Neural Response to Food Stimuli: FMRI Changes Following Cognitive Behavioral Therapy for Binge Eating Disorder

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Neuroscience Neuroimaging Center
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Center for Weight and Eating Disorders
University of Pennsylvania

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Study Summary

Title	Neural response to food stimuli: fMRI changes following cognitive behavioral therapy for binge eating disorder
Short Title	NEURAL RESPONSE BED
IRB Number	829018
Phase	Phase 4
Methodology	Randomized, waitlist controlled, open label
Study Duration	3 years
Study Center(s)	Single-center
Objectives	The purpose of this research is to conduct a randomized controlled trial (RCT) assessing the impact of CBT on neural responses to binge eating stimuli. Females with a BMI≥25 kg/m^2 and BED will be randomized to either a 16-week, one-on-one CBT intervention (n=20) or a waitlist control (WL; n=20). Both groups will have blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) scans at baseline and after the 16-week intervention. During the scans, participants will complete the following tasks: 1) food-specific stop signal task (SST), and 2) script-driven imagery of binge foods.
Number of Subjects	40
Main Inclusion and Exclusion Criteria	Key Inclusion: BMI≥25 kg/m^2; binge eating disorder as diagnosed by DSM-5 criteria; female Key Exclusion: Weight > 158.8 kg; left-handedness; pregnancy or lactation; current diagnosis of severe major depression or other psychiatric disorder that significantly interferes with daily living; active suicidal ideation; presence of conditions that may interfere with magnetic resonance imaging; use of weight loss medications or other agents known to affect body weight or blood glucose; type 1 or 2 diabetes mellitus; visual, auditory, or other impairment affecting task performance
Reference therapy	Waitlist control group
Statistical Methodology	Mixed-effects linear models
Safety Evaluations	Adverse events
Data and Safety Monitoring Plan	Drs. Chao and the co-investigators will be responsible for monitoring the data quality and the ongoing safety of subjects.

1. BACKGROUND AND STUDY RATIONALE

1 Background and Relevant Literature

Binge Eating Disorder (BED). BED is a serious public health problem. It is characterized by eating, in a discrete period of time, an amount of food that is larger than most people would consume under similar circumstances. Patients report a sense of loss of control over eating, followed by distress about their behavior.[1] The prevalence of BED is 2.8% among US adults.[2] BED effects twice as many females as males but is comparable in prevalence across racial/ethnic groups.[2] BED has a chronic course and leads to progressive weight gain if left untreated.[3,4] BED and obesity are highly comorbid, and the frequency of binge eating episodes is strongly associated with body mass index (BMI).[5] Individuals with BED have a higher prevalence of medical and psychiatric morbidities compared to individuals without BED, including metabolic syndrome, functional impairment, and lower quality of life.[6,7] Patients with BED differ behaviorally, psychologically, genetically, and physiologically from persons with other forms of obesity and eating disorders[7-11]; notably, these individuals have high levels of dietary disinhibition and food reward sensitivity.[12,13] BED represents a vulnerable phenotype of obesity for which there is an urgent need for better treatment approaches.

Critical Need for Better BED Treatment Approaches. Treatment options for BED remain limited and are often not sufficient for patients. Current available treatments include psychotherapy, behavioral weight loss, and pharmacotherapy. A specific type of psychotherapy, cognitive behavioral therapy (CBT), is the most effective treatment for BED.[14] CBT is associated with significantly higher binge eating abstinence rates than no treatment and abstinence rates are 15-44% higher in CBT than behavioral weight loss.[15-17] Unfortunately, even with CBT, roughly half of patients with BED do not achieve full remission of binge eating,[15,17-19] and there are no reliable predictors of treatment response. Further knowledge is needed about how to best prevent and treat BED. Effective prevention and treatment strategies rely on a better understanding of both the etiology and maintenance of binge eating behaviors.

Neurobehavioral Aspects of BED. Neurobehavioral studies have revealed distinct vulnerabilities in individuals with BED that may underlie the emergence and maintenance of their symptoms. Behavioral studies have demonstrated two primary deficits in people with BED relative to individuals without this disorder—disinhibition and food reward sensitivity.[12,13] Recent neurobiological evidence has provided insight into the mechanisms underlying these behavioral data. Compared to obese patients without BED, individuals with BED have diminished activation in the prefrontal cortex (PFC), orbitofrontal cortex (OFC), and inferior frontal gyrus (IFG) when completing inhibitory control tasks.[20] These regions are associated with executive functioning, decision making, and impulse control.[21] Individuals with BED, relative to those without, have increased activation in neural regions associated with reward sensitivity (i.e., PFC, OFC, insula, ventral tegmental area (VTA), and ventral striatum (VS).[22-26] Only one study has examined the relationship between neural mechanisms and BED treatment outcomes. In that study, participants completed a monetary incentive delay task during a pre-treatment fMRI. Compared to individuals who achieved remission with BED, those who continued to binge following treatment with sibutramine and/or CBT showed less activation of specific frontostriatal brain regions during pre-treatment fMRI scans.[27]

Neural Responses to CBT. To our knowledge, no studies have examined the impact of CBT on neural response in patients with BED. However, several converging lines of research have emerged that use fMRI, a safe and noninvasive way to image neural activity,[28] to assess the impact of CBT on brain function. The most common method of fMRI measures the blood oxygenation level dependent (BOLD) signal, which uses cerebral blood flow to delineate regional activity in the brain.[28] These studies have been conducted among individuals with various conditions including anxiety disorder,[29-32] major depressive disorder,[33,34] chronic pain,[35] and substance use disorder.[36,37] This literature has demonstrated that CBT, which promotes changes

in the thoughts, feelings, and behaviors of patients, also promotes neural changes that are discernible immediately after treatment.[33,34,38,39] These studies have helped to develop cognitive neuroscience models of diseases and to identify neural processes that mediate symptom expression. This research will be used to develop novel, neurobiologically-informed treatments for BED such as cognitive training interventions, which may help patients capitalize on the adaptive capacity of the brain to improve self-management behavior.

Predictors of CBT Response. A significant barrier to precisely targeting treatment for BED is that there are no reliable predictors of outcomes. This study will also form the basis of a line of inquiry that uses neural biomarkers in predictive models of BED outcomes. A growing body of literature in anxiety and depression has shown that relative to baseline demographic or clinical information, pre-treatment variance in neural activity is a better and more reliable predictor of response to both pharmacological and psychological interventions.[40-42] Identification of neuroimaging biomarkers associated with CBT intervention response can help identify vulnerable and treatment-responsive groups. Our lack of understanding of neural function in relation to BED forms a critical barrier to the development of efficacious, patient-centered treatment approaches.

This document is a clinical research protocol and the described study will be conducted in compliance with the protocol, Good Clinical Practice standards, associated federal regulations, and all applicable University research requirements. This study will be conducted in full accordance all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, and Good Clinical Practice. All episodes of noncompliance will be documented.

2 Study Objectives

The purpose of this research is to conduct a randomized controlled trial (RCT) assessing the impact of CBT on neural responses to binge eating stimuli. Females with a BMI $\geq$25kg/m^2 and BED will be randomized to either a 16-week, one-on-one CBT intervention (n=20) or a waitlist control (WL; n=20). Both groups will have blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) scans at baseline and after the 16-week intervention. During the scans, participants will complete the following tasks: 1) food-specific stop signal task (SST), and 2) script-driven imagery of binge foods.

2.1 Primary Objective

Aim 1: Compare differences between the CBT and WL groups at week 16 in changes in BOLD fMRI response to the food-specific SST.
Hypothesis 1: Since CBT for BED involves successful management of dietary disinhibition, we propose that participants will have favorable pre- to post-treatment changes in regions of interest (ROIs) that are associated with inhibitory control. We hypothesize that the CBT group, compared with the WL group, will have increased activation in the PFC, IFG, OFC, and insula during the food-specific SST.

Aim 2: Compare differences between the CBT and WL groups at week 16 in changes in BOLD fMRI response to recall of binge foods (i.e., script-driven imagery).
Hypothesis 2: CBT teaches participants how to reduce responsiveness to binge foods. Thus, we propose that CBT will alter neural responses in regions that promote food reward. We hypothesize that after treatment, the CBT group, compared to the WL group, will have decreased activation in the PFC, OFC, insula, VTA, and VS in response to script-driven imagery of binge foods.

Aim 3: Determine whether pre-treatment neural activation on the SST and script-driven imagery task predict differences between CBT responders and non-responders ($\geq$1 binge eating episode in the past 28 days).

Hypothesis 3: Results from other psychiatric disorders show that patients with greater dysfunction in neural circuitry related to their disease are less likely to respond to treatment. We predict that relative to CBT responders, non-responders will have lower pre-treatment BOLD activation in the inhibitory control ROIs during the SST and higher pre-treatment BOLD activation in the reward ROIs during the script-driven imagery task.

2.2 Secondary Objectives

Aim 4: Assess the associations between pre- to post-treatment behavioral changes in reported binge eating episodes (percent reduction and categorical response), in reward-based eating drive, and in dietary inhibition, and pre- to post-treatment neural changes on the SST and script-driven imagery task.

3 Study Endpoints

3.1.1 Primary Study Endpoints

The primary endpoints are baseline to 16-week changes in BOLD fMRI response to food-specific SST and to binge-eating script-driven imagery.

3.1.2 Secondary Study Endpoints

Secondary study endpoints include changes in binge eating episodes (percent reduction and categorical response), in reward-based eating drive, and in dietary inhibition.

4 Investigational Plan

4.1 General Design

We propose a randomized, waitlist-controlled trial of a 16-week CBT intervention for females with a BMI$\geq$25 kg/m^2 and BED as diagnosed by DSM-5 criteria (n=40).[1] We will assess the effects of CBT on neural responses to binge-eating stimuli and neural predictors of treatment response. Participants will have assessments at baseline and after 16 weeks, with each assessment including neuroimaging with BOLD fMRI. We use 16 weeks for our follow-up assessment based on previous studies in different conditions (e.g., depression[33,34] and anxiety[38]) demonstrating discernible changes in neural function immediately after CBT. Also, CBT treatment effects for BED are most robust at 16 weeks, which will maximize our effect sizes.[43-45]

5 Study Population and Duration of Participation

5.1 Total Number of Subjects and Sites

This is a single-site study. We will randomly assign 40 females with BED to either CBT or a waitlist control.

5.2 Inclusion Criteria

1. Women who meet the DSM-5 criteria for BED as diagnosed by the Eating Disorder Examination Interview
    a. Recurrent episodes of binge eating characterized by consuming an abnormally large amount of food in a short period of time compared with what others might eat in the same amount of time under the same or similar circumstances, and experiencing a loss of control over eating during the episode.
    b. These episodes feature at least 3 of the following:
        i. consuming food more rapidly than normal;
        ii. eating until uncomfortably full;

iii. consuming large amounts of food when not hungry;
iv. consuming food alone due to embarrassment;
v. feeling disgusted, depressed, or guilty after eating a large amount of food.

c. Significant distress about the binge episodes is present.
d. Binge episodes must occur, on average, at least once per week for 3 months.

2. Ages 18 to 45 years of age
3. BMI $\geq$25 kg/m^2
4. Premenopausal
5. Able to provide informed consent
6. Right-handed
7. Eligible female patients will be:
   - Non-pregnant, evidenced by a negative urine dipstick pregnancy test
   - Non-lactating
   - Surgically sterile or postmenopausal, or they will agree to continue to use an accepted method of birth control during the study
     Acceptable methods of birth control are: hormonal contraceptives; double barrier method (condom with spermicide or diaphragm with spermicide); intrauterine device; surgical sterility; abstinence.
8. Understand and be willing to comply with all study-related procedures and agree to participate in the study by giving written informed consent

5.3 Exclusion Criteria

1. Weight > 158.8 kg (350 lbs, due to scanner weight restrictions)
2. Supine abdominal width (with arms folded above) > 70 cm or sagittal diameter > 50 cm (due to scanner dimension restrictions)
3. Pregnant or nursing (or plans to become pregnant in the next 5 months)
4. Evidence of psychiatric disorder that significantly interferes with daily living
5. Active suicidal ideation
6. Self-reported type 1 diabetes or type 2 diabetes
7. Use of weight loss medications or other agents known to affect body weight (e.g., oral glucocorticoids, second-generation antipsychotic medications) in the past 3 months
8. Psychiatric hospitalization within the past 6 months
9. Self-reported alcohol or substance abuse within the past 12 months, including at-risk drinking (current consumption of ≥ 14 alcoholic drinks per week)
10. Self-reported use of illicit drugs within the past 30 days
11. Presence or history of orthopedic circumstances, metallic inserts, pacemaker, claustrophobia, or other conditions that may interfere with magnetic resonance imaging
12. Loss of ≥ 10 lb of body weight within the past 3 months
13. History of (or plans for) bariatric surgery
14. Visual, auditory, or other impairment that would affect task performance
15. Epilepsy or other brain injury
16. Participation in individual psychotherapy for BED in the prior 3 months
17. Inability to attend treatment and lack of capacity to provide informed consent
18. Any serious or unstable medical or psychological condition that, in the opinion of the investigator, would compromise the patient's safety or successful participation in the study

5.4 Duration of Study Participation

The approximate duration of study participation for subjects assigned to the CBT group is 5 months. The approximate duration of study participant for those assigned to the wait-list control is 9 months (5 months on the waitlist and then 4 months of CBT treatment).

6 Procedures

6.1 Recruitment, accrual, and retention.

We will recruit participants at a single site – the Center for Weight and Eating Disorders at the University of Pennsylvania, Philadelphia, PA, USA - through local media advertisements and news shows/outlets, as well as Internet-based advertising outlets and flyers and brochures around our community. We also will advertise using clinician referrals from primary care clinics affiliated with the University of Pennsylvania Health System. We will be recruiting from the university-based website, iConnect, which allows access to their volunteer registry data of potential participants. We will use study condition terms such as "binge eat*"; "eating disorder*"; and/or obesity. Recruitment may also use Penn media services (e.g., communications) and social media (e.g., Facebook, Twitter; please see attached for information about Facebook recruitment**).** We conservatively estimate a drop-out rate of 25% based on prior experience in our labs and will enroll 40 participants to have 30 complete the study. Based on prior studies of BED in our labs,[17,46,47] we expect to screen 50 to 75 females who respond to our advertisements per month and enroll about 5 females each month. To minimize attrition we will use multiple evidence-based strategies that improve retention rates including scheduling sessions at convenient times, maintaining close contact, and providing compensation for assessment visits and travel costs.[48] Travel compensation will be given at the end of each CBT session, as applicable. Our research group has successfully completed a number of long-term intervention and fMRI trials that have lasted >4 months with attrition rates <20%.[49-51]

6.2 Screening

Phone screening. Interested subjects will call in and be consented verbally, over the phone, by study staff to participate in the initial telephone screening. Study staff from the Center for Weight and Eating Disorders will describe the study, explain that the research is completely voluntary, and conduct a brief screening of candidates who express an interest in proceeding (e.g., check for handedness, substance use history, binge eating, and MRI eligibility). We request a waiver of written documentation of consent for the telephone and questionnaire screen. Those who appear to meet eligibility criteria and remain interested in the trial will be scheduled for an in-person interview.

Screening and intake visit. Following the initial telephone screening assessment, eligible participants will attend a 3.5-hour intake visit at the Center for Weight and Eating Disorders at the University of Pennsylvania. At the screening visit, candidates will meet individually with study staff, including a study nurse practitioner or physician. We will obtain the following:

- Informed consent (general and individual consents for audiorecording)
- MRI-eligibility checklist
- Diagnostic and psychological interview to assess for BED and frequency of binge episodes (Eating Disorder Examination[52])
- Psychiatric exam using the Mini International Neuropsychiatric Interview (MINI)[53] and Columbia Suicide Severity Rating Scale[54]
- Routine medical history and physical exam including height, weight, and urine pregnancy test
- Interview for script-driven imagery of binge foods task (described below)
- Practice session of the food-specific SST to minimize the learning effects of the experiment

- Questionnaires (emailed via REDCap or printed)
  - Eating Disorder Examination Questionnaire[52]
  - Eating Inventory[55]
  - Reward-Based Eating Drive Scale[56]
  - Loss of Control Over Eating Scale[57]
  - Yale Food Addiction Scale[58]
  - Food Craving Questionnaire – Trait and State versions[59]
  - Beck Depression Inventory-II[60]
  - Barratt Impulsiveness Scale[61]
  - Clinical Impairment Assessment Questionnaire[62]
  - Short Form 36 Health Survey [63]
  - Yale-Brown Obsessive Compulsive Scale- Binge Eating[64]
  - National Institute of Nursing Research Index of Self-Regulation[65]

Throughout the study, participants will be asked to keep a menstrual cycle diary. Individuals who do not wish to participate in the research study will receive recommendations for alternative treatments for binge eating disorder if they are interested.

6.2.1 FMRI Study Assessment Visits

After participants complete the screening procedures, provide their informed consent to participate, and are enrolled into the study, they will complete two study assessment visits (one at baseline and one after the 16 week treatment).

Planning for the Assessment Visit

Study assessment visits will be scheduled for the morning and last approximately 105 minutes (60 minutes in the fMRI scanner and 45 minutes to complete questionnaires and physical measurements; Figure 1). The visit will be held at the Hospital of the University of Pennsylvania. Participants will be asked to fast (including no caffeine or alcohol) for at least 8 hours prior to the appointment to increase the stimulus salience[67] and create a more homogeneous hunger state across participants. Participants will be asked to remove all jewelry and metal objects at the visit. Participants who require vision correction will be instructed to wear contact lenses or will be provided with MRsafe glasses in their prescription strength.

Imaging Procedures

Pre-scan preparation. Visits on imaging days will begin in the morning at the Hospital of the University of Pennsylvania. Upon arriving, participants will be greeted by research staff who will re-administer the MRI-eligibility checklist to ensure no changes have occurred that would render MRI unsafe or uncomfortable. The MRI technician will review this checklist. All participants will be asked about pregnancy status. For those who are unsure, a urine pregnancy will be completed prior to the scan. Those who attest to being pregnant or test positive will be withdrawn. Participants will change into a hospital gown and be weighed, without shoes, on a calibrated electronic scale (BWB 800S, Tanita Corp., Tokyo, Japan) and will have their waist circumference and blood pressure measured. They will then complete a self-report measure of current mood (i.e., the Profile of Mood States, Brief Form[68]) and visual analog scales for stress, hunger, food

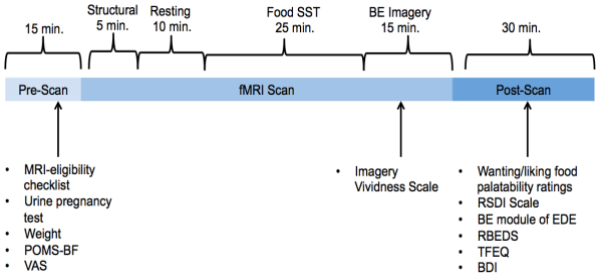

Figure 1. Summary of Assessment Visit. POMS-BF=Profile of Mood States, Brief Form; VAS=Visual analog scales for stress, hunger, food cravings, fatigue; RSDI Scale=Response to Script-Driven Imagery Scale; BE=binge eating; EDE=Eating Disorder Examination; RBEDS=Reward-Based Eating Drive Scale; TFEQ=Three Factor Eating Questionnaire; BDI=Beck Depression Inventory

cravings, and fatigue level. They also will be required to demonstrate understanding of the task and use of the response device prior to entering the scanner.

Imaging equipment. We will use a clinically approved 3.0 Tesla Siemens Prisma scanner equipped with 64-channel head coil. BOLD fMRI sequences include automatic higher order shimming and both prospective and retrospective motion correction. Gradient performance allows 4 mm isotropic voxels at TR=2 sec and 3 mm isotropic voxels at TR=3 sec (3T). The system uses a transmit/receive head coil.

The research scanner is equipped with stimulus delivery and monitoring systems for fMRI research. This includes Sanyo SXGA 4200 lumens projectors with Sanyo Long Throw zoom lens for rear-view/rear projection onto Mylar screens. Video signals are carried into the magnet room using a Lightwave FiberLynx optical-fiber VGA connection. Both the projector and the FiberLynx units are housed in custom RF shield boxes with filtered power receptacles. Images are viewed through mirrors mounted on the head coils.

Audio stimuli will be presented via air-conduction headphones and an Avotec audio system which is equipped with two different styles of head phones to accommodate variance in patient head size. Responses will be monitored using a color-coded keypad made of non-ferromagnetic components (FORP Current Design Inc., Philadelphia, PA) installed at the 3T system.

The MRI scan procedures have been designed to last 55 minutes. To ensure completion of all scans, each procedure will be timed and every effort will be made to keep as close to the designated schedule as possible. In respect of time and data quality, if necessary, scans will be skipped or re-run at the discretion of the research team.

Protocol for structural MRI (5 minutes). A magnetization-prepared, rapid acquisition gradient echo (MPRAGE) image will be acquired for anatomic overlays of functional data and spatial normalization using the following parameters: TI/TR/TE=1100/1810/3.51ms, flip=9°, matrix=256x192, FOV=240x180mm, slices=160, slice thickness=1mm.

Protocol for BOLD fMRI (~10 minutes). Resting and Task fMRI data will be acquired using a whole-brain, single-shot, multi-slice, gradient-echo EPI sequence with the following parameters: TR/TE = 3000/32 ms, flip = 90°, FOV = 192 × 192 mm, matrix = 64 × 64, 46 slices, slice thickness/gap = 3 mm/0 mm. The resulting nominal voxel size was 3.0 × 3.0 × 3.0 mm. EPI acquisitions include a 20 second dummy-scan period allowing the magnetic resonance signal to reach steady-state.

FMRI Tasks. We will use two tasks to assess the impact of CBT on neural activity to food-cue tasks. Our tasks have been selected to target relevant cognitive and neural models of BED. The timing of the stimulus presentation will be synchronized with trigger pulses from the magnet in order to ensure precise temporal integration of stimulus presentation and fMRI data acquisition. These tasks will presented in a fixed order with the food-specific SST occurring first and the binge-eating script-driven imagery second.

BOLD fMRI Task (Food-Specific SST; ~25 Minutes). The SST is a measure of response inhibition, or the ability to inhibit a prepotent response. In this task, we will use an event-related design. Participants will be asked to perform the SST using a modified version with high and low calorie food images as we have used in a current ongoing trial. Neutral items will include office

supplies. This task will be run twice including: Run 1) 2 blocks with each block consisting of high-calorie foods vs neutral items, and Run 2) 2 blocks with each block consisting of low-calorie foods vs neutral items. Participants will use the response pad and be randomized to either indicate the left most button for the food pictures and the right most button on the response pad for neutral items or vice versa. Within subjects assignment will remain the same at pre and post scans. Participants are instructed to press keys as quickly and as accurately as possible to indicate the direction of the food or the office supplies. Following a 32-trial practice, stop signals (change in the color of the frame around the image) are presented on 25% of trials for a 32-trial practice and task blocks of 64 trials each. The initial stop delay in each block is 250 ms and adjusts by 50 ms increments depending on whether the participant is able to successfully inhibit a response.[69] The adjusting stop delay allows the determination of the delay at which inhibition occurs on approximately 50% of trials. All trials consist of a 500-ms warning stimulus followed by a 1,000-ms go signal (left- and right-facing arrows) and 1,000-ms blank screen intertrial interval. Pictures have been matched for complexity, brightness, and color composition. Stimuli are digital photographs of food items depicted in the ready-to-eat state on identical backgrounds that are validated and are available in publically available databases.[70,71] Each high-calorie block will contain at least one image from each of the following categories: salty snacks; sweet snacks; fast foods; and desserts. Each low-calorie block will contain at least one image from each of the following categories: non-starchy vegetables; fruit; leafy vegetables; and starchy vegetables.

BOLD fMRI Task (Binge-Eating Script-Drive Imagery; ~15 minutes). During the intake visit we will collect information for the binge eating script-driven imagery task using methods previously established.[72,73] We will use both binge eating and neutral scripts that are customized for each participant. Binge scripts will be based on the participants' descriptions of two binge episodes that have occurred in the past year. Participants will be instructed to describe the episode in detail. Neutral-relaxing scripts will be developed by asking the participant to describe a neutral-relaxing situation that they have experienced. We will ask the participant to describe two binge situations and two neutral-relaxing situations. Scripts will be developed using a Scene Construction Questionnaire, which includes specific stimulus and response details.[74,75] A female research coordinator will then record the script on an audiotape. Each script will be 2.5 minutes in length when read aloud. Each individual will receive training on how to generate and maintain a mental image for 30 seconds during the intake visit and will be reminded of these techniques on assessment days.[73]

During the task, participants will be instructed to lie quietly with eyes closed. Each script will be presented in randomized, counter-balanced order with four trials presented using a block design (two trials each of binge eating and two trials of neutral control). Each trial will include a 1-min quiet baseline period followed by a 2.5-minute imagery period where the participant will be instructed to remember the experience as vividly as possible, in all of its details, both while the 2.5-minute recording plays (script listening) and for an additional 30 seconds after where they continue imaging the story while lying in silence (scene imagery). Next, there will be a 1-minute quiet recovery period. A beep will be played 15 seconds into the recovery period. Participants will be required to push a button on the response pad when they hear the beep to confirm accurate performance and compliance with task instructions. Participants will remain blind to the order until presentation during imaging. Personal scripts will be used as personal events trigger greater physiological reactivity than imagery of standardized nonpersonal situations.[76] The same recordings will be used during pre- and post-treatment scans.

Task Assessments, Questionnaires, and Interview. After the fMRI is completed, participants will complete questionnaires to assess response to the fMRI tasks and manipulations and

treatment outcomes. To assess the response to the tasks using the food images, participants will be asked about their liking and wanting and palatability of the presented foods on an 11-point Likert scale. To assess the response to the symptom provocation task, participants will complete the Responses to Script-Driven Imagery Scale.[77] Participants will also be asked to indicate the date of their last menstrual period at each visit to assess the current phase of their menstrual cycle as this impacts food reward response.[78] Participants will complete physical measurements and additional questions, if they have not been completed before their screening visit.

6.2.2 Post-Treatment Visit (Waitlist Group Only)

After individuals in the WL group complete their second fMRI assessment, they will be offered CBT treatment. For Specific Aim 3, the WL group will be asked to complete a brief assessment after their last CBT session to measure treatment response (i.e., the number of BE episodes in the past 28 days).

6.2.3 Allocation to Interventional Group

Subjects who meet eligibility criteria and complete their baseline assessment visit will be randomly assigned to the intervention or waitlist condition. We will use a permuted randomized block design that randomly mixes blocks of different sizes (2 to 6) to assign 40 eligible participants to CBT or waitlist conditions using a one-to-one allocation ratio. This randomization design was selected due to the need to create exactly the same group sizes with a small sample.[79] A statistician will conduct the randomization using a computer-generated algorithm.[80]

7 Study Interventions

CBT Intervention. The CBT intervention (Table 1) will consist of weekly, 50-minute individual meetings for 16 weeks with a clinician trained in CBT for binge eating disorder. The treatment will be administered using a manualized treatment protocol adapted from Fairburn[81] and Mitchell.[82] The overall goals of CBT for BED are to interrupt binge-eating behavior, learn self-management strategies to help reinstitute more normal eating habits, change erroneous beliefs about weight and shape and develop healthier attitudes towards one's body. Participants are taught a variety of skills including identifying triggers of binge eating episodes, correcting beliefs or thought patterns related to binge eating, and altering attitudes regarding food and eating. Homework is assigned at each session so participants can practice the skills that they have learned. To monitor treatment integrity and adherence, treatment sessions will be reviewed under the supervision of Drs. Wadden or Chao. This treatment has been tested in a number of trials for BED[43] and we anticipate seeing 50% of individuals with full remission from binge eating and a 68-90% reduction in the number of binge eating episodes.[83]

Table 1. CBT for BED Intervention

Stage	Aim	Weeks
1: Introduction	Jointly creating a formulation of the processes maintaining the eating disorder Establish real-time monitoring of eating and other relevant thoughts and behavior Provide education about body weight regulation and fluctuations, the physical complications and the adverse effects of dieting Introduce weekly weighing Introduce a pattern of regular eating	1-4
2: Transition	Jointly reviewing progress Identify barriers to change Modify the formulation as needed	5-6

	Plan Stage Three	
3: Main body of treatment	Address key mechanisms that are maintaining BED Overevaluation of shape and weight - Provide education about overevaluation and its consequences - Reduce unhelpful body checking and avoidance - Relabel unhelpful thoughts or feelings such as “feeling fat” - Develop previously marginalized domains of self-evaluation - Explore the origins of the overevaluation Dietary restraint - Change inflexible dietary rules into flexible guidelines - Introduce previously avoided food Event triggered changes in eating - Develop problem-solving skills to directly tackle such events - Develop skills to accept and modulate intense moods	7-14
4: Final stage	Provide education about realistic expectations Devise a short-term plan for the months following treatment Devise a long-term plan to minimize relapse in the future	15-16

Waitlist Control Group. Participants who are assigned to the wait-list group will complete their assessment visits at baseline and 16 weeks. We will request that they not seek treatment for weight or binge eating disorder during the wait period. This will be verified at a brief telephone call check-in at week 8 where we will also update the patient on their study status, as well as at the week 16 visit. After they complete their post-treatment assessment, they will be offered the 16-week cognitive behavioral therapy treatment. At their last treatment session, they will be asked to complete a brief assessment on the effect of the CBT treatment.

7.1 Vulnerable Populations:

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study. Although not directly targeted, mentally disabled persons, economically or educationally disadvantaged persons, and/or employees or students of the University of Pennsylvania will not be denied enrollment and any special protections and/or additional safeguards will be undertaken in order to protect the rights and welfare of these subjects from coercion or undue influence as appropriate.

Table 2. Study Assessment Schedule

					Waitlist Group Only	
	Screen	T1	Intervention or Waitlist (16 weeks)	T2	Intervention (16 weeks)	T3
Informed Consent- General	X					
Informed Consent- Audiorecording BED Assessment	X			X		X
Informed Consent- Audiorecording treatment sessions	X		X		X	
Demographic and Clinical Variables						
Review inclusion/exclusion criteria	X					
Demographics	X					
Medical history and physical exam	X					
Prior/concomitant medications	X			X		X
Review medication changes and updates				X		X
Vital signs (BP, HR)	X					
Pregnancy test	X					
MINI	X					
Menstrual diary	X	X	X	X		
BMI	X	X	X	X		X
Profile of Mood States (Brief Form)		X		X		
Scales for stress, hunger, food cravings, fatigue		X		X		
Responses to Script-Driven Imagery Scale		X		X		
Outcome Measures						
fMRI scan (SST, Script-driven imagery)		X		X		
Eating Disorder Examination	X			X		X
Reward-Based Eating Drive Scale		X		X		
Three Factor Eating Questionnaire		X		X		
Additional Questionnaires (described in Section 6.2)		X		X		X
Intervention adherence/fidelity						
Sessions attended, skill builders completed			X			
Adverse event/unanticipated problems assessment		X	X	X		X

Note. T1=Baseline; T2=16 week follow-up. T3=Assessment of post-CBT treatment outcomes for the waitlist group only. SST=Stop signal task.

7.2 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to intervention or study procedures or visit schedules, AEs, or due to subject pregnancy or intention of becoming pregnant. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study.

Lost to follow-up: In the case of subjects who do not return to the Center for study procedures and cannot be contacted, study personnel will make vigorous and repeated attempts (minimum of 3) to contact the subject. These attempts will include at least 1 mailing. If all attempts to contact the subject fail, that subject will be considered to be lost to follow-up and discontinued from the study.

Subject Replacement
Subjects who prematurely discontinue from the study or become ineligible will not be replaced once they have been randomized. Every effort will be made to obtain follow-up data on all participants randomized.

8 Statistical Plan

8.1 Sample Size and Power Determination

The power calculation is based on current standards in exploratory neuroimaging studies. Previous fMRI studies that used groups of 15 subjects per condition were sufficient to detect significant differences in BOLD signal response to behavioral tasks.[84,85] Due to resource limitations, our sample size will be limited. The sample size will allow us to detect effect sizes of 0.93 or larger in BOLD signal between groups with 80% power controlling for type 1 errors at 5% using a one-sided test.

8.2 Statistical Methods

8.2.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables such as age and standard percentages for categorical variables such as gender).

8.2.2 Efficacy Analysis

Baseline to 16-week changes self-report and behavioral variables will be examined using mixed-effect general linear models, fit with the between-subject factor of treatment group and the within-subject factor of time. Differences between groups in percent of participants classified as responders will be analyzed using a chi-square test. Statistical significance will be defined as $p<0.05$ in analyses.

The primary analysis will only include responses to high calorie food, since the CBT intervention is designed to improve inhibition to “bad” (i.e., high-calorie) foods. Response-inhibition-related BOLD activity will be tested using similar analytic strategies as previous trials.[86-88] Analysis of data indicating changes in each ROI will be conducted using a mixed-effects general linear model with time (baseline vs 16 weeks) and trial type (stop vs go) as within-subject factors and group (CBT vs WL) as a between-subjects factor.[89] *Percent reduction in binge eating episodes will be included as a statistical covariate*. Since no significant differences have been found between successful vs unsuccessful stops, we will not distinguish these *a priori*. [90] Exploratory contrasts will be conducted using the same analysis procedures to examine specificity to energy density (contrast with high- and low-calorie foods) and general inhibitory behavior (high-calorie food vs neutral and low-calorie food vs neutral). We will also examine differences among the CBT and WL groups in brain-behavior correlations using correlations between BOLD activation in the ROIs with the behavioral measure (SSRT).

The primary analysis for aim 2 will be the script-listening time-block. We will use a similar approach as above to examine data from recall of binge eating episodes. In the mixed-effects general linear model, analysis of data indicating changes in each ROI will be conducted using time (baseline vs 16 weeks) and trial type (binge food vs neutral) as within-subject factors and

group (CBT vs WL) as a between-subjects factor. Percent reduction in binge eating episodes will be included as a statistical covariate.

8.3 Subject Population(s) for Analysis

We will use an intention-to-treat approach of all randomized participants for all primary analyses. Additional analyses will be conducted with protocol-compliant participants.

9 Safety and Adverse Events

9.1.1 Definitions

9.1.1.1 Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

9.1.1.2 Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

10 Recording of Adverse Events

At each contact with subjects, study personnel will be responsive to reports of adverse events with specific questioning, and, as appropriate, by examination. The investigator will report all adverse events including serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSARs) (as defined below) to the Penn IRB. Information on all adverse events will be recorded immediately in the source document and reported immediately, and also in the appropriate adverse event module of the case report form (CRF). Information on study name, subject identification, event (i.e., diagnosis), and reporter identification (e.g., name) will be collected and recorded in the source document (as detailed below). All serious adverse events will be reported to the IRB within 24 hours.

All events meeting the definition of an adverse event will be collected and reported from the first trial related activity after the subject has signed the informed consent and until the end of the post-

treatment follow-up period. Serious adverse events that are still ongoing at the end of the study period will be followed up until either resolved or stable. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

11 Relationship of AE to Study

• Probable: Good reasons and sufficient documentation to assume a causal relationship
• Possible: A causal relationship is conceivable and cannot be dismissed
• Unlikely: The event is most likely related to an etiology other than the trial product
The PI will evaluate all unexpected events and adverse reactions.

12 Outcome Categories and Definitions:

• Recovered: Fully recovered or by medical or surgical treatment the condition has returned to the level observed at the first trial related activity after the subject signed the informed consent
• Recovering: The condition is improving and the subject is expected to recover from the event. This term should only be used when the subject has completed the trial
• Recovered with sequelae: As a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralysed). Any AE recovered with sequelae should be rated as an SAE
• Not recovered
• Fatal
• Unknown

13 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

All events meeting the definition of an adverse event will be collected and reported from the first trial related activity after the subject has signed the informed consent and until the end of the post-treatment follow-up period as stated in the protocol.
At a minimum the following information will be reported:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study intervention was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

Additionally all other events (unanticipated problems, adverse reactions, unanticipated adverse device effects and subject complaints will be recorded and reported with respect to institutional and federal policies as described in the Penn Manual.

14 Medical Monitoring

The Principal Investigator will oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. Medical monitoring will be performed by the Principal Investigator and study healthcare providers.

15 Study Administration, Data Handling and Record Keeping

15.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

All electronic PHI will be maintained by using an institutionally secured and managed network drive, institutionally secured and managed devices, and institutionally approved third-party computing environments. Should PHI need to be transferred, it will be done so through the use of a Penn-approved encrypted portable drive or a Penn-approved secure encrypted file transfer solution.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects who have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Where possible, data will be entered directly into our password protected database, REDCap. All data pertaining to the study will be saved on the Center for Weight and Eating Disorders' password-protected server. Paper copies of informed consent, questionnaires, interviews, lab results, and any correspondence will be kept in the case record in locked offices.

The consent form will clearly state that the research involves use of audiorecording and participants will be fully informed about the purposes, procedures, storage, security, confidentiality, and use of the recordings. Audio recording will be used to evaluate CBT intervention fidelity. They will not be transcribed. Individuals will be informed that participation in the study is not contingent upon agreeing to be recorded during CBT sessions. All participant recordings will be kept in a locked filing cabinet and password-protected computer. Participants can request that the recordings be paused or stopped at any time, and they will be informed that they have the right to refuse audiorecording at any time. Records will be maintained, retained, and destroyed per applicable Federal and local regulations. The recordings will not be used publically. Research staff will have access to recordings.

16 Privacy

Steps will be taken to protect subject privacy. Informed consent and study procedures will be conducted in a private room, and the collection of sensitive information will be limited to the minimum necessary to achieve the aims of the project.

17 Study Monitoring, Auditing, and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

18 Ethical Considerations

The principal investigator (PI) will initiate and enroll subjects only after receiving IRB approval of the protocol and the informed consent documents. All recruiting materials used in the study will have IRB approval. Progress reports regarding the study will be submitted to the IRB in accordance with institutional and regulatory guidelines.

The study will be performed in compliance with the FDA Code of Federal Regulations for Good Clinical Practice (GCP). These procedures ensure the protection of the rights and the integrity of the subjects, adequate and correct conduct of all study procedures, adequate data collection, adequate documentation, and adequate data verification.

Before being enrolled, subjects will be provided informed consent. The nature, scope, and possible consequences of the study will have been explained in a form understandable to them. A copy of the consent document will be given to the subject. The PI will retain the original signed consent document.

Subject confidentiality will be maintained throughout the study according to applicable guidelines, regulations and IRB requirements. All laboratory samples, study clinical data, and reports of results will de-identify individual subjects. Subjects will be identified by initials, date of birth, gender and subject number only for use in data collection. Published data will provide subject numbers only if needed for clarity of presentation (e.g., in individual event listings).

The study will be conducted in accordance with the Declaration of Helsinki. The study will be conducted in accordance with the ICH GCP guidelines. The investigators will comply with all applicable regulatory and legal requirements, ICH GCP guidelines, and the Declaration of Helsinki in obtaining and documenting the informed consent.

19 Risks

The risks to participants in this trial have been carefully considered and minimized to the extent possible. The known risk of receiving CBT and completing the study assessments are minimal. Every effort has been made to provide a study in which the safety of research participants is protected.

Potential Study Risks

Risks of Assessments, CBT Treatment, and Waitlist

Occasionally a person suffering from BED may find answering questions about their illness distressing. Some of the questions in the interview that assess history of psychological conditions may be of a personal nature. Additionally, some of the topics discussed and audio recorded during cognitive behavioral therapy will be sensitive and may induce emotional responses or discomfort for some participants. All such questions will be asked by trained clinicians and a licensed clinical psychologist will be available at all times to consult with the participant should this occur. Appropriate referrals will be given as necessary.

Participants in the waitlist group will be contacted at week 8 via phone by a research assistant to keep participants engaged and enhance study retention. All waitlist participants will be provided with the 16-week CBT intervention after they complete the end-of-study testing at

week 16. Though we considered other designs, a waitlist control comparison was selected as it was deemed ethical, while also permitting a non-intervention comparison and maximizing power to detect differences between groups. Patients seeking treatment for BED in the community are often on waitlists for more than 4 months due to the lack of skilled clinicians available. For the majority of participants, the waitlist will still be shorter than routine services. Attrition is no worse with waitlist control groups than with active BED treatment. [91 88 87 86]

Risks of MRI

Flying objects: The known risks associated with this study are minimal. Implanted medical devices and metallic foreign fragments inside a participant's body may pose a risk if the participant were to enter the MRI magnet room. The greatest risk is a magnetic object flying through the air toward the magnet and hitting someone. To reduce this risk, we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. No metal objects are allowed to be brought into the magnet room at any time. In addition, once participants are in the magnet, the door to the room will be closed so that no one inadvertently walks into the magnet room.

Magnetic fields health risks: There is no known health risk associated with exposure to magnetic fields during an MRI.

Discomfort. Some people become uncomfortable or claustrophobic (fearing the enclosed space) while inside the scanner. Fatigue, anxiety and discomfort are potential adverse effects associated with the fMRI study. There are minimal risks from the loud noise associated with the MRI scanner and from the discomfort of lying on a hard surface. We will attempt to minimize these risks by familiarizing participants with the personnel and setting, and by closely monitoring them during the study. In our experience, participants who are well informed of the purpose of the study and who are accompanied throughout the procedures by a responsible member of the research team tolerate the testing well and without complications. Tests are administered by trained and supervised personnel and participants are debriefed after each session. Exposure to radiation with magnetic resonance measurements is far less than that resulting from a single X-ray. Thousands of patients have been safely studied at the Hospital of the University of Pennsylvania using magnetic resonance techniques. However, some individuals become uncomfortable or claustrophobic while inside the magnet. Participants who are uncertain whether they can tolerate the scanning environment can complete a "mock" scan on similar equipment prior to the research scans. If participants become uncomfortable during completion of study procedures, they may withdraw immediately from the study.

Incidental findings: This MRI is not a clinical scan. It is possible that during the course of the research study, the research staff may notice an unexpected finding(s). In the event of abnormal findings, the participant will be contacted and Center Staff will arrange for the radioloigst's report and structural images to be sent to participants and/or their physician. These possible finding(s) may or may not be significant and may lead to anxiety about a person's condition and to further work-up by a physician.

Pregnancy: Although there are no known risks related to MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is no possible benefit from participating in this protocol for a pregnant woman, we will exclude pregnant women. At fMRI scans, participants will be asked to attest to pregnancy status. Participants who are unsure or who believe that they may be pregnant will be given a urine pregnancy test.

Computer tasks. There are no known risks associated with the computer tasks the participant will be asked to perform during the study. Participants could become tired when performing them.

During MRI scans, participants have occasionally reported tingling or twitching sensations in their arms or legs. Further, because of the strong magnetic field, participants with pacemakers, certain metallic implants, or metal in the eye cannot participate in this study. These exclusions will be reviewed carefully with the research technician prior to scanning. Although there are no known risks of MRI on pregnant women or the fetus, there is a possibility of yet undiscovered pregnancy related risks.

Loss of Confidentiality Risk
Because information about participant's identity and voice recordings will be collected and stored for research purposes, there is a chance that the information could be viewed or heard by others not associated with the research team and therefore, there is a potential for loss of confidentiality. Participants will only be audio recorded with their express permission, though there is a risk of loss of privacy or breach of confidentiality that may occur from disclosure of private information while being recorded. The study team will work to uphold the privacy of the participants in several ways. Communications made among study staff regarding participants will use ID numbers only and never include names or other personal information. All participant data and recordings will be kept in locked files. In all data sets, we will use ID numbers only. A separate dataset linking names with ID numbers will be accessible only by the primary study investigators.

If unforeseen risks are seen, they will be reported to the Office of Research Integrity and Compliance.

20 Benefits

All participants who enroll in this study will receive individual CBT for BED. Participants should have reductions in the number of binge eating episodes they experience. They may also experience an improvement in their mood and a reduction in eating disorder psychopathology. However, it is possible that they may not receive any benefits from participating in this study (i.e., they may not experience improvements in their symptoms of BED). Study participants may also gain satisfaction from the knowledge that they are contributing to a better understanding of brain function and the etiology of BED, which may lead to improved prevention and treatment options.

21 Risk Benefit Assessment

The benefits of this research to the subjects studied, and to society at large, far surpass the risks. We believe that this study poses minimal risk to participants, while providing potential benefit to women who are overweight with BED. The treatments and procedures, including fMRI, used in this study have been shown to be relatively safe. Numerous clinical trials have demonstrated the safety of fMRI scans and efficacy of CBT for BED. Research staff will monitor subjects closely during their participation. We anticipate that after CBT treatment participants will show reductions in their symptoms of binge eating disorder. Results of this study hold promise of significantly improving the management of BED and its associated complications.

22 Informed Consent Process / HIPAA Authorization

Following the screening telephone call, trained clinical assessors will meet in person with all potential participants to describe the study, its requirements, and its likely risks and benefits. Participants will be provided a written copy of the Consent Form/HIPAA Authorization at this meeting and will be given an opportunity to read it and have all of their questions answered. Persons who wish to participate in the study will be asked to give their written consent at the time

of consent discussion and will then continue with the screening visit. Participants will also be permitted to discuss the consent form and procedures and return the signed form and continue with the screening at a later date (within 2 months), if they prefer. Participants will be told that they can contact the Principal Investigator at any time if they have questions about the study. The study team member who reviews the consent document will emphasize that participation in the study is voluntary and that medical care will not be influenced by the participants decision to participate or not. The consent process will take place in a private office or exam room to help protect subject privacy. Subject comprehension of the nature of the study will be assessed using interactive conservation methods (e.g., asking the potential subject to paraphrase different points of discussion, asking open-ended questions, encouraging questions).

Audiorecordings. Study staff will ask participants if they are willing to have their eating disorder examination interview audiorecorded. This will be done at the time of recording and is optional, however it will be helpful to assess interrater reliability. Participants will also be asked if they are willing to have their CBT sessions recorded before each session. Recordings will be used to assess treatment fidelity, but are not mandatory to participate in the study.

22.1.1.1 Waiver of Written Documentation of Consent

We are requesting a waiver of the requirement to obtain a signed consent form for the phone screening. The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern.

23 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

24 Subject Stipends or Payments

Participants will be compensated $100 for each of the MRI scans completed, for a total of $200. Participants will also receive $5 at each of the 16 CBT treatment sessions (total of $80 during the study) to help cover travel costs. “Greenphire ClinCard” will be used as a payment option.

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