Grant Report

Neurofeedback during Eating: A Potential Novel and Mechanistic Treatment for Bulimia Nervosa

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ABSTRACT

Bulimia nervosa (BN) is a disabling eating disorder that is associated with costly medical morbidity and often follows a chronic course. Novel treatments are needed, particularly those that directly target symptom-maintaining mechanisms. One such mechanism may be reduced activation of the prefrontal cortex (PFC) during attempts to control behavioral responses. In this proof-of-principle project, we propose to develop, establish feasibility, and preliminarily test a novel neurofeedback procedure that is intended to increase PFC activation and enhance the ability to control the consumption of common binge foods. We will compare the effects of one session of real and sham neurofeedback during eating on neural activation, inhibitory control, and clinical symptoms in women with BN. To our knowledge, this will be the first test of neurofeedback in BN to date. Results will establish this new technique's potential to clarify causal mechanisms of BN symptoms and inform future clinical trials.

Trial Registration: NCT05614024.

KEYWORDS: bulimia nervosa; neurofeedback; functional near-infrared spectroscopy; prefrontal cortex

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ABBREVIATIONS

BN, bulimia nervosa; fNIRS, functional near-infrared spectroscopy; PFC, prefrontal cortex; lPFC, lateral prefrontal cortex; MRI, magnetic resonance imaging; CBT, cognitive-behavioral therapy; mPFC, medial PFC; EEG, electroencephalography; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition; EDE: Eating Disorder Examination; SCID-5: Structured Clinical Interview for DSM-5; WASI: Wechsler Abbreviated Scale of Intelligence; BMI: body mass index; VAS: visual analogue scales

INTRODUCTION

Bulimia nervosa (BN) is an eating disorder characterized by recurrent episodes of binge eating and subsequent compensatory behaviors (e.g., self-induced vomiting). More than half of adults with BN treated with first-line psychotherapies remain symptomatic [1–5]. Novel treatments are needed, particularly those that directly target underlying mechanisms that maintain symptoms.

Substantial evidence suggests that altered functioning of the lateral prefrontal cortex (lPFC) and medial prefrontal cortex (mPFC) contributes to behavioral disinhibition [6,7]. Such disinhibition defines out-of-control binge/purge episodes in BN, and functional magnetic resonance imaging (fMRI) data indicate that individuals with BN show reduced activation of both lateral and medial aspects of the PFC when attempting to inhibit button-pressing responses [8,9]. This reduced activation has been statistically correlated with increased BN symptom frequency [8,10]; however, it is not clear whether deficient PFC engagement drives binge eating and purging or simply represents a side-effect or correlate of repeatedly engaging in those behaviors. No controlled studies have examined whether normalizing PFC activation reduces BN symptoms. Testing this question could validate a new treatment and clarify a potential causal link between PFC dysfunction and binge eating and purging. Neurofeedback is an optimal method to fill this knowledge gap: by training individuals to change their own brain activation and continuously measuring that change, neurofeedback simultaneously serves as both an intervention and an assessment tool.

Functional near-infrared spectroscopy (fNIRS)-based neurofeedback may be ideal for the treatment and study of BN. FNIRS is an optical brain imaging technique that measures changes in cortical blood oxygenation, a signal very similar to the blood-oxygen-level dependent signal that is measured in fMRI. Although its spatial resolution is inferior to fMRI, it has higher temporal resolution, and it can reliably assess hemodynamics in cortical areas integral for inhibitory control [11]. In addition, because fNIRS has near-zero run-time costs, it is portable, and recent technical and software advancements have helped automate much of the fNIRS neurofeedback process, it is more clinically deployable than fMRI. Relative to electroencephalography (EEG), fNIRS has better spatial resolution and requires less set-up (e.g., time-consuming gel/water application is not needed for sensors over the scalp) [12]. Critically, since fNIRS sensors are wearable and less sensitive to motion than fMRI or EEG, the wearer can learn to self-regulate activation in real time during clinically relevant behaviors, like eating. FNIRS neurofeedback studies report successful PFC modulation and behavioral changes in other impulsive populations after a single session [13], supporting the method's potential utility for BN.

We have previously used fNIRS to measure PFC activation of women with BN and healthy controls while they completed a novel go/no-go task requiring the inhibition of eating (sipping and swallowing a palatable

shake) [14]. In the BN group, reduced activation of the right lPFC during attempts to inhibit eating responses was associated with more errors on the task and more frequent and severe loss-of-control eating in the real world. These findings are in line with results suggesting a pivotal role for the lPFC in the inhibition of unwanted behaviors [15] and in the exertion of control during food-related decisions [16]. They are also consistent with findings associating right lPFC dysfunction with BN diagnosis [8,9], and with results showing reduced lPFC activation in adults with BN compared with controls when instructed to focus on feelings elicited by food vs. non-food images [17]. In addition, they are in line with results suggesting that individuals with binge-eating disorder show reduced fNIRS-measured lPFC activation during a food picture go/no-go task [18]. Several studies have specifically targeted lPFC activation with neurofeedback (e.g., [19–21]). Our prior findings further suggest that neurofeedback to enhance fNIRS-measured right lPFC activation during eating may be particularly effective for BN.

Neurofeedback, and specifically fNIRS-based neurofeedback, has shown success in reducing symptom severity in other populations who experience difficulties with inhibitory control, including individuals with attention-deficit/hyperactivity disorder (ADHD; [22–24]). However, to date, there have been limited investigations of neurofeedback interventions in binge-eating populations. Initial studies have found somewhat promising effects of EEG-based neurofeedback for binge eating [25–27]. To our knowledge, only one other study has tested fNIRS-based neurofeedback for binge eating: Hilbert et al. [27] trained participants with binge-eating disorder to increase bilateral activation in the lPFC to shrink pictures of personally appetizing food pictures presented on a screen. They found that binge eating frequency in decreased slightly and not significantly (on average, 1 less episode compared to a control waitlist group) after the completion of a 12-session neurofeedback protocol. However, the waitlist control group in this study showed unusually high symptom improvement, and changes in brain activation in the target region during active regulation attempts were near-zero [27], highlighting a need for future work with additional control groups and different feedback designs.

In the current project, we propose to develop and preliminarily test a novel protocol that delivers real-time, fNIRS-based neurofeedback while participants consume a common binge food. To accomplish this goal, this “proof-of-concept” study will compare the effects of one session of real and sham right lPFC neurofeedback during eating on neural activation, inhibitory control, and symptoms in women with BN.

GRANT AIMS AND ASSOCIATED HYPOTHESES

Aim 1: To Demonstrate lPFC Neurofeedback Target Engagement in Women with BN Using fNIRS

First, we aim to establish the technical feasibility of our novel protocol and preliminarily assess target engagement. We will compare the effects of real and sham feedback on changes in right lPFC activation and connectivity over the course of one training session.

Primary Hypothesis 1: Compared with sham feedback, real right lPFC feedback will be associated with greater increases in right lPFC activation.

Secondary Hypothesis 1: Compared with sham feedback, real right lPFC feedback will be associated with greater increases in right lPFC-to-mPFC connectivity, consistent with previously observed effects of lPFC neurofeedback in individuals with obesity [21].

Aim 2: To Link Changes in PFC Activation to Changes in Inhibitory Control and Eating-Related Symptoms

Second, we aim to examine whether this novel neurofeedback protocol will enhance cognitive control and reduce core symptoms of BN. Participants will complete an inhibitory control task and symptom severity assessments before and after the neurofeedback session, and we will test for group differences in changes in these measures.

Primary Hypothesis 2: Compared with sham feedback, real right lPFC feedback will be associated with greater improvements in: food response inhibition (fewer commission errors on a food-specific go/no-go task), self-reported frequencies of loss-of-control eating and purging episodes, and the self-reported severity of the sense of loss of control over eating.

Secondary Hypothesis 2: Within the real feedback group, post-neurofeedback increases in right lPFC activation will be associated with improvements in food-specific response inhibition, which will predict decreases in bulimic symptoms.

INNOVATION

(1) This pilot study will be the first test of a relatively scalable neurofeedback intervention for BN. To our knowledge, no published studies have tested neurofeedback for BN. Clinical use of fMRI neurofeedback has been hamstrung by high costs and exclusions for entry into the MRI environment. Other promising neuromodulatory interventions (e.g., repetitive transcranial magnetic stimulation; [28–31]) rely on external stimulation to achieve their effects. FNIRS neurofeedback has near-zero run-time costs and provides patients with a learned skill—changing their own brain activation—that they can implement in everyday life.

(2) Neurofeedback will occur during eating. EEG and fMRI neurofeedback protocols have instructed other populations to imagine the taste and smell of pictured foods [21,25,32]. However, our participants will

practice increasing brain activation while consuming a common binge food, hopefully facilitating the transfer of this skill to real-world eating. The only other study to test fNIRS-based neurofeedback for binge eating [27] was not published when the current proposal was submitted for funding or when the current study was funded. In contrast to this prior investigation, the present study standardizes food consumption before neurofeedback training to minimize variations in metabolic states that could affect neural responses and asks participants to develop and employ their own strategies to increase their brain activation while they eat (rather than using visual feedback that is food specific).

(3) Results will establish this new technique's potential to clarify whether PFC dysfunction drives symptoms. Studies suggest that stimulating the PFC may decrease bulimic symptoms [28–31]; however, only one such study assessed post-stimulation neural change, and it did not include a control group [30]. In addition, the continuous relationship between increases in PFC activation and BN symptom change has not been assessed. We will train participants to increase their own lPFC activation, simultaneously measure the extent of that increase, and relate it to subsequent changes in inhibitory control and symptoms.

APPROACH

Participants

Adult females with current DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) BN (N = 30) will be recruited from ongoing observational studies of BN at Mount Sinai as well as through online, listserv, and flyer advertising. After prospective participants indicate study interest, they will complete brief phone screening procedures to ensure that they meet our inclusion and exclusion criteria (Table 1).

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria
• Age 18–45
• Female
• English-speaking
• Current body mass index ≥ 18.5kg/m^2 but <30kg/m^2
• Liking of ice cream-based shake ≥ 6 out of 9 on Likert-type scale [33]
• Ice cream included in at least one binge-eating episode in the past 3 months
• Meet DSM-5 criteria for bulimia nervosa
Exclusion Criteria
• Current major medical illness or diabetes (type 1 or 2)
• Current diagnosis of a swallowing disorder
• Current use of medication used to lower blood glucose or antidiabetic medications; medications affecting weight, appetite or gut motility

Table 1. *Cont.*

Exclusion Criteria
• Current medical treatment that may interfere with study variables (e.g., chemotherapy) • Current or past neurological disorder, history of a seizure, or history of serious head trauma with loss of consciousness ≥ 10 minutes • Pregnancy, lactation, or planned pregnancy during study • Meet DSM-5 diagnostic criteria for a current bipolar disorder, psychotic disorder, attention-deficit/hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), or obsessive-compulsive disorder (OCD) • Meet criteria for a substance/alcohol use disorder in the last 3 months • Current comorbid psychopathology affecting participation (e.g., acute suicide risk) • Current psychotherapy focused primarily on eating disorder symptoms • Current use of psychotropic medication that is not taken at a stable dose for at least 6 weeks • Full-scale IQ < 75 • Allergy to ingredients in the standardized meal or in the ice cream-based shake

Procedures (Figure 1)

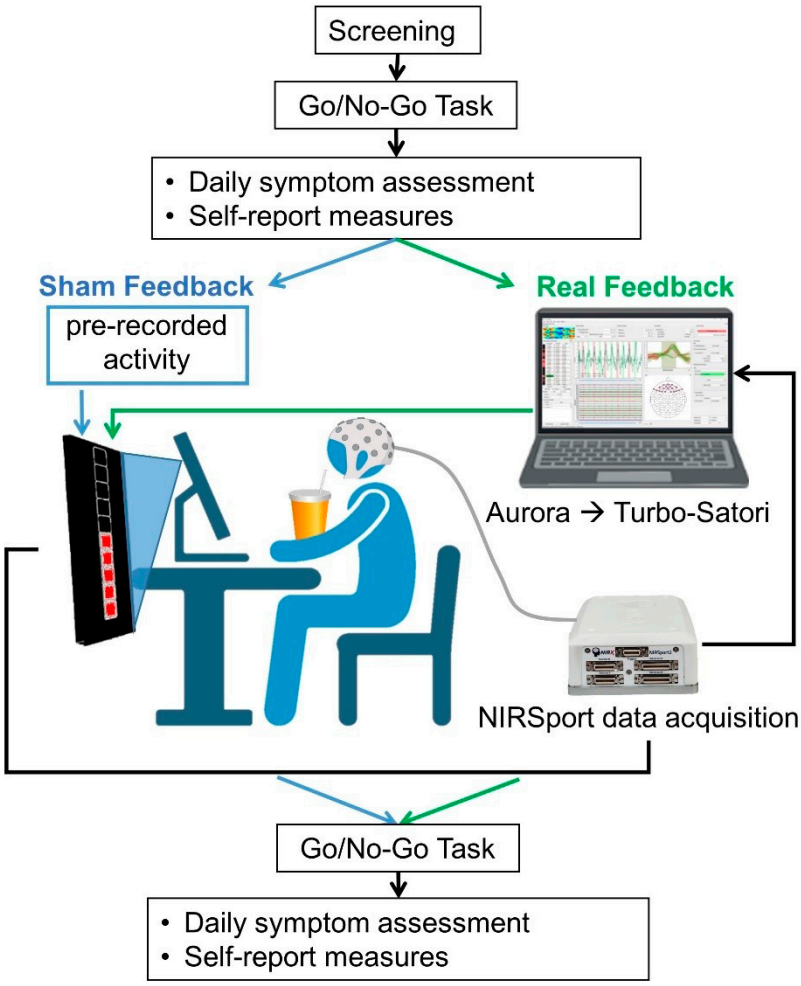

Figure 1. Overview of study procedures. Portions of this figure were generated with biorender.com.

After signing an informed consent, participants will complete several screening procedures to ensure their eligibility. Screening measures will include: the Eating Disorder Examination [34–36] to assess BN diagnosis and binge-eating and purging frequency; the Structured Clinical Interview for DSM-5 Disorders [37] to assess other psychiatric diagnoses; the two-subtest version of the Wechsler Abbreviated Scale of Intelligence [38] to assess full-scale IQ; and measured height and weight to assess body mass index (BMI; [39]). In addition, participants will taste 5 mL of the shake used during neurofeedback (see below) and rate it on a 1–9 Likert-type scale to ensure that they perceive it as palatable.

Following these initial screening procedures, participants will complete a go/no-go task to assess behavioral disinhibition in the context of salient visual food stimuli (in a food block) or non-food stimuli (in a non-food block; adapted from [40,41]). Block order will be randomized. Participants will be instructed to respond rapidly by pressing a key to "go" cues and to withhold responses to "no-go" cues (25% no-go trials, 75% go trials total). In the food block, participants will be shown high-calorie foods (no-go cues) and household objects (go cues). The non-food block, with nature images (no-go cues) and household objects (go cues), will be included to explore whether the session of neurofeedback can also enhance generalized inhibitory control (Table 2). Images across categories will be group-mean matched for red-green-blue percentages, intensity, contrast, complexity, and variations in pixel luminance. We chose a go/no-go task for multiple reasons: (1) this study builds on our previous findings of lPFC hypoactivation during eating go/no-go task inhibition in BN [14]; (2) go/no-go tasks are commonly used to measure the effects of neurofeedback and neurostimulation on response inhibition [42–46], so our use of the task will allow us to compare our results to those from other neuromodulatory interventions; (3) the use of go/no-go tasks to study response inhibition and changes in response inhibition in binge-type eating disorders is well established [47,48].

Next, participants will complete baseline questionnaires (Table 2) and one week of HIPAA-compliant online daily symptom assessments measuring the frequency of compensatory behaviors and the frequency, size, and severity of loss-of-control eating episodes via questions from previous ecological momentary assessment studies [49,50]. Research staff will carefully train participants in standard definitions of behaviors [49].

Then, participants will be randomized to complete one session of either real or sham neurofeedback (n = 15 per group). Participants will be blind to their assignment, and randomization will be stratified by age and BMI. Immediately before and after neurofeedback, participants will provide visual analogue scale (VAS) ratings of their hunger, satiety, desire to eat, sense of loss of control, and urges to binge eat and purge. After neurofeedback, participants will again complete the go/no-go task, questionnaires (Table 2), and another week of daily symptom assessments.

We will closely monitor participants for any acute changes in BN symptom severity through the week of daily symptom assessments following the neurofeedback session. If symptoms worsen significantly, we will discontinue study participation. We will discuss appropriate care options, and a study staff member will help the participant to obtain these services and provide referral resources. Participants will be informed beforehand about these procedures, and our consent forms clearly outline that, in cases of imminent risk, there is a possibility of breaching confidentiality to ensure participant safety. Any adverse events will be reported to our local IRB.

Table 2. Measures.

Exploratory Behavioral and Symptom-related Outcome Measures
• Change in Eating Disorder Symptoms Scale [51] scores • VAS ratings: loss of control over eating, urges to binge eat and purge • Non-food-specific go/no-go task commission errors • Post-training ratings of tolerability and acceptability
Potential Moderators or Confounds
Baseline Severity and Comorbidity • BN duration (months) • Eating Loss of Control Scale (ELOCS) [52] Severity Subscale score • Barratt Impulsiveness Scale-11 (BIS) [53] total score • Patient Health Questionnaire (PHQ-9) [54] score • Spielberger State Trait Anxiety Inventory (STAI) [55] trait score
State • Positive and Negative Affect Schedule (PANAS) [56] scores • VAS ratings: hunger, satiety, desire to eat
Consumption during Neurofeedback • Ratings of how typical of a binge episode the shake consumption felt [57] • Grams of shake consumed during the neurofeedback session
Modulation Strategies • Reported strategies used during neurofeedback [11,58] • Mental Strategy Questionnaire for Neurofeedback [59] for phenomenological characterization of strategies • Daily post-neurofeedback reports of attempts to change brain activation

Neurofeedback Protocol

Participants will be instructed to consume a standardized meal (apple juice, an English muffin, and butter) 4 hours before the scheduled start of the neurofeedback and to refrain from eating or drinking (except water) in this interim. To maximize compliance with these instructions, we will provide participants with the meal. Participants will be reminded of the

meal requirement and timing the day before and the morning of neurofeedback and a coordinator will contact them 4 hours prior to the start of the neurofeedback session to remind them to consume the meal on time. Participants will be instructed to avoid purging behaviors after consuming the standardized meal. Of note, this meal, which has been used in numerous past studies of eating disorders [14,60–62], is not, by volume or caloric content, an objectively large amount of food. As we have also done in our previous studies [14], we will ask participants to report at the beginning of the neurofeedback visit what they last ate, the specific time that they last consumed food, and the last time that they engaged in any purging behaviors to ensure compliance. We will compare neurofeedback groups on minutes since last food consumption to ensure they do not statistically significantly differ, and we will collect state ratings of hunger and fullness and the urge to binge and purge before neurofeedback.

Hemodynamic response signals will be assessed using a NIRSport System (NIRx Medical Technologies, LLC). We will use an optode array that covers both lateral and medial aspects of the PFC (Figure 2). Neurofeedback will be based on oxygenated hemoglobin in the lPFC [13], as measured by NIRx Aurora software and converted to a visual display using NIRx Turbo-Satori software (Figure 1) [63].

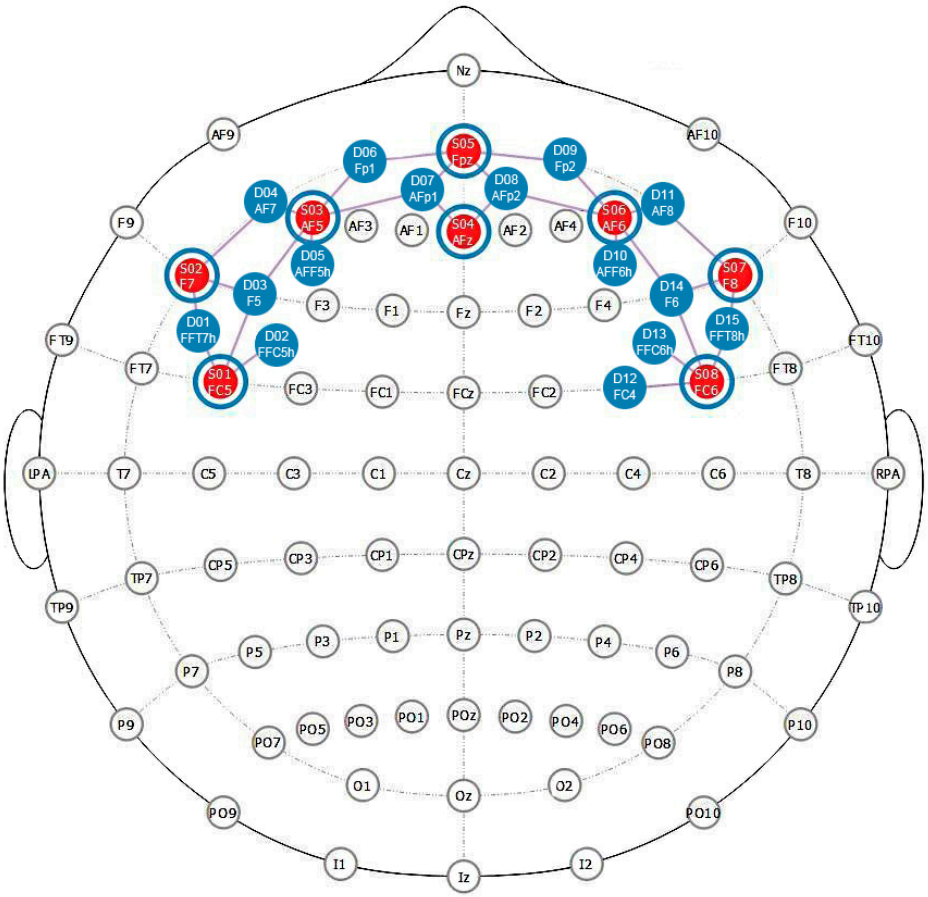

Figure 2. fNIRS Montage Map with 15 detectors (blue) and 8 sources (red). The setup also includes an accelerometer (not shown). Image generated using NIRSite software (© NIRx Medical Technologies, LLC).

Neurofeedback training sessions will consist of 4 total runs including REST and INCREASE trials (8 of each trial type per run [11]). During INCREASE trials, the height of a red thermometer bar on a screen will indicate the level of either true right lPFC activation (real feedback) or sham activation (pre-recorded activity from the real feedback group [13,64,65] (Figure 1)). This yoked sham protocol is designed so that the visual appearance of this feedback is indistinguishable from real neurofeedback. Since prior research suggests that giving participants explicit strategies to change their brain activation is unnecessary, and potentially counterproductive [13], participants will be encouraged to test out their own mental strategies to increase the height of the bar. This approach has been successful in studies of other populations who struggle with self-regulatory control [11,21,66]. During REST trials, participants will stop trying to regulate their brain activation (see Figure 3).

Consistent with recent recommendations to enhance the measurement of learning that occurs during neurofeedback [59], before each run, participants will be instructed to predefine a list of strategies that they would like to try during the run. Before each pair of REST and INCREASE trials within the run, participants will indicate a single strategy that they plan to use during the INCREASE trial. A free response "other" option will also be offered in the event that a participant would like to come up with an additional strategy in the middle of a run that was not on their list.

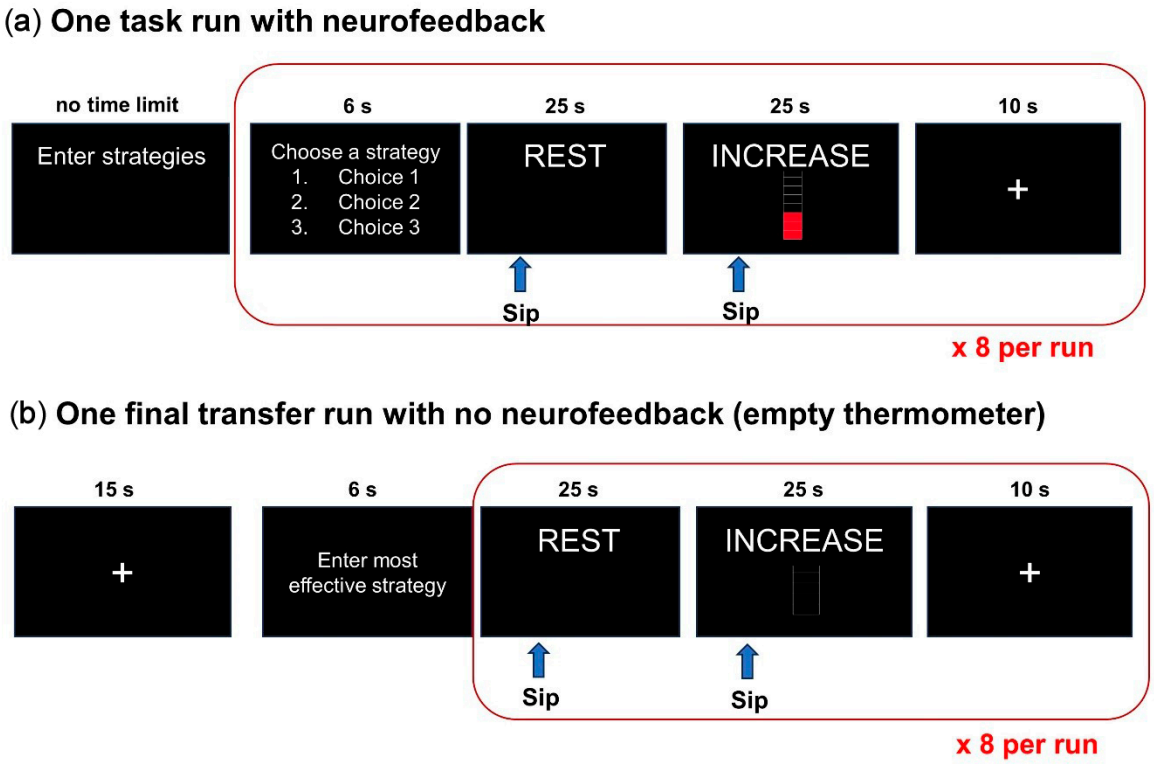

Figure 3. Neurofeedback trial design. (**a**) One example task run with neurofeedback. Participants complete four runs while receiving neurofeedback based on their right lPFC activation. (**b**) One final transfer run with no neurofeedback. Participants choose the strategy they found to be most effective to use throughout the entire run.

To assess the transfer of PFC-modulation skills after training, we will measure activation during an additional (5th) run with no neurofeedback. For this final run, participants will be instructed to use only the single most successful strategy from their past runs.

Since our goal is for participants to learn to increase their lPFC activation while eating, an ice cream-based shake in a vacuum-insulated tumbler with an opaque lid and a clear straw will be placed on a table in front of participants during neurofeedback (Figure 1). Ice cream is one of the most frequent foods included in the binge-eating episodes of individuals with BN, it is consumed significantly more during binge-eating episodes compared with non-binge-eating episodes in women with BN, and single-item ice cream meals with binge instructions have been repeatedly used to study in-lab eating behavior in binge-type eating disorders [67–72]. To minimize between-subject variance, facilitate replication, and maximize internal validity, this pilot study will focus on neurofeedback during consumption of this common binge food. We will confirm that ice cream is particularly salient for all participants by including only those who include ice cream in recent binge-eating episodes and like the shake (see Table 1). To ensure that participants eat at a consistent rate across training, an auditory signal and the word “SIP” on the screen will cue participants to sip and swallow the shake at standard intervals during both INCREASE and REST trials. Video-analysis software used in the principal investigator’s pilot work [14] will cross-check sipping across groups, and we will weigh the container pre- and post-training to measure shake consumption.

Analyses

Offline, fNIRS data will be preprocessed and analyzed for hypothesis testing. We will model task-related changes in activation with boxcar functions for INCREASE and REST (implicit baseline) trials.

Hypothesis 1: Compared with sham feedback, real right lPFC feedback will be associated with greater increases in right lPFC activation.

Mixed-effects models (robust versions, if needed) will assess Group (real vs. sham feedback) × Run (1–4) interactions for lPFC activation. *T*-tests (Wilcoxon tests if parametric assumptions are violated) will assess group differences in activation during the 5th (no-feedback) run.

Exploratory Hypothesis 1: Compared with sham feedback, real right lPFC feedback will be associated with greater increases in right lPFC-to-medial PFC connectivity, consistent with previously observed effects of lPFC neurofeedback in individuals with obesity [21].

Mixed-effects models (robust versions, if needed) will assess Group (real vs. sham feedback) × Run (1–4) interactions for lPFC connectivity coefficients with all other fNIRS channels. *T*-tests (Wilcoxon tests if parametric assumptions are violated) will assess group differences in connectivity during the 5th (no-feedback) run.

Hypothesis 2: Compared with sham feedback, real right lPFC feedback will be associated with greater improvements in: food response inhibition (fewer commission errors on a food-specific go/no-go task), self-reported frequencies loss-of-control eating and purging episodes, and the self-reported severity of the sense of loss of control over eating.

Mixed-effects models (robust versions, if needed) will assess Group (real vs. sham feedback) × Time (pre vs. post-training) interactions for primary behavioral and symptom-related outcome measures (Table 2).

Exploratory Hypothesis 2: Within the real feedback group, post-neurofeedback increases in right lPFC activation will be associated with improvements in food response inhibition, which will predict decreases in bulimic symptoms.

Robust regressions in the real feedback group will test whether the increase in lPFC activation from run 1 to run 4 predicts reduced outcome measures. Regressions will also test whether a decrease in commission errors from pre- to post-training is associated with a decrease in bulimic symptoms.

Within each family of tests, results will be FDR-corrected for multiple comparisons ($q < 0.05$).

Aim 2 analyses will be repeated using secondary outcome measures for additional exploratory analyses, and we will explore influences of potential moderators or confounds (Table 2).

Power considerations

Prior studies of populations with high impulsivity have reported moderate to large effect sizes of PFC-focused fNIRS neurofeedback on brain activation [13]. The proposed sample size ($N = 30$) for this proof-of-concept study provides 90% power to detect moderate effects ($d = 0.50$) and 99% power to detect large effects ($d = 0.80$) for our primary hypothesized Group × Run interaction (two-tailed $\alpha = 0.05$).

IMPACT AND FUTURE DIRECTIONS

This randomized controlled proof-of-concept study will be the first, to our knowledge, to test fNIRS neurofeedback for BN, and results will inform a mechanistic understanding of the disorder and set the stage for future clinical trials. We plan to use the data from this project to initiate a program of research examining fNIRS neurofeedback for eating pathology. First, these pilot data will lay critical groundwork for a larger and longitudinal study that will test longer-term effects and the impact of dosage. Given the modest sample sizes in this pilot study, we aimed to minimize potential confounds by excluding some relatively common comorbidities and medications. Next-step studies will need to test whether preliminary findings from this study generalize to a more diverse and representative cohort of individuals with BN. Generalizability of our results also may be limited by all participants having ice cream in recent binge-eating episodes and the use of an ice cream shake during

neurofeedback. In future studies, we plan to explore neurofeedback during the consumption of other foods to ensure that our findings are more broadly applicable and can be, ideally, personalized for more effective intervention. These larger projects may also benefit from including more comprehensive pre- and post-neurofeedback task batteries that assess impulsive choice, impulsive action, and inattention, to determine how each of these domains is affected by the intervention. Future work should also consider asking participants to consume the standardized meal in the lab before neurofeedback and collecting measures of hormonal factors that may influence findings (e.g., glucose, insulin; [73]). Finally, as binge eating is a shared symptom of BN, binge-eating disorder, and the binge-eating/purging subtype of anorexia nervosa, the current project will also inform studies testing the effects of fNIRS-based neurofeedback across eating disorder diagnoses.

ETHICAL STATEMENT

Ethics Approval

The study was approved by the Institutional Review Board of the Icahn School of Medicine at Mount Sinai (STUDY-22-00063, initially approved 4/28/2022). Written informed consent will be obtained from all participants prior to engaging in any study procedures.

Declaration of Helsinki STROBE Reporting Guideline

This study adheres to the Helsinki Declaration. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guideline was followed.

DATA AVAILABILITY

No data were generated from this grant report.

AUTHORS' CONTRIBUTIONS

Conceptualization and Methodology, LAB and ML; Software, ML; Writing—Original Draft Preparation, Review & Editing, LAB, JLQ, AP, and SL; Visualization, LAB, ML, JLQ; Funding Acquisition, LAB and MAP.

CONFLICTS OF INTEREST

LAB is a scientific advisor to Juniver, Ltd. ML is employed by the research company Brain Innovation (B.V., Maastricht, The Netherlands). The authors declare that they have no other conflicts of interest.

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