Deep Brain Stimulation for Treatment-Resistant Depression

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TITLE: **Deep Brain Stimulation for Treatment-Resistant Depression**

PRINCIPAL INVESTIGATOR: Patricio Riva Posse, MD (Psychiatry)

CO-INVESTIGATORS: **Helen Mayberg, MD (Psychiatry and Neurology)**
Robert Gross, MD, PhD (Neurosurgery)
Andrea Crowell, MD (Psychiatry)

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SCHEMA

Recruitment:	Telephone screening
Screening:	Eligibility assessment Informed consent and videotaping of consent process
Pre-operative Evaluation: (4-6 weeks pre-op)	Confirmatory psychiatric interview Neurosurgical evaluation 2-4 Behavioral Activation evaluations Neuropsychological testing #1 Emotional response testing #1 Activity Monitoring and GPS Route Logging #1 EEG testing #1 High-resolution anatomical MRI Diffusion tensor imaging Resting BOLD fMRI Weekly mood ratings
Surgery:	Pre-operative anatomical MRI Implantation of bilateral deep brain stimulators Intraoperative testing of DBS contacts with electrophysiological recordings LFP, EEG, HRV, SCR, EMG Implantation of pulse generator and lead extensions Post-operative anatomical MRI
Post-operative evaluation: (4 weeks post-op)	Stimulation OFF Weekly mood ratings for 4 weeks Emotional response testing #2 Activity Monitoring, GPS Route Logging #2 EEG #2 High resolution computed tomography (CT) scan
Open Stimulation:	Bilateral, open-label chronic stimulation (24 weeks) Emotional response testing #3-5 (1,3,6 months) Activity Monitoring, GPS Route Logging (1,3,6 mos) EEG #3-5 (1,3,6 months) Weekly mood ratings for four weeks Bi-weekly to monthly mood ratings for next 20 weeks Behavioral Activation therapy sessions (up to 30)
Ten Year Follow-Up:	Mood Ratings every month for 3 months, then Mood Ratings every 3 months for 9 months then Mood Ratings every 6 months EEG #6 Optional EEG at 6 months and at annual visits Gait assessment (once) Emotional response testing (once)

INTRODUCTION

Major Depression is one of the most common and costly of all psychiatric disorders [1]. It ranks among the top causes of worldwide disease burden and is the leading source of disability in adults in North America under the age of 50 [2]. While depression can be effectively treated in the majority of patients by either medication or some form of evidence-based psychotherapy [3], up to 20% of patients fail to respond to standard interventions [4, 5]. For these patients, trial-and-error combinations of multiple medications and electroconvulsive therapy are often required [6, 7]. For patients who remain severely depressed despite these aggressive approaches, new strategies are needed.

Converging clinical, biochemical, neuroimaging, and post-mortem data suggest depression is unlikely to be a disease of a single brain region or neurotransmitter system. Rather, it is now generally viewed as a systems-level disorder affecting integrated pathways linking select cortical, subcortical and limbic sites and their related neurotransmitter and molecular mediators [8-12]. While mechanisms driving this 'system dysfunction' are not yet characterized, they are likely to be multi-factorial, with important and synergistic contributions from genetic vulnerability, developmental insults, and environmental stressors [13-15]. Treatments for depression can be similarly viewed within this limbic-cortical system framework, where different modes of treatment modulate specific regional targets, resulting in a variety of complementary, adaptive chemical and molecular changes that re-establish a normal mood state [12, 16, 17].

Functional neuroimaging studies have played a critical role in characterizing these limbic-cortical pathways [17-20]. Previous studies have demonstrated consistent involvement of the subgenual cingulate (Cg25) in both acute sadness and antidepressant treatment effects, suggesting a critical role for this region in modulating negative mood states [21, 22]. In support of this hypothesis, a decrease in Cg25 activity is reported with clinical response to different antidepressant treatments including specific serotonin reuptake inhibitor (SSRI) antidepressant medications, electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and ablative surgery [23-28]. In addition, Cg25 connections to the brainstem, hypothalamus, and insula have been implicated in the disturbances of circadian regulation associated with depression (sleep, appetite, libido, neuroendocrine changes) [29-33]. Reciprocal pathways linking Cg25 to orbitofrontal, medial prefrontal, and various parts of the anterior and posterior cingulate cortices form the neuroanatomical substrates by which primary autonomic and homeostatic processes influence various aspects of learning, memory, motivation and reward – core behaviors altered in depressed patients [31, 34-36].

Recent advances in the surgical treatment of Parkinson's disease have demonstrated that chronic high frequency deep brain stimulation (DBS) in pathologically active brain circuits produces profound clinical benefits [37-39]. It has also been shown that clinically effective DBS in the basal ganglia produces both local and remote changes in neural activity as assessed by positron emission tomography (PET) [40, 41].

Based on these observations, Dr. Mayberg has studied DBS of the white matter adjacent to Cg25 as a treatment for treatment-resistant depression in 13 patients. Of these 13 patients, 9 have mood ratings at 3 months post-surgery and 6 have mood ratings at 6, 9 and 12 months post-surgery. At 3 months, 3 of 9 patients met response criteria (>50% decrease in Hamilton Depression Rating Scale [HDRS] score). At 6 months, 4 of 6 patients met response criteria. Of these four patients, 2 were in remission (HDRS less than 8) and one was near remission at the 6 month time point. Also, all of these 4 responders (at 6 months) maintained this response out to 12 months post-surgery. In addition to improvements in depressive symptoms, patients with an antidepressant response have spontaneously reported improvements in sleep and

changes in visual perception. Although three patients had post-operative local wound infections, no other behavioral or medical adverse events were noted.

This pilot study supports the hypothesis that high-frequency DBS in Cg25 white matter can be used to treat depression, but further data is needed to confirm these findings. We propose a replication study at Emory University that will help further test the efficacy, safety and potential mechanisms of action of DBS for treatment-resistant depression (TRD).

OBJECTIVES

We propose to test whether high frequency DBS of the subgenual cingulate white matter (Cg25-DBS) is a safe and efficacious antidepressant treatment in forty TRD patients, and to investigate potential mechanisms of action of this intervention. Importantly, this study will be used to assess the need for and assist in planning a larger, more definitive trial of Cg25-DBS for TRD. We will address the following specific aims.

Specific Aim 1. To assess the safety and tolerability of acute and chronic Cg25-DBS. Rates of complications (surgical complications, hemorrhage, stroke, infections, and seizures) will be assessed and compared to known rates for DBS surgery in other disorders.

Specific Aim 2. To assess the antidepressant efficacy of active Cg25-DBS in treatment-resistant depressed patients. We hypothesize that 24 Weeks of open Cg25-DBS will yield statistically significant antidepressant effects.

Specific Aim 3. To assess the possible mechanisms mediating Cg-25 DBS effects on depression. This will include behavioral and psychophysiological measures of emotional response and perception, motor activity and electrophysiological measurements with acute intra-operative testing of DBS.

Secondary Aim 1. To assess long-term effects of Cg25-DBS in patients with Major Depressive Disorder. Patients will be followed naturalistically over 10 years.

Secondary Aim 2. To assess for variables that predict antidepressant response, remission and relapse over time.

Secondary Aim 3. Changes in mood and behavior associated with DBS will have both immediate effects and slowly evolving, delayed effects, our experimental protocol will assess mood and behavior at several time points post-surgery. This will include behavioral and psychophysiological measures of emotional response and perception, motor activity and electrophysiological measurements.

PROTOCOL

1.0 Clinical Care Costs

1.1 Patients or their third party payers will be responsible for the costs of the following procedures:
- 1.1.1 Initial surgery and any subsequent battery replacements
- 1.1.2 Pre & post-operative MRI,
- 1.1.3 post-op Xray CT
- 1.1.4 Psychiatric screening
- 1.1.5 Psychiatric follow-up visits
- 1.1.6 Neuropsychological assessment
- 1.1.7 Labs
- 1.1.8 Behavioral activation therapy
- 1.1.9 EKG (if required)

1.2 The following procedures will be covered by the study:
- 1.2.1 Research fMRI scan
- 1.2.2 Research assessments
- 1.2.3 Emotional Response Testing[46-50]
- 1.2.4 Actigraphy and GPS Route Logging[51-53]
- 1.2.5 EEG[54]
- 1.2.6 Gait Assessment

1.3 We currently have approval from the local CMS director for Medicare to cover the clinical costs associated with this study. We will pursue pre-authorization from other third party payers as appropriate.

2.0 Patient Selection

2.1 Eligibility Criteria. Patients can be included if they have:
- 2.1.1 Age 18-70 years old.
- 2.1.2 Ability to provide written informed consent.
- 2.1.3 Current Major Depressive Episode (MDE), secondary to either Major Depressive Disorder or Bipolar Disorder (I, II or NOS), diagnosed by structured clinical interview for DSM IV-TR[42]. Diagnosis will be confirmed by two independent psychiatrists.
- 2.1.4 Current MDE at least two years duration OR a history of more than 4 lifetime depressive episodes.
- 2.1.5 Minimum score at study entry of 20 on the 17-item Hamilton Depression Rating Scale (HDRS-17)[43].
- 2.1.6 Average pre-operative HDRS-17 score of 20 or greater (averaged over four weekly pre-surgical evaluations during the four weeks prior to surgery) and an average pre-operative HDRS-17 score no more than 30% lower than the baseline screening HDRS-17 score.
- 2.1.7 A maximum Global Assessment of Functioning of 50.
- 2.1.8 Treatment-resistant depression defined as:
  - 2.1.8.1 Failure to respond to a minimum of four different antidepressant treatments, including at least three medications from at least three different classes, evidence-based psychotherapy or electroconvulsive therapy (ECT) administered at adequate doses and duration **during the current episode**. We will require

documentation (i.e., statement from the treating psychiatrist) that a treatment trial has failed (either no response to maximum tolerable doses for a minimum of 4 weeks, or side-effects at sub-maximal doses) as coded by a revised Antidepressant Treatment History Form (ATHF). The study investigators will confirm each treatment via review of records from referring psychiatrists.

2.1.8.2 Failure or intolerance of an adequate course of electroconvulsive therapy (ECT) **during any episode** (confirmed by medical records)**,** or refusal of ECT due to a reason considered to be valid by the study psychiatrist. Such reasons might include concern regarding the impact of cognitive side effects of ECT on current ability to work or function, or inability to obtain third-party payment for a course of ECT. Additionally, it is recognized that the probability that a patient who has failed four medications in the current episode will achieve a lasting response with ECT is about 18% (60% probability of an acute response and 30% chance of maintaining this for at least 24 Weeks); patients who have refused ECT because this chance of benefit does not outweigh the risks associated with ECT will be considered eligible.

2.1.9 A patient may remain on psychotropic medications during this study. However, doses must remain stable during the 4 weeks prior to surgery, the four weeks post-operatively, and the 24 weeks open stimulation phase. Medications will be changed only if intolerable side effects clearly attributable to the medications develop.

2.1.10 All patients must have an established outpatient psychiatrist and be willing to sign a written release to allow study investigators to give and receive information from this psychiatrist.

2.2 Ineligibility Criteria. Patients will be excluded if they have:

2.2.1 Inability to tolerate general anesthesia.

2.2.2 Significant cerebrovascular risk factors or a previous stroke, documented major head trauma or neurodegenerative disorder.

2.2.3 Other currently active clinically significant Axis I psychiatric diagnosis including schizophrenia, panic disorder, obsessive-compulsive disorder, generalized anxiety disorder or post-traumatic stress disorder. Patients with severe Axis II personality disorders will also be excluded if the personality disorder is likely to interfere with cooperation and adherence to the study protocol.

2.2.4 Current psychotic symptoms.

2.2.5 Evidence of global cognitive impairment.

2.2.6 Substance abuse or dependence not in full sustained remission (i.e., not active for at least one year).

2.2.7 Active suicidal ideation with intent; suicide attempt within the last six months; more than three suicide attempts within the last two years.
2.2.8 Pregnancy or plan to become pregnant during the study period.
2.2.9 General contraindications for DBS surgery (cardiac pacemaker/defibrillator or other implanted devices).
2.2.10 Inability or unwillingness to comply with long-term follow-up.
2.2.11 History of intolerance to neural stimulation of any area of the body.
2.2.12 Participation in another drug, device or biologics trial within the preceding 30 days.
2.2.13 Conditions requiring repeated MRI scans.
2.2.14 Conditions requiring diathermy.
2.2.15 Conditions requiring anticoagulant medication.
2.2.16 Terminal illness associated with expected survival of <12 months.

2.3 Final patient selection will be made by consensus of the primary study team.

3.0 Pre-operative Clinical Evaluation

3.1 Telephone screening. To increase the efficiency of the screening process, interested patients will first be contacted by telephone to complete an initial telephone screening. This screening will confirm the patient's interest and review the major inclusion/exclusion criteria. Insurance status will be collected. Medical records will be requested and reviewed. Patients who continue to be eligible and interested will be scheduled for a screening visit. A copy of the informed consent form will be mailed to patients for careful review.

3.2 Screening visit. Potentially eligible and interested patients will have an initial screening visit to obtain informed consent and confirm eligibility. This visit will last approximately 8 hours including breaks, and may occur over more than one day. During this visit, the patient will meet with a study psychiatrist and a research coordinator. The following will be performed:

3.2.1 Informed consent (120 minutes). Patients will first be given an informed consent to be videotaped during the informed consent process for the DBS study. If patient's agree, the entire informed consent discussion will be videotaped. The patient will also be given the request to interview family member consent. If the patient chooses to sign, we will contact the family member (chosen by the patient) to see if they are willing to consent to be interviewed regarding DBS. The DBS study will be explained in detail and all questions from the patient will be answered to the greatest degree possible. The patient will demonstrate understanding of the study protocol verbally and will sign the informed consent form if they choose to participate. As part of the informed consent process, questions will be asked to assess how well the participant understands the consent using a validated questionnaire (the MacArthur Competence Assessment Tool for Clinical Research [MacCAT-CR]). Additionally, a brief questionnaire assessing how well the participant understands key differences between research and usual clinical care, and the effects of these differences on their participation in this study, will be administered. Patients will also have the opportunity to consent for us to contact a family member of their choosing. That

family member would then give us consent to interview them about their understanding and expectations of the study. Responses taken from the family member will be used to compare to those taken from the patients. The interview will be videotaped. That family member will also complete an interview/questionnaire form. Family members will be asked to do the interview/questionnaire again 7 months after their family member has received the DBS surgery. As a separate part of this study, videotapes will be reviewed by up to three outside psychiatrists with expertise in decision-making capacity. Videotapes of the consent discussion and capacity assessment will be kept confidential. The outside experts will obtain separate IRB approval from their home institutions to review these videotapes for the purpose of studying capacity to consent to research involving deep brain stimulation. A repeat, videotaped MacCAT-CR/consent assessment will be done at the end of the 24 weeks open active stimulation phase. As a separate part of this study, audio files will be extracted from the patient videos before surgery and after 24 weeks of active stimulation and sent to collaborators at the Nathan Kline Institute for analysis of changes in speech and language. Grammatical complexity, frequency of vocabulary, and conversational expressions will be analyzed as part of the language analysis. Audio files of the consent discussion and capacity assessment will be kept confidential. The outside experts will obtain separate IRB approval as necessary.

3.2.2 Diagnostic interview and mood ratings (120 minutes). The following will be administered:

- 3.2.2.1 Structured Clinical Interview for DSM-IV Diagnoses (SCID-I)
- 3.2.2.2 Structured Clinical Interview for DSM-IV Diagnoses, Axis II (SCID-II)
- 3.2.2.3 Shedler-Westen Assessment Procedure (SWAP)
- 3.2.2.4 28-item Hamilton Depression Rating Scale (HDRS-28)
- 3.2.2.5 Hamilton Anxiety Scale (HAS)
- 3.2.2.6 Montgomery-Asberg Depression Rating Scale (MADRS)
- 3.2.2.7 Young Mania Rating Scale (YMRS)
- 3.2.2.8 Mini-Mental Status Examination (MMSE)
- 3.2.2.9 Edinburgh Handedness Inventory (EHI)
- 3.2.2.10 Beck Depression Inventory (BDI-2)
- 3.2.2.11 Inventory of Depressive Symptomatology – Subject Rated (IDS-SR)
- 3.2.2.12 Beck Anxiety Inventory (BAI)
- 3.2.2.13 NEO-PR Personality Inventory (NEO)
- 3.2.2.14 Dysfunctional Attitude Scale (DAS)
- 3.2.2.15 Revised Dimensions of Temperament Survey (DOTS-R)
- 3.2.2.16 Beck Hopelessness Scale (BHS)
- 3.2.2.17 Toronto Alexithymia Scale (TAS)
- 3.2.2.18 Health and Labor Questionnaire (HLQ)

3.2.2.19 Quality of Life Expectation Satisfaction Questionnaire (Q-LES-Q)
3.2.2.20 Klein trauma & abuse-neglect (KLEIN)
3.2.2.21 Stressful Life Events Questionnaire (SLEQ)
3.2.2.22 Columbia Suicide Severity Scale (C-SSS)
3.2.2.23 Clinical Global Impression – Severity (CGI-S)
3.2.2.24 Patient Global Impression – Severity (PGI-S)
3.2.2.25 Global Assessment of Function (GAF)
3.2.2.26 Antidepressant Treatment History Form (ATHF)

3.2.3 Psychiatric examination (60 minutes). If the patient continues to meet inclusion criteria, a study psychiatrist will perform a detailed, diagnostic examination. Current psychiatric and physical symptoms, current medications and treatments, past psychiatric history, past medical and surgical history and substance use history will be reviewed. A physical examination will be performed as indicated.

3.2.4 Medications. Medications can be adjusted during the first part of the screening/pre-operative phase. However, doses must remain stable during the four weeks prior to surgery.

3.2.5 Release of information (ROI). Patients will sign an ROI so that study investigators may share health-related information with the patient's psychiatrist.

3.3 Follow-up screening visits. Patients who continue to be eligible will be scheduled for follow-up screening visits to include:

3.3.1 Evaluation by a second study psychiatrist to confirm psychiatric diagnosis and degree of treatment resistance (60 minutes).

3.3.2 Evaluation by the study neurosurgeon including review of appropriateness for surgery, physical and detailed neurological examination (60 minutes).

3.3.3 Labs (10 minutes). Blood and urine will be obtained for the following tests: complete blood count (CBC), comprehensive metabolic panel (CMP), thyroid screening tests, coagulation studies, high-sensitivity C-reactive protein, genotyping, urinalysis, urine drug of abuse screen, pregnancy test (if applicable). A small amount of blood will be stored for further genetic testing – cell lines will be immortalized so that blood can be stored indefinitely for future studies.

3.3.4 EKG (20 minutes). An EKG will be performed if the neurosurgeon determines this is necessary as part of the pre-surgical screening.

3.3.5 Magnetic Resonance Imaging (MRI)(60 minutes). This pre-operative scan will help rule out intracranial abnormalities that might explain the patient's level of treatment resistance or preclude the patient from surgery. During this scan, we will also acquire diffusion tensor imaging (DTI) to assess white matter tract integrity and resting BOLD functional MRI data to assess regional connectivity.

3.3.6 Neuropsychological testing (4 hours). A comprehensive neuropsychological battery will be administered by a trained psychometrist under the supervision of a board-certified neuropsychologist. This battery will take approximately 4 hours to

complete but can be done over more than one day if needed to prevent patient fatigue. The study will be performed prior to surgery and repeated at the end of 6 months of active stimulation

3.3.7 Behavioral Activation: In an effort to provide rehabilitation to our patients, behavioral activation therapy will be performed. There will be 2-4 sessions pre-op to establish a relationship with the patient. Therapy will begin post operatively when stimulation is started and will occur weekly for approximately 30 weeks.

3.4 Mechanism of Action Studies. To help assess mechanism of action (MOA) of DBS for TRD, several MOA experiments will be performed throughout the study beginning in the pre-operative evaluation period. All of the following will be repeated 1 month after surgery during acute DBS testing and again after 1,3, and 6 months of active DBS. :

3.4.1 Emotional response testing with psychophysical meaures. *Eye-Tracking and Pupilometry:* Eye-tracking will be used to measure the visual attention of the participant, The participant sits in front of a computer monitor and simply watches as pictures or sounds are presented. While they view the image or screen, a light beam is used to track the position and size of the pupil and cornea over time in order to estimate position of gaze.

3.4.1.1.1 *Emotional Pictures:* Emotional pictures will be selected from the International Affective Picture System, a standardized, widely available dataset, normed for content and emotional valence (IAPS; Lang, Bradley, and Cuthbert, 2008).

3.4.1.1.2 *Emotional Sounds:* The set of emotional sounds will include emotionally evocative and neutral musical excerpts (from classical and popular sources) as well as standard sounds from the International Affective Digital Sounds set (IADS; Bradley and Lang, 1999) which contains. short audio clips associated with pleasant (e.g., laughing) and unpleasant (e.g., crying, a barking dog) events.

3.4.1.1.3 *Emotional Videos:* The set of emotional videos will include up to twelve two-minute video clips from movies, documentaries, and instructional videos.

3.4.1.1.4 *Emotional Memories:* Participants will be asked to remember an experience that made them feel sad, feel happy, and feel angry for two minutes per experience. These emotional memories will be interspersed with 2 minutes spent imagining common, emotionally-neutral experiences, such as going grocery shopping.

3.4.1.1.5 *Image and sound ratings and questions*: Participants will rate emotional valence (how positive or negative a stimulus is) and emotional arousal (strength of emotional response), using a numeric scale. To verify that

participants attended to each stimulus, memory for selected items will be assessed with standard recall (e.g., “what stimuli did you experience”) and recognition tests (e.g., “is this stimulus one that you experienced in the experiment?”).

3.4.1.1.6 *Psychophysiology:* Galvanic Skin Response (GSR) will be measured using two sensors placed on the palm surface of the index and middle finger. (Andreassi, 2000). Electromyography (EMG) will be measured using two pairs of sensors placed on two separate locations of the face. (above the left eye brow corrugator supercilli muscle—frowning; midway between the corner of the mouth and the ear lobe (zygomaticus major muscle--smiling), Cardiac measures (ECG): Heart rate acceleration, heart rate variability (HRV) will be used using 3 lead ECG. Blood pressure will be measured simultaneously using a finger sensor..

3.4.2 Motivation and activity levels. Q-Sensor mobile wrist sensor 3-dimensional accelerometer to assess somatic activity movement), Garmin mobile personal GPS tracking to assess large-scale daily activity via tracking of routes (20).

3.4.2.1 Actigraphy. We hypothesize that decreased depressive symptoms will be associated with an increase in patients' average level of somatic movement, Patients will wear a mobile wristband-style 3-D accelerometer sensor that continuously logs arm and body movement levels.

3.4.2.2 GPS logging. We also hypothesize that decreased depressive symptoms will be associated with an increase in patients' average level of daily life activities including amount of travel outside the home. This will be assessed by a wristband-style GPS route logger, which periodically logs the individual's GPS location, forming a connected route map of daily travels.

3.4.2.3 Security. Patients will be fully informed about the nature of the information that will be recorded, its purpose and use, and will be able to stop, pause, or start the GPS logging function whenever they wish, by pressing a button (patients will receive training on these functions). The GPS logging information will be securely transmitted to a cloud server that will store the route logging information associated with a random study identification number, not the individual's name or other identifying information. The information on the server is only retrievable using a login and password. The route logging information will be used to determine

the number, length, and complexity of travel outside the home.

3.4.2.4 Gait Assessment. We hypothesize that decreased depressive symptoms will be associated with increased gait speed and endurance. Patients will engage in a self-paced walk for six minutes while wearing sensors attached to the trunk and limbs (APDM Wearable Technology).

3.4.3. Electroencephalography. (EEG) (1 hour). This data will be tested in conjunction with the resting bold fMRI as a predictive biomarker of antidepressant response to chronic DBS and as as index of ongoing brain changes with short term and chronic DBS. This study will be performed at baseline, 1 month after surgery and during acute testing of optimal DBS contacts, after 1, 3 and 6 months of active DBS, and at one time point during the naturalistic follow up phase.

3.4.3.1. EEG Recording and Analysis. During the EEG session, cortical field potentials will be continuously recorded at 1000 Hz (1kHz) from 32-64 active electrodes distributed over the scalp and held in place using an elastic cap. Electrodes will be placed so as to maximize scalp coverage and labeled according to the International 10-20 System for localizing EEG electrodes. Additional bipolar leads will be placed around the eyes to record the horizontal and vertical electrooculogram (H-EOG and V-EOG respectively). All electrophysiological data will be recorded using a BioSemi ActiveTwo biopotential measurement system (Amsterdam, Netherlands) and digitized on a laptop computer. Raw EEG data will be collected continuously during the testing session and segmented and filtered offline (0.01 – 100 Hz bandpass) prior to analysis. Positioning the electrodes and ensuring good electrical contact with the scalp will take an estimated 20-30 minutes for each patient. The total EEG session, including set-up and clean-up time is expected to be approximately 1 hour in duration.

3.4.3.2 Behavioral Tasks. EEG will be recorded in two conditions: (1) resting state; (2) a mood induction/emotion regulation task;

3.4.3.2.1 Resting Baseline: Previous research with patients receiving DBS for Parkinson's Disease (PD) has revealed a significant effect of DBS on EEG coherence in a resting condition in which no task was required of the patients. To facilitate comparison with this existing literature we will replicate their recording conditions. During this recording, the patient will be asked to sit still and maintain visual fixation on a marker on the computer screen for 150 seconds (2.5 minutes). Because DBS in our patients is expected to primarily influence prefrontal circuits we expect to find an overall increase in EEG coherence at frontal electrode sites and possibly between frontal and more posterior sites. However, the lack of a defined task in this baseline period may make interpretation difficult. To this end, we will record resting activity during different DBS states (ON versus OFF).

Additionally, we will collect EEG during an emotional behavioral tasks designed to explore the effects of DBS on the engagement of prefrontal circuits. Preliminary data using this task and a previously approved protocol demonstrates feasibility and results in support of the current hypotheses [54]

3.4.3.2.2 Mood Induction/Emotion Regulation Task: This task assesses the ability of the patients to regulate negative emotions. Words describing a variety of negative (e.g., "greedy") or positive (e.g., "kind") personality traits will be presented on a computer monitor. In two separate task runs, the patients will be asked to decide: (1) whether each word describes themselves or not, and (2) whether it would be a desirable trait in someone else or not. This task, particularly the condition in which patients make judgments about whether negative traits apply to themselves, requires patients to actively engage in mood regulation, presumably by engaging prefrontal circuits that may be compromised by depression. Because we expect DBS to alleviate depression and thus to facilitate mood regulation we will compare patterns of EEG coherence between conditions (self vs. other; positive vs. negative traits) during each session. We expect that successful emotion regulation will be manifested by increases in EEG coherence in prefrontal circuits, and that those circuits will be more engaged following successful DBS treatment.

3.5 Weekly mood ratings. During the pre-operative phase, patients will have assessments every 1 to 4 weeks. Assessments will occur weekly during the 4 weeks prior to surgery. Assessments will include:

- 3.5.1 HDRS-28
- 3.5.2 HAS
- 3.5.3 MADRS
- 3.5.4 YMRS
- 3.5.5 BDI-2
- 3.5.6 IDS-SR
- 3.5.7 BAI
- 3.5.8 PGI-S
- 3.5.9 Patient Global Assessment of Improvement (PGI-I)
- 3.5.10 DAS
- 3.5.11 DOTS-R
- 3.5.12 BHS
- 3.5.13 Q-LES-Q (every 4 weeks)
- 3.5.14 HLQ (every 4 weeks)
- 3.5.15 TAS
- 3.5.16 C-SSS
- 3.5.17 CGI-S
- 3.5.18 Clinical Global Assessment of Improvement (CGI-I)
- 3.5.19 GAF
- 3.5.20 Medication Log

3.6 Pre-surgical visit. On the last weekly mood rating visit prior to surgery, the patient will again meet with a study psychiatrist and PI to confirm continued

interest in participation and to review the surgical and post-surgical procedures.

3.7 Videotaping: Videotaping: At several time points in this study the patient will be briefly videotaped to document their appearance, speech and behavior. Additionally a more extensive videotaped interview will be performed prior to surgery and at the primary endpoint date to further document overall change in symptoms, appearance, speech and behavior, supplementing quantitative measures.

4.0 Surgery

4.1 Target Identification. Patients will come to Emory University Hospital on the morning of surgery. A CRW stereotactic frame (Radionics, Inc., Burlington, MA) will be affixed to the patient's head and preoperative MRI obtained (Signa, 1.5 tesla; General Electric, Milwaukee, WI). The x, y, and z coordinates of the anterior (AC) and posterior commissures (PC) will be determined using axial 3D T1 MR images. To reach the intended target within the subgenual cingulate white matter, a midline T2 sagittal image will be selected and the cingulate gyrus below the genu of the corpus callosum identified. A line will be traced from the most anterior aspect (genu) of the corpus callosum to the anterior commissure and the midpoint selected. The T2 coronal section corresponding to the plane of this midpoint will be identified and the coordinates of the transition point between the gray and white matter identified.

4.2 DBS Surgery. In the operating room under local anesthesia, a burr hole will be drilled 2 cm from the midline immediately anterior to the coronal suture. The underlying dura mater will be opened, and the exposed pial surface coagulated. A mixture of fibrin glue and cryoprecipitate will be used to prevent cerebrospinal fluid egress and minimize brain shift. The CRW arc will be attached to the head frame and set to the pre-determined target coordinates. Micro-electrode recordings will commence at 10 mm above the target using electrodes made from parylene-C-insulated tungsten wires and plated with gold and platinum (FHC, Inc., Bowdoinham, ME). Cellular activity will be amplified (DAM 80 WPI Instruments) with a gain of 1000 and initially filtered to 0.1-10 kHz. The signal will be displayed on an oscilloscope (Axon Instruments) and directed to an audio monitor (Grass AM 8, with noise clipping circuit). Microelectrode mapping will be used mainly to confirm the anatomic location of the gray and white matters of area 25, characterized respectively by the recording of neuronal activity and cell sparse areas. The transition between these two regions will be chosen as the final target for the implantation of the electrodes. DBS quadripolar electrodes (St. Jude Medical Neuromodulation; Plano, TX) will be implanted bilaterally. Each of the 4 electrode contacts will be tested for adverse effects and clinical benefits. These contacts will be numbered from 1-4 (left hemisphere) and 5-8 (right hemisphere), with 1 and 5 being the most ventral and 4 and 8 the most dorsal contacts. The Positive And Negative Affect Scale (PANAS) and visual analog scales will be used to test mood intraoperatively as each contact is tested. This portion of the surgery will be videotaped.

4.3 Intraoperative Recording. We will record electrical activity (single cell recording and local field potentials) in the vicinity of the surgical target and along the electrode trajectory. We will also record scalp EEG, facial EMG,

Skin conductance (SCR), and heart rate intraoperatively.. Recording will occur prior to, during and after stimulation at each DBS contact. This will provide comparable measures to those measured in the lab during the Emotional testing sessions.

5.0 Post-operative care. Prophylactic antibiotics will be administered for 24 hours after the surgical procedures. An 1.5T MRI will confirm DBS electrode placement and absence of intraoperative complications (e.g., intracranial air, hemorrhage, edema), Patients will be discharged 1-3 days following surgery.

6.0 Post-operative, Stimulation Off Phase (4 weeks)

6.1 Patients will discharged with the DBS system off (patients will be told the system is off).

6.2 Patients will be evaluated weekly for four weeks to assess for behavioral changes following DBS surgery but prior to receiving active, chronic stimulation.

6.3 Clinical Assessments. During this phase, clinical assessments will include:

- 6.3.1 HDRS
- 6.3.2 HAS
- 6.3.3 MADRS
- 6.3.4 YMRS
- 6.3.5 BDI
- 6.3.6 BAI
- 6.3.7 IDS-SR
- 6.3.8 DAS
- 6.3.9 DOTS-R
- 6.3.10 BHS
- 6.3.11 Q-LES-Q (every 4 weeks)
- 6.3.12 HLQ (every 4 weeks)
- 6.3.13 TAS
- 6.3.14 C-SSS
- 6.3.15 SDS
- 6.3.16 PGI-S
- 6.3.17 PGI-I
- 6.3.18 CGI-S
- 6.3.19 CGI-I
- 6.3.20 Medication log

6.4 High Resolution x-ray CT scan: this study will be used to verify the final location of DBS electrode contacts needed for selection of the optimal contact for chronic stimulation.

6.5 Emotional response testing, actigraphy and GPS logging, EEG #2: Patients will return for repeat testing (sam as 3.4.1-3).

7.0 Open Stimulation Phase (4-30 weeks post-op)

7.1 Clinical Assessments. During this phase, patients will return every two to four weeks for clinical assessments to include:

- 7.1.1 HDRS
- 7.1.2 HAS
- 7.1.3 MADRS
- 7.1.4 YMRS
- 7.1.5 BDI

7.1.6 BAI
7.1.7 IDS-SR
7.1.8 DAS
7.1.9 DOTS-R
7.1.10 BHS
7.1.11 Q-LES-Q (every 4 weeks)
7.1.12 HLQ (every 4 weeks)
7.1.13 TAS
7.1.14 C-SSS
7.1.15 PGI-S
7.1.16 PGI-I
7.1.17 CGI-S
7.1.18 CGI-I
7.1.19 Medication log

7.2 Behavioral Activation Therapy: Patients will begin BA with the onset of stimulation. There will be a maximum of 30 sessions over the course of the first 6 months.

7.3 Emotional response testing #3-4: Patients will return for repeat testing at 1 month and 3 months of DBS. SCR and activity will be monitored continuously for the first month using the Q-Sensor mobile wrist sensor, 3-D accelerometer and Garmin mobile GPS devices. Weekly testing will be performed monthly for months 2-6.

7.4 EEG #3 and #4: EEG will be repeated at 1 month, 3 months of DBS.

7.5 End of Phase MOA Assessment. At the end of this 24 Week phase, patients will be evaluated as follows (see above for details):
7.5.1 Neuropsychological testing #2
7.5.2 Emotional response testing, actigraphy, GPS logging and EEG #5.

7.6 Programming Adjustments. Initial stimulation settings will be 130 Hz, 91 μs pulse width, 4mA monopolar bilateral stimulation (one contact per electrode array per side). Every 4 weeks, after the clinical evaluation, a decision will be made whether to continue at these settings or make an adjustment. Adjustments will be made based on whether a patient is considered IMPROVED (>10% change in the 17-item HDRS score from the previous assessment and/or at least minimally approved on the CGI-I), UNCHANGED (≤10% change in the 17-item HDRS score from the previous assessment and/or unchanged on the CGI-I) or WORSE (>10% increased in the 17-item HDRS score from the previous assessment and at least minimally worse on the CGI-I) using the following algorithm:
7.6.1 If IMPROVED, make no change and re-assess in 4 weeks.
7.6.2 If UNCHANGED or WORSE, go through the following sequence of steps:
7.6.2.1 Increase amplitude to 6 mA and reassess in 4 weeks.
7.6.2.2 Increase amplitude to 8 mA and reassess in 4 weeks.
7.6.2.3 Re-evaluate contact location and consider a contact switch; remain at 8 mA; re-assess in 4 weeks.
7.6.2.4 Re-evaluate contact location and consider adding a second contact; remain at 8 mA; re-assess in 4 weeks.
7.6.3 To date, there has been no association with stimulation of this brain region or increased amplitude of stimulation with a worsening of depression. When patients have had a worsening of

depression, this has consistently been determined to be due to environmental stressors or the natural history of the patient's illness (normal fluctuations). However, if a patient experiences a >30% increased in the 17-item HDRS score within 4 weeks of a stimulation setting change AND there is no other cause identified for this worsening, then the stimulation parameters will be returned to the previous settings and the patient will be re-evaluated in 4 weeks (or sooner if clinically indicated).

8.0 Ten Year Naturalistic Phase

8.1 Rationale. The long-term effects of DBS are not known. This will be evaluated over ten years.

8.2 Length. The overall length of this phase will be ten years and will begin at the end of the 6 month open stimulation phase.

8.3 Clinical Assessments. During this phase, patients will return every month for the first three months, every 3 months for the next 9 months, then every six months for clinical assessments:

- 8.3.1 HDRS
- 8.3.2 HAS
- 8.3.3 MADRS
- 8.3.4 YMRS
- 8.3.5 BDI
- 8.3.6 BAI
- 8.3.7 IDS-SR
- 8.3.8 DAS
- 8.3.9 DOTS-R
- 8.3.10 BHS
- 8.3.11 Q-LES-Q (every 4 weeks)
- 8.3.12 HLQ (every 4 weeks)
- 8.3.13 TAS
- 8.3.14 C-SSS
- 8.3.15 PGI-S
- 8.3.16 PGI-I
- 8.3.17 CGI-S
- 8.3.18 CGI-I
- 8.3.19 PANAS-X
- 8.3.20 Hope Scale
- 8.3.21
- 8.3.22 Medication log
- 8.3.23 Depressive Experiences Scale (once)
- 8.3.24 Brio acceptability questionnaire
- 8.3.25 CAT MH

8.4 Medication Adjustments. Medications can be adjusted during this phase based on clinical judgment.

8.5 DBS programming adjustments. DBS programming adjustments will be allowed based on clinical judgment.

8.6 Assessment of long-term stable response: Patients will be invited to undergo a brief EEG subsequent to the 6 month study period and in conjuction with annual visits. After several years of stimulation, when a long-term, stable response has been attained, subjects will be reassessed with EEG #6, emotional response testing, psychophysiology, and gait assessment.

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9.0 Data Analyses and Statistical Consideration

9.1 Definitions. Standard criteria for antidepressant response, remission, relapse and recurrence will be applied[45].

9.1.1 **Response** will be defined as a decrease in the HDRS-17 score of 50% or greater from the average pre-surgical baseline.

9.1.2 **Non-response** will be defined as a <30% decrease in HDRS-17.

9.1.3 **Partial response** will be defined as a decrease in HDRS-17 >30% but less than 50%.

9.1.4 **Remission** will be defined as an HDRS-17 score <10.

9.1.5 Depressive **relapse** will defined as meeting DSM-IV criteria for a MDE (i.e., meeting 5 of 9 DSM-IV criteria for 2 consecutive weeks with at least one symptom being depressed mood or anhedonia) in the absence of a 2 month period of remission. **Recurrence** will be defined as meeting DSM-IV criteria for a MDE following at least a 2 month period of remission.

9.1.6 **Study Success** will be defined by the number of patients meeting individual patient success criteria (HDRS-17 decrease of ≥50% between baseline and 24 Weeks) after 6 months of active DBS. The study will be considered a success if 30% or more of enrolled patients meet the response criteria after 6 months of active stimulation. This threshold would exceed that seen for Vagus Nerve Stimulation, the only currently approved treatment for this degree of treatment refractory depression.

9.2 Statistical Analyses.

9.2.1 **General analysis issues.** Given that this is a preliminary study of safety and efficacy (SE), the primary focus of the analyses is to determine the size of the treatment effect and its clinical relevance as a basis for future comparative trials. Thus, the sample size is expected to be small. Even so, all exploratory analyses of mechanisms of action will use the assumed distribution of the outcome variables and the appropriate analysis method that would be expected in the population. However, careful attention will be paid to outliers that may affect the validity of the estimates. This will be done through careful analysis of model residuals and influence statistics. If outliers or variance issues are apparent, we can substitute nonparametric procedures, and in some case small-sample exact methods, for those analyses outlined below. Multiple measures will be handled using appropriate multivariate analyses, or with data reduction techniques such as PCA which are not model dependent (i.e., do not assume a distribution and therefore are not as sensitive to sample size issues).

9.2.2 **Power Analysis.** The sample size calculation is based on the demonstration of efficacy of the treatment (SA2). Our purpose is to estimate the response rate with a given level of precision, thus we used the 6 month response rate for the pilot data (4/6=0.67) and determined the sample size necessary to estimate a similar rate with specified levels of precision (i.e., the width of the confidence interval). For the given rate, a sample size of 11-19 patients would be required to estimate the response rate plus or

minus 20-25%. For the purposes of the exploratory analyses, a sample size of 19 should be adequate to detect larger effect sizes (differences equal to 68% of the standard deviation (ES=0.68)), though more patients will be needed to detect smaller effect sizes and to evaluate for predictors of response.

9.2.3 **Specific Aim 1.** We will record all surgical complications in addition to any other adverse events in order to get a reasonable estimate of the risks of the treatment. We will examine specific complication rates in addition to rates of "any" adverse event. We will separately document serious adverse event rates. If possible, we may also do a formal statistical comparison of these sample rates to those associated with DBS surgery in other disorders to determine if the sample rates are comparable. Rates of the first occurrence of all adverse events and device and procedure related adverse events within 24 Weeks following the initial bilateral implants will be summarized along with exact one-sided 95% upper confidence bounds. Similar analyses will be conducted for serious adverse events.

9.2.4 **Specific Aim 2.** We will estimate of the 24 Week response and remission rates; we will quantify the magnitude of the response using repeated measures analysis of variance on the depression scores (HDRS-17) comparing the levels at baseline with those after 24 Week of open DBS treatment.

9.2.5 **Specific Aim 3**. This aim is exploratory and will assess for intraoperative electrophysiological changes associated with stimulation at specific DBS contacts.

9.2.6 **Secondary Aim 1**. The purpose of this maintenance phase will be to attempt to quantify the level of treatment (dose) that is sufficient to sustain the antidepressant effect.

9.2.7 **Secondary Aim 2**. Analyses will include evaluating a variety of measures, including demographics, clinical characteristics, brain morphology and cognitive function, as possible mediators of the antidepressant effect over time. This will be formally carried out in two ways: 1) by comparing these measures in 6 month responders and nonresponders using appropriate two-sample tests (e.g, t-tests for continuous data, chi-square for categorical data) and 2) by using longitudinal analysis to see if either baseline measures of these variables or changes in these variables with treatment are significantly associated with the change in depressive symptoms over time. This can be performed using repeated measures analysis of covariance, or more simply, using linear regression predicting the change in depression (pre-post). Given the nature of the study these analyses will be underpowered but will provide useful data for future comparative trials.

9.2.8 **Secondary Aim 3**. Analyses will evaluate EEG, emotional reactivity and psychophysiological variables over time, as possible mediators of the antidepressant effect. This will be formally carried out in two ways: 1) by comparing these measures in 6 month responders and nonresponders using appropriate two-sample tests (e.g, t-tests for continuous data, chi-square for categorical

data) and 2) by using longitudinal analysis to see if either baseline measures of these variables or changes in these variables with treatment are significantly associated with the change in depressive symptoms over time. This can be performed using repeated measures analysis of covariance, or more simply, using linear regression predicting the change in depression (pre-post). Given the nature of the study these analyses will be underpowered but will provide useful data for future comparative trials.

10.0 Data and Safety Monitoring

10.1 Expected Side Effects/Potential Adverse Events. The complications of DBS surgery are well established and relate to surgical complications at the time of implantation and secondary complications due to failure of the device, infection or stimulation of structures adjacent to intended target structures. Effects of acute and chronic Cg25-DBS in depressed patients are largely unknown. No unanticipated psychiatric, neurological or other medical adverse effects have been observed in 20 patients studied to date in Toronto, or the 23 patients implanted thus far as part of this protocol. Three out of the first five patients in the Toronto series developed local wound infections; however, these infections occurred in the context of two separate surgeries separated by one week with externalization of the electrodes for testing. This prompted a switch to performing both surgical procedures at the same time and no infections have occurred since (in the next eight patients). Risks of general anesthesia are well-known include a less than 1/200,000 risk of death. Based on data collected to date on DBS in Parkinson's Disease patients, the rate of serious surgery-related adverse events (e.g., hemorrhage, seizures, hemiparesis/hemiplegia, serious infection) is approximately 10%. The rate of all serious adverse events is approximately 53%, and the rate of all (including minor) adverse events is approximately 88%.

10.2 Adverse Event Rates Leading to Study Discontinuation. Based on the DBS in PD event rates listed above, study discontinuation will be considered in the following situations:

- 10.2.1 If the serious surgery-related adverse event rate is more than double the above rate (>20%), the study will be halted and the DSMB will carefully review the data to determine if the risks of the study outweigh benefits.
- 10.2.2 If the rate of all serious adverse events is greater than the rate for PD (>53%), the study will be halted to allow the DSMB to carefully review the data to determine if the risks of the study outweigh benefits.
- 10.2.3 If the rate of all adverse events is greater than the rate for PD (>88%), the study will be halted to allow the DSMB to carefully review the data to determine if the risks of the study outweigh benefits.

10.3 Data and Safety Monitoring Board (DSMB). In light of the limited experience with this procedure in psychiatric patients, we will use the Data Safety Monitoring Board (DSMB) for the Department of Psychiatry and Behavioral Sciences as a third-party oversight committee.

10.3.1 DSMB Composition. The DSMB for this study will consist of the Clinical Research Oversight Committee members including co-chairs Larry Tune, M.D. and Boadie Dunlop, M.D., Bobbi Woolwine, L.C.S.W and Tanja Mletzko, M.A. Should the DSMB require additional specialized expertise to evaluate safety issues related to the performance of this study, a relevant specialist will be consulted.

10.3.2 Frequency of meetings/review. The frequency of DSMB review for this protocol will follow recommendations from the IRB based on the assessed risk status of the study. Currently, it is expected that the DSMB will meet quarterly.

10.3.3 This protocol will be submitted to the DSMB simultaneously with this initial submission to the Emory IRB. The DSMB will review the research protocol and plans for data and safety monitoring. Twice per year, the DSMB will review a report from the study's data manager that includes the following information: the number of participants who signed consent forms for the study and were subsequently randomized to study arms, the number of post-randomization dropouts, the reasons for withdrawal from the study, and any safety concerns, adverse events, an up-to-date consent form, and measures taken to protect confidentiality (e.g., data and tape storage, use of coded ID numbers, etc.). The DSMB will also review the Principal Investigator's summary of any new data or evidence that might alter the risk/benefit ratio for participating in the study (e.g., newly published studies, etc.). After reviewing this information, the DSMB will issue its own report summarizing any serious and unexpected adverse events or other unanticipated problems that involve risk to study participants, and whether these appear related to the study-based interventions or research assessment protocols.

10.3.4 There will be regular, ongoing communication between the PI, Emory's IRB, and the DSMB. The PI will take responsibility for reporting any serious and unexpected adverse events or other unanticipated study problems to Emory's IRB within 24 hours, according to standard regulations. A copy of each report will be sent to the DSMB. Actions taken by the IRB in response to adverse event reports will be immediately reported to the DSMB, which will review all serious adverse events as they arise. DSMB reports will be shared with the IRB.

10.3.5 A Serious Adverse Event (SAE) in this study will be defined as an event that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability or incapacity. The degree of probable relation between study procedures and the SAE will be carefully evaluated and documented.

10.3.6 Unexpected adverse events in this study will be defined as any adverse events for which the nature and severity are not consistent with expected adverse events resulting from the surgery, pre- or post-operative evaluation, or deep brain stimulation.

10.3.7 The DSMB will have the authority to stop the study at any point.

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