.

- The ethicist (Dr. William Allen) will review the case and summary recommendations as well as the inclusion and exclusion criteria and will make a final determination as to whether the candidate can proceed to DBS implantation as part of this protocol.

- Following approval by the multidisciplinary team and the ethicist, eligible subjects will, within approximately four weeks, receive bilateral CM and aGPi lead implantation surgery. The intent is that all 4 leads will be placed during one surgery. However, the neurosurgeon may determine with the patient that 2 surgeries are necessary for the best outcome. In that case, 2 leads will be placed (one in CM and one in aGPi) in one hemisphere of the brain. Approximately 4 weeks later a second surgery will be performed to place 2 leads on the other hemisphere of the brain (in the CM and aGPi). Ultimately subjects will have 4 leads surgically placed, 2 in bilateral CM and 2 in bilateral aGPi.

- Approximately one month after all 4 leads are implanted, two implantable pulse generators (IPG) will be placed under the collar bone in the subject's chest in an outpatient procedure under general anesthesia.

- The multidisciplinary team's surgical safety assessment for each patient along with regular safety updates will be providedto the Data Safety Monitoring Board (DSMB) based on the schedule of the formal DSMB plan.

- **Months 1-3** post-implantation of IPG will focus on recording physiology from both the CM and aGPi brain targets. One brain target in each hemisphere will be used for recording and the target used for stimulation will be chosen solely based on the physiology (i.e. the target with the highest quality physiological signal will be chosen as the "sensor" target and the remaining target will be used as the "suppressor" or stimulation delivery target). The suppressor target will apply electrical stimulation and be triggered to fire by the physiology detected by the "sensor" target. These configurations may be different in each brain hemisphere.

- **Survey Collection:** Participants will be asked to complete a REDCap survey on their mobile device or computer tracking a variety of symptoms no more than once a day during the study period. Participants will be sent a unique link via text message. A reminder text message with the survey link may be sent again until the participant has submitted their daily survey. Survey results will be stored in REDCap. The purpose of this daily survey is to collect important data that is often missed during the

30 days between study visits. This information will help study team members tailor DBS programming to each individual participant.

- **Details of the physiology collection procedure:** At each visit the subject will be asked to put on EMG sensors (taped skin sensors like EKG leads) and signals from this device will stream into the research host computer (RHC). The signals from the device (brain signals) will also be downloaded. Video recordings will also be performed. Stimulation and brain activity data collected will be reviewed and analyzed on an individual basis. Study participants may be asked to collect physiology at home using the event tracking capabilities of the Percept device.

- Following the three-month physiology collection period, programming and optimization of the DBS devices will then occur for the next 6 months **(months 4-9)** and stimulation settings will need to be kept stable and unchanged for one month prior to the primary outcome variable measurement at month 9. During months 4-9 participants will complete one YGTSS assessment per week via UF telemedicine with the study coordinator to track real time progress.

- All subjects will undergo once a month programming visits for months 4-9 (+/- 14 days). Additional visits may be added in an effort to **obtain optimization of settings by month 8.** Physiological data will be collected from both the CM thalamus and the aGPi during all protocol visits. Subjects may also choose to come to the clinic for "unscheduled visits" as they deem necessary for any management issue or discussion on any topic. The activities performed at these visits will be at the discretion of the principal investigator.

- The DBS programmer will be permitted to adjust stimulation parameters during **months 4-8 to achieve** maximal tic suppression with minimal to no side effects. The programming that will be employed will be identical to procedures used for Parkinson's disease and essential tremor which are common indications for DBS surgery.

- The CM or aGPi neurostimulators for each subject will be programmed in an outpatient setting **(months 4-8)** to **deliver closed-loop stimulation** in all patients following activation. In the unlikely event that an appropriate signal has not been found by this time, we will use open-loop stimulation settings until the appropriate signal is determined. Stimulation parameters will be adjusted as necessary to provide maximal tic reduction.

- **At day 270 (9 months +/- 14 days),** the primary and secondary outcome variables will be collected. **There must be a 30day period of stable stimulation settings before primary outcomes are assessed.**

- **Primary and secondary outcomes and physiology collection will be assessed**

over approximately 2-3 outpatient days. The "on" responsive stimulation response will be compared by validated scales to the pre-operative baseline.

- Following the 9-month outcome variable measurement visits for the primary study, if any subject has a primary outcome of <30% improvement on the YGTSS motor scale, the subjects will be **offered to switch to a continuous (open loop) stimulation regimen** in one or both hemispheres which will be guided by the clinical neurologist. The goal will be to provide the best possible outcome. The subject may also be **offered closed loop DBS by flipping the "sensor" and "suppressor" target.** This may only be offered in cases where there exists a potential physiological control signal "sensor" in the alternate target.

- Subjects will be followed for approximately 24 months post-implant.

Inclusion and Exclusion Criteria

Subjects for this study will include 8 individuals with medication refractory and severely disabling TS. We expect to screen 24 individuals to enroll 8 subjects. The primary outcome variable will be ≥ 30% individual improvement on the YGTSS from baseline in 4/8 subjects (50% responders). Effectiveness, tolerability, and safety will be assessed as a secondary outcome as well as the appropriate programming parameters.

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 ≥35/50 and the motor tic sub score ≥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[4-6] 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[5]) either 1-4 mg/day of haloperidol, 2-8 mg/day of pimozide, risperidone (1-3 mg/day), or aripiprazole (2.5-5 mg/day)]. There must be at a minimum[7] single trial with an alpha-2 adrenergic agonist (0.1-0.3 mg/day).

- Clinically relevant depression if present 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 subject responds satisfactorily to botulinum toxin, and their quality of life significantly improves, they will be excluded from the study.

- Must be 18 years of age or older.[8]

Exclusion Criteria

- Any previous neurosurgical intervention such as DBS or ablative brain lesions. Participants with previous DBS system that have been explanted will still be excluded from the study.

- Any metal in the body that would preclude the patient from receiving an MRI scan.

- Untreated or unstable anxiety, depression, bipolar disorder or other Axis I psychiatric disorder.

- Presence of psychotic features.

- Significant psychosocial factors that may impart an 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 on the brain scan.

- 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.

- A positive urine drug screen for illicit substances (a urine drug screen is required), not to include marijuana/cannabinoid use.

- Patients who do not have access to a site that can program the device if they cannot come to The University of Florida for clinical re-programming follow-up appointments after completion of the study.

- 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 as judged by the neurosurgeon).

- Women of child-bearing potential who are pregnant or who wish to become pregnant during the study (a urine pregnancy screen required).

- History of multiple surgical procedures with poor outcomes.

- Unexplained gaps in medical history.

- Pending lawsuits or other legal action.

The study will be conducted at the **University of Florida Fixel Institute for Neurological Diseases** located at 3009 SW Williston Rd, Gainesville, FL 32608. The surgery will be completed at the University of Florida Neuromedicine Hospital.

Recruitment: There are approximately 600 TS patients actively followed with yearly appointments at the combined 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. From this pool, we anticipate being able to recruit 8 patients (2-3 per year) over 5 years to complete this study.

Subjects will receive a $200 stipend to help compensate for their time and travel. This will be payable on a prepaid Visa card at the conclusion of each study visit, except the post implant visit (as it does not require a separate trip to the study site). If they complete all required research visits, they could receive up to $3200.00. One unscheduled visit will be compensated ($200) per calendar year, though the study participants may request as many as needed. Any unscheduled visits requested by the study team will be compensated ($200).

Subjects will be recruited in one of three ways:
1) the neurology clinic
2) the psychiatry clinic, or
3) through referral by the Tourette Association of America (TAA) and the combined UF TAA 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 at UF. Additionally, the PI of this protocol is also the PI for the International Tourette Syndrome DBS database project, and receives many TS DBS referrals, which will also aid in study recruitment.

Obtaining Informed Consent: Prior to any intervention, the informed consent form (ICF) will be reviewed with the patient which will explain the protocol and study procedures as well as the risks and benefits of the surgical procedure. The ICF will also cover device related complications, medical related complications, the risk of not obtaining the "perceived benefit" from surgery. Additionally, the ICF 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) discontinuing stimulation, and 3) 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 one of the Movement Disorders Neurologists at the Fixel Institute. These items will also be reviewed with the subject by the Neurosurgeon during the Neurosurgery evaluation at the Screening Visit.

The study coordinator will explain the time commitments for each study visit (both research clinic and hospital visits for surgeries), as well as potential time commitments for any study related adverse events. Finally, the coordinator 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. Additionally, it will be explained that the cost of neurostimulator (battery) replacements following the study will be the responsibility of either the individual's insurance plan, out of pocket expense or the individual may apply for a device donation (from the hospital and/or Medtronic Corporation). In cases where a battery replacement is necessary within the study window, the study will cover the costs of the replacement and will replace with the Percept RC. These items will also be reviewed with the subject by the Neurologist during the

Neurological Evaluation at the Screening Visit. Finally, participants will be able to approve or disapprove of a letter being sent to their Primary Care Physician informing them of their patients' enrollment in this clinical study.

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, unless they are followed by a UF Health Movement Disorders Neurologist and have been seen within the last 3 months, and a psychiatrist, who 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 neurologist will perform a physical and neurological exam. 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. The study coordinator will collect information and complete scales and questionnaires. The subject will also receive a whole brain MRI during this screening visit which will be used for pre-operative surgical planning. Subjects may be sedated or placed under general anesthesia for MRI scans to prevent movement in the scanner. This decision will be made by study physicians and the anesthesiologist. 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, medical history, family medical 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 diagnostic 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 study team member.

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.

Beck Anxiety Inventory (BAI): The BAI is a 21 item self-reported measure of anxiety. A total score is calculated by finding the sum of the 21 items. A score of 0-21 signifies low anxiety, 22-35 moderate anxiety, and 36 and above correlates to potentially concerning levels 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.

***Evaluation by Neurosurgeon*:**
A DBS fellowship-trained neurosurgeon will perform a complete history and a physical examination, evaluate medical co-morbidities, obtain and examine any previous 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[9].

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.

Meeting of the Multidisciplinary DBS Team Following Screening:

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.

All of the data from the screening evaluation will be provided to the **study ethicist** who will review and make a recommendation as to whether or not it is ethically reasonable to offer surgery. Only individuals deemed ethically reasonable to receive DBS surgery will progress to implantation.

Surgical Procedure:

Pre-Surgery Planning Meeting: Approximately 2 weeks prior to surgery Connectomic analysis of the high resolution, volumetric, three tesla MRI scan obtained during the Screening Visit will be conducted and provided to the neurosurgeon to aid in the identification of optimal targets for DBS lead implantation.

On the morning of the surgery, 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 higher quality MRI images. Only imaging procedures that adhere to the DBS manufacturer's guidelines will be used in this study. The targeting 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. Stereotactic targeting will be used in addition to pre-surgery target selection based on neuroanatomy, brain circuitry and connectivity to allow for optimal placement of electrodes.

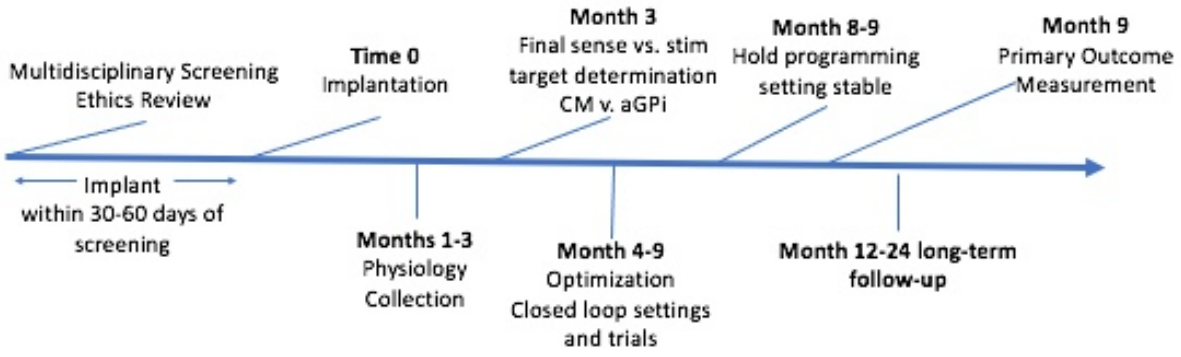
CM and aGPi Target Localization:

The stereotactic target of CM and aGPi targets 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 approximately at 5 mm lateral, and 4 mm posterior to the midcommissural point and refined by direct visualization of the neurosurgeon. The aGPi target will be stereotactically targeted approximately at 15 mm lateral, and 6mm anterior to the midcommissural point and refined by direct visualization of the neurosurgeon. 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 and aGPi will be located by imaging, and by fusion to our 3-dimensional atlas which can be morphed to the subject's MRI and morphed atlas. The study team is experienced in targeting DBS cases and will determine the correct location and depth of the final lead. Lead implantation (4 leads, 2 in each hemisphere of the brain) is intended to be completed in one surgery. However, the neurosurgeon may determine that two surgeries are necessary for the best outcome. In that case, 2 leads will be placed in one hemisphere of the brain and approximately 4 weeks later the remaining two leads will be placed in the other hemisphere of the brain. If lead implantation is completed in one surgery (all 4 leads) it will take place under general anesthesia. In the case of 2 surgeries the neurosurgeon and anesthesiologist will decide on the method of anesthesia on the day of surgery for the best patient outcome. The level of anesthesia could range from local anesthetic to sedation of different levels to general anesthesia. This is the typical procedure for the Neurosurgeons listed on this study. The lead may be tested by macro-stimulation (turning the lead on and checking for benefits and side effects) to obtain thresholds for benefit and side effects. Using an O-ARM Surgical Imaging System, a fluoroscopic X-ray will be obtained intro-operatively and the leads secured using the plastic cap provided in the DBS kit (Medtronic, Minneapolis, MN). Following lead implantation surgery subjects will spend 1-2 nights in the hospital for recovery.

One month after lead implantation surgery patients will undergo a final surgery to implant two neurostimulators, at this appointment patients will also receive a post-operative CT scan to assess lead localization. During the neurostimulator placement surgery, two neurostimulators will be implanted bilaterally in the patient's chest under the collar bone. The neurostimulators will be connected to the DBS leads by extension wires. The CM and aGPi on each side of the brain will be connected to an ipsilaterally located neurostimulator. Once the operative procedure for lead insertion and the follow-up procedure for the neurostimulators are completed each subject will have a total of 4 DBS leads and two neurostimulators.

Timeline of the study events:



Subject Follow-up Schedule:

Subjects will have study visits once a month for 9 months post-implant. The protocol will focus on recording physiology from both the CM and aGPi brain targets for the initial 3 months. After the first 9 months subjects will be seen for an additional 15 months with appointments every 3 or 6 months for follow-up.

If primary outcome is not achieved by 9 months, the subjects will be offered to switch to a continuous (open loop) stimulation regimen in one or both hemispheres guided by the clinical neurologist with the goal to provide the best possible outcome. The subject may also be offered closed loop DBS by flipping the "sensor" and "suppressor" target. This may only be offered in cases where there exists a potential physiological control signal "sensor" in the alternate brain target.

Table 2. Schedule of Assessments/Events

Study Events (monthly visits to occur +/- 14 days, except month 1, which will occur +/- 7 days)	Screening	Baseline **	Lead Implant Surgery ***	IPG Implant	Mo 1	Mo 2	Mo 3	Mo 4	Mo 5	Mo 6	Mo 7	Mo 8	Mo 9	Mo 12	Mo 18	Mo 24
Informed Consent	X															
Movement Disorders Neurologist Evaluation *	X															
Neurosurgery Evaluation (including co-morbidities and risk assessment)	X															
Neuropsychological Battery (Weschler abbreviated scale of intelligence, digit span and spatial span, California Verbal Learning Test-2, 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	
Psychiatry Evaluation	X															
Review by Multidisciplinary DBS Panel and Ethicist	X															
Mini International Neuro-psychiatric Interview (MINI)	X															

Study Events (monthly visits to occur +/- 14 days, except month 1, which will occur +/- 7 days)	Screening	Baseline **	Lead Implant Surgery ***	IPG Implant	Mo 1	Mo 2	Mo 3	Mo 4	Mo 5	Mo 6	Mo 7	Mo 8	Mo 9	Mo 12	Mo 18	Mo 24
Medical History	X	X														
Neurological Exam	X															
Urine Testing (Illicit Drugs & Pregnancy for Females)	X															
Physical Exam	X	X												X		X
Demographics (age, disease duration, family history, smoking history, alcohol history and substance abuse history)	X															
Hamilton Rating Scale for Depression (HAM-D)	X												X	X	X	X
Beck Anxiety Inventory (BAI)	X	X			X	X	X	X	X	X	X	X	X	X	X	X
SF-36® Health Survey	X							X	X	X	X	X	X	X	X	X
Yale Global Tic Rating Scale (YGTSS)	X	X			X	X	X	X	X	X	X	X	X	X	X	X
Yale-Brown Obsessive Compulsive Scale (Y-BOCS)	X	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	X
Modified Rush Tic Rating Scale (MRTRS)	X				X	X	X									
Blinded Modified Rush Tic Rating Scale (MRTRS) with device turned off and on "responsive" setting								X	X	X	X	X	X	X	X	X

Study Events (monthly visits to occur +/- 14 days, except month 1, which will occur +/- 7 days)	Screening	Baseline **	Lead Implant Surgery ***	IPG Implant	Mo 1	Mo 2	Mo 3	Mo 4	Mo 5	Mo 6	Mo 7	Mo 8	Mo 9	Mo 12	Mo 18	Mo 24
Young Mania Rating Scale (YMRS)	X												X	X	X	X
The Conner's Attention Deficit Questionnaire (CAARS)	X												X	X	X	X
Premonitory Urge for Tics Scale (PUTS)	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														
Brain MRI with Contrast †	X															
CT scan prior to surgery			X													
CT scan for lead localization				X												
Fluoroscopic X-ray Intra-Operatively			X													
General Anesthesia			X	X												
Hospitalization			X													
Thresholds								X								
Device Programming								X	X	X	X	X	X	X	X	X
Concomitant Medication Log	X	X	X	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	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* This is not necessary if the subject is followed by a Movement Disorders Center Neurologist at the Fixel Institute, but the Neurologist will perform the Physical and Neurological exam.

** Baseline visit will only occur if Screening assessments were performed more than 45 days prior to surgery.

*** Study Neurosurgeon may opt for 2 lead implantation surgeries rather than 1 in which the level of anesthesia will be decided by the study neurosurgeons and anesthesiologists on the day of surgery (this could range from local anesthetic to general anesthesia)

† Participants may be sedated or placed under general anesthesia during MRI scans

Description of the Device

We will use the Medtronic Percept PC neurostimulator with the SenSight leads. The Percept PC device features BrainSense technology, designed to capture brain signals (local field potential, or LFP) using the implanted DBS lead. These signals can be recorded simultaneously while delivering therapeutic stimulation, inside and outside the clinic. The Medtronic Percept PC neurostimulaor received FDA approval in 2020, and the SenSight leads received FDA approval in 2021. In 2024 Medtronic received FDA approval for the Percept RC (rechargeable) neurostimulator. We will initially implant all study subjects with the Percept PC for continuity however, in the event that a battery replacement is necessary within the study window we will replace with the Percept RC as it offers a longer potential battery life.

7. Possible Discomforts and Risks:

Monitoring Plan

This study will have a designated Data Safety Monitoring Board (DSMB) composed of three members (a neurologist, a neuropsychologist, 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 twice a year to discuss all of the adverse events for the study. The safety experience will be frequently reviewed by the 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 Investigators will designate each adverse event as mild, moderate, or severe; as device related, uncertain to be device related or not device related; and as anticipated or unanticipated. The DSMB will review these designations and approve them or request changes. Once the first subject is enrolled, the DSMB will meet by teleconference or email twice a year until all subjects have completed the first 6-months of the study. The DSMB has the authority to suspend further enrollment pending investigation of safety concerns raised by severe adverse events occurring in the trial.

The DSMB has a stopping rule for more than one death or more than 1 suicide within the 6-month post-operative period if deemed to be device related.

Adverse Event Reporting:

Once a subject is enrolled into the study, continuous close monitoring will be conducted by the principal investigator and other investigators as well as the UF IRB. Adverse events will be monitored and information regarding the nature of the adverse event, the relationship to the device itself or implantation, severity, subsequent treatment, and resolution status will be collected. This information will be detailed through annual reports of progress and by immediate notification of serious and unanticipated adverse events by the principal investigator 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 neurological or neuropsychological 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 difficulty to treat depression
- Additionally, the DSMB has a firm stopping rule for more than a single death or suicide attempt in cohort during the 6-month post-operative period.

***Possible risks of surgical implantation of the device*:**

Possible risks associated with DBS surgery:

1. Bleeding or fluid inside of the brain, on the surface of the brain, or in the space between the skull and brain during your surgery that could result in change in consciousness, paralysis (not being able to move), stroke, or death.
2. Cerebrospinal Fluid (CSF) leakage during surgery could result in a dull or throbbing headache or need for additional surgery.
3. There is the possibility of complications, injury and even death from all forms of surgical anesthesia.
4. Meningitis, encephalitis, or brain abscess resulting from infection involving the brain and/or central nervous system
5. Swelling of a small part of the brain around the DBS lead
6. Bleeding into the brain or stroke-like conditions resulting in temporary or permanent injury to the nervous system, or death; these could occur at any time after the DBS leads are placed
7. Non-infected cyst of the brain around the end of the DBS lead

Possible risks immediately after DBS surgery:

1. CSF leakage after surgery could occur and might result in a dull or throbbing headache or need for additional surgery.
2. Short-term pain in the head and neck might occur.
3. Infection could occur after surgery, including meningitis which has the potential to cause brain damage or hearing loss.
4. Allergic reaction to the implanted parts is possible but rare.
5. Discomfort or lack of healing of the skin area could occur at or around the site of the implanted parts.
6. Surgery could cause swelling under the skin of the scalp or a mass of clotted blood inside or on the surface of the brain or in the space between the skull and brain that may apply pressure to the brain.

7. There is a risk of seizure post-operatively.

Possible risks with the DBS system:

1. Although pain and negative changes in mood during stimulation could occur, test stimulation

is performed to determine stimulation settings that do not cause pain, discomfort, or negative changes in mood.
2. Pain or discomfort that lasts a long time and/or additional sensitivity may occur where the implanted parts were placed.
3. Movement of the lead from where it should be in the brain or loose electrical connections could cause therapy to stop working, could cause pain, or possibly cause a sensation of pricking, tingling, or creeping on the skin.
4. Stimulation has the potential to cause a seizure and there is a possibility that this could bring about a seizure disorder.
5. Certain therapy settings may cause involuntary movements (i.e., eyelid blinking, twitching). These movements usually go away after the therapy settings have been adjusted.
6. Changes in the brain cells or reduced sensitivity of the brain to stimulation could cause therapy to stop working.
7. The effects of long-term brain stimulation are not completely known and there could be some risk of brain tissue damage.
8. There could be battery life issues for the device used in this study. These will be explained so participants can reasonably anticipate battery replacement. The battery (A Medtronic Corporation product called the Percept DBS battery) is labeled to last about 5 years after implant, depending on use. However, frequent and/or high current stimulation may shorten the "life" of the battery. When the battery runs out, an additional surgery for replacement will be required for the device to work. The risks for this procedure are expected to be lower than those of the first implant since the replacement surgery does not involve cutting into bone or placement of leads in the brain.
9. As with any electronic device, the DBS System may not work. A system malfunction may be because the battery is running low or is out of energy. It could also be because of an electrical short, open circuits, lead fractures, or lead insulation failures, or damage as a result of head trauma. These malfunctions are unpredictable, and may result in too little stimulation. A malfunctioning pacemaker may require minor surgery to replace. Although the pacemaker is designed to turn off if over stimulation or excess current occurs there is a possibility that product failure could result in brain tissue damage.

Other Possible Risks Associated with this Study:

1. The device can be removed or left implanted until the battery runs out. Device removal (explantation) will be paid for by subject's private insurance and/or Medicare or CMS. Device explantation may involve the removal of the battery in your chest, while the DBS electrodes could be left in place. Study participants may also choose to have the DBS electrodes removed as well. One publication by Liu and colleagues published in the Journal of Neurosurgery in 2012 reported 12.8% chance of bleeding within the skull when DBS electrodes were removed. These bleeds were detected by postoperative CT scans. However, they were reported to be asymptomatic.
2. Worsening of TS and other psychiatric symptoms, such as those associated with mania, could possibly occur and might require medical treatment.
3. Worsening of suicidal thoughts or impulses.
4. Replacing or permanently removing any or all implantable parts may be medically necessary.

The implanted parts may cause fibrosis that could get in the way or stop their removal. With any surgery involving removal of such parts, there is a risk of intracranial bleeding (bleeding inside the brain).

5. The following risks have been reported with the use of systems that provide chronic stimulation to deep brain structures. These reported risks may be related to areas of your brain that will be stimulated.
    a. In a study of 160 people treated for Parkinson's disease with another deep brain stimulator (DBS), serious side effects included bleeding in the brain (7.5%), infection related to the deep brain stimulator (10.6%), weakness or loss of energy (10%), and weakness or paralysis affecting one side of the body (8.1%). There were ongoing serious side effects related to the stimulation in 3.1% of the patients, including pain, problems with speech, and worsening of the Parkinson's disease symptoms. Serious on-going side effects related to the device occurred in 6.3% of the patients and included problems with the DBS system, infection, skin breakdown in the area where the device was implanted, and worsening of Parkinson's disease symptoms.
    b. In another study of 424 patients with tremor who were implanted with the same deep brain stimulator used for the patients with Parkinson's Disease, side effects related to the surgery to implant the device included pain (6.6%), bleeding in the brain (3.1 %), infection (2.6%), skin breakdown in the area of the device (1.9%) and a change in skin sensation (1.4%). Side effects related to brain stimulation included a change in skin sensation (33%), difficulty saying words (9%), difficulty with balance (5%), and weakness (5%). Most of these side effects were tolerable and did not require any change in the treatment.
6. While the following potential risks have not been reported with the use of the DBS System, they have been reported with systems that provide chronic stimulation to deep brain structures. These reported risks may be related to the area being stimulated, and include: abnormal dreams, thinking and vision; amnesia; apathy; chest pain; delusions; encephalopathy; deep thrombophlebitis; difficulty breathing, swallowing and walking; dizziness; drowsiness; dysesthesia; fainting; hallucination; hostility; increased salivation; paresthesia; paresis/paralysis; pneumonia; postural hypotension; rapid heart rate; speech disorders/difficulty speaking; vomiting/nausea.
7. While the following potential risks have not been reported with the use of the DBS System, they have been reported with systems that provide stimulation to deep brain structures in an acute environment, like in the doctor's office. These reported risks include all those risks listed above as well as:
   Changes in cognitive function; changes in movement, standing or walking; changes in smell/taste; encephalopathy; gastrointestinal symptoms; increased depression or worsening of depressive symptoms; memory experiences.

8. Possible Benefits:

The possible benefits from study participation would be suppression of vocal and motor tics.

9. Conflict of Interest:

None. The devices are paid for by the NIH UH3 grant.

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