The Influences of Eating and Fasting on Inhibitory Control in Bulimia Nervosa:
A Computational Neuroimaging Study
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The Influences of Eating and Fasting on Inhibitory Control in Bulimia Nervosa: A Computational Neuroimaging Study

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CONFIDENTIALITY STATEMENT

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: The Influences of Eating and Fasting on Inhibitory Control in Bulimia Nervosa: A Computational Neuroimaging Study

IF Number
TE00000667 (Year 4)
IF2706030 (Year 3)
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IF2452740 (Year 1)

Study Description

Bulimia nervosa (BN) is a serious eating disorder characterized by a cycle of binge eating and behaviors designed to undo or counteract the effects of binge eating. In the past, studies have linked BN to problems with self-control, but it is not yet understood how individuals with the disorder can show both out-of-control binge eating and dangerously overly controlled dietary restriction, like fasting. The purpose of this study is to investigate areas of the brain responsible for self-control in adult women with BN compared to women who have never had an eating disorder. More specifically, investigators are interested in whether individuals with BN show abnormal changes in brain activation (e.g., changes in blood flow and oxygen use) when they are trying to control their behaviors, and whether brain activity depends on how recently eating or fasting has occurred. Data collection will rely on a technology called functional magnetic resonance imaging (fMRI).

Objectives:

Primary Objective: To determine whether eating and fasting abnormally interfere with the capacity of individuals with BN to adaptively exert inhibitory control

Secondary Objective: To identify associations of BN symptom severity with state-specific frontostriatal activation

Endpoints:

Primary Outcome: Frontostriatal activation
We will compare the impact of fasting and eating on neural activation in women with BN and healthy controls. Specifically, we will compare groups on the influence of fasted and fed state on: 1) frontostriatal activation when correctly inhibiting responses and 2) frontostriatal signals for the anticipated need to stop (P(stop)) and inhibitory control prediction errors.

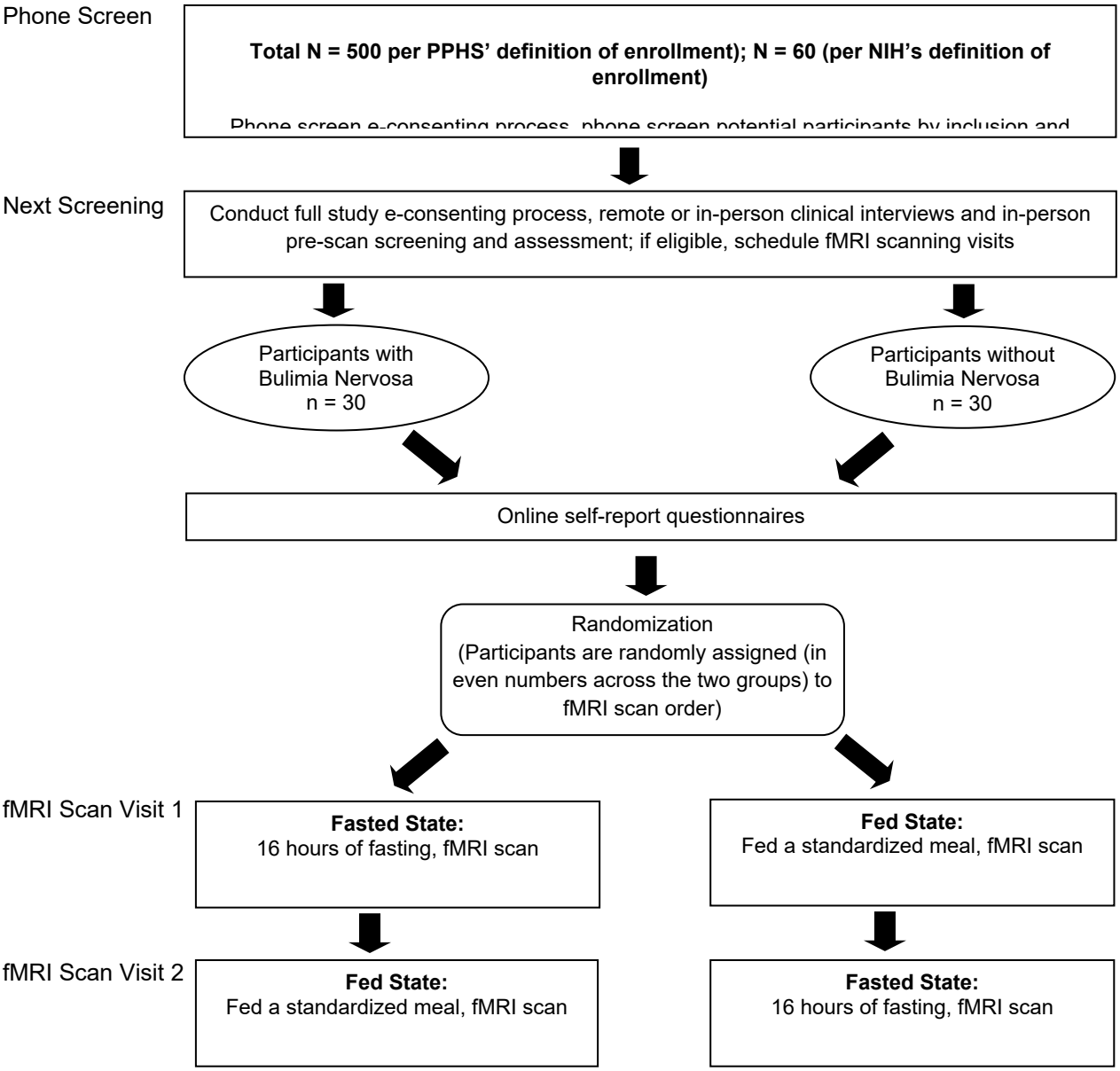
Secondary Outcome:

- Stop signal task performance: We will compare the impact of fasting and eating on behavioral task performance in women with BN and healthy controls. We will specifically compare groups on stop signal reaction times and the percentage of correct stop trials.

- Eating disorder symptom severity: We will examine, with the BN group, whether more severe binge eating/purging is associated with frontostriatal signals for P(stop) and inhibitory prediction errors in the fed vs. fasted state, and whether more severe dietary restriction is associated with frontostriatal signals for P(stop) and prediction errors in the fasted vs. fed state.

Study Population:	**Other/Exploratory Outcome: Resting cerebral blood flow** We will compare the impact of fasting and eating across our two groups on resting cerebral blood flow, as measured by arterial spin labeling (ASL). **Estimated Enrollment): 5**00 **Targeted Populations:** Adults – Healthy Controls, Adults – Patients with Bulimia Nervosa **Age Ranges:** 18 to 35 years **Sexes Eligible for Study:** Female **Gender Based Eligibility:** Yes **Gender Eligibility Description:** The prevalence of bulimia nervosa is substantially greater in women than in men. Moreover, prior research suggest that men and women show different neural response patterns during the engagement of inhibitory control, and that satiety differentially impacts the neural function of men and women.
Phase or Stage:	N/A
Description of Sites/Facilities Enrolling Participants:	Icahn School of Medicine at Mount Sinai
Description of Study Intervention/Experimental Manipulation:	**Fasting state:** 16 hours of fasting **Fed state:** Fed a standardized meal
Study Duration*:	5 years of grant
Participant Duration:	Anticipated over 7-10 days, but participants will be allowed up to 3 months for scheduling based on their availability for procedures.

1.2 SCHEMA



2 INTRODUCTION

2.1 STUDY RATIONALE

Every year, 1.4 million years of healthy life are lost to disability or premature death associated with bulimia nervosa (BN), and up to half of adults with BN treated with first-line psychotherapies do not recover. Treatment-resistant binge eating and purging may be perpetuated by inhibitory control deficits linked to reduced activation in lateral prefrontal cortices (LPFC), anterior cingulate, and striatum. To date, however, neurocognitive studies of BN have not accounted for 1) the dynamic computational processes underlying inhibition or 2) the fact that individuals with BN oscillate between two extremes—under-controlled, excessive eating and over-controlled, restricted intake. This study proposes to examine the neurocomputational underpinnings of inhibitory control in fed and fasted states to test an explanatory model of BN symptoms and inform future context-dependent, targeted interventions for BN.

2.2 BACKGROUND

Bulimia nervosa (BN) affects 1-3% of women [3-6] and is associated with high rates of disability and premature death [6-8]. Up to half of adults with BN treated with first-line psychotherapies do not recover, and characterization of the neural underpinnings of BN symptoms is essential to develop novel, targeted treatments. Data to date suggest out-of-control binge eating and purging (e.g., self-induced vomiting) [6] in BN may result, in part, from impaired control over behavioral responses (i.e., deficits in inhibitory control) and related reduced activation in frontostriatal circuits. However, our understanding of the role of inhibitory control in BN is limited in two critical ways. First, inhibitory control is a complex process that requires individuals to a) update expectations based on experience, and b) use updated expectations to adaptively adjust behavior [9]. These dynamic subcomponents of inhibitory control have not yet been studied in BN. Second, it is not clear how deficient frontostriatal activation could explain both out-of-control binge eating and the overcontrolled, dangerous restriction that typically occurs between binge/ purge episodes. Biologically-based explanatory models for the full spectrum of BN symptoms are lacking. This study hypothesizes that just as temporary fluctuations in disinhibition, in addition to stable, disinhibited traits, may contribute to substance use disorders [10], state-specific alterations in adaptive inhibitory control processes could contribute to BN. Metabolic state, or how recently a person has eaten, is a well-established modulator of inhibitory control in healthy individuals, yet surprisingly little is known about how metabolic state and inhibitory control interact in BN. This study is the first systematic test of whether eating and fasting influence inhibitory control abnormally in BN. This knowledge has potential for substantial impact, as it will 1) identify elements of the inhibitory control process that specifically may maintain problematic eating, and 2) pinpoint when interventions designed to bolster inhibitory control may be most effective.

Neural Substrates of Inhibitory Control Processes in BN are Understudied. An imbalance between control and reward-related processes may contribute to BN [11, 12], but most neuroimaging research in BN to date has focused on reward circuitry [13-19]. Cognitive and motor cortico-striato-thalamo-cortical (CSTC) loops involved in anticipating the need to control our cognitions and behavior [20] and ultimately inhibiting responses are understudied in BN. These control-related processes recruit overlapping frontostriatal, cingulo-opercular, and frontoparietal networks, including dorsolateral and ventrolateral prefrontal cortices (DLPFC, VLPFC) [21-24], anterior cingulate cortex (ACC), dorsal striatum, the pre-supplementary motor area, insula, and

parietal regions.[25-31] When making food- related decisions that require control, DLPFC is specifically engaged [32]. Data from existing case-control studies of adult BN suggest reduced activation in frontostriatal regions (VLPFC, DLPFC, ACC, caudate and putamen) during inhibition, and that this dysfunction is associated with binge/purge symptoms [33, 34]. However, very few functional neuroimaging studies have focused on adults ill with BN, much less non-food-specific inhibitory control. Further, brain-behavior relationships are not consistent across studies: One study found reduced activation and impaired inhibitory performance in BN [33], while one adolescent study [35] and one adult study [34] found reduced activation in the context of intact performance. Reduced activation could thus reflect deficient or efficient processing during inhibition in BN. More nuanced behavioral measures and careful control of state-based factors are needed to clarify these inconsistencies. Moreover, past BN research that has focused on neural activation during successful and failed inhibition alone has likely missed subtle alterations in the dynamic inhibition process.

Dysfunctional Components of Adaptive Inhibitory Control May Perpetuate BN. Adaptive inhibitory control requires moment-to-moment decision-making about whether to engage in or stop a behavior, and using experience to update beliefs about how likely it is that inhibition will be required in the subsequent moment.[9] These computations can be quantified using Bayesian models. Such models, combined with fMRI, have identified blunted signals for the expected need to inhibit in the VLPFC, DLPFC, ACC, and caudate that distinguish substance users from controls and predict the onset of and relapse to problematic substance use.[36-38] Similarly altered frontostriatal signals for these computations may maintain BN. Prior work has documented attenuated signals for food-reward-related prediction errors in BN,[19] and individuals with BN show decision-making deficits [39-41] correlated with impaired control [40]. However, no study has investigated how altered signals for inhibitory control prediction errors and expectations may contribute to BN.

BN is a Disorder of Extreme Under- and Over-Control. Our understanding of inhibitory control processes in BN has been further limited by a sole focus on deficiencies. Indeed, hallmark loss-of-control eating and frequent co-occurring impulsive behaviors [6, 42-44], along with most neurocognitive task performance findings [45], point to inhibitory control impairments in BN. However, some neurocognitive studies report intact inhibitory control abilities in BN [46]. Moreover, BN is characterized by rigid dietary restriction between binges and is associated with "traits" typical of "overcontrolled" populations—perfectionism and harm avoidance [47-50]. Data also suggest that impulsive "traits" decrease after binge/purge frequency reductions [51]. These discrepancies raise the possibility that control-related alterations in BN are state-dependent, rather than trait-like.

The Influences of Fasting and Eating on Inhibitory Control in BN are Unknown. Perhaps the most basic and relevant state changes in BN are the characteristic fluctuations between under-controlled, excessive eating and over- controlled rigid restriction. Restraint theory and cognitive-behavioral therapy (CBT) models of BN assume that these metabolic states are causally related—that fasting and attempts to excessively control eating ("dietary restraint") precipitate binge eating and purging [52-54]. Supporting this notion, self-reported dietary restriction has been associated with binge/purge frequency [55-57], and reduced dietary restraint scores partially mediate improvements in binge eating and purging with CBT [58]. However, some studies have found an inverse or no association between restraint and binge eating [59-61], caloric restriction has been associated with reduced binge eating [62-64], and acute fasting does not increase intake at subsequent ad libitum meals in BN [2, 65, 66]. Conflicting findings may relate to the conflation of physiological states (e.g., fasted) and psychological states (e.g., deprived). Key variables in traditional models (restraint, restriction, binge eating, and purging) are clearly interrelated and

salient for BN [67], but 30-50% of patients do not achieve symptom abstinence after completing the first-line, empirically-supported treatments based on these models [68, 69]. As BN is defined by cycles of avoidance and excessive consumption of food, imaging studies that investigate the neurobiological influence of metabolic state fluctuations are needed to refine models and improve interventions [70]. However, the state-specific imaging methods used to study other cyclical disorders (e.g., substance use, bipolar)[71, 72] have not yet been used to study individuals ill with BN.

One possibility is that BN is maintained by the same disinhibiting impact of fasting seen in healthy controls (HC). Higher hunger levels in HC are associated with poor inhibition on stop signal and food go/no-go tasks.[73, 74] After fasting, the cognitive control of desires for food requires greater DLFPC activation,[75] which may reflect an increased inhibitory demand. In BN, an exaggerated version of this increase in neural inhibitory demand may make sustained control especially difficult in a fasted state. An inability to successfully recruit frontostriatal resources to meet this demand could precipitate disinhibited behavior, including binge/purge episodes.

A second possibility is that prolonged periods of restriction in BN are maintained by abnormally enhanced control in a fasted state, but once eating has started, inhibitory control is abnormally compromised. Consistent with this possibility, women with BN show an abnormally reduced startle response (reflecting increased emotion regulation) to food cues after a fast, and an abnormally increased startle response (reflecting emotion dysregulation) after eating. [2] In addition, binge-eating episodes are preceded by lower hunger ratings than are normal eating episodes,[76, 77] suggesting that loss-of-control eating may be uniquely precipitated by satiety. Other populations who struggle with overeating (e.g., obese individuals) show reduced lateral PFC responses to food images relative to controls when fed,[78] and women with obesity [79] and women with BN do not show normal increases in resting cerebral blood flow (CBF) in PFC regions after eating [1, 80-83]. Thus, failure to effectively recruit inhibitory circuitry after eating initiation could leave urges to continue eating unchecked.

Proposed Theoretical Model: This application represents a critical next step for understanding the role of control- related abnormalities in the maintenance of BN. Existing theories view binge eating as the result of psychological effects of overcontrolled eating but do not 1) specify mechanisms that may maintain prolonged fasting, 2) account for changes in physiological state that occur with fasting and eating, or 3) directly specify the role of inhibitory control in symptom maintenance. The proposed model complements existing theories with hypotheses grounded in BN, obesity, and substance use neuroimaging literatures. Specifically, the model posits that individuals with BN have increased frontostriatal signals for the predicted need to inhibit (P(stop)) and prediction errors, and increased frontostriatal activation during response inhibition in the fasted state, all of which facilitate behavioral control and prolonged periods of dietary restriction. However, after eating, decreased frontostriatal signals for the predicted need to inhibit, decreased frontostriatal prediction error signals, and deficient frontostriatal activation contribute to impaired inhibition, a sense of loss of control over eating, and subsequent out-of-control purging. This combination promotes a cycle of extremes—prolonged fasting versus dysregulated eating and purging—maintained by problematic, state- dependent neurocomputational mechanisms of adaptive control. Of note, this novel maintenance model only focuses on dietary restriction (not "dietary restraint"). It also does not specify factors that influence eating initiation, nor does the model focus on reward processes that closely interact with control processes and have been the focus of most prior BN imaging and preclinical studies [13, 19, 84-88]. These elements should be examined after the impact of fasting and eating on inhibitory control-related processes are studied. Longitudinal studies with individuals at risk for BN development will be critical in determining whether these hypothesized neural abnormalities precede or follow the onset of BN symptoms.

Testing this model in adults with current BN will 1) help delineate when and what control- related neural alterations should be targeted with new treatment approaches (e.g., fed-state inhibitory prediction deficits) and 2) identify neurocomputational markers that can be investigated next as predictors of treatment outcome.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Risk of Targeted Advertising. There is a risk for participants who click on our study advertisement to receive additional information related to eating disorders, given how Facebook/Instagram and Google use their users' behavior to target them with future ads.

Risk of Breach of Confidentiality. There is a risk that information collected in our study could become known to individuals not involved in our study.

Risks of Fasting and Standardized Meal. There is a potential risk that fasting as part of pre-scan study procedures could result in mild discomfort (e.g., tiredness, weakness, headache, dizziness) or might exacerbate eating disorder cognitions and increase distress in participants with eating disorders. In addition, although the standardized meal before the fed-state scan is not objectively large, participants with BN may be upset if they feel that they have overeaten during the standardized meal before the fed-state scan.

Risks of Venipuncture (for medical screening for BN participants) and Glucose Finger Prick (for all participants). There is minor discomfort associated with venipuncture, as well as potentially significant psychological distress, if the procedure is not well-handled. There is a small chance of bruising and a very small risk of infection with venipuncture and possibility of fainting.

Risks of Psychological and Cognitive Assessments/Standardized Meal. One possible risk is feeling uncomfortable while completing self-report or interview measures or the standardized meal. While most individuals do not experience such feelings, some may feel sad or anxious. In our experience with a wide range of patient and control populations, such feelings are typically transient and resolve before the completion of the testing.

Risks of MRI. According to the FDA, there is currently no evidence that MRI with approved scanners of up to 4 Tesla signal strength are associated with adverse effects. The specifications of the 3.0 T scanners at TMII (and the specific pulse sequences used for each protocol) meet all the stringent safety requirements of the regulatory bodies within and outside TMII. The risks associated with MRI scanning are as follows:

1) Exposure to MRI magnetic fields is not associated with any known adverse health effects. The primary risk of MRI is the possibility of undisclosed metal in the participants' body (pins, pacemakers, metal fragments in the eye) that could become dislodged by the magnet. Some individuals (10-15%) may experience unexpected claustrophobia when entering the magnet bore, or may notice the change in magnetic field upon entering or leaving the bore.

2) The acoustic noise associated with MR imaging is related to the mechanical movement of the gradient coils during the scanning process. The acoustic noise levels perceived by human subjects when undergoing MRI examination in our 3.0 Tesla magnet constitutes a non-significant risk; specifically, our system will not be operated in a way that will present more noise to human subjects than is recommended by the FDA.

3) There is also the potential for RF-induced local heating and for mild electric stimulation due to induced currents from rapidly switching gradients.

2.3.2 KNOWN POTENTIAL BENEFITS

Expected Direct Benefit to Subjects
Participants are not expected to derive benefits from participation.

Benefit to Society
Understanding the causes of eating disorders has been difficult because of the inaccessibility of the brain. Now neuroimaging technologies, such as fMRI, hold the promise of new insights into neurocircuit dysfunction that contributes to BN. This study may provide information about brain alterations that contribute to BN symptoms. Even our best treatments for BN fail to achieve remission in up to half of those treated, and a better understanding of the pathophysiology of BN may ultimately lead to better therapies.

2.3.3 DESCRIPTION OF PROCEDURES TAKEN TO LESSEN THE PROBABILITY OR MAGNITUDE OF RISKS

Informed Consent
Individuals who are interested in participating will undergo an initial phone screen. After an authorized member of the research team describes the research study to the potential participant (see attached Study Description), if the potential participant is still interested, a REDCap link to the electronic version of the approved phone screen consent will be sent to the prospective research subject for review. An authorized member of the research team will be on the phone with the potential participant as the e-consent form is reviewed using the attached script. If a written informed consent is obtained, the potential subject will provide their e-signature and name as well as the date of the consenting process on the e-consent form. After the subject submitted the form, the study staff member obtaining the consent will provide their signature, name, and the consenting date on the signed e-consent form and send a copy of the form to the participant via an encrypted email.

Individuals who are eligible to participate after the phone screen will be sent a REDCap link to the electronic version of the full-study consent form. These participants will first be scheduled for full-study informed consent and psychodiagnostic screening interviews, either in person or via a HIPAA-compliant videoconference (Zoom), as specified in the HRP 503 form section **3. Study Design → Inclusion and Exclusion Criteria → How Participants will be Screened**. At the start of this appointment, Dr. Berner or her delegate listed on this protocol will review the study protocol and obtain written informed consent using the full-study e-consent form. Voluntary written informed consent will be completed prior to completing study procedures in accordance with the PPHS of Mount Sinai. The consent process includes a description of the remaining screening procedures and pre-scan assessments, fMRI scanning procedures, and other study requirements and will be obtained in a closed office with only members of the research group present. No reference to the potential subject's identity will be made outside of closed quarters. The consent form includes an explanation of study procedures, their time commitments, risks and benefits, alternatives to participation, the confidentiality of information, and the rights of research subject. Participants will be given the opportunity to have all their questions answered. Participants' understanding of the protocol will be examined by direct questioning prior to their signing the consent forms. In addition, participants will be made aware that if they choose to participate, they must give consent to be audio-recorded as needed in the protocol. Again, if a written informed

consent is obtained, the potential subject will provide their e-signature and name as well as the date of the consenting process on the e-consent form. After the subject submitted the form, the study staff member obtaining the consent will provide their signature, name, and the consenting date on the signed e-consent form and send a copy of the form to the participant via an encrypted email. All study related questions from study participants that a research staff member is unable to address will be referred to the Principal Investigator (Dr. Berner), or other co-investigators. No further information will be gathered until participants have provided written, signed informed consent.

Participants with BN will be informed that choosing not to participate in the study will not change or restrict their eligibility for treatment in the EWDP and will not jeopardize their relationship with any Mount Sinai subspecialist (if they were referred from within the health system). The ability of the participant to withdraw from the study at any time without consequence will be clearly stated and indicated in the consent form itself. After the participant consents and signs the informed e-consent form, the psychodiagnostic screening interviews will be initiated. A copy of the consent form is provided to all participants. If the individual decides not to participate in this study, a project staff member will provide reasonable and timely assistance in obtaining an alternative referral, if applicable and so desired.

In summary, in the consent forms and discussions with study staff, participants are advised fully of the procedures to be used, the time commitments they require, the possible risks and benefits of the procedures, their right to refuse participation in the study without prejudice, and the name and telephone number of the Principal Investigator.

Confidentiality of Subjects' Responses

To minimize possible risk of breach of confidentiality, each study participant will be assigned, after consenting to phone screening (i.e., at the time of enrollment), a numeric code which will be used as the identifier for subsequent research related activities. All information collected, including self-report questionnaires, psychological assessments, and imaging data will be identified solely by these ID numbers without any personal identifiers. No identifying information is printed on subject data forms or in individual data files. Access to the numbering system will be limited to Dr. Berner and research staff directly involved in the study. All research files are kept in locked file drawers and encrypted computer files on a secure server made available only to qualified personnel for research purposes. No verbal or written information concerning a subject will be released to anyone without expressed written consent by the subject. All audio-recorded interviews will be labeled with study ID numbers. Recordings will be stored for 5 years after the completion of the research study, and destroyed thereafter. Clinical data from optional treatment at the EWDP's clinical program will be kept in separate file cabinets from the study data. The clinical team at the EWDP will not be informed of the research findings about specific patients unless clinically indicated (e.g., threat to the patient's life) or the participant asks us to reveal the information via a written, signed release of information. However, an exception to confidentiality is a previously unreported or ongoing case of abuse (state agencies may need to be involved) or in cases where participants are judged to be a danger to themselves or others (see below). Participants are made aware of these exceptions in the consenting process.

No published or presented materials will identify patients by names, initials, or any other means that could be used to identify the participant. We quote information only by number in conference discussions, scientific reports, or publications, in order to maintain anonymity.

As part of consent procedures, participants will be advised of precautions taken to preserve confidentiality. Further, all individuals involved in data collection procedures (i.e., research staff)

will be instructed to not divulge any information concerning participants to any person or agency without the written and explicit consent of the participant. All study staff will receive Human Subjects Protection training as well as HIPAA privacy training as required by the ISMMS PPHS before working with any participants. This approach to data security and confidentiality has been very effective in our past studies.

Risks specific to research procedures will be managed as follows:
Fasting and Standardized Meal
It is unlikely that fasting overnight (16 hours before both scan visits, and, by the end of the fasted-state scan, a total of 18 fasting hours) will be associated with significant risk, as prior research studies have demonstrated that individuals with BN can abstain from eating safely for 20-24 h (Mauler et al., 2006; Moreno-Domínguez et al., 2012). Nevertheless, we will take steps to protect against both physiological and psychological risks of fasting. All participants will be informed during screening that they will be asked to refrain from eating anything for up to 18 h total during study participation and will be able to decline participation if they are unwilling to abstain from eating for that amount of time. All participants will be provided with instructions about the fasting protocols for both scan visits (see attached) at the time of consenting and scheduling and will be reminded that they can discontinue their participation at any time.

We will protect against physiological risks of fasting for participants with BN by only including participants with BN who are medically stable in the study. A licensed MD's determination of medical stability will be based on vitals sign assessment, anthropometric measurements, review of medical history, and, for participants with BN, review of lab results including a chemistry panel and complete blood count panel. In addition, participants will be provided with a handout (see attached) listing potential physical symptoms during the fast (tiredness, irritability, headaches, general weakness, mild nausea, constipation or diarrhea, bad breath, sleep disturbances, dizziness, water retention). Consistent with prior research, participants will be instructed to contact the research team in the event of minor side effects, but if more severe problems occur, or if they feel sick or uncomfortable continuing to fast, to stop fasting and eat something first, then contact the research team. If participants call us after business hours, our voicemail will remind participants of these instructions. In addition, this voicemail will instruct participants to eat something if they are unsure about whether their symptoms are mild enough to continue fasting. Participants will be informed of this in fasting instructions, as well.

Several study design decisions were specifically made to minimize psychological distress associated with the fasting periods: First, fasting is common for many women with BN, and the 16-18-h duration of fasting across visits in this study falls in the middle of the 8-24 h range of the definition for the BN symptom of "fasting" used in self-report studies of BN (Fairburn, Cooper, & O'Connor, 2008; Stice et al., 2008). Therefore, it is unlikely that this duration of fasting will be atypical for the women with current BN included in our study. Second, because participants are asked to stop eating between 5:00 and 9:00 PM the night before scan visits, participants will likely be sleeping during half of the fasting period. Shift workers will be explicitly excluded from participating. Thus, participants will effectively only be missing one meal (breakfast) before the scans. Self-report data indicate that breakfast is the most frequently skipped meal of the day among both women with BN and controls (Masheb Robin, Grilo Carlos, & White Marney, 2010). Therefore, given the frequency of this behavior in the natural environment, we do not believe that it will affect the safety of the 16-18-h fasting periods. In addition, we will provide participants with a snack after post-scan self- report questionnaires are completed to minimize any fasting beyond the period necessary for study design. Study staff will conduct de-briefing at the conclusion of both scan visits to address any residual distress. Participants will be asked to notify research staff

immediately should they start to feel excessively distressed as a result of fasting for the study, and will be encouraged to stop fasting and study participation will be discontinued if persistent distress is experienced.

Although the standardized meal before the fed-state scan is not objectively large, participants with BN may be upset if they feel that they have overeaten during the standardized meal before the fed-state scan. A member of the staff will be present during the standardized meal, and will be available to the subject if she does become upset.

Participants with BN who are not patients in the EWDP will be provided with treatment referrals during de-briefing at the end of participation, if participants are interested.

Risks of Venipuncture and Glucose Finger Prick
We have a firm policy to only attempt venipuncture/finger prick a maximum of twice on one occasion. In addition, we allow adequate time for the procedure, as necessitated by the individual subject. Very rarely will a subject be so anxious about venipuncture/finger prick that these studies are not feasible.

Psychological and Cognitive Assessments
Some study participants may become anxious or tearful because of the personal nature of questions asked during clinical interviews. All research team members are well trained in strategies to help alleviate and manage any participant distress that may be associated with responding to research questions and interviews. Clinical interviewers will exercise caution and sensitivity and terminate the interview as necessary to protect the emotional well-being of the study participant. Similarly, study participants who experience frustration during cognitive assessments will be reassured that they are there to do their best and that it does not matter how well they score.

They will be encouraged to continue but can stop completing these procedures at any time. If a participant becomes anxious or uncomfortable during the testing session and would like to discontinue her participation, the session will be terminated. In addition, participants will be offered periodic 5-minute breaks to minimize fatigue.

MRI-Related Issues
Computers and the interfacing devices will be checked regularly for proper and safe operation. Typically, 3 Tesla scanners have been measured to produce noise between 122-131 db. The potential risk of hearing loss associated with the noise generated during MRI is eliminated by using ear plugs (rated to reduce noise by 32 dB) and through the use of headphones (rated to reduce noise 30 dB).

Subjects will be strongly encouraged to move slowly when entering or exiting the magnetic field. The scanner bed has been designed to slowly move the subject to minimize the possibility of vertigo. Participants are assisted in exiting from the MRI gantry to prevent a possible stumble or fall.

RF-induced local heating is unlikely due to the software requirement that subject's weight is accurately recorded and used in determining the appropriate changes in gradients. Subjects are warned of the possibility of mild electric stimulation and are monitored throughout the session.

Exclusions will be made for the following: cardiac pacemaker, metal fragments in eyes/skin/body (shrapnel), history of being a metal worker/welder, history of eye surgery/eyes washed out because of metal, aortic aneurysm clips, prosthesis, by-pass surgery/coronary artery clips, hearing aid, heart valve replacement, subjects with a metallic IUD (birth control device), a shunt (ventricular or spinal), electrodes, metal plates/pins/screws/wires, or neuro/bio- stimulators (TENS unit), vision problems uncorrectable with lenses, claustrophobia, inability to lie still on one's back for approximately 90 minutes, prior neurosurgery, older tattoos with metal dyes, bigen hair dye and micro-bladed eyebrows, tattooed eyeliner or other makeup, unwillingness/inability to remove nose, ear, tongue or face jewelry, hair weaves or extensions, braces or permanent dental retainers, and women with a positive urine pregnancy test or who are currently lactating.

Participants will be carefully screened by our staff and again by research staff for any metal that could pose a danger, and the importance of this screening will be repeatedly emphasized. If there is a possibility of metal being present in the participant's body, the participant will be excluded. Participants' informed consent will be reviewed prior to scanning, and an additional safety check (for metal in the body) will be obtained prior to scanning. A metal detector will be used to confirm that participants are not carrying or wearing material (e.g., keys, coins, jewelry, clothing containing metal) that may be affected by the presence of a magnetic field. To prevent accidental entry of metallic objects into the imaging room/magnetic field during an MR imaging session, there are large warning signs at the entrance to the area of higher field strength.

Study participants will be asked questions pertaining to fear of closed spaces during the screening stage. However, should the participant become claustrophobic during the study or for any reason be unable to endure remaining in the scanner, the study will be terminated, and the participant will be removed from the scanner.

In addition, a urine pregnancy test will be performed immediately before study participation. No studies will be performed on pregnant or potentially pregnant women.

During scanning, subjects will be in voice contact with the research staff at all times and they are encouraged to promptly report any discomfort. Furthermore, our clinically trained research staff will be on the watch for signs of distress, anxiety or fatigue and terminate the study procedure should a subject display signs of distress.

Incidental Findings and Other Potential Issues

1. If there is an indication that a participant needs immediate assistance, intervention, or a referral (e.g., suicidality, medical instability), the study staff member will help the participant to obtain these services or provide a referral. All participants will be informed that if they tell a study staff member or indicate on any assessments that they are thinking about hurting or killing themselves, research staff will ask more questions about these thoughts, and, based on their responses, staff may provide the participant with help to get treatment. This may include providing participants with information about treatment options, encouraging the participant to pursue treatment, working with the participant to contact her doctor or mental health provider, or working with the participant on a plan that may include getting her to an emergency room for safety. If this information is revealed during an in-person assessment or visit, the psychiatry fellow on call will be paged. If necessary, the participant will be taken to the emergency room or admitted. Although Dr. Berner will assist in this procedure, the primary decision about the best course of care will be made by clinical providers in these settings, not by the research team, in order to ensure that the participant gets the clinical attention that is

customary in these cases and that the treatment is not biased. Some of these actions involve a breach of confidentiality to ensure participant safety, and this may be upsetting. This risk will be described ahead of time to participants in both the phone screen and full study e-consent forms. All study staff will be trained by the principal investigator, a clinical psychologist, on procedures for the occurrence of suicidality among study participants to ensure that such cases are responded to in a clinically sensitive manner. If the research staff member conducting the research procedures feels unequipped to manage clinical issues that arise, Dr. Berner and/or Dr. Hildebrandt, also a licensed psychologist, will be contacted for consultation or supervision, or to directly intervene.

2. The discovery of a previously unknown psychiatric disorder during evaluation: If safety is compromised or could potentially be compromised, the procedure above will be followed. If safety is not compromised (e.g., the discovery of PTSD producing functional impairment in addition to BN), the patient will be notified and encouraged to seek help. If the patient agrees, a referral for evaluation by the C/L service or outpatient department will be made.

3. All subjects in this study will be asked to provide a urine sample at both scan sessions to assess recent drug use and pregnancy. Participants are notified in advance that if they test positive for recent drug use or pregnancy they will not complete the scan. Unanticipated findings of potential medical significance uncovered during the course of the study, including a positive pregnancy test or an abnormal MRI, will be reported to Dr. Berner (the principal investigator) and Dr. Hildebrandt (co-investigator). The study participant will be informed of the test result and then referred to her physician. If the participant does not have a regular physician, an appropriate referral will be made.

All members of the study team will be trained by the principal investigator on study procedures for handling incidental findings.

Targeted Advertising

BUMP's approach provides the highest level of data security and HIPAA compliance. Study advertisements distributed through Facebook, Instagram, and Google.com are linked to a landing page that provides additional information on the study. If a candidate is interested, they click on a button that takes them to a pre-screening form via REDCap. While BUMP manages the landing page, our research team entirely manages the REDCap survey.

With this approach, BUMP has no access to any candidate information, including names, ePHI, or IP addresses, and therefore do not require a HIPAA Business Associate Agreement (BAA), nor a Data Use Agreement (DUA).

Facebook, Instagram (owned by Facebook), and Google provide their users with control over how they are targeted with ads and what ads they see. Therefore, when individuals agree to these platforms' user agreements, they consent to be targeted for various types of targeted advertisements.

We will specifically target candidates via advertisements on these platforms using basic information provided by the user directly, such as gender, age, location, and interests. However, note that neither BUMP nor the study team has any access to any personally identifiable information during ad targeting. They also cannot capture any of this information when participants click on the study's ad. BUMP only receives anonymous and group-level summary information on total ad impressions, ad reach (i.e., the number of unique individuals reached), number of ad clicks/ landing page views, and "results" (i.e., the number of candidates who clicked

on a landing page button and were sent to the research team's REDCap page). The only time a person's identity can be known is if they choose to post a public comment or question on Facebook or Instagram. BUMP always responds privately via Facebook or Instagram Messenger, never publicly on Facebook or Instagram itself.

Although the user agreements for Facebook, Instagram, and Google clearly indicate policies regarding how user information will be used for targeted advertising, we will provide all potential participants who inform us that they heard about our study from an online advertisement with additional information about the implications of seeing these advertisements. Specifically, we will remind these individuals that the information they provided in these online platforms may have matched their profiles with our study's advertisement and that there is a possibility that they could be shown additional advertisements related to eating disorders as a result of their clicking on our ad. We will also remind participants that they can change their user settings to change how advertisements are shown to them. We also provide this information to all participants in the phone screening consent form as well as the study consent form.

3 OBJECTIVES AND ENDPOINTS

3.1 OBJECTIVES

Every year, 1.4 million years of healthy life are lost to disability or premature death associated with bulimia nervosa (BN), and up to half of adults with BN treated with first-line psychotherapies do not recover. Treatment-resistant binge eating and purging may be perpetuated by inhibitory control deficits linked to reduced activation in lateral prefrontal cortices (LPFC), anterior cingulate, and striatum. To date, however, neurocognitive studies of BN have not accounted for 1) the dynamic computational processes underlying inhibition or 2) the fact that individuals with BN oscillate between two extremes—under-controlled, excessive eating and over-controlled, restricted intake. This study proposes to examine the neurocomputational underpinnings of inhibitory control in fed and fasted states to test an explanatory model of BN symptoms and inform future context-dependent, targeted interventions for BN.

Inhibitory control requires individuals to update expectations based on experience, and use updated expectations to adaptively adjust behavior. Neural signals for these dynamic subcomponents of inhibitory control can be quantified with computational neuroimaging and robustly predict outcome in other psychiatric disorders. However, they have not yet been used to study BN. In addition, it is not clear how inhibitory control deficits in BN could explain both out-of-control binge eating and the over-controlled, dangerous restriction that typically occurs between binge/purge episodes. As has been proposed in substance use, BN may be associated with aberrant, state-based fluctuations in control that maintain bulimic behaviors. Metabolic state, or how recently a person has eaten, is an established modulator of inhibitory control in healthy individuals, yet surprisingly little is known about how metabolic state and inhibitory control interact in BN. In healthy adults, fasting deactivates LPFC and impairs inhibition, whereas eating increases LPFC activation and enhances inhibition. An exaggerated version of this normal fasted-state disinhibition may increase the risk for binge/purge episodes when individuals with BN restrict their intake, but a neurobiological basis for this theory has not been tested. Conversely, in BN and other conditions characterized by overeating (e.g., obesity), neuroimaging and psychophysiological data suggest that food intake and satiety may in fact be abnormally

disinhibiting. This could create a fed-state vulnerability and make it difficult to stop eating after starting.

The overarching hypothesis of this research study is that in BN, frontostriatal function and inhibitory control are enhanced in the fasted state, but impaired in the fed state. This study proposes that this aberrant state-dependent activation promotes prolonged periods of dietary restriction punctuated by out-of-control binge/purge episodes. To test this hypothesis, this project will compare neural responses of 30 women with BN to 30 group-matched healthy controls (HC) at two counterbalanced scans (after a 16-h fast and after a standardized meal) using Bayesian ideal observer modeling of stop-signal task inhibition. To assess the clinical significance of metabolic-state sensitivity, this project will examine associations of neural response with symptom severity. This project will serve as a vehicle for formal training and mentorship in repeated-measures neuroimaging methodology and analysis, computational modeling in psychiatry, and the neurobiology of BN symptoms. Characterizing the influences of eating and fasting on the control-related dysfunction that may contribute to maladaptive BN symptoms is critical to developing precise pathophysiological models and more accurate and effective treatments.

Aim 1: To determine whether eating and fasting abnormally interfere with the capacity of individuals with BN to adaptively exert inhibitory control
Hypothesis 1.1: Women with BN in the fed relative to fasted state will demonstrate impaired performance and deficient frontostriatal activation when inhibiting responses, whereas HC will show the opposite pattern. Hypothesis 1.2: In BN, frontostriatal signals for the trial-level anticipated need to stop (P(stop)) and Bayesian prediction errors will be reduced in the fed relative to fasted state. HC will show the opposite pattern. Associated Training: Goal 1: To develop expertise in repeated-measures neuroimaging and analysis, including measurement of potential state-based fMRI normalization factors (e.g., resting perfusion); Goal 2: To learn to independently conduct computational model-based analysis of fMRI data in eating disorders

Aim 2: To identify associations of BN symptom severity with state-specific frontostriatal activation
Hypothesis 2.1: In BN, more frequent binge eating and purging will be associated with lower frontostriatal signals for
P(stop) and prediction errors in the fed state relative to the fasted state.
Hypothesis 2.2: In BN, more severe dietary restriction will be associated with increased frontostriatal signals for P(stop) and prediction errors in the fasted state relative to the fed state.
Associated Training: Goal 1: To develop expertise in analysis and integration of repeated-measures neuroimaging and clinical data; Goal 3: To expand my knowledge of the neurobiological mechanisms involved in the full spectrum of bulimic behaviors, specifically dietary restriction.

Findings are expected to inform novel treatments by 1) pinpointing which components of the inhibition process are altered in BN and 2) identifying states in which control-focused interventions may be most effective at interrupting the cycle of BN symptoms. We also may detect state-independent neural alterations that represent stable BN biomarkers. This research and training are critical to launching my independent career as a translational clinical investigator who combines behavioral, psychological, and neuroimaging tools with sophisticated analytic approaches to inform treatment optimization. The proposed study will serve as the basis for a longitudinal R01 application powered to examine brain-based phenotypes over time and state-specific predictors of outcome among a wider diagnostic spectrum of individuals who binge eat and purge.

3.2 STUDY ENDPOINTS

Primary Outcome: Frontostriatal activation
We will compare the impact of fasting and eating on neural activation in women with BN and healthy controls. Specifically, we will compare groups on the influence of fasted and fed state on: 1) frontostriatal activation when correctly inhibiting responses and 2) frontostriatal signals for the anticipated need to stop (P(stop)) and inhibitory control prediction errors.

Our sample size was selected based on the most rigorous analysis of this primary outcome measure (a Group x Visit x Trial Type linear mixed effects model). We simulated 1,000 datasets with a 3-way interaction (Group x Visit x Trial Type) and fitted a mixed effects model to each dataset; power to detect a large (d = .80) 3-way interaction with 30 women per group was estimated at over 80% with a two-sided alpha =.05. Results will serve as essential preliminary data for a larger, fully powered R01 application.

Secondary Outcomes:

- Stop signal task performance: We will compare the impact of fasting and eating on behavioral task performance in women with BN and healthy controls. We will specifically compare groups on stop signal reaction times and the percentage of correct stop trials.
- Eating disorder symptom severity: We will examine, with the BN group, whether more severe binge eating/purging is associated with frontostriatal signals for P(stop) and inhibitory prediction errors in the fed vs. fasted state, and whether more severe dietary restriction is associated with frontostriatal signals for P(stop) and prediction errors in the fasted vs. fed state.

Other/Exploratory Outcome: Resting cerebral blood flow
We will compare the impact of fasting and eating across our two groups on resting cerebral blood flow, as measured by arterial spin labeling (ASL).

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study uses a two-group, repeated-measures design to investigate whether eating abnormally influences inhibitory control processes in BN. We propose to test this hypothesis in adult women with currently symptomatic BN compared with healthy controls and will probe inhibitory control circuits at two counterbalanced scans using computational modeling of stop-signal task inhibition (Aim 1). To assess the clinical significance of sensitivity to fasting and eating, we will examine whether state-specific altered neural function is associated with the severity of binge eating, purging, and fasting (Aim 2).

4.2 END-OF-STUDY DEFINITION

Completing the research described in this protocol will include a phone screening assessment, psychodiagnostic assessment, one in-person evaluation, online questionnaires, and two fMRI scans on two separate days.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

All Participants

- Female
- Aged 18 to 35 years
- Currently between 85 and 130% of the expected weight for height based on the Metropolitan Life Insurance tables (attached)
- Right-handed
- English-speaking

Additional Inclusion Criteria for Women with BN

- Meet DSM-5 criteria for bulimia nervosa (at least one binge eating episode and compensatory behavior episode per week on average for the past three months)
- Medical stability, as determined by a licensed MD listed on the study protocol, based on vitals assessment and blood draw for complete blood count and chemistry panel

5.2 EXCLUSION CRITERIA

All Participants

- Vitals outside of the following limits:
  - Temp: < 97 degrees F
  - Pulse: <40 or >100 bpm
  - BP lying, sitting, standing: Blood pressure < 90/60 mmHg and/or orthostatic increase in pulse of > 20 bpm or a drop in blood pressure of > 10-20 mmHg
- Personal history/diagnosis (self-reported) of any metabolic disorder (i.e., diabetes (type 1 or 2)) or gastrointestinal disorder
- Reported current or past diagnosis of a chronic disease, defined as:
  - symptomatic coronary artery disease o coronary revascularization
  - myocardial infarction o unstable angina
  - stroke
  - transient ischemic attack o pulmonary embolism
  - peripheral vascular thromboembolism
  - chronic kidney disease stage III or higher o kidney stones
  - gallstones or gallbladder disease
  - chronic obstructive pulmonary disease o immunodeficiency
  - solid organ transplant o thyroid dysfunction
  - cancer of any type other than cancer of the skin excluding melanoma o blood disorder
  - uncontrolled asthma
- Current fever, upper respiratory infection, vertigo, regular fainting spells (at least once monthly), persistent diarrhea, blood in stools, vomiting blood
- Any medication used to lower blood glucose or antidiabetic medications (metformin, sulfonylureas, Glucagon-like peptide-1 GLP-1 analogues [i.e. exenatide], thiazolidinediones or DPP-IV inhibitors [i.e. 'gliptins']); medications affecting weight, appetite or gut motility (i.e. domperidone, cisapride, orlistat, phentermine, topiramate)

- Undertaking any form of medical treatment which may interfere with study variables (e.g. chemotherapy)
- Shift work
- Pregnancy or planned pregnancy during the study period, or lactation
- Current or past neurological disorder
- History of a seizure or history of head trauma with loss of consciousness
- Full Scale IQ under 75
- Allergy to any of the ingredients in or unwillingness to consume the standardized meal or unwillingness to drink water during the fasting period
- Any contraindication for fMRI (e.g., non-removable metallic objects in the body, known claustrophobia)

Additional Exclusion Criteria for BN Women

- Meet DSM-5 diagnostic criteria for any current comorbid Axis I diagnosis except: depressive disorders (Persistent Depressive Disorder (PDD) or Major Depressive Disorder (MDD)), Generalized Anxiety Disorder (GAD), or Social Anxiety Disorder (SAD)
- Primary diagnosis of MDD, GAD, or SAD, as assessed by the Structured Clinical Interview for DSM-5 Research Version
- Meet criteria for a substance/alcohol use disorder in the last 3 months
  Change in psychiatric medication or dose within the past 6 weeks

Additional Exclusion Criteria for Healthy Controls

- Current or past diagnosis of any Axis I psychiatric disorder
- Current or past binge eating (including any endorsed history of a sense of loss of control over eating, regardless of eating episode size) or compensatory behaviors (including self-induced vomiting, laxative or diuretic misuse, weight- loss medication use) or fasting to control shape or weight
- Any active attempts at weight loss in the last 3 months (including dieting, elimination or restriction of certain foods to lose weight, fasting, weight loss medications)
- Reported weight loss or gain > 4 kg in the last 3 months
- Psychotropic medications in the last 3 months

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Please see the HRP 503 form section **3. Study Design → a) Recruitment Methods** for detailed recruitment strategies.

6 STUDY EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

6.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. Please further details in the HRP 503 form section **3. Study Design → i) Procedures for Subjects to Request Withdrawal.**

The Principal Investigator, the sponsor, or the institution may stop subjects' participation at any time without their permission. Please further details in the HRP 503 form section **3. Study Design → i) Procedures for Investigator to Withdraw Subjects.**

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 DESCRIPTION OF PROCEDURES BEING PERFORMED

Screening Procedures

Please see the HRP 503 form section **3. Study Design → Inclusion and Exclusion Criteria → How Participants will be Screened** for further details on the study's screening procedures.

Interested individuals will first complete a brief initial screening (~15 min via phone). The purpose of this brief screen is to quickly exclude individuals who meet clear-cut exclusion criteria.

Individuals who are still interested in and are eligible to participate after phone screening will next complete full study consenting (please see HRP 503 form section **9. Consent Process → Where and When Consent Will Be Obtained**) and, after providing written informed consent, semi-structured psychodiagnostic interviews in person at the EWDP clinic or via a HIPAA-compliant videoconference (Zoom).

The standardized structured diagnostic interviews are designed to assess past and present eating disorder symptomatology and concomitant psychopathology. Individuals eligible after these initial assessments will also complete the Borderline Personality Disorder (BPD) Module from the Structured Clinical Interview for DSM-5 Personality Disorders to assess for comorbid BPD symptoms and diagnosis. The full battery of interviews takes about 2.5 hours to complete. The clinical interviews will be audio-recorded, and 15% will be randomly selected for interrater reliability assessment.

Participants who are deemed eligible after phone screening and diagnostic interviews will be asked to complete remaining screening assessments and pre-scan procedures in person at the EWDP clinic. These remaining assessments take approximately 1.5 hours total and include height and weight measurement and a neuropsychological test that assesses Full-scale IQ (WASI-II; designed to assess general cognitive ability as groups will be matched on full scale IQ and individuals with IQ under 75 will be excluded). In addition, height and weight will be measured for all participants. For participants with BN, the in-person screening will also include a medical stability screening that includes vitals assessment and drawing 2 teaspoons of blood for basic laboratory tests (e.g., CBC, Chem7).

At the end of the first in-person visit, participants will also complete the Patient Health Questionnaire–9 (PHQ-9) and will practice and complete computerized decision-making tasks, and pre-task state measures:

- Generalized labeled magnitude scale (gLMS) ratings of hunger and satiety
- VAS ratings of fatigue, urge to overeat, urge to binge eat (BN only), urge to purge (BN only)
- Positive and Negative Affect Schedule (PANAS)

- Spielberger State-Trait Anxiety Inventory (STAI-S)
- State Difficulties in Emotion Regulation Scale (S-DERS)

Self-Report Battery
Between the first in-person visit and the scanning visits, participants will be asked to complete a battery of self-report questionnaires online via REDCap to provide timely symptom measures. These surveys will be administered online to avoid transcription errors and allow participants to complete questionnaires when most convenient for them. These widely used, well-validated self-report questionnaires take approximately 1 hour to complete. The battery includes standardized psychological measures designed to assess current anxiety symptoms, personality pathology and temperament, impulse control and eating-disorder related symptoms (see below). Data collected from the questionnaires will be used to measure the severity of any current symptoms in the BN versus healthy controls and correlate these scores with neural responses and behavioral task performance.

Neuroimaging Scans
Participants will be asked to refrain from using alcohol or any substances they may occasionally use (e.g., marijuana), for 7 days prior to scanning.

Methods will closely replicate those used to study anorexia nervosa and bulimia nervosa: Fasted and fed-state scans will be scheduled no more than one week apart in a counterbalanced order between groups. Participants will be instructed to consume nothing besides water the night before scans. Therefore, the only difference between counterbalanced fasted and fed-state scan days will be the consumption of a standardized meal immediately before scanning on the fed-scan day. To balance feasibility and safety with ecological validity, we will conduct scans on both fasted-state and fed-state visits starting between 9:00 AM and 1:00 PM.

Several studies of BN and obesity have successfully implemented similar at-home fasts (9 h-20 h in duration). On fed scan days, participants will consume a standardized meal over 15 min [30% daily caloric needs (30 kcal/ kg), ~450–500 kcal] 45 min before scanning. As in prior research in remitted eating disorder samples, portions will be adjusted for each participant based on their body mass index. Scanning will begin 30 minutes after meal completion. Participants will be informed of these eating schedule requirements over the phone during pre-screening and will only eligible to participate if they are willing to comply with these study procedures and (in the case of BN participants) if their vitals and labs indicate that they are medically stable. Participants will be instructed to consume their last food 16 hours before their scheduled scan start (i.e., between 5:00 and 9:00 PM the night before, depending on scheduled scan time). Participants with BN will be instructed to refrain from purging (self-induced vomiting or laxative or diuretic use) during the fasting periods before scanning.

Upon arrival at the TMII, at both scan visits, participants will first complete a Scan Day Visit Questionnaire, and overnight fasting status will be confirmed via interview regarding food intake. We will also measure blood glucose via finger-prick. Criteria for interpreting blood glucose will be consistent with that used in our prior studies: Specifically, glucose levels that are 70-100 mg/dL are considered a normal fasting glucose range. Participants will be informed that upon arrival for each session they will be asked to report on their recent food consumption, and that they will be asked to provide a blood sample to demonstrate compliance.

All subjects in this study will be asked to provide a urine sample at the scan session to assess recent drug use and pregnancy. Participants are notified in advance that if they test positive for recent drug use or pregnancy they will not complete the scan.

Before and after the fMRI scan, subjects will complete self-reports on their current state in targeted areas such as mood, anxiety, fatigue, and feelings of hunger or satiety:

- Generalized labeled magnitude scale (gLMS) ratings of hunger and satiety, fatigue, urge to overeat, urge to binge eat (BN only), urge to purge (BN only)
- Positive and Negative Affect Schedule (PANAS)
- Spielberger State-Trait Anxiety Inventory (STAI-S)
- State Difficulties in Emotion Regulation Scale (S-DERS)

Information collected will be examined in correlation with behavioral performance and neural responses to decision- making tasks. Subjects will perform an inhibitory control task and two decision-making tasks at both scanning study visits. During the scan, visual stimuli are projected from a computer onto a screen in the scan room, and participants hear auditory stimuli via headphones and log their responses to visual and auditory stimuli using a button response box for both tasks. The remainder of scan time consists of structural sequences and resting state sequences during which the subject is asked to lie still and stay awake. A fixation cross is displayed during this portion. The imaging procedure involves lying quietly on a table for approximately 1.5 hours. No pain or discomfort results from this procedure.

On both scan days, participants will be offered a granola bar snack after scanning is complete.

At the conclusion of study participation, we will provide a customized written set of referrals, which includes low-fee, full-fee, and insurance-based options that include both Mount Sinai and external treatment sources. We are available to discuss follow-up with any of these options and communicate this availability to participants. However, as we are not providing treatment in this study, we will not engage in formal case management for participants.

During these cognitive tasks, participants will have the opportunity to earn a bonus between $0 and $15. Monetary bonuses are a common technique in behavioral economics that help to ensure that participants' behavior is ecologically valid and as true to life as possible. It also helps to minimize the risk of boredom and fatigue that participants will face when playing these games. Depending on the task, these bonuses are either calculated based upon a cumulative score, meaning participants bank up small rewards over the course of the task, or they receive the full payout from a randomly selected trial. The full details for how these bonuses are calculated is made clear to the participants in the instruction screens of the individual tasks.

7.2 DESCRIPTION OF THE SOURCE RECORDS THAT WILL BE USED TO COLLECT DATA ABOUT SUBJECTS

Names of Standardized Instruments (Psychiatric Measures):

- Structured Clinical Interview for DSM-5, Research Version (SCID-5-RV)
- Eating Disorder Examination (EDE; abbreviated version that only includes the diagnostic items for BN)
- Borderline Personality Disorder (BPD) Module from the Structured Clinical Interview for DSM-5 Personality Disorders
- Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II), 2-subtest version
- Patient Health Questionnaire –9 (PHQ-9)
- Spielberger State-Trait Anxiety Inventory (STAI-T)

- Restricting Subscale of the Eating Pathology Symptoms Inventory (EPSI)
- Behavioral Activation System Scales (BIS/BAS)
- Barratt Impulsiveness Scale-Version 11 (BIS-11)
- Difficulties in Emotion Regulation Scale (DERS)
- UPPS-P Impulsive Behavior Scale
- Affective Lability Scale
- Eating Expectancies Inventory (EEI)
- Eating Disorders Inventory (EDI) weight history questions
- Power of Food Scale (PFS)
- Eating Loss of Control Scale (ELOCS)
- Eating Disorder Examination Questionnaire (EDE-Q)
- Eating Disorder Flexibility Index Questionnaire (EDFLIX)
- Multidimensional Assessment of Interoceptive Awareness (MAIA)
- Loss-of-control over eating scale, brief version (LOCES-B)
- U.S. Household Food Security Survey Module
- Self-Reported Behavior Automaticity Index (SRBAI)
- Cash Choice Task
- Generalized labeled magnitude scale (gLMS) ratings of hunger, satiety, fatigue, urge to overeat, urge to binge eat (BN only), urge to purge (BN only)
- Positive and Negative Affect Schedule (PANAS)
- Spielberger State Anxiety Inventory (STAI-S)
- State Difficulties in Emotion Regulation Scale (S-DERS)
- Coronavirus Anxiety Scale (CAS)

Description of Instruments Created by Research Team:
All instruments created by the research team are included with this submission.

- Supplemental interview to evaluate eating disorder history adapted from SCID Eating Disorders Module: This form provides a more structured scoresheet for information collected during the eating disorders section of the SCID-5, and includes specific boxes for the collection of information about worst, past, and current eating disorder symptom frequencies. The interview also includes a timeline to facilitate determination of whether a participant meets criteria for BN or may instead meet criteria for another eating disorder based on their history (e.g., the binge-eating/purging subtype of anorexia nervosa, in partial remission)
- Scan Visit Day Questionnaire: This brief questionnaire assesses sleep, caffeine consumption, menstrual status, and last eating disorder behaviors before scanning
- Medical screening form: This form assesses current and past medical diagnoses and includes a review of systems relevant to the study. It also includes space to log results of measured vitals. A licensed MD listed on the study protocol will review this form for all participants.
- COVID-19 Testing Questions: These questions assess subjects' COVID-19 testing and status in the past 3 months

Neurocognitive Tasks:
- Stop signal task
- Go/no-go reinforcement learning task

- Demand selection task
- Social decisions task
- Flexibility task

Magnetic Resonance Imaging:

- MRI data will be acquired following Human Connectome Project (HCP) Young Adult protocols on a Siemens 3T MAGNETOM Skyra scanner.
- The session includes:
    1) a whole brain T1-weighted anatomical scan
    2) a whole-brain resting ASL scan
    3) a whole-brain resting BOLD scan
    4) task-based T2*-weighted multiband EPI scans (1 if a neuromelanin-sensitive scan is conducted, 2 if not)
    5) phase maps to correct field inhomogeneities.
    6) a neuromelanin-sensitive (gradient-echo pulse with magnetization transfer) scan

7.3 ADVERSE EVENTS, INCIDENTAL FINDINGS, AND OTHER POTENTIAL ISSUES

Please see the HRP 503 form section **4. Provisions for Research Related Harm/Injury → Incidental Findings and Other Potential Issues** and **Provisions for Research Related Harm / Injury** for details on the procedures the research team will implement to handle and report adverse events, incidental findings, and other potential issues.

8 STATISTICAL CONSIDERATIONS

8.1 DATA ANALYSIS PLAN (INCLUDING ANY STATISTICAL PROCEDURES)

8.1.1 HYPOTHESIS TESTING

Hypothesis 1.1) BN in the fed relative to fasted state will demonstrate impaired performance and deficient frontostriatal activation when inhibiting responses, whereas HC will show the opposite pattern. Behavioral analyses will examine state-dependent group differences in stop signal reaction time and % correct stop trials. Neuroimaging analyses will examine the impact of eating on activation during successful inhibition, regardless of the anticipated probability of the upcoming need to stop (P(stop)). Linear mixed effects (LME) models will be used for both sets of analyses.

Hypothesis 1.2) In BN, frontostriatal signals for the anticipated need to stop (P(stop)) and inhibitory prediction errors will be reduced in the fed relative to fasted state. HC will show the opposite pattern. Group x Visit x Trial Type LME analyses will examine how eating impacts group differences in P(stop)-modulated inhibitory activation (i.e., activation during Stop versus Go trials) and group differences in P(stop) activation, regardless of trial type. Group x Visit LME analyses will examine how eating impacts group differences in signed and unsigned prediction errors. We will examine both signed and unsigned prediction errors as each may provide unique information to inform behavioral adjustment: Unsigned prediction errors capture the overall mismatch between one's internal model of prediction and the actual outcome, whereas signed prediction

errors provide additional information about the directionality of this mismatch, which may bias an individual to be more or less cautious (i.e., oriented more toward stopping or going).

Hypotheses 2.1 & 2.2) More severe binge eating and purging will be associated with lower frontostriatal signals for P(stop) and inhibitory prediction errors in the fed vs. fasted state; more severe dietary restriction will be associated with increased frontostriatal signals for P(stop) and prediction errors in the fasted vs. fed state. Within the BN group, Symptom Severity x Visit generalized LMEs will test how eating impacts the relations between self-report measures (binge eating, purging, and fasting frequencies) and activation associated with each neurocomputational regressor of interest. We will examine whether areas from this analysis overlap with clusters identified in Aim 1 to assess the potential contribution of illness severity to group differences in activation.

8.1.2 EXPLORATORY ANALYSES AND POTENTIAL CONFOUNDS

1) Resting CBF: ASL data will be subjected to Group x Visit LMEs a) restricted to masks of Aim 1 LME results and b) across the whole brain. If whole-brain mean CBF differences are observed, Aim 1 analyses will be repeated covarying for CBF.7 However, localized differences in CBF that overlap with Aim 1 results will further inform BOLD signal interpretation.
2) Illness Duration: We will test the association between months with BN and neural measures of interest.
3) BN Comorbidity and Treatment: Depending on final sample composition, post-hoc tests will examine a) group differences controlling for MDD, GAD, and SAD b) group differences excluding comorbid MDD, GAD, and SAD or c) associations of PHQ-9 and STAI-T scores with group differences in activation. Potentially confounding effects of treatment-seeking status will be evaluated in a similar manner.
4) Additional Measures of BN Symptom Severity and State Emotion/Arousal: Analyses described for Hypotheses 2.1 and 2.2 will be repeated using the pre-scan state measures.
5) Functional Connectivity: Psychophysiological interaction analyses will interrogate state-specific frontostriatal connectivity during stop-signal inhibition.
6) We will explore group differences in performance and/or brain activation during the other decision-making neurocognitive tasks and associations of these measures with BN clinical symptoms.

8.2 POWER ANALYSIS (SAMPLE SIZE DETERMINATION)

Our sample size was selected based on the most rigorous analysis of our primary outcome measure (a Group x Visit x Trial Type LME). FMRI studies using inhibitory control tasks report large BN vs. HC effect sizes (mean striatum d = .82; mean PFC d = .96),62, 167 and our pilot data from remitted BN and HC suggest a large Group x Visit x Inhibitory Difficulty interaction in the DLPFC (d = .83). Prior work using the proposed Bayesian models to study substance dependence report large Group x P(stop)-modulated Trial Type (Stop*P(stop), Go*P(stop)) interactions in the DLPFC (d = .90) and caudate (d = .81).20 Based on these prior data, we expect large Group x Visit x Trial Type frontostriatal interactions. Using computed Stop*P(stop) and Go*P(stop) regressors from the DLPFC and caudate from this prior study of substance dependence, we determined beta estimates were normally distributed with homogeneous variance across groups. We simulated 1,000 datasets with a 3-way interaction (Group x Visit x

Trial Type) and fitted a mixed effects model to each dataset; power to detect a large (d = .80) 3-way interaction with 30 women per group was estimated at over 80% with two-sided alpha =.05.

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.1 INFORMED CONSENT PROCESS

The study involves two consenting processes: phone screen and full study consenting processes. Please see the HRP 503 form section **9. Consent Process → Where and When Consent will be Obtained** for details on these consenting processes.

9.1.2 CONFIDENTIALITY AND PRIVACY

Please see the HRP 503 form section **3. Study Design → f) Data Storage, Transmission and Confidentiality** and section **6. Provisions to Protect the Privacy Interests of Subjects** for details.

9.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

Please see the HRP 503 form section **3. Study Design → e) Specimen Banking for Future Uses Not Part of This Project,** and **f) Data Storage, Transmission and Confidentiality** for details.

9.1.4 SAFETY OVERSIGHT

Please see the HRP 503 form section **3. Study Design → g) Data and Safety Monitoring Plan**, and **h) For Other Projects With Greater Than Minimal Risk A Monitoring Plan Must Be Provided** for details.

9.1.4.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Please see the HRP 503 form section **3. Study Design → f) Data Storage, Transmission and Confidentiality → Data Storage** for details

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