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To: Chair, IRB, NICHD

Recommended by: _____, Clinical Director, NICHD
_____, Clinical Director, NIDDK
_____, Clinical Director, NIMH
_____, Clinical Director, Clinical Center

Study Title: Pilot Study of Mobile Attention Training in Overweight Female Adolescents

Abbreviated Title: Mobile Attention Training

Investigators: Please see "Attention Retraining Study Personnel List"

Identifying Words: obesity, binge, loss of control eating, adolescents

Study type (check all that apply):

___X___Archived biological specimens/medical information
_____Natural history; definition of phenotype, genotype/phenotype correlation
_____Prospective linkage/gene identification, NOT providing information to participants
_____Prospective linkage/gene identification, providing information provided to participants
___X____Social science; assessments of knowledge, attitudes and behavior
_____Genetic counseling
_____Drugs or devices
_____Gene transfer
___X____Other interventions

Estimated Duration of Study: 2 years

Subjects of Study:

Description	Number	Sex	Age
Overweight youth <u>with</u> loss of control over eating	40	Female	12-17 y/o at baseline
Overweight youth <u>without</u> loss of control over eating	40	Female	12-17 y/o at baseline
Screened but not randomized	40	Female	12-17 y/o when screened

Project Uses Ionizing Radiation: ☐ No ☒ Yes

☐ Medically-indicated only
☒ Research-related only (*attach RSC/RDRC documentation)*
☐ Both (*attach RSC/RDRC documentation)*

Durable Power of Attorney ☒ No ☐ Yes

Multi-institutional Project ☒ No ☐ Yes

Data and Safety Monitoring Board ☒ No ☐ Yes

Technology Transfer Agreement ☐ No ☒ Yes

Agreement type and number ___MOUs for Research Collaborators at USUHS_____ Expiration Date___August 2017_____

Samples are being stored ☐ No ☒ Yes

Flesch-Kincaid reading level of consent form:
Assent Form (youth): 68 (7^{th} – 8^{th} grade)
Consent Form (parent/guardian): 60 (9^{th} grade)

Research participants to be seen at:

_____x___NIH only*
_____Off-site only
_____Both NIH* and off-site

**Includes participants who physically come to the NIH Clinical Center and/or for whom specimens/data are analyzed by Clinical Center departments. If participants will be seen at NIH, a Medical Advisory Investigator must be indicated on the 1195 form, unless this is a social science project with no clinical interventions.*

Collaborative Project:

• FWA for each Institution:___X_not applicable_____
see http://ohrp.cit.nih.gov/search/asearch.asp#ASUR for assurance #s

Version Date: July 14, 2022

Précis:

Over 30% of adolescents are overweight and 20% are obese, but the mechanisms that produce excessive weight gain in youth remain incompletely elucidated. Some overweight youth appear to have an attention bias (AB: a tendency to attend selectively to stimuli that have acquired salience or meaning) toward highly palatable food that may lead to overeating. AB involves distinct cognitive processes, (1) unconscious reactions (UCR), reflecting initial attention capture evoked by salient stimuli, and (2) continued attention deployment (AD) to stimuli relevant to current goals. These rapidly evolving processes are associated with unique neurocircuitry best measured using high spatial resolution and temporal sensitivity. Magnetoencephalography (MEG) is a novel neuroimaging technology that has *both* excellent temporal and good spatial resolution, thus is uniquely and ideally suited to study neurocognitive mechanisms of AB. Reducing AB to palatable foods may help some overweight youth curb their consumption of energy-dense options. Attention retraining (AR) programs can be used to reduce AB and have been effective in reducing AB to unhealthy food in adults. Although most AR studies involve computers in the laboratory, using smartphones in the natural environment may be a particularly effective method to deliver AR to adolescents and measure AB using ecological momentary assessment. The first aim of the proposed study is to examine the impact the a 2-week smartphone AR program on AB in overweight adolescent (12-17 y/o) girls with and without loss of control (LOC) eating, defined as a subjective experience of a lack of control over what or how much one is eating. LOC is a distinct eating behavior phenotype in youth that is a risk factor for excess weight gain and disordered eating, and is much more prevalent among girls (vs. boys). Overweight youth who report LOC may be particularly susceptible to AB. Additionally, adults with LOC demonstrate AB toward socially threatening cues, such as angry or disapproving faces, and the AB to social threat may be relevant to the relationship between AB to food and overweight. The second aim is to examine, using MEG, the effect of a 2-week smartphone AR program on neural responses to food cues. The third aim is to examine the effect of the AR program on food intake and body composition. An exploratory aim is to examine whether AB to socially threatening cues, moderates the effects of this novel intervention on AB to food cues, food intake, and body composition. The proposed study is innovative because no study to date has examined the impact of AR delivered in the natural environment on AB and its associated neurocircuitry using MEG in a group of youth prone to AB. These studies may help further characterize phenomenology of distinct obesity subtypes and may potentially identify an approach that could prevent undue weight gain in adolescent girls at risk for obesity.

II. Outline/Table of Contents: **Page**

III. Introduction:

List of Abbreviations:

BMI:	Body Mass Index
LOC:	Loss of control
MEG:	Magnetoencephalography
AB:	Attention bias
AR:	Attention retraining
EMA:	Ecological momentary assessment

Obesity and Adolescence

More than one-third of youth between ages 2 and 19 are overweight, defined as BMI (kg/m^2) ≥ 85^{th} percentile for age and sex, and 17% are obese, defined as BMI ≥ 95^{th} percentile for age and sex (1, 2). These numbers are alarming because excess weight places adolescents at high risk for impaired metabolic function (3), type 2 diabetes (4), and adult obesity (5-7). Adolescent obesity is also associated with psychological problems. Overweight and obese adolescents experience greater emotional, social, and behavioral problems compared to their non-overweight peers (8-10). There are positive associations between adolescent obesity and depression, anxiety, eating disorders, low self-esteem, and poor weight-related quality of life (10-12).

A time of considerable biological, social, and cognitive change (13, 14), adolescence is a critical developmental stage for establishing behavior patterns. Unlike the eating behaviors of younger children that are largely under parental influence, adolescents typically exercise greater independence with regard to their food choices and eating habits (15). Adolescence is also a period when many disordered eating patterns manifest, particularly among girls (16). Understanding the mechanisms underlying eating behaviors and designing more effective interventions to decrease excessive food intake and reduce excess weight among adolescents are thus of paramount importance. The proposed study, of a novel and age-appropriate intervention, develops a targeted approach that may hold promise for wide dissemination. Targeted therapeutic approaches for subgroups with specific phenotypes have been recommended (17), and have the potential for greater effects.

Attention Bias and its Neurocircuitry

Attention bias (AB) refers to the tendency to attend selectively to stimuli that have acquired salience or meaning (18). ABs have been theorized to predispose individuals to psychopathology (19, 20), causing and/or maintaining anxiety (21), overeating (22, 23), and disordered eating attitudes (24). Incentive sensitization models (25, 26), based primarily on animal studies, propose that palatable food cues capture attention more readily and trigger food cravings when they carry a heightened incentive value. AB is hypothesized to lead to a pathological motivation for food and stimulate compulsive, out-of-control eating behavior in individuals who are biologically prone towards obesity (25, 26). Research generally finds a positive relationship between AB for palatable foods and overweight in adults (27-30). However, data in children are less clear (31, 32).

Imaging studies of AB map neural correlates of two component processes: 1) unconscious reactions (UCRs) reflecting initial attention capture evoked by emotionally salient stimuli, and 2) attention deployment (AD) to stimuli relevant to current goals (33, 34). The UCR involves rapidly deployed sub-cortical circuitry encompassing medial temporal and striatal circuitry (25, 26, 33, 34), depending on whether salient stimuli are attributed a negative or positive emotional valence. The AD involves brain regions that support task-related goal attainment, including the anterior cingulate cortex (ACC), orbital frontal cortex (OFC), and ventrolateral prefrontal cortex (vlPFC) (34). The neural processes involved in UCR and AD evolve in sequence and over short time scales (1-2 seconds), and are optimally captured by temporally sensitive methods (35).

LOC Eating and Overweight

LOC eating is defined as a subjective experience of a lack of control over what or how much one is eating, regardless of the amount reportedly consumed (36). LOC eating is endorsed by approximately 30% of overweight adolescents (37, 38) and is a salient risk factor for excess weight gain (39, 40), metabolic complications (41) and partial or full-syndrome binge eating disorder (42, 43). LOC eating is a distinct eating behavior phenotype in youth. Compared to their peers without LOC, youth who report LOC are at twice the risk for overweight or obesity (39) and prospectively gain over 5 lbs. more per year (beyond healthy growth) (40). Although LOC eating has been reported with similar prevalence among Non-Hispanic White and minority groups including Non-Hispanic Black and Hispanic youth (44, 45) some laboratory data demonstrate that non-Hispanic Black adolescent girls consume more during a laboratory meal compared to their non-Black counterparts (45). Thus, given that the childhood obesity rates have increased dramatically among Black youth (1, 46), it is important to consider the effects of race on LOC eating.

LOC Eating and Attention Bias

Notably, youth with LOC eating appear to have a bias toward highly palatable foods that may lead them to engage in LOC eating episodes. Our data (15, 47) and those of others (48) have demonstrated via self-report (15) and in the laboratory (49, 50), that youth with LOC eating select and consume more highly-palatable snack and dessert foods than youth without LOC. Similar to binge eating in adults (51, 52), the LOC phenotype involves overconsumption of palatable foods. Recent studies indicate that youth who binge eat demonstrate increased AB to food cues in laboratory tasks (53). Our data suggest that among youth with LOC eating, BMIz is positively associated with AB to highly palatable foods (Figure 1a), while the reverse is observed among youth without LOC (Figure 1b) (54).

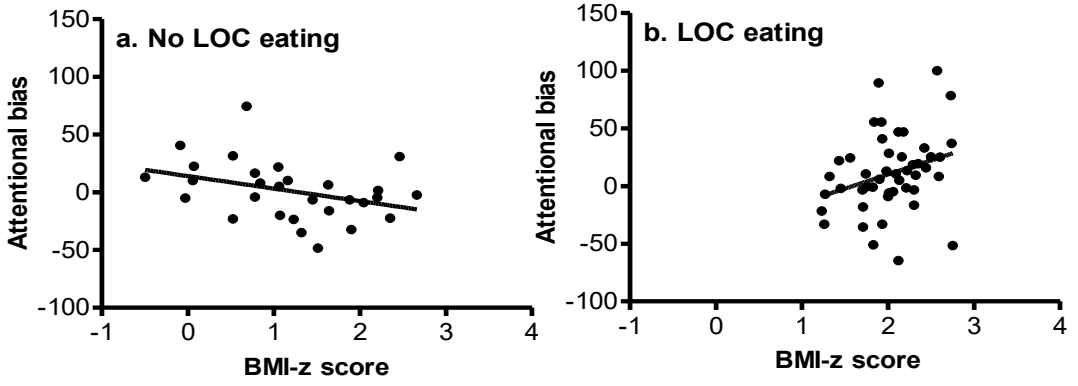

Fig 1a. Youth with LOC eating have a positive association between AB and BMI-z, p<.05. Fig 1b. No LOC eating youth have a non-significant negative association between AB to high palatable foods and BMI-z; Interaction p=.01, N=77.

In adolescents, LOC severity is associated with cravings for palatable foods (55, 56), a self-reported index of food cue AB. Youth with LOC eating report frequent eating in response to external food cues (16, 57-59), which is linked to food AB (60). The current obesogenic environment likely further strengthens AB to highly palatable foods and may lead to an irresistible, compulsive desire to eat that overwhelms self-regulatory capacity in youth with LOC. Thus, AB to palatable foods may provide an important mechanism by which LOC eating promotes excess weight gain.

Youth with LOC eating may also be susceptible to attending selectively to socially threatening stimuli in the environment. ABs to threatening stimuli have been shown to contribute to the development and maintenance of anxiety disorders (61). There is also evidence that adults who engage in binge eating behaviors demonstrate greater AB toward socially threatening stimuli (such as angry faces) compared to healthy control participants (62, 63). This may be explained by interpersonal models of eating dysregulation that posit that social stressors, particularly interpersonal evaluation and conflict, precipitate LOC eating (64, 65). Thus, attentional bias toward socially threatening cues (e.g., disapproving facial expressions) might contribute to LOC eating via the interpersonal model (34). Youth with LOC eating report greater anxiety and social stress than youth without LOC eating (58, 66), and there is emerging evidence from neuroimaging studies that girls with LOC demonstrate heightened sensitivity toward social cues (67). Thus, it appears that heightened attention to threatening cues may moderate the relationship between food cue exposure and overconsumption, but the neurocognitive processes related to the potential ABs to social threat have not been examined in relation to eating patterns in youth.

Neurocircuitry of Attention Bias and LOC Eating. To date, AB research has used either event-related potentials to elucidate the temporal sequence of neural activity, or functional MRI (fMRI), providing high spatial resolution to determine key brain regions. In fMRI studies with adolescent girls, neural circuitry of the UCR (insula, ACC, OFC) and AD (vlPFC) were implicated during a food cue AB task (68). The striatum has also been shown to be central to food cue processing, reward value encoding, and AB (69-75). Upon exposure to palatable food (vs. neutral) cues, adults with binge eating have OFC, insula, and striatal hyperactivation – brain regions essential to UCR

– relative to those without binge eating (76-78). There is also preliminary evidence that neural activation associated with exposure to social stress may be related to dysregulated eating patterns. In studies using fMRI, individuals with dysregulated eating patterns demonstrate hyperactivation in regions implicated in social threat processing, specifically the amygdala (AMY), ACC and the OFC (79). These regions are also implicated in the initial attention capture processes in attention bias literature (80). Compared to those without LOC, overweight adolescent girls with LOC eating demonstrate hypoactivation in the ventromedial PFC following an experience of interpersonal rejection (67). Thus, it is possible that AB to socially threating cues is one moderator of the neural response to appetizing and rewarding food cues, and subsequent overconsumption. The neurobiology of the ABs to socially threatening cues and the impact of such biases on the correlates of LOC eating have not been explored to date.

Magnetoencephalography to examine Neural Mechanisms of Attention Bias

Magnetoencephalography (MEG) is a novel neuroimaging technology that has *both* excellent temporal and good spatial resolution (81-83). MEG studies focusing on other types of ABs confirm the utility of MEG for differentiating between the neural components of these two consecutive AB processes (84). Thus, the use of MEG can help elucidate the neural bases of ABs toward food and threat in youth susceptible to such biases.

Attention Retraining

Attention bias modification methods have been studied in other fields, such as anxiety and substance use disorders. Attention retraining (AR), a method to reduce an unwanted AB, is effective at reducing AB to problem cues in other fields, such as anxiety and substance use in adults (85-87) and pediatric anxiety (88). AR has been shown to effectively reduce AB and intake of chocolate, a palatable food (89, 90), or to increase biases for and intake of healthy foods (91). Among adults, five retraining sessions had a lasting effect of reducing AB to food for at least a week after training was concluded (92). Additionally, there is preliminary evidence among adults with LOC eating that AR is effective in reducing attention bias and LOC eating episodes immediately and 3-months following delivery (93). There are no data in adolescents. One preliminary study of 20 overweight and obese children found that a single session of AR in the laboratory reduced AB and food intake (94). Yet, there are no data among youth with reported LOC eating – a subgroup that appears to have a particularly robust AB to palatable foods (54).

Given the initially promising results from single sessions of AR to reduce AB youth (94), it is plausible that AR in the natural environment may have a potent effect. Learning theory posits that the development of new behaviors is strongly context dependent (95). The ubiquity of palatable unhealthy foods makes it necessary to provide an AR intervention that will generalize outside of the laboratory in order to impact AB and, ultimately, body weight.

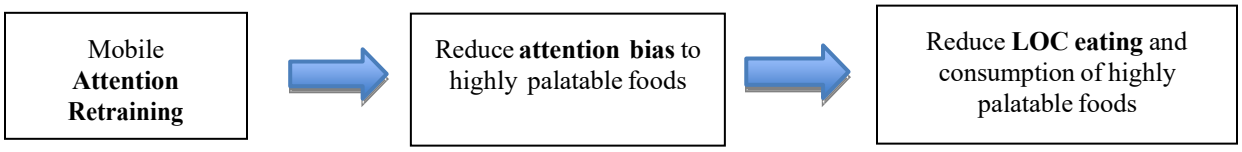

Fig 2. Attention retraining in the natural environment reduces biases to highly palatable foods that, in turn, decreases LOC eating and consumption of highly palatable foods.

Theoretically, interventions that occur in the natural environment may be more accessible, ecologically valid, and have greater impact on the key constructs that influence the outcome variable of interest (95). Importantly, adolescents use handheld technology as part of their daily communication and activities (60). Thus, AR delivered on a mobile phone will be less intrusive in, and more compatible with, their lifestyles than the inconvenience of multiple trips to the laboratory. Administering AR on smartphones may be a particularly promising approach because it is easy to administer multiple trainings per day. Additionally, more "doses" of AR may lead to greater reductions/reversals, or more sustained reductions/reversals, in AB (a reversal occurs when participants attend away from salient cues and toward neutral cues). For example, Hakamata and colleagues (96) and Beard and colleagues (97) reported that number of training sessions was associated with degree of reduction in AB or symptoms. "Distributed practice" over multiple sessions is generally more effective than "massed practice" at a smaller number of sessions in skill acquisition (98), and a primary feature of computer-based cognitive remediation interventions for both adults and adolescents is the use of a large number of individual training sessions (99). Therefore, retraining youth to attend away from palatable foods in their natural environment may have more robust impact on AB and consequently reduce LOC episodes and energy intake (Figure 2).

Attention Bias Retraining in Overweight Youth: Identifying Neural Underpinnings

Loss of control (LOC) eating is a distinct behavioral phenotype in youth (36) and it is associated with AB toward highly palatable food (40, 49, 54), adiposity (37, 38), and weight gain over time (39, 40). Attention bias (AB) involves complex cognitive processes, unconscious reactions (UCR) and attention deployment (AD) (33, 34), each associated with unique neural correlates, best measured using high spatial resolution and temporally sensitive methods (35). Understanding the differences in neurocognitive mechanisms of AB to highly palatable food in youth with LOC eating compared to those without will help inform tailored treatments. These youth may also be at higher risk of AB to social threat, thus examining neurocognitive processes associated with appraisal of socially threatening cues may further the understanding of distinct subtypes of obesity. In the proposed study, we will examine the differences in neurocognitive responding to cues of highly palatable foods in youth with and without LOC eating using MEG, which offers both high spatial resolution and excellent temporal sequencing (84). It is also unknown how these neurocognitive processes are affected by an intervention aimed at modifying AB. Using MEG, the proposed study will elucidate the neurocognitive mechanisms of AB in youth with LOC eating, prior to and following a novel, age-appropriate intervention aimed at modifying AB. Additionally, we will explore whether AB to social threat is more pronounced in overweight youth with LOC compared to those without, and whether, if present, it moderates response to intervention.

IV. Study Objectives

Primary objective

No study to date has examined the impact of AR delivered in the natural environment on AB in a targeted group of youth specifically prone to ABs. Similarly, no study has examined the effect of AR on neurocircuitry of ABs to food using MEG. Overweight adolescent girls (age 12-17y) with and without LOC eating will be studied at baseline and again after completion of a 2-week double-blind, randomized controlled trial of AR away from palatable (trigger) foods. The longer-term effects of AR on AB, neural responding, food intake, and body composition will also be examined at 3-month follow-up.

Secondary objectives (Exploratory)

To improve retention, *all* participants will receive the AR intervention and be followed for an additional 3 months. One exploratory objective of this study is to examine whether dose-response effects are present when the AR program is re-administered 3 months later. The effects of the AR received as a booster vs. AR received for the first time on AB and body composition will be examined. Given that ABs to social threat appear to be more pronounced in adults with LOC eating compared to those without LOC eating (62, 63), the second exploratory aim is to examine the moderating effects of AB to social threat on intervention effects. The third exploratory aim is to examine the LOC status (LOC vs. No-LOC girls) as a moderator of changes in AB, neural responsivity, food intake, and body composition following the AR program. Finally, given the increase in obesity among Black youth and some findings indicating that Black girls consume more in laboratory meals (45), the fourth exploratory objective is to explore the moderating effects of race on the study outcomes.

V. Specific Aims

Specific Aim #1: To examine the impact of a 2-week AR or control program on AB in overweight girls with and without LOC.

> **Hypothesis 1:** Youth randomized to AR will demonstrate a reduction in AB to palatable foods compared to those in the control condition in: (**A**) The laboratory based on visual probe task and eye tracking; (**B**) The natural environment based on smartphone data.

Specific aim #2: To examine changes in neural responsivity following a 2-week AR or control period in overweight girls with and without LOC.

> **Hypothesis 2A**: Youth randomly assigned to AR will have improvements in "bottom-up" attention circuitry in response to palatable food images (striatum) during UCR: AR will lead to less activation, whereas there will be no change in "bottom-up" attention circuitry in youth given the control condition.
>
> **Hypothesis 2B**: Youth randomly assigned to AR will have improvements in "top down" attention circuitry (dorsal ACC, vlPFC, dlPFC) during AD: AR will lead to greater activation, whereas there will be no change in "top down" attention circuitry in girls given the control condition.

Specific aim #3: To examine the effect of AR on food intake and body composition.

Hypothesis 3A: Youth randomized to AR will (i) Consume less energy from palatable foods in the laboratory test meal; (ii) Report lower levels of LOC eating in the natural environment (based on smartphone data); **Hypothesis 3B**: Youth randomized to AR will demonstrate less weight gain and adiposity compared to youth in control condition at 3-month follow-up.

Exploratory aim #1: Examine whether dose-response effects are present for AB to palatable foods and body composition in participants who receive the AR program at 3 months as a booster compared to those who receive it for the first time.

Exploratory aim #2: Examine the moderating effects of ABs to social threat (reaction times on the visual probe task, neural activation during the MEG session) on intervention effects (AB to food cues, food intake in the laboratory, and body composition).

Exploratory aim #3: Examine the moderating effects of LOC status (LOC vs. No-LOC) on the effects of AR program on "bottom-up" and "top-down" attention circuitry, AB reaction times, food intake, and body composition.

Exploratory aim #4: Examine the moderating effects of race on the effects of the AR program on attention bias, laboratory consumption, and weight/adiposity.

VI. Study Design and Methods

a. Subject Enrollment

A maximum of 120 overweight/obese but otherwise healthy adolescent girls, age 12-17y, (in order to randomize 40 with LOC eating and 40 without LOC eating), will be recruited through mailings to families in the Washington, D.C. greater metropolitan area, a method that has shown success in our previous community-based and intervention studies of youth with LOC eating (40, 43, 47, 58, 100).

Eligibility Criteria

Inclusion Criteria:

Volunteers will qualify if they meet the following criteria:

1. Age between 12 and 17 years (at the start of the study).
2. Female sex.
3. BMI at or above the 85th percentile for age and sex according to the Centers for Disease Control US Standards (101).
4. Right handedness.

LOC sample only:

5. ≥1 episodes of LOC eating during the past month prior to assessment*, assessed using a clinical diagnostic interview for eating disorders*

No-LOC sample only:

6. No episodes of LOC eating during the past month prior to assessment*, assessed using a clinical diagnostic interview for eating disorders*

Exclusion Criteria:

Individuals will be excluded (and provided treatment referrals as needed) for the following reasons:

1. An obesity-related health comorbidity requiring medical treatment, such as hypertension (defined by age-, sex-, and height-specific standards) or fasting hyperglycemia consistent with diabetes.
2. Presence of other major illnesses: renal, hepatic, gastrointestinal, most endocrinologic (e.g., Cushing syndrome, untreated hyper- or hypothyroidism), hematological problems or pulmonary disorders (other than asthma not requiring continuous medication). Non-serious medical illnesses, such as seasonal allergies, will be reviewed on a case-by-case basis.
3. Regular use of any medication known to affect body weight or eating behavior (e.g., stimulants prescribed for attention deficit hyperactivity disorder, or ADHD). Medication use for non-serious conditions (e.g., acne) will be considered on a case-by-case basis.
4. Current pregnancy or a history of pregnancy.
5. A significant reduction in weight during the past three months, for any reason, exceeding 5% of body weight.
6. Presence in the child of any significant, full-threshold psychiatric disorder based on DSM criteria (102), such as schizophrenia, bipolar disorder, alcohol or substance abuse, anorexia or bulimia nervosa, or any other disorder that, in the opinion of the investigators, would impede competence or compliance or possibly hinder completion of the study. These individuals will not be permitted to enroll in the current study and will be referred for treatment. Individuals who present with other psychiatric disorders, including sub-threshold psychiatric disorders, will be permitted to enroll in the study. If, based on the opinion of the investigators, a participant requires treatment for his/her psychiatric symptoms, the individual will be referred for treatment. Participants who develop any psychiatric disorder or significant psychiatric symptoms at any follow-up assessment during the study will be excluded and be provided with treatment referrals.
7. Current and regular substance use, including the use of alcohol and/or tobacco products (including e-cigarettes).
8. A history of significant or recent brain injury that may considerably influence performance (i.e., any history of loss of consciousness ≥30 minutes associated with a head injury, any history of memory loss or hospitalization associated with a head injury, or ≥2 concussions within last year).
9. Current involvement in a weight loss program, participating in psychotherapy aimed at weight loss or treatment of eating behavior (e.g., binge eating).
10. All parents/guardians will be asked to indicate if their child has any food allergies. To be conservative, children who report allergies to gluten, nuts, dairy, fruit, or any other item in the array, will be excluded from the test meal portion of the study.
11. A condition under which MEG is contradicted (e.g., metal in the body, pregnancy, claustrophobia, history of significant neurological insult or injury).

12. Non-English speaking participants will be excluded from the study as they may be unable to complete questionnaires and follow the instructions which are only provided in English.

Appendix 1 provides the Eligibility Checklist.

b. Procedures

Study overview: **Appendix 2** provides a schematic of the chronology of experimental procedures. The study will consist of a total of six visits.

Visit #1: Screening. Following a 20-minute phone screen with the parent and the child (**Appendix 3**), potentially eligible participants will be invited to the NIH for a screening visit to determine eligibility for the experimental portion of the study. The screening visit will be a half-day appointment. The following procedures will take place:

1. **Consent/assent**. Study purposes, all testing procedures, and possible study risks will be described in detail. Interested families will sign IRB-approved assent and consent forms (see also Consent/Assent Process, page 36).
2. **Brief history, physical exam, and body measurements** will be conducted by a trained practitioner (see **Appendix 4** for the screening visit physical exam form). A brief psychiatric and health history of the participant will be obtained from a parent or guardian in order to identify medical issues prior to study participation. This will include the assessment of current parental (guardian) medical and/or psychiatric illness, in addition to birth history of participants and factors associated with prenatal stress. Waist circumference (in cm) will be measured, as will pubertal development according to the stages of Tanner (103, 104). Tanner breast staging (by inspection and palpation) and pubic hair staging (by inspection) will be used to categorize youth as those in pre-puberty (Tanner stage 1), early to mid-puberty (Tanner stages 2–3), or late puberty (Tanner stages 4–5). In cases in which the stage is discordant between the right and left breasts, the higher stage will be assigned. Measurements of vital signs (blood pressure, pulse, and temperature) height in triplicate by stadiometer, and weight by calibrated scale will be conducted. BMI will be calculated as weight in kilograms divided by the square of height in meters (kg/m^2). BMI percentiles will be used to categorize participants as overweight ($\geq 85^{th}$ percentile) or obese ($\geq 95^{th}$ percentile) (105). A urine sample will be obtained from all participants and tested for pregnancy in postmenarcheal girls.
3. **Whole body Dual-Energy X-ray Absorptiometry (DXA)** will assess fat, lean, and bone mass (Lunar iDXA, GE Healthcare) in a fasting state. DXA involves 0.003 mrem of radiation exposure per scan (total exposure for 3 scans: .0009 mrem).
4. **Youth Interviews**.
    a. Eating Disorder Examination (EDE), Version 14 (106) (see **Appendix 5**) or the EDE adapted for children (children age < 14 years) (107) is a semi-structured psychodiagnostic interview of eating disorder psychopathology. The EDE is the "gold

standard" interview for diagnosing disordered eating. The overeating section will be administered to determine LOC presence and severity. The EDE is reliable and valid in adolescent samples (38, 59, 108, 109). Participants who report at least one episode of LOC eating in the past 28 days on the EDE, will be assigned to the LOC group. Participants who deny LOC episodes in the past 28 days will be assigned to the non-LOC group.

b. Physical Activity. To determine the average amount of moderate-to-vigorous physical activity each participant has engaged in within the previous week, children will be asked two items from the International Physical Activity Questionnaire (IPAQ) screening form (110). These data will be used to help determine the amount of the standardized breakfast shake for each participant in subsequent visits. See **Appendix 6** for the list of items.

5. **Youth Questionnaires**. Youth will complete a battery of self-report questionnaires including the following (see **Appendix 6** for the measures):

   a. Beck Depression Inventory (BDI) (111) is a widely used valid and reliable (112) questionnaire that measures self-reported severity of depressive symptoms. It has been shown to be internally consistent (alphas = .86 for psychiatric patients and .81 for nonpsychiatric subjects). Concurrent validity with other measures of depression for psychiatric patients has ranged between .72 and .73 and for nonpsychiatric individuals between .60 and .74. If participant endorses a positive screen (BDI $\geq$ 20), she will be further assessed for depression symptoms according to the DSM-5 criteria using a semi-structured interview (see *Supplemental Assessment* section below). Only girls who are at least 14-years-old will complete the BDI.

   b. Children's Depression Inventory (CDI) (113, 114) assesses the presence and degree of childhood depressive symptoms and is a widely used measure with very good reliability and validity.

   c. DSM-5 Cross-Cutting Symptoms Measure (DCSM) (115) assesses mental health domains that are important across psychiatric diagnoses. The measure consists of 25 questions that assess 12 psychiatric domains, including depression, anger, irritability, mania, anxiety, somatic symptoms, inattention, suicidal ideation/attempt, psychosis, sleep disturbance, repetitive thoughts and behaviors, and substance use. Each item asks the child to rate how much he or she has been bothered by the specific symptom during the past 2 weeks. The measure was found to be clinically useful and had good test-retest reliability in the DSM-5 Field Trials in pediatric clinical samples across the United States. If the participant endorses symptoms consistent with the presence of one of DSM-5 disorders above threshold levels, she will be further assessed using a semi-structured interview (see *Supplemental Assessment* section below).

   d. Food Preference Questionnaire (FPQ): This measure contains the foods that will comprise the buffet used for the test meals. These food items are embedded within a larger, general food preference list. The questionnaire evaluates whether foods used in the test meal array are acceptable (graded 5 or above on a 10-point Likert scale) to the

participant and has been shown to successfully identify food preferences in children (116). This measure is used to ensure that participants like (i.e., rated them 6 or above) at least 50% of the food items offered during their lunch test meals.

e. State-Trait Anxiety Inventory for Children–A trait scale (STAIC) is a 20-item self-report measure of trait anxiety with very good psychometric properties (117). A meta-analysis revealed very good internal consistency for the trait scale (mean alpha coefficient = .89).

f. Emotional Eating Scale - Children (EES) (118, 119) is a 25-item self-report measure used to assess the urge to cope with negative affect by eating. It generates 3 subscales including: Anger/Anxiety/Frustration, Depression, and Unsettled. The EES-C has demonstrated good internal consistency, discriminant validity and construct validity.

g. Eating in the Absence of Hunger Questionnaire for Children (EAH-C) consists of 14 total items from which 3 subscales are factor-analytically derived: i) Negative Affect (6 items), ii) External Eating (4 items), and iii) Fatigue/Boredom (4 items). Items will be rated on a 5-point Likert scale ranging from 0="never" to 4="always." The measure has demonstrated good internal consistency, convergent validity and temporal stability for all scales (120).

h. *The Reward-based Eating Drive Scale (REDS)* (121) is a 9-item self-report questionnaire that is designed to measure reward-based eating symptoms. Individual items capture constructs of lack of control over eating, lack of satiety, and preoccupation with food. The REDS yielded a total score. The REDS has demonstrated excellent internal consistency, good test-retest reliability, and incremental validity to other reward-driven eating measures in adults (121). In the current study, participants' responding to rewarding stimuli will be measured at the neural level (with MEG) and the cognitive level (with the food AB task), thus we will be able to validate this brief self-report scale against presumably more objective indices of reward-based eating.

i. Questionnaire on Eating and Weight Patterns – Adolescent Version – DSM-5 (QEWP-A-DSM-5) is a self-report measure based upon the adult Questionnaire on Eating and Weight Patterns – Revised to assess frequency of reported binge eating (122)(1). The QEWP-A has been adapted to capture LOC eating as well as binge episodes. The QEWP-A was been adapted to capture DSM-5 (102) eating disorders. This questionnaire is a screening tool designed to identify children with possible bulimia nervosa and binge eating disorder.

j. Perceived Stress Scale (PSS) is a 14-item self-report questionnaire designed to measure the extent to which life events impact an individual's level of perceived psychological stress. The scale is not used as a diagnostic tool, but as a comparison tool for intra-sample participants. The items refer to life events that have occurred within the past month, targeting general events during this period (e.g. "In the last month, how often have you found that you could not cope with all the things that you had to do?") The scale has been validated in both laboratory and community samples (123).

k. Mindful Attention and Awareness Scale – Adolescents (MAAS-A). Mindful attention

or clear, present-moment awareness has gained increasing attention as a cognitive state highly relevant for stress and coping/stress-response (124). Adolescents will complete the 15-item MAAS questionnaire (125), adapted for adolescents (126), which assess one's tendency to attend to present-moment experiences in everyday activities. The MAAS is internally reliable, distinguishes practitioners of mindfulness, and has concurrent and predictive validity for diminished negative affect (125-127).

l. UPPS-P Impulsive Behavior Scale – Child Version (UPPS-R – C) is a 40-item self-report questionnaire designed to measure features of impulsive behavior in adolescents (128). The UPPS-P (129) generates 4 subscales: a) Negative Urgency; b) Lack of Planning; c) Lack of Perseverance; and d) Sensation Seeking. Items will be rated on a 4-point response scale ranging from 1 = "Not at all like me" to 4 = "Very much like me." It has good psychometric properties (130).

m. Monetary Choice Questionnaire (MCQ) (131) is a well validated and widely used self-report measure of delayed reward discounting (DRD). Adolescents will make 27 choices between smaller immediate rewards and larger delayed rewards.

n. Anxiety Sensitivity Index – Revised (ASI-R): Anxiety sensitivity (AS) is a trait defined by fear of anxiety-related physical sensations (132, 133). The ASI-R is a 36-item self-report measure assessing AS and is a revised and expanded version of the original 16-item Anxiety Sensitivity Index (134). Individuals are presented with statements describing reactions to physical symptoms of anxiety (e.g. "It scares me when I feel faint") and are asked to rate how strongly each item applies to them on a Likert scale ranging from 0 ("very little) to 4 ("very much"). Higher scores indicate greater AS, with scores ranging from 0 to 144. The ASI-R has demonstrated high internal consistency, good content validity, and adequate criterion validity in prior studies of nonclinical populations (135). Prior research suggests that AS is a distinct construct from trait anxiety and may contribute to the development or maintenance of a variety of psychological disorders, including social anxiety (136, 137). By assessing AS among a sample of healthy youth, we will be able to further examine the relationships between AS and other trait and state facets of anxiety.
For participants who did not complete this questionnaire at screening, it will be completed at a later timepoint. Participants who have completed study visits will be contacted, re-consented and re-assented as required, and invited to complete the questionnaire via mail or the NIH Secure Email and File Transfer (SEFT) system.

o. Supplemental Assessment (conducted *only* if the participant endorses items on the CDI or the DCSM suggestive of a DSM-5 disorder):

The Schedule for Affective Disorders and Schizophrenia for School-Age Children (KSADS) (138). Portions of the KSADS will be used to assess psychiatric functioning and exclude participants with significant psychiatric co-morbidities that, in the opinion of the investigators, would impede competence or compliance or possibly hinder completion of the study. It will only be administered to participants who endorse a positive screen for depression, suicidal ideation, mania, psychosis, or substance use disorder on the DCSM. Individuals with these disorders will be referred for treatment

and excluded. Both current and lifetime history will be assessed. This measure is a reliable and valid diagnostic interview with good inter-rater reliability (93-100%) and excellent test-retest reliability for present and lifetime diagnoses of childhood and adolescent major depression, bipolar disorder, generalized anxiety, conduct disorder, and oppositional defiant disorder (k coefficients .77 to 1.00) listed in the DSM-IV-TR (139). See **Appendix 7** for a copy of the KSADS.

6. **Parent study questionnaires**. Parents/guardians will have access to computers and/or paper copies to complete these surveys about their child during their child's visit (see **Appendix 8** for measures).
    a. Child Behavior Checklist (CBCL) is a reliable and well-validated Child Behavior Checklist to assess their perceptions of their child's internalizing and externalizing symptoms, as well as overall behavioral problems.
    b. Hollingshead Four-Factor Index of Socioeconomic Status (HI) (140) is a measure that assesses social status based upon four domains (marital status, employed status, educational attainment, and salary).
    c. Questionnaire on Eating and Weight Patterns – Parent about Child (QEWP-P-DSM-5): The QEWP-P-DSM-5 assesses parents' perceptions of their children's binge eating behaviors (141). This measure has been widely used and demonstrates sound psychometric properties (141). Items were modified slightly to ensure that criteria for binge eating disorder according to DSM-5 (102) are captured.
    d. Eating in the Absence of Hunger Questionnaire for Children – Parent Report about Child (EAH-P): Parents will report on their perceptions of their children's EAH on the EAH-P. This form is a parallel version to the Eating in the Absence of Hunger Questionnaire for Children (EAH-C) (142). It consists of 14 total items from which there are 3 factor analytically-derived subscales that assess EAH in response to: i) Negative Affect (6 items), ii) External Eating (4 items), and iii) Fatigue/Boredom (4 items). The EAH-P has demonstrated good internal consistency, convergent validity and temporal stability for all scales (143). The EAH-P also demonstrates good construct validity as parents' reports of children's EAH in response to external cues has been significantly correlated with greater energy intake in laboratory EAH paradigms (120).

Visit #2: Baseline Laboratory Session. The baseline lab will be scheduled within a week of the screening session. The baseline lab visit will be a half-day appointment that starts in the morning (from approx. 8AM to 1PM). Participants will be instructed to engage in an overnight fast starting at 10:00PM the night prior to the visit. The following procedures will take place:

1. **Phlebotomy**. Blood will be drawn from participants by a phlebotomist or registered nurse for obesity-related measurements (e.g., acute care panel, hepatic panel, lipid panel, mineral panel, insulin, c-peptide, glycosylated hemoglobin, TSH, free T4, ESR, hsCRP), appetite-regulating hormones (e.g., leptin, ghrelin, oxytocin), nutritional status (e.g., 25-hydroxyvitamin D, iron), and hematological status (e.g., CBC), and samples to save for future research (75 mL). If desired, we will use ELA-Max cream so that the blood draw will hurt less. Total blood withdrawal will be within NIH pediatric guidelines (3.5mL/kg

per single draw, 7 mL/kg per 6 weeks) since participants will have minimum age 12y and will be eligible to join the study only if BMI exceeds the 85th percentile for age (BMI must be more than 20.9 kg/m^2), weight will always exceed 40 kg; thus up to 140 cc may be obtained at a single blood draw.

2. **Standard breakfast shake.** Participants will receive a standard breakfast shake, the amount of which (21% of estimated daily energy needs) is determined by measured body weight, height, age and average activity level in the previous week. The shake will consist of 17% protein, 16% fat and 67% carbohydrate. This is a standardized procedure to reduce the effect of hunger on AB to food. If the participant has lactose intolerance, lactase pills will be administered at the beginning of the visit or a lactose-free shake will be offered.

3. **Hunger/satiety and mood rating**. Immediately before and after the breakfast shake, and after the food cue attention bias task, youth will rate their hunger and satiety states using the visual analog scales, ranging from 1 to 10 ("not at all" to "extremely). Mood will be assessed using the validated and reliable Brunel Mood Scale (BRUMS) (144, 145). The respondent indicates to what extent they feel a variety of different mood descriptors "right now." The mood descriptors in the BRUMS are rated on 5-point Likert scales. Guilt, an emotion that may be particularly salient for LOC episodes (146), will be assessed using items from the Guilt subscale of the PANAS-X (147) following procedures from prior EMA studies (146). Copies of these measures can be found in **Appendix 6**.

4. **MEG Session with the Food Cue and Social Threat AB Visual Probe Task and Eye-Tracking**. Eligible youth will participate in both the food cue and the social threat AB task while undergoing the MEG scan (see **Appendix 9**). The order of exposures will be counterbalanced across participants.

    a. The Food Cue AB task (see **Appendix 10**) will consist of 180 trials in which pairs of color photographs are presented on a computer screen (10). Pairs are drawn from high palatable (HP) foods, low palatable (LP) foods, and non-food (NF) control stimuli consisting of emotionally neutral images of household items. Across the task, the 180 trials were divided into three pairing categories (60 of each): HP-LP, HP-NF, and LP-NF. There are 15 such pairings and each pair is presented 4 times with location of stimuli and location of probe fully crossed. The order of stimulus will be randomized. For each trial, stimuli are presented side-by-side (500 ms) after which both images disappear and a probe appears in a location previously occupied by 1 of the 2 pictures (500 ms). The probe consists of a left or a right arrow, and participants are instructed to press the left arrow button if pointing left, and the right arrow button if pointing right and told to respond as quickly and accurately as possible. To minimize automaticity, the inter-trial interval will be randomly jittered across 3 durations of 100ms, 150ms, or 500ms.

    b. The Social Threat AB task (84) (see **Appendix 11**) will examine neural responses during a social threat visual-probe paradigm with angry, happy, and neutral faces (11), which have been used extensively in pediatric samples between the ages of 9-17 years (148-150). Normed face images will be taken from the NimStim Face Stimulus Set (151). Visual-probe paradigms assess attention bias by presenting stimulus pairs

followed by a probe that requires a response. Pairs of each face combination (angry-neutral, happy-neutral, neutral-neutral) will be presented in randomized order. After the image pair disappears, a probe appears in one of the previously occupied photo locations. Youth respond with a right or left sided key-press to indicate the orientation of the probe. The response mapping of probe orientation will be counterbalanced across participants. Youth will be instructed to respond as quickly and accurately as possible to the probe. Trials consist of a mixture of incongruent trials (when the probe replaces the neutral face image), congruent trials (when the probe replaces the emotional face image), and neutral trials (when two identical neutral facial expression appear and the probe location is insignificant).

c. Eye-tracking will be performed with the Tobii TX300. This system uses infrared reflections from the pupil and a 300 Hz camera and can withstand substantial head movements within a restricted area that eliminates the need for chin rest or other head restraint. Tobii software interfaces with Eprime, which enables flexible experimental design implementation. Duration, frequency and latency of fixations will be tabulated in each experimental condition and combined with reaction time (RT) measures. The combination of RT and visual fixation metrics will provide a detailed portrait of attention allocation under these experimental conditions.

d. **MEG Recording.** Brain magnetic fields will be recorded with the 275-channel OMEGA system. Participants will sit in the magnetically shielded recording room with their heads in a helmet covered with 275 SQUID sensors. Head position within the magnetometer will be determined before and after each MEG session by digitizing the position of three indicator coils that are attached to the preauricular and the nasion fiducial points. The positions define the coordinate system for the signals and allow for post-hoc correction of head movement artifacts. Digital photographs of the fiducial points will also be taken to localize the same points on the participant's anatomical MRI scan. Consistent with prior MEG studies in pediatric samples and in populations not previously studied (84, 152), MEG data will be sampled at 600 Hz (bandwidth 0-150 Hz). MEG recording will last for approximately 45 minutes (**Appendix 9**).

5. **Laboratory test meal**. Youth will complete rating scales for hunger, fullness, state mood, and food craving (47, 48). They then receive tape-recorded instructions to "Let yourself go and eat as much as you want" from a multi-array test meal (9,835 kcal). This well-validated paradigm has been used in pediatric (47) and adult (52) studies. Rating scales are repeated post-meal. Consumption is calculated by weighing each item before and after the meal. Energy content and macronutrient composition for each item will be determined according to data from the U.S.D.A. Nutrient Database for Standard Reference and information supplied by food manufacturers. The sample meal is presented in a photograph in **Appendix 12**.

6. An **Anatomical MRI** will be performed on one of the Clinical Center's Phillips 3T scanners (MR2 or MR4). Standard imaging parameters will be used including acquisition of T1 weighted structural images for co-registration (see **Appendix 9** for details on MRI acquisition and preprocessing). If the MRI scanner is not available during participant's

second session, participants will be asked to return for a brief visit to perform the anatomical MRI scan. Contingent on the availability of the scanner, the participants may be scheduled to complete the anatomical MRI on a day separate from their study visit. They will be compensated for their time. A urine sample will be obtained from all participants and tested for pregnancy on the day of the participant's anatomical MRI scan. If a participant has undergone an anatomical MRI scan at the NIH of sufficient quality in the preceding two months, she will not be required to complete another MRI anatomical scan as part of this study.

7. **Smartphone training.** Participants will be given the mobile devices with attention retraining or the control program. Before they leave the laboratory, they will be trained in the use of the mobile devices and provided with contact information of the study staff to aid with troubleshooting of any problems that might arise. The training will take approximately 20 minutes.

Attention Retraining or Control Program with Ecological Momentary Assessment (EMA) in the Natural Environment for 2 Weeks. Participants will be randomized in blocks of 8 with stratification for LOC status (LOC vs. no-LOC), race/ethnicity (Hispanic/Non-Hispanic, Black/White), and age (12-14; >14) to attention retraining or control programs carefully matched for intensity of interaction. In addition to three attention retraining or control trials administered on the smartphone each day, attention bias will be assessed once a day. Each of the four daily trials will also include an EMA component in which participants answer questions regarding their eating patterns and mood in real time. A sample administration schedule for a school day is presented in Figure 3.

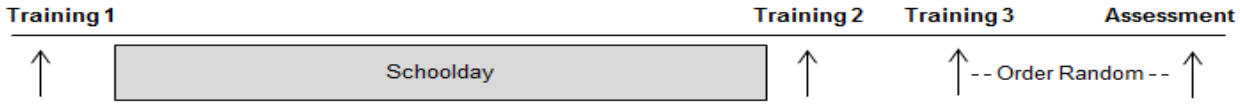

Figure 3. Sample administration schedule.

On school days, youth will be signaled to complete AR/control trainings and EMA assessments pre-school (Training 1) and immediately post-school (Training 2). They will also be signaled 2 more times (at random) between 3:30 pm (or end of school day) and bedtime, once for training (Training 3) and once for AB assessment (in random order). Bedtime will be set individually with each participant based on the participant's and participant's parent's preference. Adolescents tend to go to sleep between 10:45PM and 11PM on school nights (153), therefore the latest bedtime offered will be 10:30PM. Bedtimes will be offered in 30-minute increments and the earliest bedtime available will be 7:30PM. ,. In sum, on each study day participants will be scheduled to complete 3 AR/Control trainings (80 trials each) and one AB assessment (40 trials). On non-school days, the same schedule will be used except that the first training may be delayed by up to 2 h. A different picture set will be used on each day (order randomized over time), and assessments will occur using pictures on which youth were scheduled to receive training. With

>70% compliance, participants will complete ~30 AR/Control trainings during the two weeks, and AB will be assessed ~10 times during the study.

1. **Attention retraining / control program on smartphone.** For the attention retraining task, the probe always replaces the neutral picture. There is a perfect correlation between picture type and probe location. Over time, individuals assigned to the attention retraining group should learn to attend away from the highly palatable pictures. For the control, the probe is equally likely to replace the food picture and the neutral picture. There is no correlation between picture type and probe location, and no training of attention should occur. This control has been used in previous attention retraining studies (154, 155). It ensures that: 1) the duration of attention retraining and control trials should not differ; 2) attention retraining and control participants receive equal practice on the motoric aspects of the visual probe tasks; and 3) attention retraining and control participants are exposed to the same food and neutral stimuli.
2. **Attention bias assessment on smartphone.** Attention bias assessed via a visual probe task will be a difference score (measured in msec) reflecting the difference in response times to probes that replace highly palatable food with neutral stimuli. Attention bias data from assessments with >25% errors will be excluded. Following Kerst & Waters, an item will assess how many times the participant reported being interrupted during trainings/assessments (Response options: No, 1, 2, 3, 4+ times), so that data from assessments with a large number of interruptions can be excluded (155). On the attention bias assessments, faster responses to probes that replace highly palatable food pictures indicates an attention bias toward highly palatable food (i.e., attention has shifted to highly palatable food stimuli leading to faster responses on probes that replace highly palatable food), whereas faster responses to probes that replace neutral pictures indicates an attention bias away from highly palatable food.
3. **Ecological Momentary Assessment.** LOC eating ("since the last assessment") will be assessed during EMA with previous methods using items assessing the adolescent's perceived "level of control," "loss of control," and the sensation of "out of control" if they ate (on a 1-5 scale, "No, not at all" to "Yes, very much," with 4 or 5 on any item coded as presence of LOC eating). Mood will be assessed using visual analog scales (see **Appendix 13** for a list of EMA questions).

Visit #3: Post-Smartphone Program Laboratory Session. This visit will take place two weeks after Visit #2, at the conclusion of the 2-week attention retraining protocol. Procedures will be a combination of those from Visits #1 and #2, and will be conducted using the same methods and procedures described above:

1. BMI and waist circumference.
2. MEG Session with the AB Visual Probe Tasks and Eye-Tracking.
3. Laboratory test meal.

Visit #4: 3-month follow-up. This visit will take place approximately 3 months following visit

#3. Changes in weight/fat mass and eating behavior will be assessed at this visit. To increase retention, all girls will be offered the attention retraining program if they complete Visit #4. All the procedures will be conducted using the same method as in the previous visits:

1. BMI and waist circumference; a urine sample will be obtained from all participants and tested for pregnancy in postmenarcheal girls.
2. DXA scan.
3. MEG session with the AB Visual Probe Tasks and Eye-Tracking.
4. Laboratory test meal.
5. Eating Disorder Examination (EDE), Version 14.

AR for all: Attention Retraining with EMA in the Natural Environment for 2 Weeks. Participants will be offered the attention retraining program for two weeks as a "booster." All participants will receive attention retraining at this point in the study. The attention retraining will be conducted using the same method as in the previous intervention.

Visit #5: Post-AR for all follow-up. This visit will take place 2 weeks after Visit #4, at the end of the 2-week booster attention retraining intervention. All the procedures will be conducted using the same method as in the previous visits:

1. BMI and waist circumference.
2. MEG session with AB Visual Probe Tasks and Eye-Tracking.

Visit #6: 6-month follow-up. This visit will take place approximately 3 months following Visit #5, and/or 6 months following Visit #3. All the procedures will be conducted using the same method as in the previous visits:

1. BMI and waist circumference; a urine sample will be obtained from all participants and tested for pregnancy in postmenarcheal girls.
2. History and physical exam as done in Visit #1 (see **Appendix 14** for follow-up physical exam form).
3. DXA scan.
4. MEG session with AB Visual Probe Tasks and Eye-Tracking.
5. Laboratory test meal.
6. Eating Disorder Examination (EDE), Version 14.

Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and NICHD Clinical Director and will provide the reason(s)

for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the NICHD Clinical Director and IRB.

VII. Analysis of the Study/Oversight

a. Study Administration and Data Collection, Management and Storage

Roles and Responsibilities of Study Investigators and Key Research Personnel are specified in the Monitoring Plan (see below). Data collected from participants in this research study will be saved and may be used for future analyses related to eating behavior, attention bias and neural circuitry related to both. This testing may be done by research laboratories that are not at the NIH. Prior to transfer of data to non-NIH collaborators, a material transfer agreement (MTA) with the outside institution will be established. The PI will provide the IRB with a listing of MTA's that have been established under these provisions at the time of the Continuing Review, but including a record of each such collaboration in the study protocol.

Data collected from all components of the current protocol will be coded with identifying information stored in a protected database to which only the NIH research team will have access. This code will be used for labeling samples and data for storage. The purpose of retaining the code is to permit the NIH research team to link clinically-significant findings with a subject so that the subject can be informed and appropriate follow-up arranged if medically indicated and to allow for examination of additional research questions in the future. Scientific collaborators (non-investigators), to whom coded samples and data may be sent for future studies, will not have access to subject names or other identifying information. If unauthorized disclosure of identifying information linked with samples or data occurs, the IRB will be notified by the Principal Investigator.

The principal investigator and the co-investigators will have access to all identifiable participant records. Records containing personal identifiers will be maintained consistent with the security measures required by the NIH. We will follow guidelines developed by the NIH for projects funded by the Federal Government. Prior to managing data, all identifying information including name and address will be removed.

The smartphone attention bias data and the ecological momentary assessment (EMA) data will be collected via the "Colors" software. "Colors" runs on a Windows-based or Android-based smartphones. The "Colors" software has been reviewed by Mr. William Hermach (NIMH ISSO) and received a Certification to Operate on February 18, 2016 (see **Appendix 15**). The smartphones

compatible with the "Colors" software will be purchased by the NICHD. The "Colors" program can administer reaction time (RT) tasks, individually or in combination, to include the visual probe (VP) task, Stroop, Implicit Association Test, Go No-Go task, and Rapid Visual Information Processing Task. A native code app is currently used, written in C# in the Windows Mobile environment. Data are collected in a local database and transmitted to the Cloud Server in near real time. De-identified participant and study profiles are created on the Cloud Server via a .NET browser based application. The "Colors" application data can be protected by 2048 bit SSL encryption for all participant submitted data. The administration of the application is protected by dual authentication to servers behind a network firewall. Reliability of reaction time and attentional bias assessed on mobile devices has been good (156, 157). An app in an ongoing attention retraining study of smokers using the proposed platform has generated nearly 10,000 completed trainings and assessments (as of December 2015). On this platform, the estimated internal reliability of mean reaction time computed using split-half r is >.95 (see also (156, 157). The program has been used successfully in non-smokers, smokers, heroin/cocaine addicts undergoing detoxification, and recovering alcoholics. The program has also been used successfully to administer attentional retraining (155). To the best of our knowledge, this is the most sophisticated software currently being used for the assessment of cognitive biases in ecological momentary assessment studies. The attention bias smartphone data will be co-managed by Dr. Andrew Waters, an Associate Investigator on this protocol, at the Uniformed Services University. The EMA data will be co-managed by Drs. Andrew Waters, an Associate Investigator on this protocol, at the Uniformed Services University. Dr. Scott Engel will provide consultation to the research team regarding the set-up of the EMA protocol, data collection, and analysis. Dr. Engel will have access to no identifiable participant information and will assist in interpretation of the data being collected throughout the study. Consultation with Dr. Engel will occur primarily via phone and email, as he is located off-site at the Neuropsychiatric Research Institute in Fargo, ND. Dr. Crosby will provide statistical support working with de-identified data.

Data from the MEG acquisition computer will be transferred to the analysis computer and then copied to DVD and external hard drive. DVD's will be labeled with the assigned participant ID, date, and session type (i.e., social threat or food cue). Each participant's data will be stored on the secure RAID serve for several weeks and then permanently deleted. All participant data files will be labeled with the participant's ID. Electronic data will be password protected and accessible only by authorized study personnel. Electronic (de-identified) data will be backed up daily and stored at a secure server. All hardcopy data will be locked in Dr. Yanovski's storage cabinets in research offices at the NIH CRC and will be accessible only by authorized study personnel. All data will be collected specifically for the purpose of the current proposed research project.

Data will be stored for a minimum of 3 years after completion of analyses for this study. Furthermore, in compliance with federal law, records will be maintained until all subjects enrolled in the study have reached a minimum age of 23 years. Subjects may choose to withdraw from the study at any time and may request for stored data to be destroyed. All withdrawals from the study will be documented and included in the annual report for continuing review by the IRB.

b. Publication of Research Findings

We estimate that several publications will result from this study; for example, comparison of

changes in neural responding and attention bias in LOC and No-LOC girls assigned to the AR vs. control condition, as well as the impact of these potential changes on eating behaviors and body composition over time. The impact of the booster intervention will also be evaluated. Findings will be submitted to peer-reviewed journals, and data will be deposited as required by governmental rules.

c. Primary Outcomes

Specific Aim 1: Examine change in attention bias following a 2-week attention retraining or control period.

i. **Primary outcomes**: Change in laboratory measured attention bias (i.e., reaction times to palatable foods at the baseline laboratory visit vs. the post-EMA visit),

ii. **Secondary outcomes:** Change in EMA-measured attention bias over time (2-week period), laboratory measured AB to social threat (i.e., reaction times to threatening stimuli at the baseline laboratory visit vs. the post-EMA visit),

Specific Aim 2: Examine changes in neural responsivity following a 2-week attention retraining or control period.

i. **Primary outcomes**: Change in neural activity during attention bias task paradigm at the baseline laboratory visit vs. post-EMA visit.
ii. **Secondary outcomes**: Neural activity during the social threat AB task.

Specific Aim 3: Examine the effect of attention retraining on food intake and body composition.

i. **Primary outcomes**: Change in the energy intake at the buffet meal, change in adiposity/body composition (DXA) from the baseline visit to the post-EMA visit.

ii. **Secondary outcomes**: Change in self-reported eating patterns (EDE), number of LOC episodes measured via EMA and clinical interview,

Exploratory Aim 1: Examine whether dose-response effects are present for attention bias to palatable foods and body composition in participants who receive the attention retraining program at 3 months as a booster compared to those who receive it for the first time.

i. **Primary outcomes**: Change in laboratory measured attention bias (i.e., reaction times to palatable foods at the baseline laboratory visit vs. the post-EMA visit), adiposity/body composition (DXA)

ii. **Secondary outcomes**: Change in EMA-measured attention bias over time (2-week period), self-reported eating patterns (EDE), number of LOC episodes measured via EMA and clinical interview.

Exploratory Aim 2: Examine ABs to social threat (measured as reaction time, eye tracking, and neural activation on the AB to social threat visual probe task at baseline), and potential moderating effects of AB to social threat on intervention effects.

i. **Outcomes:** Change in energy intake at the buffet meal, adiposity/body composition (DXA).

Exploratory Aim 3: Examine LOC status (LOC vs. No-LOC) on primary outcomes.

i. **Outcomes**: Change in neural activity during attention bias task paradigm at the baseline laboratory visit vs. post-EMA visit, change in laboratory measured attention bias (i.e., reaction times to palatable foods at the baseline laboratory visit vs. the post-EMA visit), change in food intake, change in adiposity/body composition (DXA)

Exploratory Aim 4: Examine effects of race on primary outcomes.

a. **Outcomes**: Laboratory measured attention bias (i.e., reaction times to palatable foods at the baseline laboratory visit vs. the post-EMA visit), the energy intake at the buffet meal, adiposity/body composition (DXA).

d. Reasons for Withdrawal/Adverse Event Reporting: Participants will be examined briefly on the phone during the initial screening, and more extensively during the screening visit (Visit #1) as well as the follow-up visits. Participants will be excluded and/or referred for treatment if appropriate, as previously described. Identification of a current and significant psychiatric disorder at the time of enrollment will result in an appropriate referral to a mental health professional and study exclusion. Noncompliance with study procedures may lead to withdrawal of study participants. Other events that may lead to study withdrawal include pregnancy or serious unanticipated complications, including development of any medical problem listed in the exclusion criteria. Please see Section 16: *Reporting of Unanticipated Problems, Adverse Events and Protocol Deviations* for more details regarding adverse event reporting.

f. Determination of Sample Size and Analytic Plan

Sample Size: Sample size estimation is based on the power analysis for the first Specific Aim. This is a pilot study to test a novel promising intervention for a targeted group of youth at high risk for adult obesity. Eighty overweight girls, 40 with LOC eating and 40 without LOC eating, will be randomized, out of 120 recruited. Meta-analytic studies of AR effect on attention bias (e.g., to appetite [food, alcohol], or threatening stimuli) in adults found large effects of AR (d = .80–1.41) on attention bias reductions (96, 97) and medium effects (d = .51-.61) of AR on behavioral outcomes (96, 97). Based on recommended equations for estimating sample size (158, 159) when using general linear model, and assuming 35% attrition due to unusable visual probe or MEG data (based on pilot data and prior MEG studies in youth), this sample size will provide >80% power to detect medium to large effects (83, 152, 160).

Preliminary Analyses:

1. Anatomical MRI data processing will be done with AFNI software (see **Appendix 9**). Structural scans will be spatially normalized to standard Talairach space.
2. Raw MEG data will be filtered using third gradient reference coils with fixed weights. A broad frequency band (1-30 Hz) will be used for primary analyses, following procedures from prior MEG studies in new populations (83, 152, 160). Fixed frequency smoothing

and transformation will be applied to obtain oscillatory power estimates. Oscillatory power activity will be calculated by subtracting the baseline activity (1000ms immediately prior to stimulus onset) from the activity evoked during the UCR and AD periods, respectively (84). The synthetic aperture magnetometry (SAM) beamformer technique (161) will be applied to produce a 3D representation of brain activity by calculating the oscillatory power activity for individual voxels (7 mm). Using the anatomical MRI, normalized SAM data will be co-registered and transformed into Talairach space in AFNI software. Based on our hypotheses, a priori brain regions will be selected for examination. Pseudo F-ratios – an index of 3D oscillatory power activity – for the regions-of-interest will be used in analyses (see **Appendix 9**).

3. EMA data will be collected using a specialized platform designed to collect EMA on mobile devices. Data are collected in a local database and transmitted to the Cloud Server in real time. Participant and study profiles are created on the Server and exported from the Server by an administrative user. On this platform, the estimated internal reliability of mean RT computed using split-half r is >.95 (156, 157).
4. *Missing Data and Attrition*: AR and control will be compared on study completion vs. early termination using logistic regression controlling for age, sex, race, lean mass, adiposity, and height ("covariates"). Multiple imputation based upon fully conditional Markov chain Monte Carlo modeling (162) will be used to impute missing data on non-EMA assessments. Primary analyses will be based upon imputed data except for EMA analyses. Sensitivity analyses will use all available data (i.e. no imputation) and maximum likelihood imputation and results will be compared across methods. Although data preprocessing and analytic methods can mitigate artifacts to some extent, excessive participant movement remains a problem. Structural MRI / MEG will be excluded if there is movement > 2.5 mm during respective sessions. At NIH, pediatric fMRI / MEG studies typically have 30-40% attrition in youth due to excessive movement. Thus, attrition rate of 35% is assumed in power analyses.

Primary Analyses:

Specific Aim 1

a. **Hypothesis 1:** Youth randomized to AR and control conditions will be compared on:
    1. Post-smartphone program lab visit and the 3-month follow-up visit reaction time data from dot probe task will be using a general linear model (or appropriate generalized linear model depending upon distribution diagnostics) controlling for baseline visit reaction time data from dot probe task, and covariates (order effects, age, race, and BMIz).
    2. Reaction time data from EMA

Specific Aim 2

a. **Hypothesis 2**: General linear model adjusting for baseline neural activity and covariates (order effects, age, race, and BMIz), will be used to analyze

1. Post-smartphone visit amd 3-month follow-up visit neural activity in response to palatable food cues in the "bottom-up" attention circuitry (ventral ACC, OFC, insula, and striatum) in the unconscious reaction period.
2. Post-smartphone visit and 3-month follow-up visit neural activity in response to palatable food cues in the "top-down" attention circuitry (dorsal ACC, vlPFC, dlPFC) in the attention deployment period.

Specific Aim 3

a. **Hypothesis 3A**: Youth randomized to AR and control groups will be compared on
    1. Post-smartphone program lab energy intake from laboratory test meal using a general linear model (or appropriate generalized linear model depending upon distribution diagnostics) controlling for the baseline visit energy intake and covariates
    2. The daily number of LOC episodes using a generalized estimating equations (GEE) model with a negative binomial response function controlling for baseline LOC episodes and covariates. The model will include a main effect for group, and a group-by-time interaction. Analyses use all available data (no imputation). We will also examine LOC as a continuous daily dependent variable (mean of 3 LOC items).
    3. BMI and adiposity at the 3-month follow-up visit using a general linear model (or appropriate generalized linear model depending upon distribution diagnostics) controlling for baseline lab visit and the post-smartphone program lab visit BMI and adiposity.

Exploratory Aim 1

a. Youth randomized to AR (who receive the AR program at 3 months as a booster) will be compared to controls (who receive AR for the first time) at post-booster visit and the 6-month follow-up visit on BMI, adiposity, and energy intake using a general linear model (or appropriate generalized linear model depending upon distribution diagnostics) controlling for Visit #2 measurement

Exploratory Aim 2

b. Moderation analyses will be conducted using reaction times from the baseline social threat AB task as well as neural correlates of social threat ABs when the outcome variable is change in AB to food cues following the intervention, energy intake, and body composition.

Exploratory Aim 3

c. Moderation analyses will be conducted considering LOC status (LOC vs. no-LOC) when the outcome variables are: change in neural activity, change in reaction times on the food AB task, and change in food intake during the laboratory test meal from

baseline to post-intervention/3-month follow-up in AR vs. control condition, as well as and change in body composition from baseline to 3-month follow-up in AR vs. control condition.

Exploratory Aim 4

d. Moderation analyses will be conducted considering race (Black vs. non-Black) when the outcome variable is AB to palatable food, energy intake, and adiposity/body composition.

VIII. Human Participant Protection

a. Rationale for Subject Selection

Girls ages 12-17 years with BMI $\geq 85^{th}$ percentile are included in the present study. To test the effects of the intervention on particular subtypes of overweight youth, half of the participants will have to endorse LOC eating episodes. The rationale for the inclusion of youth between the ages of 12 and 17 years is because LOC eating behaviors often emerge during this developmental period (163-165). Adolescence is also a period when many disordered eating patterns manifest, particularly among girls (16). Youth who endorse even infrequent LOC episodes are at higher risk for gaining excess weight in prospective studies (40, 100), placing them at risk for developing more severe health complications of the cardiovascular and endocrine systems in later life. Understanding the mechanisms of eating behaviors and designing more effective interventions to decrease excessive food intake and reduce excess weight among adolescents are thus of paramount importance. The proposed study, of a novel and age-appropriate intervention, develops a targeted approach that may hold promise for wide dissemination. Targeted therapeutic approaches for subgroups with specific phenotypes have been recommended (17), and have the potential for greater effects. Should this pilot study have positive results, other groups, including boys and younger children, should be studied.

Youth of all races and ethnicities will be eligible. LOC eating is reported with similar prevalence among Non-Hispanic White and minority groups including Non-Hispanic Black and Hispanic youth (44, 45). Of particular concern are data indicating that childhood obesity rates have increased dramatically among Hispanic and Non-Hispanic Black youth (1, 46). Thirty-six percent of Non-Hispanic Blacks (2-19y), for example, are currently overweight or obese compared to 32% of Non-Hispanic White youth (166). Non-Hispanic Blacks remain at a higher risk for serious obesity-related health comorbidities (46, 167). Some laboratory studies have found that Black girls consume more during a laboratory meal compared to their non-Black counterparts (45). Despite these important racial/ethnic variations in weight-related concerns, there are limited data on eating behavior-related endophenotypes for pediatric obesity among non-White youth. Historically, non-White girls have been underrepresented in psychological research, and limited sample sizes may preclude meaningful investigations of racial/ethnic differences. Our previous studies have consistently attracted about equal proportions of Non-Hispanic White and Non-Hispanic Black youth. It is expected, given our recruitment procedures targeting individuals living in the greater metropolitan Washington D.C. area, that we will recruit similar rates of minority participants. Indeed, Washington, D.C. is very diverse: 35% Non-Hispanic White, 48.8% Non-Hispanic Black,

9.9% Hispanic, and 3% Asian, among others. Therefore, we expect to continue our ability to recruit substantial numbers of racially/ethnically diverse youth (see Planned Enrollment Table for estimates of minority enrollment).

b. Participation of Children and Other Vulnerable Populations

The study involves many procedures that have previously been approved by IRBs as minimal risk, including anthropometric and body composition measurements, psychological testing, brain imaging, and laboratory cognitive tasks. The cognitive tasks and questionnaires are of no greater risk than that of taking a mathematics examination at school. The physical measurements are likewise not considered to be outside of usual activities that children normally undergo. The protocol takes into account psychological as well as physical discomfort, and provisions have been made for soliciting the assent of children and the permission of parents. The PI and all members of the study team will emphasize to participants that they are able to withdraw from the study at any time without penalty. All participants are carefully debriefed and written procedures for managing unusual circumstances (e.g., subject distress or suicidality) are in place. We request that consent from one parent is sufficient unless there is joint legal custody for medical decision-making of a child, in which case both parents must give their permission. Exceptions may include if one parent has since died, become incompetent, or is not reasonably available. Consent forms include waivers of confidentiality for suicidality, homicidal ideation, and child and elder abuse, for which we are mandated reporters. The screening portion of the study protocol will begin with a discussion of confidentiality and its limitations. Specific written procedures have been developed for handling cases that necessitate a breach of confidentiality. Children's screening questionnaires and interviews will be reviewed by a research team member conducting the appointment before participants leave the NIH. Participating youth will be immediately referred for a psychiatric consultation at the NIH and referred for outside treatment as recommended if the child endorses suicidality or psychosis at any point. The study team will work with the psychiatrist to ensure that all distressed participants are given a list of referrals that include hotlines and crisis centers, and we also will facilitate referrals to counseling services if the situation calls for this. Depending on the individual circumstances, the appropriate authorities such as a parent/guardian will be contacted. Jack Yanovski, MD, PhD or Marian Tanofsky-Kraff, PhD will be immediately contacted for consultation if suicidality, suspected child abuse, or homicidal ideation issues arise. Suspected child abuse is reported to Social Services; the Social Work department will be contacted to assist with needed evaluation and referrals. Given the small and temporary nature of risks posed to participants, we believe that the knowledge to be gained outweighs the risks and inconveniences of this study.

c. Screening Methodology

A number of methods will be used to screen for the psychiatric and health concerns noted above, including a brief phone screen (during which we will ask parents/guardians about their children's psychiatric and medical concerns) and a screening visits at the Clinical Center (during which a medical and psychiatric history interview and physical exam will be conducted, and a questionnaire assessing DSM-5 psychological disorders will be administered). Research staff facilitating the psychiatric interviews will review youths' surveys for critical item endorsement (e.g., suicidal ideation) and follow-up as appropriate. If suicidality is endorsed, research staff will

conduct a follow-up evaluation to determine the appropriate course of action (i.e., referrals for treatment or request onsite psychiatric consultation). Urinary analyses will be used to ensure that postmenarcheal girls are not pregnant. If they are, they will not be eligible to participate in the current study. Parents will be informed that girls who are found to be pregnant become emancipated minors for the purpose of health care decision-making, and that the child, not the parent, will be told about a positive pregnancy test.

d. Risk/Benefits Analysis

Risks: We do not anticipate that the current study will pose serious risks to participants' physical or psychological/emotional health. Potential mild risks and inconveniences are:

1. The completion of **questionnaires, behavioral paradigms and interviews** involves no appreciable risk. However, it is possible that participants may experience slight discomfort as a result of being asked to fill out questionnaires or respond to queries about stress, mood, and eating. They may also become frustrated while completing the behavioral tasks designed to assess their attentional processes. If the wording of some questions makes the child uncomfortable, the participant is not required to answer that particular question. Similarly, participants will be informed of their right to not complete any test or task during any visit. Additionally, questionnaires, behavioral paradigms and interviews may cause inconvenience because of the time required for testing.
2. **Psychiatric issues**. If, based upon the study team's opinion, there is evidence of the development of a serious psychiatric disorder or signs of suicidality, participants (including children and parents/caregivers) will be immediately referred for a psychiatric consultation at the NIH and referred for outside treatment as recommended. If a participant is in need of an urgent evaluation (e.g., is actively suicidal with a plan to carry out such actions) while on the NIH premises, an on-call NIH attending psychiatrist will be contacted for an immediate consultation and intervention until the participant can be safely referred for outside treatment.
3. **Confidentiality** of discussions during the screening, experimental, and ecological momentary assessment portions of the study will be honored. The materials obtained from the participants will be used exclusively for this research project. All personal information on participants will be kept confidential and stored in locked filing cabinets and password protected computers in the laboratory and offices of Dr. Yanovski. All offices are secured with locks. However, each participant will be informed that if the PI or any other study team member learns of any planned actions or current behaviors that may be detrimental to his/her health or the safety or health of others, the information will be shared with the participant's parent/guardian and/or the appropriate authorities.
4. **Body fat measurements by dual-energy x-ray absorptiometry (DXA)** have no significant known risk, other than the inconvenience of the time required. Volunteers undergo DXA scanning using the iDXA system (GE Healthcare, Madison WI). To perform the DXA scan, the subject will be placed between the collimated X-ray source and the detector. This is achieved by having the subject lie down on a cushioned table and

remaining still for 5-10 minutes. The X-ray source and detector are contained in a C-arm construction that is moved to cover the participant. At all times, the child can see, and be seen by, a person standing nearby. A parent may safely be in the room and be in visual and auditory contact with the child. The participant is also in constant voice contact with the operating personnel. Fat, bone, and muscle will be determined during a total body scan. An external standard, simulating bone, fat, and muscle, is scanned along with the participant. This standard allows calculation of total body fat, muscle, bone, and percentage body fat. DXA involves passing a collimated X-ray beam of 45 and 105 keV through the subject and collecting the X-rays that pass through the participant with a standard X-ray detector. Since the delivery and attenuation of the X-rays are measured separately for the two principal energies, the procedure allows the differentiation of substances in their path if the attenuation coefficients of these substances are known. According to the manufacturer's specifications, DXA scanning for body composition using the array beam delivers 0.003 mrem total body radiation.

5. **Radiation exposure**. This research study involves exposure to radiation from three DXA scans (at baseline, 3-months, and 6-months). This radiation exposure is not necessary for medical care and is for research purposes only. Although each organ will receive a different dose, the total amount of radiation exposure participants will receive yearly from this study each year is equal to a uniform whole-body exposure of 0.009 mrem for child subjects This calculated value is known as the "effective dose" and is used to relate the dose received by each organ to a single value. The amount of radiation participants will receive in this study is well below the dose guideline established by the NIH Radiation Safety Committee for child (less than 500 mrem per year) or adult (less than 5000 mrem per year) research subjects. For comparison, the average person in the United States receives a radiation exposure of 300 mrem per year from natural background sources, such as from the sun, outer space, and from radioactive materials that are found naturally in the earth's air and soil. The effective dose that participants will receive from participation in this research study is less than the amount normally received in one day from these natural sources. For more information about radiation and examples of exposure levels from other sources, participants will, upon request, be given a copy of the pamphlet called, An Introduction to Radiation for NIH Research Subjects. This protocol has been submitted for approval by the Radiation Safety Committee.
6. **Urine collection** methods involve no risk but may be inconvenient because of the time required for collection. If participants have difficulty voiding, they will be offered water and asked to try again at a later time. Parents will be informed that girls who are found to be pregnant become emancipated minors for the purpose of health care decision-making, and that the child, not the parent, will be told about a positive pregnancy test.
7. **Phlebotomy** procedures involve <75 mL of blood withdrawal once over the course of the study, which is below the NIH guideline for a safe amount of blood withdrawal. This guideline is based upon body weight, and for a 70 pound child, the maximum amount of blood that can be taken is 1⁄2 pint (225 mL) every six weeks. Drawing blood may be painful, and a small bruise may form at any site where the blood is taken. The risk of infection or fainting is very small. Inflammation or clotting of a vein also may rarely occur.

We will offer ELA-Max cream in an effort to reduce any pain. An area of white or a red rash that usually goes away within a few hours may be seen after use of ELA-Max.

8. **Structural MRI**. Individuals are at risk for injury from the MRI magnet if they have implanted electrical devices, brain stimulators, some types of dental implants, metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), aneurysm clips, permanent eyeliner, implanted delivery pumps, or shrapnel fragments. For this reason, participants will be screened for these contraindications before having any scan. If they have any risk for injury, they will not receive an MRI scan. In addition, all magnetic objects (for example, watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room. Individuals with fear of confined spaces may become anxious during an MRI. The noise from the scanner is loud enough to damage hearing; therefore, participants having an MRI scan will be fitted with hearing protection. On the day of the MRI scan, a urine sample will be obtained from all participants and tested for pregnancy. There are no known long-term risks of MRI scans.
9. **Magnetoencephalography (MEG)** recording is not associated with special risks or inconveniences. MEG recording is a risk-free, non-invasive technique. The sensory stimuli (images of objects and food) are carefully controlled and well below discomfort or seizure inducing levels. However, some youth might get anxious during the recording, from being in a new testing environment, or might find the 20-minute attention bias paradigm stressful or tiresome. Prior experience with 37 anxious and non-anxious children and adolescents indicate that the MEG session is not distressing. Similarly, prior experience with 103 children and adolescents has revealed no such instances of distress during either of the attention bias paradigms using social threat and food cue stimuli. There could be mild discomfort with cleaning the scalp to put the electrodes on or with washing hair after the test. Should a participant become distressed, a psychiatrist or on-call attending will be available.
10. **Attention Retraining (AR)/Control and Ecological Momentary Assessment (EMA)** on the smartphone, as implemented in the current protocol, should involve no risk. Participants' EMA responses are password protected to ensure the security of the information they provide. A participant may be asked why she is responding to one of the scheduled recordings in the study. Study staff will discuss this possibility and brainstorm with the participant what an acceptable response may be for her in this situation. It is possible that someone could see a participant's responses by taking the phone away or peering over a shoulder before he or she finishes submitting responses. Participants may feel uncomfortable if someone else sees their responses. As such, participants will be encouraged to respond in a private setting. Research staff as needed, will stay in close contact with the participants during the two weeks of momentary data collection. If the participant has any problems or concerns, she can contact study staff immediately.
11. **Food ingestion under controlled conditions** involves no risk and is not expected to cause any participant discomfort. Participants who indicate they do not like the foods to be offered will not be studied. Participants will feel somewhat hungry and possibly irritable if they typically eat before approximately 9-10AM, when the breakfast shake is roughly

scheduled to be administered. When conducting feeding studies, participants may suffer from food allergies that restrict the types of foods they are able to eat. If the participant has lactose intolerance, lactase pills will be administered at the beginning of the visit. Similarly, certain ethical and religious beliefs may limit participants from eating foods on the array. In these cases, we will substitute foods that are of equivalent nutritional value and within the same food group. The proposed study will be carried out at the NIH CRC, where there are ample medical resources (including the NIH critical care team) should an unanticipated event occur. Metabolic cooks preparing and measuring foods for test meals have yearly HACCP food safety training that focuses upon safe food handling, proper temperatures, hand washing, and using gloves when handling food. All dietitians also have had training in weighing/processing foods for controlled feeding studies to ensure consistency in the method and presentation.

12. **Time required**. Time commitment will vary depending on the parts of the study participants decide to participate in, as well as eligibility. The screening visit (Visit #1) requires approximately 5 hours on the part of the study participant and their parent/guardian. If they are eligible following this visit, youth will be asked to return to the NIH CRC within one week for a baseline laboratory session (Visit #2) to participate in the attention bias and MEG component of the protocol. This visit will take approximately 4 hours to complete. At the end of that visit, youth will receive instructions on completing the attention training and EMA portion of the protocol using the smartphones. For that portion of this protocol, youth will be asked to respond to various prompts on their smartphones 4x/day for approximately 5 minutes, for 14 days. Estimated time required to respond to all of these prompts is 20 minutes per day (for a total of 280 min or nearly 5 hours). Time commitment for the post-EMA visit (Visit #3) is approximately 4 hours, 4 hours for follow-up 1 (Visit #4), and 4 hours for follow-up #3 (Visit #6).

Participants and their parents/guardians will be informed in detail of all potential risks during the informed consent/assent process.

Benefits: While the psychiatric screening measures and the structural MRI scan may uncover potential health problems, these procedures are not intended to provide participants with information above and beyond data gleaned from their providers' standard health-related assessments. The attention retraining program is an experimental intervention, thus a change in eating patterns as a result of participation cannot be guaranteed. Thus, individuals may not directly benefit from participating in the current protocol. Nonetheless, this research has the potential to help others by defining risk factors for excessive weight gain among children. This research has the potential to inform prevention and intervention efforts for a significant subset of children.

Assessment of Risk/Benefit Ratio: Overall, there are a number of potential benefits, not just to study participants but also to the larger population of child and adolescent girls who are at higher risk for excessive weight gain by virtue of their engagement in disinhibited eating behavior. The risks for participants include possible distress related to thinking about mood and problematic eating behaviors. We do not anticipate this to occur in most participants, and frequent contact with participants during the study visits will enable early detection of potential distress in study

participants. If a participant reports, or demonstrates symptoms suggestive of, increased distress related to her participation in the study, the study team will consider whether it is in her best interest to continue study participation. Participants have the right to withdraw from the study at any time. For both physical and psychological problems, study participation will enable the participant to be screened for clinically-significant pathology, and in cases where identified, may facilitate treatment.

In the literature, there are reports of healthy children who have undergone each of these tests in IRB-approved studies. Individually, all of the procedures proposed as part of this protocol are of low risk. The investigators have further taken many steps to minimize potential discomfort, for instance by providing the lead investigators' extensive contact information to the participant in the event that problems arise outside of office hours while completing the EMA assessments. Furthermore, children are routinely required to complete cognitive tests during school. We believe the study outlined in this protocol is reasonably commensurate with those children may be exposed to in their actual or expected medical, dental, psychological, social, or educational experiences. Additionally, all participants are offered the attention retraining program at their 3-month follow-up, regardless of their original group assignment at baseline. This is to ensure that all participants may receive the potential benefit of this experimental program. We therefore believe that the benefits to both individual participants as well as the larger population of adolescents with eating-pathology outweigh the risks to individual participants.

We believe that the IRB should indicate that permission of one parent is sufficient for this research to be conducted.

Alternatives to Participation: Participants in this study may receive a brief experimental intervention – an attention retraining program – or a control program. They will be randomly assigned to either the intervention or the control condition in a double-blind design. At the 3-month follow-up (Visit #4), participants will be offered a booster intervention and if they elect to complete it, and all participants will receive the intervention regardless of the initial group assignment.

Participants and their families will be informed that they may be eligible for other studies in children who are at risk for adult obesity. The study team will inform the participants of any such studies taking place at the NIH. They will also be provided with the link to www.clinicaltrials.gov to review the ongoing clinical studies. For participants interested in treatment for mood, disordered eating or weight management, treatment referrals will be provided.

e. Privacy and Confidentiality

Data obtained from the participants will be used exclusively for this research project. Samples and data will be coded. The PI and the co-investigators will have access to identifiable participant records. Records containing personal identifiers will be maintained consistent with the security measures required by the NIH. We will follow guidelines developed by the NIH for projects funded by the Federal Government. Prior to managing data, all identifying information including name and address will be removed. All data for the project will be processed and stored by the study team. Electronic data will be password protected and accessible only by authorized study personnel. Electronic (de-identified) data will be backed up daily and stored at a secure server. All hardcopy data will be locked in Dr. Yanovski's storage cabinets in research offices at the NIH

CRC and will be accessible only by authorized study personnel. All data will be collected specifically for the purpose of the current proposed research project. Finally, despite that a number of precautions will be taken to ensure participant confidentiality, data collection in any study is accompanied by threat to privacy and confidentiality. Precautions to be taken against violation of confidentiality are described.

Participants will receive mobile devices (i.e., smartphones) that they will be asked to carry with them and complete assessments, either self-initiated or randomly signaled, as part of the ecological momentary assessment (EMA) portion of the protocol. Regarding AR/Control Program and EMA, Dr. Waters has worked closely for a number of years with a Houston-based company to develop the "Colors" software to administer cognitive assessments and cognitive interventions using EMA. The "Colors" software has been issued a Certification to Operate by the NIMH ISSO on February 18, 2016 (see **Appendix 15**). The software can administer reaction time tasks on mobile devices, individually or in combination, to include the visual probe task to measure attention bias, Stroop, Implicit Association Test, and Go No-Go task. For the proposal, a "native code" app will be used, written in C# in the Windows Mobile environment, using an Android-based smartphone. Data are collected in a local database and transmitted to the Cloud Server in realtime. De-identified participant and study profiles are created on the Cloud Server via a .NET browser based application. The "Colors" application data can be protected by 2048 bit SSL encryption for all participant submitted data. The administration of the application is protected by dual authentication to servers behind a network firewall. The smartphones that participants receive for the duration of the study will be purchased by NICHD.

All research activities will be conducted in as private a setting as possible. Only the staff essential to the research procedures will be present during the visits.

f. Research and Travel Compensation

Participants will be compensated for any burden endured via study participation, including time and inconvenience. Adolescents will receive $70 for each visit, for a potential total of $420. The check for each session will be sent upon completion of the procedures for the respective session. Participants also receive up to $172 for completing the training program: $30 per week (if at least 80% of assessments are complete) and $2 for each completed smartphone assessment (there are 56 assessments total). This applies to the baseline program and the "booster" program 3 months later, for a potential total of $344. This amount is calculated when the participant returns to NIH for the post-EMA session and the check is sent when the procedure for the respective post-EMA sessions are completed. The total compensation that the participants may receive as a result of completing all the procedures in the study is $764. Additionally, some participants may be scheduled for the anatomical scan on a day separate from their study visit, contingent on the availability of the scanner. Those participants will be compensated an additional $50 for their time and inconvenience. If a participant withdraws early from any component of the study, she will be paid $20 per hour of study protocol completion.

g. Consent/Assent Process and Documentation

In obtaining and documenting informed consent, all study staff will comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and will adhere

to ICH GCP.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent and Assent forms will be Institutional Review Board (IRB)-approved and the participant (and/or parent/guardian) will be asked to read and review the documents. The principal investigator or associate investigators/Key Study Personnel with appropriate expertise will obtain written, active consent before the Screening Visit or as the first activity conducted at the Screening Visit (Visit #1). The purpose of the project, all testing procedures, and study components, and of their rights as research participants, will be described in detail in terms suited to the participant's comprehension. Potential participants will be informed that the purpose of the study is to explore how the brain works during cognitive tasks and whether training attention away from unhealthy foods might help youth consume less of those foods. The NIH informed consent and assent forms will be signed. Potential participants and their parents will also be informed of the possible risks and inconveniences of the study. The investigator will answer any questions that may arise. The investigator will also explain the study assent form to minors using appropriate language. Sufficient time and opportunity will be given for discussion of the research as well as to answer any questions all may have, taking care to minimize or eliminate the perception of coercion or undue influence. Consent forms include waivers of confidentiality for suicide, child abuse, and homicide, for which we are mandated reporters.

Participants will have the opportunity to carefully review the written consent form and ask questions before signing. The participants will have the opportunity to discuss the study with their family or surrogates and given time to think about it prior to agreeing to participate. The participant (or parent/guardian) will sign the informed consent document prior to any procedures being done specifically for the study. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The informed consent form (and assent if applicable) will be signed before the participant undergoes any study-specific procedures. The investigator-designated research professional obtaining the consent (and assent if applicable) must also sign the informed consent and assent form (if applicable). A copy of the informed consent/assent documents will be given to the participants for their records. The informed consent process will be documented in the medical record (including the date), and the original completed forms will be kept in the participant's medical record with a copy in their research chart.

Informed consent documents (and assent documents, if applicable) may be printed to sign and date in ink, or the electronic documents may be signed with a hand signature using a finger, mouse or stylus via an approved platform. Participants may be asked to complete the consent process electronically via iMed and Docusign, which are both 21 CFR Part 11 compliant. Once identity is confirmed, consents can be electronically signed, date-stamped, and routed to the PI for electronic signature. Once the PI has logged into the secure site and digitally signed the consent, a pdf of the signed consent is created. As is done for forms signed in ink, the participant will be provided with a copy of the signed document, and can also contact our study staff to obtain a hard copy of the consent at any point in this process.

Parents or guardians will be given a signed copy of the consent and assent form for their records. Youth will be required to sign an informed consent form confirming their desire to continue their participation in the current protocol should they turn 18 years during the course of the study. In the unlikely event that the parents/guardians of protocol-eligible subjects cannot travel to the NIH Clinical Center for a considerable period of time, the PI or other protocol staff designated to obtain consent will obtain informed consent by a telephone conversation. Consent may be obtained via telephone and/or another electronic process, rather than in person. In such cases, the written signed consent will be faxed and/or mailed and made part of the patients' NIH records. No research procedures will commence until the investigator has confirmed that written, legally effective consent has been obtained.

For assent of children

All adolescent participants are expected to be able to comprehend and be included in all discussions about the trial. Age-appropriate language will be used to describe the procedures and tests involved in this study, along with the risks, discomforts, and benefits of participation. All child study participants, who will be between age 12 and <18 years will be asked to sign an age-appropriate assent form. The consent/assent process will be documented in the child's medical record. All children will be contacted after they have reached the age of 18y to determine whether they wish to continue participating in the trial; informed consent will be obtained from them at that time.

Telephone consent

In certain instances, the PI or designee will obtain informed consent by a telephone or video conversation with a protocol-eligible subject who cannot travel to the NIH Clinical Center for a considerable period of time. A parent/guardian will be involved if the subject is <18 years of age.

The informed consent document will be sent to the subject by mail, email, or fax. An explanation of the study will be provided over the telephone or other electronic media after the subject has had the opportunity to read the consent form. The informed consent form will be signed and dated.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was returned.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator.

The investigator will confirm that, when required, written legally effective consent has been obtained prior to initiating any study interventions.

Telephone assent

The informed consent and assent documents will be sent to the parents/guardian and child. An explanation of the study will be provided over the telephone after the parents/guardian and child have had the opportunity to read the documents. Age-appropriate language will be used to discuss the study with the child. The parents/guardian will sign and date the informed consent. The child will sign and date that form. All children will be contacted after they have reached the age of 18y to determine whether they wish to continue in the trial and informed consent will be obtained from them at that time.

The original signed informed consent and assent documents will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was returned.

A fully executed copy will be returned via mail to the subject.

The informed consent and assent process will be documented on a progress note by the consenting investigator.

Consent for minors when they reach the age of majority

When a pediatric subject reaches age 18y, continued participation (including ongoing interactions with the subject or continued analysis of identifiable data) will require that consent be obtained from the now adult with the standard protocol consent document to ensure legally effective informed consent has been obtained.

If reconsent is not feasible, we request waiver of informed consent to continue to use data and/or specimens for those individuals who become lost to follow up or who have been taken off study prior to reaching the age of majority.

Requirements for Waiver of Consent consistent with 45 CFR 46.116 (d):

(1) The research involves no more than minimal risk to the subjects.
    a. Analysis of samples and data from this study involves no additional risks to subjects.
(2) The research could not practicably be carried out without the waiver or alteration.
    a. Considering the length of time between the minor's last contact with the research team and their age of majority, it will likely be very difficult to locate them again. A significant reduction in the number of samples analyzed is likely to impact the quality of the research.
(3) As the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

a. Though the purpose of future studies cannot yet be known, they often involve the correlation of clinical outcomes and clinical interventions with laboratory studies. Such information would be unavailable if access to medical record numbers was unavailable.

(4) The waiver or alteration will not adversely affect the rights and welfare of the subjects.
   a. Retention of these samples or data does not affect the welfare of subjects.

(5) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
   a. We only request a waiver of consent for those subjects who have been lost to follow-up or who have been taken off study prior to reaching the age of majority.

Non-English-Speaking Participants

Non-English-speaking participants will be excluded from the study as they may be unable to complete questionnaires and follow the instructions which are only provided in English. If an English-speaking participant with a non-English speaking parent is eligible for enrollment, the parent will be provided with the CC Short Written Consent Form for Non-English-Speaking Research Participants in the participant's native language and a verbal explanation of the purpose, procedures and risks of the study as described in MAS Policy M77-2, NIH HRPP SOP 12 and 45 CFR 46.117(b)(2). The IRB-approved English consent form will serve as basis for the verbal explanation of the study. The investigator will obtain an interpreter unless the investigator is fluent in the prospective participant's language. The interpreter will be someone who is independent of the participant (i.e., not a family member). Interpretation services provided by the CC will be used. The interpreter will interpret all oral communications (English to target language and conversely) between Investigator and Participant, facilitate discussions, and ensure understanding.

The IRB-approved English consent form will be signed by the investigator obtaining consent and a witness to the oral presentation. The CC Short Written Consent Form will be signed by the participant and a witness who observed the presentation of information. The interpreter may sign the consent document as the witness for both documents and, in this case, will note "Interpreter" under the signature line. A copy of both signed forms will be provided to the participant to take home. The investigator obtaining consent will document the consent process in the participant's medical record, including the name of the interpreter.

h. Pharmaceutical, Biological, and Device Information

Participants will receive mobile devices (i.e., smartphones) that they will be asked to carry with them and complete assessments, either self-initiated or randomly signaled, as part of the ecological momentary assessment (EMA) portion of the protocol. Regarding EMA, Dr. Waters has worked closely for a number of years with a Houston-based company to develop the "Colors" software to administer cognitive assessments and cognitive interventions using EMA. The software can administer reaction time tasks on mobile devices, individually or in combination, to include the

visual probe task to measure attention bias, Stroop, Implicit Association Test, and Go No-Go task. The program been used successfully in non-smokers, smokers, heroin/cocaine addicts undergoing detoxification, and recovering alcoholics. The program has also been used successfully to administer attentional retraining (155). To the best of our knowledge, this is the most sophisticated software currently being used for the assessment of cognitive biases in ecological momentary assessment studies.

i. Recruitment Strategies

Participants will be recruited through mailings to families in the Washington, D.C. greater metropolitan area, a successful method for our community- and intervention-based studies of youth with LOC eating (40, 43, 47, 58, 100). The advertisements will also be distributed on the local school and youth organization listservs (with permission), posted on the local bulletin boards (e.g., libraries, supermarkets, fitness clubs) with permission, and posted on free online social media (e.g., Facebook, Twitter, Instagram, LISTSERVs, ResearchMatch, CC News/NIH Record) and online services such as "Craigslist" and "Facebook." These recruitment strategies have been highly effective in previous studies. Participants will call the phone number associated with the study and be pre-screened on the phone before attending the screening session. It is anticipated that on average three participants per week will be screened, and two participants per week will be enrolled. See **Appendix 16** for a study recruitment methods. See **Appendix 17 and Appendix 18** for the sample recruitment materials.

j. Description of Criteria for Withdrawal from the Study

Participants will be examined briefly on the phone during the initial screening, and more extensively during the screening visit (Visit #1) as well as the follow-up visits. Participants will be excluded and/or referred for treatment if appropriate, as previously described. Identification of a current and significant psychiatric disorder at the time of enrollment will result in an appropriate referral to a mental health professional and study exclusion. Noncompliance with study procedures may lead to withdrawal of study participants. Other events that may lead to study withdrawal include pregnancy or serious unanticipated complications, including development of any medical problem listed in the exclusion criteria. Please see Section 16: *Reporting of Unanticipated Problems, Adverse Events and Protocol Deviations* for more details regarding adverse event reporting.

k. Re-evaluation of the Study

During and after the first several participants participate in the proposed procedures, data collection will be monitored closely to ensure that data are being collected as proposed. For example, we will download data from our first participant's computerized attention bias tasks and magnetoencephalography, as well as her smartphone reaction time task data to ensure that these data are computing as expected. Adjustments, as needed, will be made to the procedures to obtain the data proposed in the current protocol. In such cases, a request to amend the protocol will be submitted to the IRB.

l. Collection, monitoring, analysis and reporting of adverse events

1. **Data and Safety Monitoring**: Since the study does not involve administration of any

pharmaceutical agents, but rather administration of a low-risk cognitive intervention, and the procedures are of little risk, we propose that a formal DSMB is not required, and the investigators and IRB can adequately supervise this study. Data and safety will be monitored by Dr. Jack Yanovski, the Principal Investigator. Dr. Yanovski is responsible for coordinating data collection and will review the data for accuracy and completeness within 30 days of each subject visit, including review of patient consent documents. An evaluation of patient recruitment, accrual, and retention as specified in the protocol will be ongoing. Review of literature and results of related studies will be assessed throughout the study for any impact on patient safety or ethical questions.

All IRB documentation can be found in the NIH Integrated Research Information System (iRIS). Dr. Jack Yanovski is responsible for maintaining IRB documentation, including records of all reviews of the study and submissions to the IRB. Dr. Tanofsky-Kraff is responsible for facilitating the sending of paperwork (e.g. Amendments to the protocol) for review by USUHS as per the established IRB Authorization Agreement), to ensure that Department of Defense requirements are met. Dr. Tanofsky-Kraff will also be responsible for returning paperwork from USUHS regarding protocol actions to Dr. Yanovski. This protocol does not meet the criteria as outlined in the NIH HRPP SOP 17 for data to be submitted to a monitoring committee. Clinical Trial Studies (non IND/IDE) will have random audits performed by the NICHD Office of the Clinical Director (https://science.nichd.nih.gov/confluence/display/ocd/Protocol+Navigation). Dr. Yanovski will maintain subjects' records for at least three years after completion of the study.

2. Quality Assurance: The Principal Investigator, Dr. Jack Yanovski, will perform the quality assurance monitoring. The NICHD Standard Operating Procedure for Intramural Clinical Protocol Monitoring (rev. 5.20.2015) will be followed.

3. Reporting of unanticipated problems, adverse events, and protocol deviations:

Adverse events: We expect that the risk for an adverse event during this protocol will be below the "Rare but Serious (Event Rate < 1%)" category.

Event Characterization and Reporting to the IRB and Clinical Director (CD): Unanticipated problems, non-compliance, and other reportable events will be reported to the NIH IRB as per Policy 801. All adverse events occurring during the study, including those observed by or reported to the research team, will be recorded. All adverse events (serious and non-serious, expected and unexpected) will be reported to the IRB at the annual continuing review in the form of electronic data sheets or summary language.

This study involves an intervention/social science protocol, with multiple participant encounters. The six-month protocol may involve up to 6 separate encounters (depending on eligibility for participation in experiments), all of which involve little risk. Thus, we expect few adverse events to occur as a direct result of participating in our research protocol. However, the majority of our participant will report recent disordered eating behavior (specifically LOC eating), which has been prospectively associated with onset of threshold binge eating disorder and psychosocial problems. Thus, we would expect that a significantly higher proportion of youth in our LOC eating group would experience the onset of threshold

mental health disorders. Thus, we will anticipate and monitor for the following adverse events: 1) onset of threshold psychiatric disorders, and 2) suicidal thoughts. Should any of these events occur, youth (and their parents/guardians if under 18 y) will be notified and they will not be considered reportable adverse events.

m. Conflicts of Interest:

NIH guidelines on conflict of interest have been distributed to all investigators. There are no conflicts-of-interest to report for NIH investigators. Non-NIH investigators will abide by the conflict-of-interest policies of their own institutions.

n. Monitoring Plan:

1. Purpose

The purpose of this Monitoring Plan is to describe the rationale and process for the collection, recording, and verification of data for NICHD Protocol "Mobile Attention Retraining."

2. Objectives

a. To establish a monitoring plan to ensure the protocol data are in compliance with Good Clinical Practice (GCP), Institutional Review Board (IRB) and Data Safety Monitoring Committee policies, and Federal regulations.
b. To ensure the validity, accuracy and integrity of the data

3. Study Staff Responsibilities

Jack A. Yanovski, MD, PhD *(the principal investigator) is responsible for all aspects of the study. Some responsibilities may be delegated to the current Associate Investigators*.

Delegation of responsibility will be documented on a study staff ***Signature and Delegation of Responsibility Log.***

4. Source Documentation and Case Report Forms

The Principal Investigator (***Jack A. Yanovski, MD, PhD) and co-investigators as specified above,*** are responsible for coordinating data collection and will review the data for accuracy and completeness within seven days of each subject visit, including review of patient consent documents.

The Principal Investigator (***Jack A. Yanovski, MD, PhD)*** along with study co-investigators will conduct the monitoring. Patient consent documents, primary outcome and safety laboratory results and diagnostic test results will be monitored for accuracy, correct dating, and agreement between case report forms and source documents. As case report forms are entered electronically into the NICHD Clinical Trials Database, the

computer system contains logs indicating changes made and the circumstances leading to these changes.

5. IRB and DSMC Documentation

All IRB documentation can be found in iRIS. The Principal Investigator, ***Jack A. Yanovski, MD, PhD***, is responsible for maintaining IRB correspondence related to this protocol, including records of all reviews of the study and submissions to the IRB.

Dr. Tanofsky-Kraff is responsible for IRB documentation at USUHS, which also reviews this research.

This protocol does not meet the criteria as outlined in the NIH HRPP SOP 17 for data to be submitted to a data safety monitoring committee. The PI and IRB can provide adequate oversight for this trial.

Clinical Trial Studies (non IND/IDE) will have random audits performed by the NICHD Office of the Clinical Director (policy: https://science.nichd.nih.gov/confluence/display/ocd/Protocol+Navigation).

6. FDA Documentation

Not Applicable – no IND.

7. Adverse Event Procedures and Documentation

Unanticipated problems, non-compliance, and other reportable events will be reported to the NIH IRB and the Clinical Director (CD) using iRIS, in accordance with Policy 801. When iRIS is not available, the NIH Problem Report Form will be used. (https://federation.nih.gov/ohsr/nih/ohrdocs/NIH_Problem_Report_Form_Fillable_DDIR_v1_6-11-13_508.pdf).

An aggregated summary of all UP's, PD's, UADE's, and AE's will be reported to the IRB at the time of Continuing Review (CR).

8. Study Completion

Upon completion of the study ***Jack A. Yanovski, MD, PhD*** will retain possession of the electronic Protocol Binder in a secure location. HHS regulations require that subjects' records be maintained for at least three years after completion of a study. Since subjects of this investigation are children, even longer record retention is required. All records will be retained until all participants have reached age 23.

IX. List of Appendices

- Appendix 1: Eligibility Checklist
- Appendix 2: Timeline of Procedures
- Appendix 3: Phone Screen
- Appendix 4: Screening Visit Physical Exam Form
- Appendix 5: Eating Disorder Examination (EDE) and Eating Disorder Examination adapted for Children (ChEDE)
- Appendix 6: Youth Questionnaires

- Appendix 7: Supplemental Assessment
- Appendix 8: Parent Questionnaires
- Appendix 9: MEG and MRI
- Appendix 10: Food Cue Attention Bias Task
- Appendix 11: Social Threat Attention Bias Task
- Appendix 12: Laboratory Meal Image
- Appendix 13: EMA Questions
- Appendix 14: Follow-up Physical Exam Form
- Appendix 15: Certification to Operate for "Colors" software
- Appendix 16: Study recruitment methods
- Appendix 17: Recruitment materials
- Planned Enrollment Table

X. Consent Documents

- Adult consent for minor subject
- Child subject assent
- Consent for child who becomes 18-years-old during the study

XI. References

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