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Brain-Responsive Neurostimulation for Loss of Control Eating: Early Feasibility Study

BACKGROUND: Loss of control (LOC) is a pervasive feature of binge eating, which contributes significantly to the growing epidemic of obesity; approximately 80 million US adults are obese. Brain-responsive neurostimulation guided by the delta band was previously found to block binge-eating behavior in mice. Following novel preclinical work and a human case study demonstrating an association between the delta band and reward anticipation, the US Food and Drug Administration approved an Investigational Device Exemption for a first-in-human study.

OBJECTIVE: To assess feasibility, safety, and nonfutility of brain-responsive neurostimulation for LOC eating in treatment-refractory obesity.

METHODS: This is a single-site, early feasibility study with a randomized, single-blinded, staggered-onset design. Six subjects will undergo bilateral brain-responsive neurostimulation of the nucleus accumbens for LOC eating using the RNS® System (NeuroPace Inc). Eligible participants must have treatment-refractory obesity with body mass index $\geq$ 45 kg/m^2. Electrophysiological signals of LOC will be characterized using real-time recording capabilities coupled with synchronized video monitoring. Effects on other eating disorder pathology, mood, neuropsychological profile, metabolic syndrome, and nutrition will also be assessed.

EXPECTED OUTCOMES: Safety/feasibility of brain-responsive neurostimulation of the nucleus accumbens will be examined. The primary success criterion is a decrease of $\geq$1 LOC eating episode/week based on a 28-d average in $\geq$50% of subjects after 6 mo of responsive neurostimulation.

DISCUSSION: This study is the first to use brain-responsive neurostimulation for obesity; this approach represents a paradigm shift for intractable mental health disorders.

KEY WORDS: Responsive neurostimulation, DBS, Deep brain stimulation, Nucleus accumbens, Loss of control, Eating disorders, Binge, Obesity

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GENERAL INFORMATION

Trial Acronym: BITES—Brain Intervention Therapy for Eating Suppression

Study dates: February 27, 2019 to January 1, 2025

Registry: NCT03868670 (registration date: March 11, 2019)

ClinicalTrials.gov website: https://clinicaltrials.gov/ct2/show/NCT03868670?term=NCT03868670&rank=1

Research protocol personnel: Derived from Protocol Draft of October 30, 2018

Study sponsor and Principal Investigator: Casey H. Halpern, MD

ABBREVIATIONS: BED, binge-eating disorder; **BITES,** Brain Intervention Therapy for Eating Suppression; **BMI,** body mass index; **DBS,** deep brain stimulation; **DSMB,** Data and Safety Monitoring Board; **EDC,** electronic data capture; **EDE-Q,** Eating Disorders Examination Questionnaire; **IRB,** Institutional Review Board; **LFP,** local field potential; **LOC,** loss of control; **MacCAT-CR,** modified MacArthur Competence Assessment Tool for Clinical Research; **NAc,** nucleus accumbens; **SAE,** serious adverse event; **SPIRIT,** Standard Protocol Items: Recommendations for Interventional Trial

Research site: Stanford University Medical Center, Stanford, California

More details are given in Table 1.

Obesity is a serious medical condition affecting hundreds of millions of people worldwide, and loss of control (LOC) eating is a critical risk factor.[1,2] This paper aims to describe a clinical protocol utilizing a novel neurostimulation technology to alleviate LOC eating in treatment-refractory obesity.

Over the past several decades, obesity has gained epidemic proportions worldwide. In the United States alone, more than 90 million adults are categorized as obese (body mass index [BMI] $\geq$ 30 kg/m^2), at a socioeconomic cost of over $150 billion annually.[3,4] Alongside, the United States has experienced a concomitant rise in obesity-related comorbidities, including cardiovascular disease and type 2 diabetes,[5] adversely affecting quality of life and lifespan. Despite preventative and treatment efforts, obesity remains a major public health crisis, and is especially life-threatening for a subset of individuals who are morbidly obese (BMI $\geq$ 40 kg/m^2) despite prior treatments (including gastric bypass surgery), contributing to up to 20 yr of lost life in young males with a BMI $>$ 45 kg/m^2.[6] While bariatric surgery can significantly decrease mortality for some, many patients continue to live with morbid obesity.[7] Thus, novel neurostimulation methods may provide a paradigm shift in obesity management.[8]

LOC eating, which is common in obesity and a defining characteristic of binge-eating disorder (BED),[9] involves the subjective sense that one cannot stop eating, or control what or how much one eats. LOC eating detected postbariatric surgery has been found to be associated with significantly worsened weight loss outcomes,[10,11] eating-disorder psychopathology, depression, and lower quality of life.[12-14] An extensive array of basic and clinical research has provided insight into the neural mechanisms of LOC eating; it involves the hedonic properties of highly palatable foods mediated in part by the mesolimbic dopamine system's projections to the nucleus accumbens (NAc).[15,16] Deep brain stimulation (DBS) of the NAc region is being increasingly explored for a multitude of disorders in which LOC plays a major role.[17,18] Table 2 provides a brief overview of NAc DBS procedures that have been reported to impact human LOC eating and/or obesity.[19-21] These studies investigated promising DBS effects in its most traditional form: open-loop, chronic, and continuous electrical stimulation, regardless of temporally or behaviorally specific changes in NAc physiology. However, our preclinical data have demonstrated that traditional DBS effects on LOC eating may not be sustained over time and even alter social behavior, raising concern for developing this specific approach for humans further.[17,22] These unwanted effects were not seen with closed-loop NAc DBS, in which stimulation was delivered in response to a behaviorally specific fluctuation in NAc physiology.

Given this work, we intend to leverage the availability of the RNS® System (FDA-approved for epilepsy; NeuroPace Inc., Mountain View, California), to develop a closed-loop, brain-responsive neurostimulation therapy for LOC eating in treatment-refractory obesity. The RNS® System has already been proven to detect and respond to a predefined electrographic pathophysiological signature.[23] Similar to epilepsy, in which epileptiform activity can precede electrographic and clinical seizures, temporally specific activity within the NAc as measured via numerous modalities has been reported to occur during anticipatory periods preceding consummatory behavior.[22,24,25] This brief window in time during an at-risk and vulnerable moment, when these physiological changes are detectable, represents a critical opportunity for intervention (Figure 1), as demonstrated by our preclinical studies (Figures 2 and 3). Notably, utilizing a behaviorally specific, electrophysiological signal to guide stimulation delivery is not expected to impact normal behaviors, as found in these preclinical studies. The possibilities provided by brain-responsive neurostimulation to restore inhibitory control during vulnerable moments are expected to revolutionize neurosurgical treatments for a wide range of disorders, not the least of which are epilepsy and LOC eating.[26]

STUDY GOALS AND OBJECTIVES

The primary objective of this first-in-human early feasibility study is to assess device function and safety, with secondary objectives including the feasibility of brain-responsive neurostimulation by investigating NAc physiological correlations with LOC eating. Time series and spectral analysis methods will be used. Signal identification, including the function of signal-specific detection algorithms, will be assessed, and the safety of responsive

TABLE 1. Research Protocol Personnel

Role	Specialty	Name	Institution
Principal Investigator	Neurosurgery	Casey H. Halpern[a]	Stanford University
Principal Investigator	Psychiatry	James Lock	Stanford University
Principal Investigator	Neuroscience and Electrophysiology	Robert Malenka	Stanford University
Principal Investigator	Device and Regulatory	Tara Skarpaas	NeuroPace Inc

[a]Contact Principal Investigator.

TABLE 2. Brief Literature Review on the Effects of Nucleus Accumbens DBS in Human Morbid Obesity

Study	Procedure (target)	No. of pts (sex)	Results for obesity	Additional effects or complications
Harat et al, 2016[19]	DBS (NAc, bilaterally)	1 (F)	Weight loss Reported feelings of increased energy	Improvement in the emotional state Gradual improvement in psychomotor performance in visual-spatial working memory
Mantione et al, 2010[20]	DBS (NAc, bilaterally)	1 (F)	Weight loss	Improved obsessive compulsive symptoms Improved depression and anxiety
Tronnier et al, 2018[21]	DBS (NAc, bilaterally)	1 (F)	Weight loss Increased ability to resist LOC eating	Improved depression and quality of life Difficulties falling asleep

DBS: deep brain stimulation, F: female, NAc: nucleus accumbens, M: male; YBOCS: Yale-Brown Obsessive-Compulsive Scale scores, LOC: loss of control.

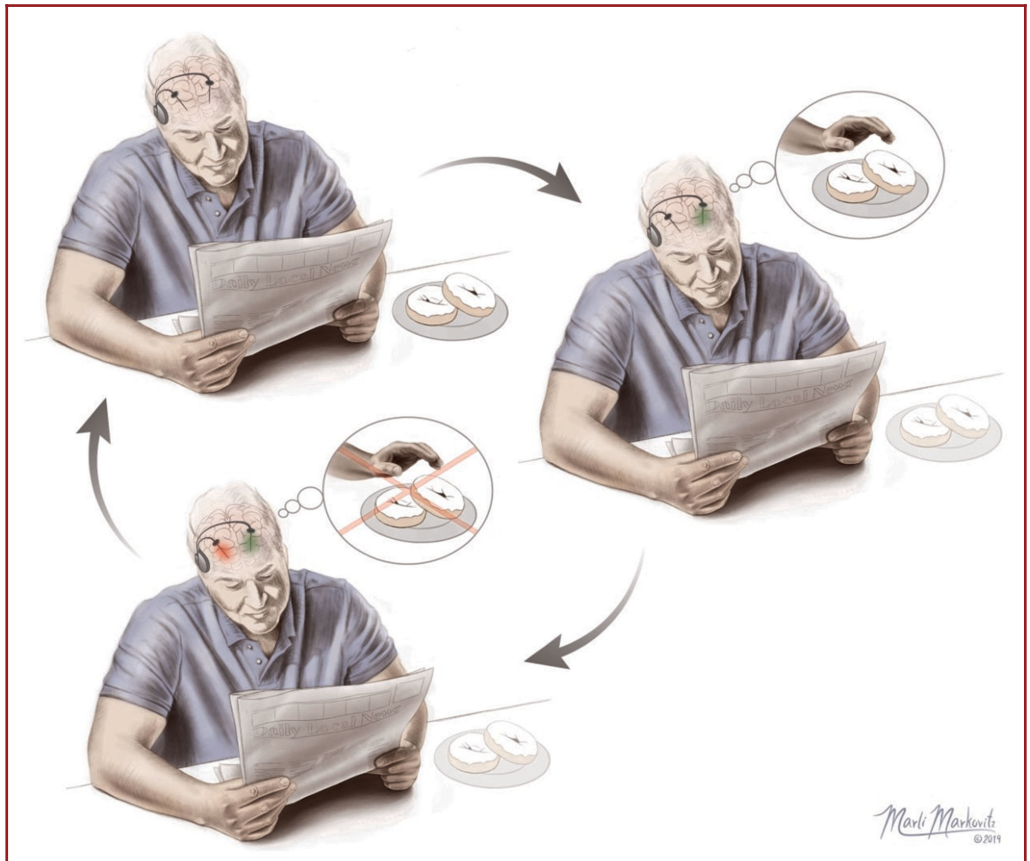

FIGURE 1. *Schematic representation of the RNS® System detecting (green) and then immediately curbing the impulse to eat a donut with triggered electrical stimulation (red). Note that this schematic simply represents unilateral detection and contralateral brain-responsive neurostimulation. Our study will include the possibility for both bilateral recordings and stimulation, depending on the perceived need and benefit for each individual subject. ©Marli Marcovitz. Used with permission.*

NAc DBS will be measured. Moreover, this study is expected to provide proof-of-concept and feasibility data; in at least half of the participants, a decreased mean weekly frequency of LOC eating episodes assessed by ecological momentary assessment (ie, the primary endpoint measure) as well as self-report Eating Disorders Examination Questionnaire (EDE-Q)[27] and the 3 other ambulatory measures described below is expected to be observed. Secondary outcomes will include other assessments of

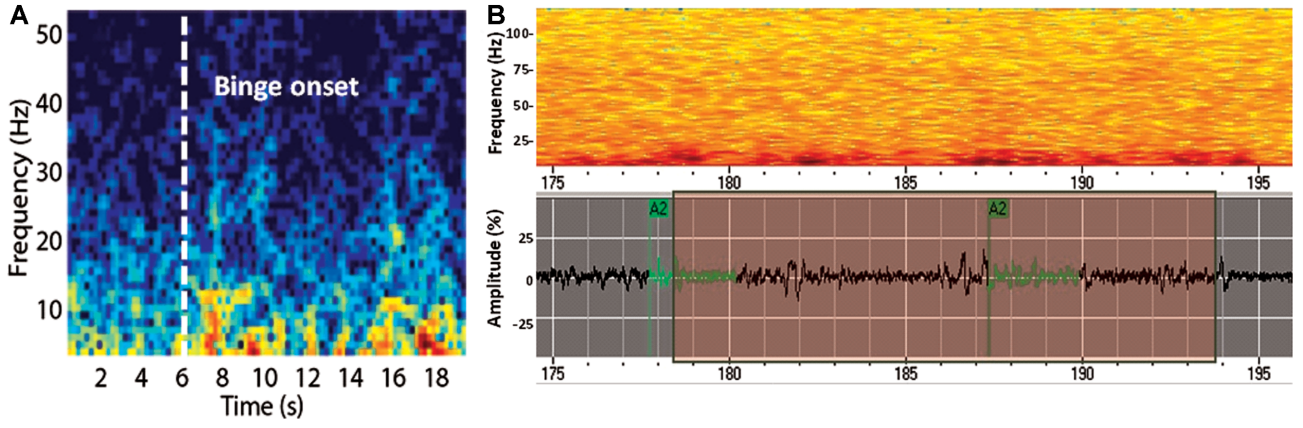

FIGURE 2. *Example of LFP signal detected by the RNS® System in a mouse model of binge-eating behavior in which LOC is pervasive:* **A**, *Continuous time-frequency spectrogram indicating a candidate signal (in this case, increased power in low frequency) prior to onset of a binge on high fat food (dashed white line) using an off-the-shelf system,* **B**, *our corresponding power spectrogram (top) and LFPs (bottom) recorded by the integrated RNS® System revealing similar changes during LOC period (red box). This change in the delta band range specifically was detected by a predefined signal detector, indicated by marker "A2," and was used to trigger stimulation.*

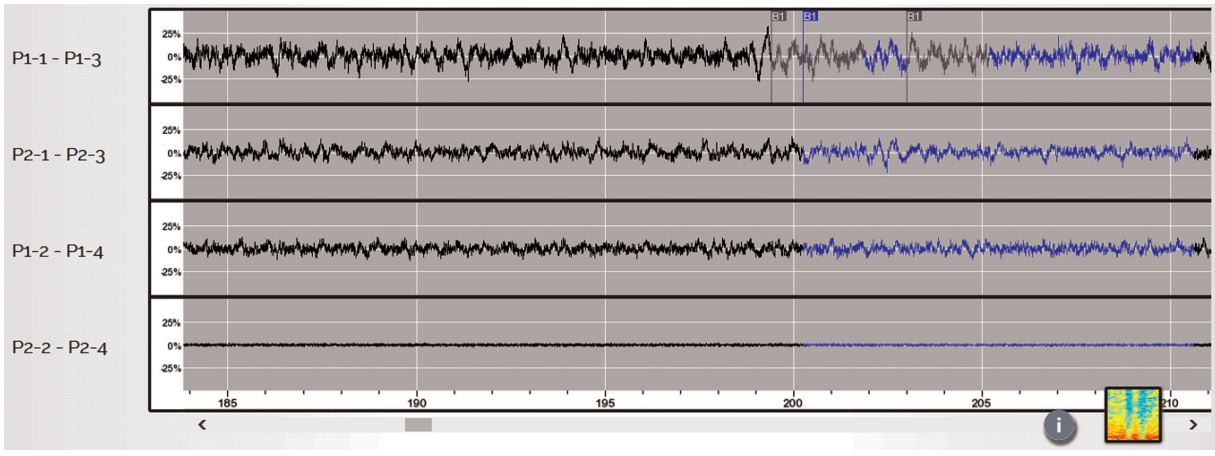

FIGURE 3. *Raw LFP recording data from the human NAc obtained from a patient undergoing prior awake DBS and partaking in a brief computer task designed to elicit NAc activity were run through a benchtop RNS® Neurostimulator. Delta power increases were indeed detected and correlated in time to the anticipation of financial rewards. Blue trace represents detection of the LFP signal of reward anticipation. Adjusting parameters resulted in earlier detections (purple trace).*

eating disorder severity, body weight, nutritional status, metabolic signals, and neuropsychological profile.

STUDY DESIGN

This is a single-site, randomized, single-blinded, early feasibility trial, designed in accordance to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[28] The objective is to support the development of a novel therapeutic approach for utilizing NeuroPace's RNS® System to reduce LOC eating in treatment-refractory obesity. Six subjects will be implanted. Inclusion and exclusion criteria are detailed in Table 3.

METHODOLOGY

Recruitment

The FDA approved the Investigational Device Exemption (IDE) (#G180079) in May 2018, followed by Stanford University Institutional Review Board (IRB #46563) approval in November 2018; all subjects will be enrolled as per the approved protocol guidelines and with appropriate informed consent. A multitude

TABLE 3. Inclusion, Exclusion, and Discontinuation Criteria

Inclusion criteria
1. Male and female patients, 22 to 64 yr of age.
2. BMI 45 to 60 kg/m^2.
3. Failure of at least one pharmacological agent intended for weight loss or binge eating disorder (minimum trial of 6 mo), one form of behavioral therapy (such as weight loss therapy and cognitive behavioral therapy; minimum trial of 6 mo), and gastric bypass surgery. Failed bariatric surgery is determined using the modified Reinhold classification as patients who lost less than 50% of excess weight by 24 mo after a technically successful surgery.
4. Assessment by a Stanford bariatric surgeon prior to referral to this study to rule out technical explanations for suboptimal outcome with an upper gastrointestinal series within months prior to consent (ie, a pre-study referral assessment). The upper gastrointestinal series would be evaluated by a bariatric surgeon for 3 purposes: (1) to rule out an obstruction, stricture or gastro-gastric fistula, or other anomaly; (2) to confirm the anastomosis size $\geq$2 cm and/or gastric pouch size of $\geq$6 cm in length and $\geq$ 5 cm wide; (3) if these features characteristic of technical failures cannot be well assessed on the upper gastrointestinal series, an esophagogastroduodenoscopy would be requested.
5. Presence of loss of control (LOC) over eating ($\geq$4 LOC episodes per week or 16 per month (ie, 28 days) and confirmed with a clinical evaluation by a Stanford eating disorder specialist.
6. The assessment of the presence of LOC will be made during the initial screening visit based on assessments of binge-like eating episodes ascertained from the Eating Disorder Examination (EDE) interview. Subjects will be asked to report the numbers of LOC episodes per week they recall over the past 28 d. All standard measures, including the EDE (which is the gold standard measure used in all major studies of eating disorders), depend on patient recall. While self-report is a limitation, studies have found the measure to be reliable (Mason et al. 2018; Berg et al. 2015).[29,30] Both objective binge episodes (defined by the combination of a subjective sense of LOC and an intake of unusually large amounts of food) and subjective binge episodes (defined the combination of experiencing a subjective sense of LOC during the intake of small or normal amounts of food) will be classified as LOC episodes. This recollection will be confirmed using the Eating Loss of Control Scale (ELOCS), a validated scale assessing LOC features. Item 2a from the ELOCS is the most relevant question for this inclusion criterion: During the past 4 wk, how many times have you felt helpless to control your eating urges?
7. Any medical (including psychiatric) conditions must be monitored actively by appropriate discipline and stable for the past 6 mo. Related therapies or medications should be held stable for the study duration.
8. Surgical suitability confirmed by a psychiatric examination.
9. Subject is able to attend all scheduled clinic appointments on their own or with a caregiver.
10. Adequate social support (eg, stable housing, identified family member or close friend as emergency contact) without acute or subacute psychosocial stressors based on screening interview.
11. Premenopausal women must agree to use acceptable methods of birth control.
12. Subjects have decision-making capacity and provide voluntary and appropriately informed consent. Subject is able to comply with all testing and follow-up requirements defined by the study protocol.
13. Subjects have no immediate plan for relocation beyond 6 hours of the study site.
14. Proficiency with the English language.
Exclusion criteria
1. Subject has an implanted medical device that delivers electrical energy to the brain.
2. Subject has an implantable cardiac pacemaker, defibrillator, or neurostimulator.
3. Subject requires diathermy treatments.
4. Subject requires transcranial magnetic stimulation or electroconvulsive therapy.
5. Subject is likely to require repeat MRI after implant of the RNS® Neurostimulator and Leads.[a]
6. Subject is unable to fit into CT scanner (500 lb upper weight limit for CT scanner).
7. Subject is pregnant or intends to become pregnant during the course of the study.
8. Subject is participating in a therapeutic investigational drug or device study.
9. Medical contraindications for surgery including but not limited to severe cardiovascular, pulmonary, renal, liver, hematological disease, severe coagulopathy, or an acute infectious process.
10. Evidence of neurological disorders, eg, seizure disorder, multiple sclerosis, severe acquired brain injury, severe brain atrophy, subdural hematoma, history of hemorrhagic stroke, or other clinically relevant abnormality on preoperative imaging.
11. Current physical or medical condition that could affect eating behavior (eg, cancer, pregnancy).
12. Active use of medication known to affect eating (eg, appetite suppressants).
13. Clinically significant or unstable psychiatric condition based on psychiatric screening interview.
14. Clinical diagnosis (past or present) of severe anxiety disorder, major depression, psychosis, or anorexia based on diagnostic interview.
15. Any lifetime history of suicide attempt, intent, or engagement in other forms of self-harm behaviors (eg, cutting).
16. History of drug abuse or dependence, including nicotine and alcohol.
17. Current use of alcohol at the rate of >14 drinks per week or >4 drinks per occasion or any diagnosis of substance abuse/dependence disorder based on Diagnostic and Statistical Manual of Mental Disorders, Edition 5.

TABLE 3. Continued

Exclusion criteria
18. Evidence of incipient dementia or cognitive impairment on neuropsychological assessment by any score on memory, executive functioning, intellectual functioning, language, or visuospatial domains falling 2 standard deviations below the normative mean.
19. Evidence of comprehension difficulties (Token test < 36).
20. Inability to provide informed consent to treatment.
21. Obesity secondary to another medical condition, a medication side effect, or a genetic syndrome.
22. Less than 80% compliance with ecological momentary assessment at the baseline or preoperative visit.
23. Subject is a candidate for revision of their bariatric surgery.
Criteria for discontinuing
1. Electrical stimulation of the nucleus accumbens not tolerated.
2. Serious adverse event in 1 patient (defined as a concerning effect requiring hospital admission, or that is irreversible or life-threatening).
3. Lack of adherence to the protocol by the patient.
4. Lack of reliable electrographic signal of LOC eating.

[a]MRI-conditional approval has been granted by the U.S. FDA since development of this protocol and exclusion criterion

of advertising strategies are currently underway. Internal and external recruitment using print and online methods will be used to encourage participation in the study. Patients of Stanford's BMI Clinic identified as gastric bypass nonresponders or relapse after appropriate initial weight loss, as well as external patients, will be contacted by the research coordinator to complete prescreening and determine initial eligibility, prior to on-site consent and screening.

Screening and Consent

A systematic and multidisciplinary approach to our patient screening will be used with a focus on contributory dietary, psychiatric, neuropsychological, medical, and surgical factors. A modified MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) will be used as a semistructured interview instrument designed to assist in the assessment of capacity to consent to clinical research. The tool will be administered in tandem with a full consent discussion. Each consent and MacCAT-CR session will be videorecorded (a separate consent for videorecording will be performed) for post hoc review by our Ethics Advisory Committee.[31] All patients enrolled into our study will have blood work to assess for metabolic syndrome, as well as hormonal alterations and vitamin deficiencies. A full list of investigational assessments and treatments can be found in Table 4. Subjects will be evaluated by our bariatric team to rule any abnormality related to the prior bariatric surgery that would require further investigation. All patients who are deemed qualified for this study otherwise will undergo an esophagogastroduodenoscopy as a final confirmation of their suitability.

Additional critical parts of our multidisciplinary screening protocol involve 2 psychiatric assessments on 2 separate visits: one with an eating disorders psychiatrist and the other with an interventional psychiatrist. The eating disorders psychiatrist will perform a comprehensive assessment of contributing mental health factors. Our interventional psychiatrist will focus more on suitability for an invasive surgery and device programming over time. A neuropsychological assessment will then take place followed by an evaluation by the study neurosurgeon.

Surgical Procedure

Consented participants will be implanted with the RNS® System (NeuroPace Inc) with depth leads in the NAc bilaterally. This surgery will require a standard, awake frameless robot-assisted stereotactic procedure targeting the NAc.[25,32] Each depth lead has 4 independently programmable cylindrical electrode contacts. The distal-most contact (0) is expected to be in ventral NAc based on a tractographic analysis previously performed (Figure 4).[33] Once the electrodes are implanted, intraoperative imaging is obtained to confirm accuracy (<2 mm radial error). Leads are then secured in place, and a small right parietal craniotomy (2 cm × 4 cm) is made for the neurostimulator. The depth leads are connected to the device, and real-time recordings are performed to confirm a functioning system. Next, an intraoperative monopolar assessment will be performed as is standard for DBS for obsessive-compulsive disorder.

Enrollment Plan

Participant enrollment will be staggered. After implantation, the initial 2 subjects (group 1) will enter a 6-mo recording period, with continuous, real-time NAc local field potentials (LFPs) performed in the ambulatory setting using multiple modalities to target time-stamped LFP analyses and in the LOC laboratory with video surveillance. Congruence of the controlled and ambulatory assessments of LOC eating and LFPs will be measured. During this phase, recording/detection parameters will be set based on prior experience with the RNS® System and signals obtained in prior mouse and human studies. An interim analysis will begin to identify the LFP candidate signal. If a signal is identified, these data will be submitted to the Data and Safety Monitoring Board (DSMB) for review. An additional 12 mo will follow in which brain-responsive neurostimulation is activated. After this period a database lock will occur, and safety data will be sent to the DSMB to confirm the feasibility and safety of further

TABLE 4. Study Procedures and Assessments

Screening phone call
Upper gastrointestinal series (UGI)
Informed consent form (ICF)
MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR)
Eating disorder/loss of control interview
Structured psychiatric interview
Interventional psychiatric interview
Neuropsychology interview
Eating Disorder Examination Questionnaire (EDE-Q)
Dutch Eating Behavior Questionnaire-Emotional Eating Subscale (DEBQ)
Grilo Eating Loss of Control Scale (ELOCS)
Beck Depression Inventory II (BDI-II)
Columbia Suicide Severity Rating Scale (C-SSRS)
Structured Clinical Interview 1 and 2 Summary
Demographics
Medical history
Family history
Concomitant medications
Substance use – smoking and alcohol
Vitals, urine tox screen, pregnancy test
Bariatric monitoring appointment
Esophagogastroduodenoscopy
Nutrition appointment
Nutrition panel
Glucose tolerance testing
Monetary incentive delay (MID)
Milkshake paradigm
Bite counter training
Ecological momentary assessment (EMA) training
Physical exam
Neurological exam
Fiducial placement
CT
MRI
PI eligibility confirmation
Multi-item buffet/loss of control (LOC) lab
Monopolar assessment
Recording initiation
Neurostimulator programming

enrollments. These data will be submitted to the NIH and FDA prior to continuing with enrollment. Group 1 will continue to be stimulated for the 12-mo period, assuming there are no serious or unexpected adverse events. Subjects 3 and 4 (group 2) will be implanted after 6 mo of tolerated stimulation in group 1 (and after an IDE supplement is approved). The same stimulation protocol will apply for the following group(s). A database lock will occur after all 6 subjects have completed the study, and final analysis will occur.

Recording Phase

Following surgery, the recording-only phase (6 mo) will be initiated. Subjects will maintain time-stamped logs of eating patterns using 3 ambulatory assessments: (1) ecological momentary assessment, (2) bite counting, utilizing a commercially available wrist-worn counter, and (3) magnet swiping. Subjects will be instructed to swipe the RNS® Magnet over the neurostimulator to trigger LFP storage whenever LOC is sensed, similar to what epilepsy patients routinely do when they sense an upcoming seizure. Most commonly, prior to LOC eating, studies have reported a sense of negative affect. Subjects will be informed to swipe when this "aura" is sensed. The neurostimulator will be programmed to store LFP activity in response to (1) this magnet swipe, as well as (2) scheduled times of day, and (3) detecting the candidate LFP signal. Additionally, a variety of laboratory assessments including a validated laboratory and computer tasks, namely the monetary incentive delay task[34] and milkshake taste reward paradigm,[35] as well as the multi-item buffet,[36] will be utilized to examine aspects of and provoke LOC eating under surveillance and optimize LFP detection (and stimulation testing to be initiated only in the next phase) in controlled settings with video synchronized to the RNS® System recording. Then, a 12-mo brain-responsive neurostimulation phase will test feasibility/safety of intermittently delivering stimulation to the NAc in this population.

Stimulation Phase

A monopolar survey will precede activation. Patients will be blinded to test conditions and asked to report mood, anxiety, and alertness verbally. Anticipated side effects of NAc stimulation are known to abate over time or quickly respond to parameter adjustment. Prior to initiating stimulation in the ambulatory setting, a multi-item buffet validated as a means to provoke LOC eating will be used to assess effects of initial parameters in a setting that is designed to mimic an at-risk environment. Stimulation will only be continued in the ambulatory setting if no adverse effects are seen. Stimulation will be initiated in the ambulatory setting in half of the patients, via randomized, staggered-onset, single-blinded design for 1-wk duration (6 wk later for the other half of patients), followed by a 1-wk evaluation period by our study's interventional psychiatrist and investigators. If there are no serious adverse effects, stimulation will be re-initiated for 4 wk, followed by another 1-wk evaluation period for Principal Investigator (PI) review. If there are no serious adverse effects, stimulation will be re-initiated for the remainder of the 12-mo assessment in both groups. Any serious adverse event (eg, hospitalization) will lead to stopping and review by the DSMB.

DISCUSSION

This study intends to develop a neuromodulation alternative for severely obese patients with LOC eating, whose past treatments have failed. This trial will apply a clinically validated strategy to provide electrical stimulation to a specific brain region in an on-demand basis to prevent LOC eating. This investigation represents a paradigm shift in the way intractable psychiatric disorders may be approached as well. While LOC eating in the current study refers to specifically to food-related

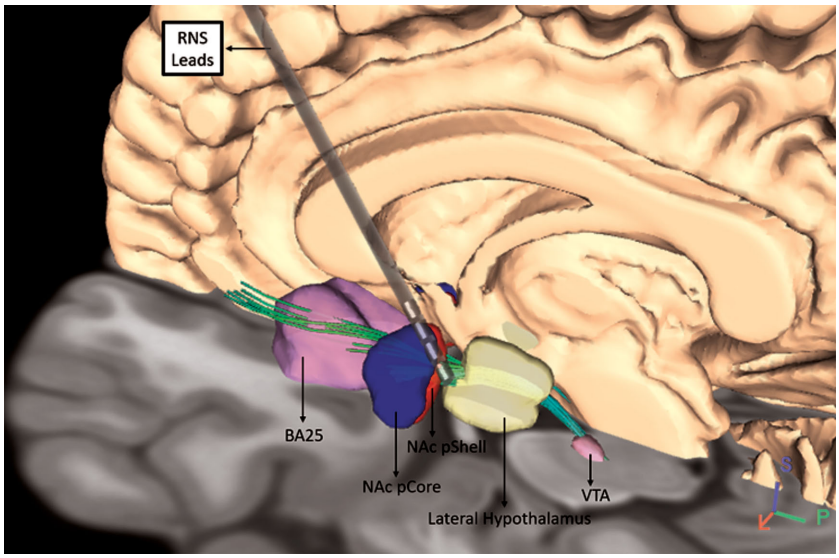

FIGURE 4. *3D rendering of optimized NAc targeting based on deterministic tractography to critical structures of the mesolimbic system in the Human Connectome Project diffusion MRI template. The presumed NAc shell/core (pNAcSh and pNAcCo; red/blue) were used as seed regions and the lateral hypothalamus (yellow) as region of interest. Streamlines not intersecting Brodmann's area 25 (BA25) (purple) and ventral tegmental area (pink) were excluded. The analysis was conducted using DSI Studio (http://dsi-studio.labsolver.org).*

behavior, LOC may represent a transdiagnostic process.[37] LOC is a component of impulsivity, and so is common not only to BEDs but also to many often-refractory mental health disorders; these include substance abuse disorder, obsessive-compulsive disorder, and impulse control disorders. Therefore, there is great potential for the targeted intervention of LOC to have a broad clinical impact.

As this is the first time that NAc brain-responsive neurostimulation is attempted in human subjects with LOC eating, the design chosen for this study focuses on establishing safety and feasibility, as well as initial nonfutility testing. This study will be used to inform future power analysis calculations for more advanced trials.

TRIAL STATUS

The trial is open to accrual at the time of manuscript submission (ClinicalTrials.gov Identifier: NCT03868670).

SAFETY CONSIDERATIONS

This study will utilize a DSMB composed of independent arbitrators with expertise in the protocol-specific surgery, obesity, and eating disorders. The DSMB will be assembled to monitor the safety of the study and to make recommendations about safeguarding the interests of subjects regarding stopping, modifying, or continuing the study. The DSMB will review the effectiveness data after 6 mo of stimulation in each subject to determine if there is enough evidence of nonfutility to justify the risk. Outcome data will also be shared with the FDA prior to proceeding with subsequent groups.

Data to support safety of the surgical procedure, the implants, signal detection, and stimulating the NAc region are widely available from studies on the RNS System and DBS studies.[18,26] In addition to clinical observations of stimulation side effects, weekly-monthly visits with the contact PI and psychiatrist, bariatric, neuropsychology, and nutrition visits are planned throughout the study. All serious adverse events (SAEs) will be reported to the independent DSMB and to the IRB. Unanticipated adverse device effects will be reported to the FDA and IRB as soon as possible, but no later than 10 working days, after learning of the event. If medical complications from participating in this study arise, the Protocol Director (CHH) and research study staff will assist the participant in obtaining appropriate medical treatment.

FOLLOW-UP

Figure 5 summarizes study timeline. Briefly, subjects will be evaluated throughout the study period once the surgery is performed to ensure safety, manage the neurostimulator, detect electrographic correlates of LOC behavior, assess eating disorder pathology and obesity, and meet study milestones. Follow-up evaluation will be performed at approximately 18 different time

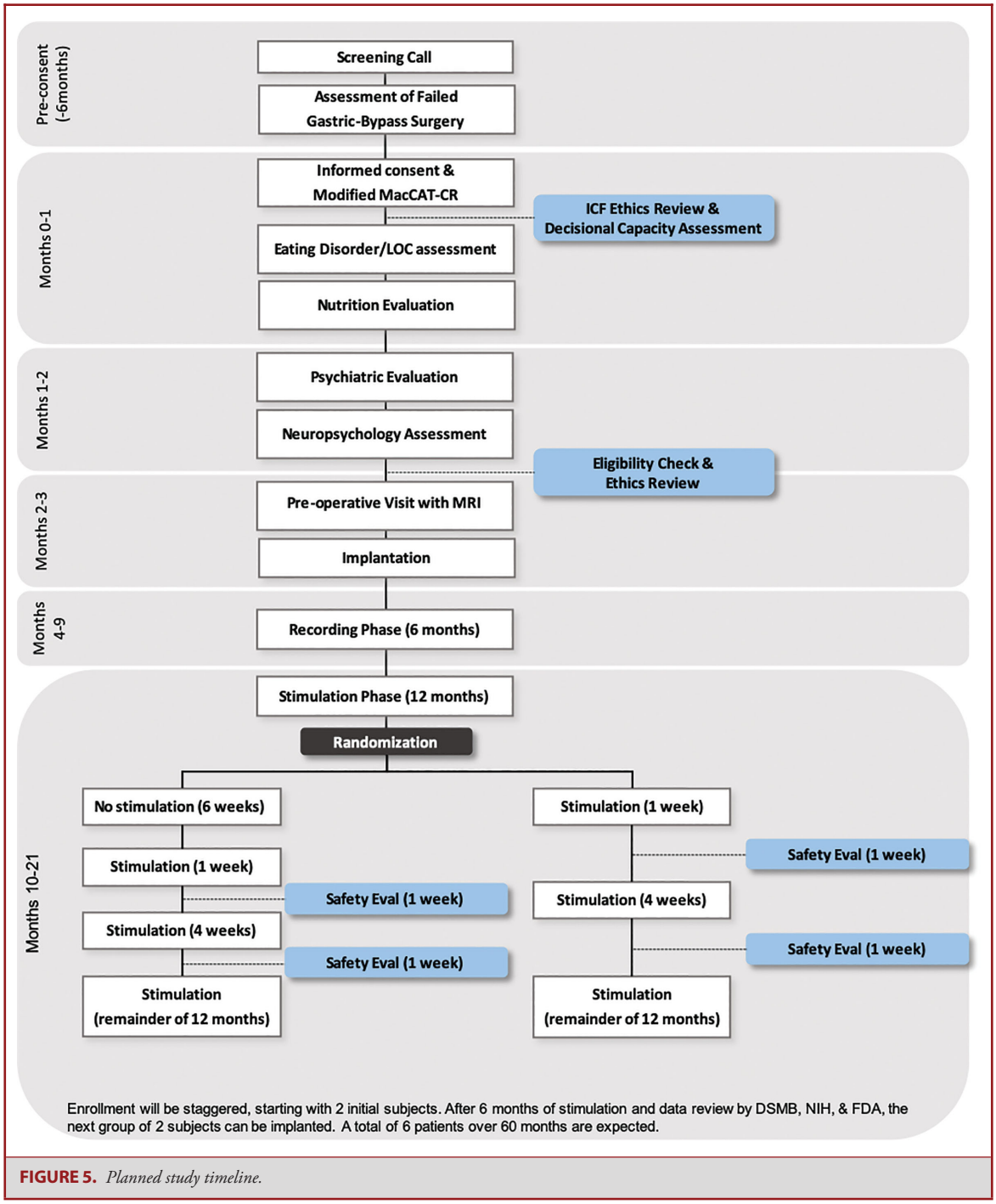

FIGURE 5. *Planned study timeline.*

points. Six times during the recording phase (M4-M9) to include psychiatric assessment, nutritional evaluation, LOC behavior, and to review compliance with study procedures; 12 times during the stimulation phase (M10-M21) to include the same evaluations as M4-M9 in addition to the management of the neurostimulator and neuropsychology assessment. To minimize loss to follow-up, contacts via phone, text, and/or email will be made to remind subjects of follow-appointments and to reschedule any missed appointments.

The importance of reporting adverse events will be discussed with the participant and companion (if applicable) at consent and the baseline appointment, and will be reiterated throughout

the duration of the trial Following surgery, participants will be prompted to report adverse events at each follow-up appointment or phone call and reminded to call and report adverse events or SAEs as soon as they occur and schedule additional visits as needed in case adverse effects are noted in the period between the visits. The only potential additional care that subjects may pursue during this study is to attend support groups. Patients and their insurance providers are responsible for post-trial care. At the close of the study, patients have the options of either having the device turned OFF (1), explanted (2), or continue to receive stimulation (3) within a new protocol (subject to sponsorship/funds availability).

DATA MANAGEMENT AND STATISTICAL ANALYSIS

The study cohort size is small. Outcome measures will be included as described above, but this is not a controlled trial, limiting statistical comparisons. Results, per patient, will be described using standard summary statistics, including evaluating outcomes at each visit and assessing changes from baseline. Summary statistics will also be generated for results across the 6 subjects.

QUALITY ASSURANCE

The Protocol Director will be responsible for data management, including quality checking. The data collected by the RNS System will be sent to a secure server at NeuroPace Inc, as is performed routinely for epilepsy patients. The raw LFP files will also be shared with the researchers at Stanford for offline analyses. The research team is responsible for entering the required data into the data collection forms on the electronic data capture (EDC) system in a timely manner. Data collected during the study are captured using this EDC system, which requires source documents to verify the accuracy of submitted data. Data revisions are captured within the EDC system, which provides a complete audit trail. After completion of the trial, source data files and regulatory records will be maintained according to federal requirements.

EXPECTED OUTCOMES OF THE STUDY

This study is intended to support the development of a novel therapeutic approach for utilizing the NeuroPace RNS® System for NAc modulation to ameliorate LOC eating in patients with treatment-refractory obesity, specifically those who have failed gastric bypass surgery. Feasibility of this novel treatment will be defined by investigating NAc physiology and possible correlation with LOC eating using time series and spectral analysis methods. The function of subject-specific signal detection algorithms will be assessed and refined during this recording phase based for each individual subject. The primary endpoint is expected to demonstrate at least 50% of subjects exhibiting a decrease in the number of LOC episodes per week calculated over a 28-d period.

DURATION OF THE PROJECT

The project's staggered enrollment and recording and stimulation phases are expected to be executed in 6 patients over a period of 60 mo.

PROJECT MANAGEMENT

The neurosurgeon, bariatric surgeon, psychiatrists, and clinical research coordinator will recruit the subjects and check for eligibility. The Principal Investigators will be responsible for explaining the study principles, including the details of the investigational treatment, experimental schedule, potential risks, and benefits. The neurosurgeon will be responsible for gathering consent signature, performing examinations, procedure, programing, and collecting data. The neurosurgeons and psychiatrists will be responsible for follow-up. The psychiatrists will be responsible for managing the behavioral science protocol. The electrophysiologists and basic scientists will be responsible for ensuring the scientific integrity of the electrographic data analysis. The device and regulatory specialist will be responsible for managing any and all compliance needs.

ETHICS

The ethical justification for the presented innovation in the context of LOC eating and neurosurgery is that for some patients whose past less-invasive treatments have failed, the possibility of neuromodulation has potentially life-saving importance.[38] Justification for invasive brain neuromodulation trials has hinged upon the devastating nature of certain disorders combined with treatment refractoriness. We argue that clinical investigation of the novel approach described here can be ethically justified when specific conditions (including patient selection, informed consent procedures, and a host of additional research safeguards) are in place.[39] Our protocol has been carefully designed to meet these conditions. This study will be conducted in full conformance with the ICH E6 Guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, as well as with FDA regulations and the Stanford IRB. Before initiating the trial, the investigator will have written and dated approval from the IRB for the trial protocol, informed consent and competence assessment documents, subject recruitment procedures (eg, advertisements), and any other written information to be provided to subjects. Ethical reviews and safety evaluations are made at several points throughout the study (Figure 5). Research results and accomplishments from this study will be made available to participants, healthcare professionals, the public, and other relevant groups. Results, analysis code, and data generated from this research proposal will be freely shared through publications in academic journals and presentations at scientific meetings.

Disclosures

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COMMENT

We congratulate the authors on a well-designed study and appreciate the tremendous effort it takes to assemble industry, IRBs, and regulatory agencies to bring novel neuromodulation interventions to the operating room. Obesity has become a global problem for which neuromodulation holds promise and our work with deep brain stimulation has shown that continuous open-loop stimulation can be safely used in this patient population and has the potential to alter both appetite and resting metabolic rate.[1]

The RNS closed-loop system was designed for intractable epilepsy, and this appears to be the first planned use of RNS in another disorder. We do feel that there is still great potential for traditional, open-loop DBS for treating obesity and agree that the nucleus accumbens deserves further study as a target for obesity and other disorders such as addiction. One criticism for choosing the currently available RNS system is the lack of MRI compatibility. Postoperative MRI remains important for determining lead location accuracy since CT and image fusion techniques still have limitations. We also have some concerns that cranially based pulse generator of RNS may have more risks and complications compared to DBS hardware, which has a more established safety record. Finally, we question how the RNS system might be programmed if a good candidate LFP signal is not identified in an implanted patient. With all of these concerns noted, this study offers the potential for significant advancement in an area of study in its infancy.

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