NEURAL UNDERPINNINGS OF ANXIETY IN RELATION TO EATING BEHAVIORS IN ADOLESCENCE

by:

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Uniformed Services University of the Health Sciences

Dissertation submitted to the Faculty of the
Medical and Clinical Psychology Graduate Program
Uniformed Services University of the Health Sciences
In partial fulfillment of the requirements for the degree of
Doctor of Philosophy 2021

Distribution Statement

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April 13, 2021

MEMORANDUM FOR ASSOCIATE DEAN OF GRADUATE EDUCATION

SUBJECT: Doctor of Philosophy Defense

1. Meghan Byrne, a Medical and Clinical Psychology student, has submitted the Dissertation to the Committee Members and is ready to defend. Therefore, I would like to schedule the Doctoral Defense.

2. Committee members:

Tracy Sbrocco, PhD, Department of Medical and Clinical Psychology
(Committee Chair)

Marian Tanofsky-Kraff, PhD, Department of Medical and Clinical Psychology
(Dissertation Advisor)

Andrew Waters, PhD, Department of Medical and Clinical Psychology

Jack Yanovski, MD, PhD, National Institute of Child Health and Human Development
(outside member - where, i.e., NIH, FDA. If not at USU, provide email address)

3. Date and time of Private Defense:

1, April, 2021 at 1300 via Zoom

4. Date and time of Public Defense:

29, April, 2021 at 1500 via Zoom

5. Title of Dissertation: "Neural Underpinnings of Anxiety in Relation to Eating Behaviors in Adolescence"

Marian Tanofsky Kraff
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Advisor

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Graduate Education Office (A 1045), 4301 Jones Bridge Road, Bethesda, MD 20814

April 14, 2021

MEMORANDUM FOR: **DR. TRACY SBROCCO**
DR. MARIAN TANOFSKY-KRAFF
DR. ANDREW WATERS
DR. JACK YANOVSKI

SUBJECT: Appointment to the Final Doctoral Examination Committee for Meghan Byrne

In accordance with the School of Medicine Graduate Program Guidelines, you are formally appointed to the Final Examination Committee of Meghan Byrne, doctoral student in the Department of Medical and Clinical Psychology.

This Committee will evaluate the scope and quality of the student's Dissertation and certify the document's acceptability.

In addition, the Committee will conduct an Oral Examination of the student's scientific knowledge, as well as the knowledge and understanding of the research project and Dissertation. This examination constitutes the Private Defense.

The Private Defense for Meghan Byrne will take place on Thursday, April 1, 2021 at 1:00 PM via Zoom meeting.

Dr. Tracy Sbrocco is appointed Chair of the Examination Committee. Dr. Sbrocco will oversee the examination. Passage of the Private Defense will be by majority vote. If corrections to the Dissertation are needed, the Chair may oversee this process and sign-off after the corrections are made.

The Committee Chair should return the signed and dated Final Examination/Private Defense Form and the Dissertation Approval Form to the Graduate Education Office.

GEO thanks you in advance for your participation in the SOM Graduate Program process.

[redacted]

Saibal Dey, Ph.D.
Associate Dean for Graduate Education

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FINAL EXAMINATION/PRIVATE DEFENSE FOR THE DEGREE OF DOCTOR OF PHILOSOPHY
IN THE DEPARTMENT OF MEDICAL AND CLINICAL PSYCHOLOGY

Name of Student: Meghan Byrne

Date of Examination: April 1, 2021
Time: 1:00 PM

DECISION OF EXAMINATION COMMITTEE MEMBERS:

	PASS	FAIL
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APPROVAL OF THE DOCTORAL DISSERTATION IN THE DEPARTMENT OF MEDICAL AND CLINICAL PSYCHOLOGY

Title of Dissertation: "Neural Underpinnings of Anxiety in Relation to Eating Behaviors in Adolescence"

Name of Candidate: Meghan Byrne
Doctor of Philosophy Degree
April 1, 2021

DISSERTATION AND ABSTRACT APPROVED:

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ACKNOWLEDGMENTS

First and foremost, I would like to wholeheartedly thank my advisor, Dr. Marian Tanofsky-Kraff. Her warm guidance, brilliance, and tenacity over the past five years have pushed me farther in my accomplishments than I ever imagined possible. Not only has her mentorship afforded me opportunities I could have never dreamed of, but she has also proven to be a lifelong role model from whom I will continually learn and grow. I will always be incredibly grateful for knowing her, being taken under her wing, and being guided by her. I look forward to many years of traversing alongside Marian and basking in her glow. I would also like to thank Dr. Jack Yanovski for generously affording me such unparalleled and thrilling research opportunities at the National Institutes of Health. I am exceedingly thankful to have simply been in proximity to his wisdom and to have absorbed so much knowledge from his exceptional direction. I will forever be a more capable scientist because of working with him. Additionally, my graduate school experience would not have been quite the same without the tremendous support of my wonderful fellow lab mates at USU. I would like to thank them for their generosity of time, collaborative and inviting nature, and for sharing their brilliant insights. Outside the walls of my academic experience, I of course want to thank my family for their loyalty and unwavering love throughout my long academic journey. They have watched me grow from someone full of self-doubt into a woman who seeks out challenges and pursues her passions fearlessly. I never take for granted the ideals they have instilled in me. In thinking of my family, I especially want to acknowledge all the strong and resilient generations of women who have come before me, whose sacrifices made it possible for me to tread this exciting path. Lastly and especially, to my fiancé, Kareem, thank you for always being my rock. Whether or not you anticipated the many long nights of studying, writing, presentation preparations, vacillating emotions, and cross-country moves when you first

encouraged me to consider graduate school, you have graciously and effortlessly shouldered me through this entire journey. From day one, you have emboldened me when I had doubts, cheered my successes, and have unshakingly believed in my abilities even when I didn't believe in myself. It has not always been an easy path, but your radiating positivity, strength, and unmatched perspective has energized me to consistently look forward. You make me better every day.

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ABSTRACT

Title of Dissertation: Neural Underpinnings of Anxiety in Relation to Eating Behaviors in Adolescence

Meghan E. Byrne, M.S.

Thesis directed by: Marian Tanofsky-Kraff, Ph.D., Professor, Department of Medical and Clinical Psychology

Loss of control (LOC) eating, a hallmark feature of binge eating disorder, involves the subjective experience of being unable to control what or how much is being consumed. LOC eating in youth is highly comorbid with anxiety, suggesting shared neural underpinnings and/or etiologies. Data suggest youth with LOC eating may have an attention bias to socially threatening stimuli. Heightened sensitivity to incoming social cues and abnormalities in anxiety processing socio-emotional neural circuits may partially account for this relationship. The interpersonal model of disordered eating may help to explain this pattern of attention bias; however, the interpersonal model has not been directly tested making use of a task to assess attention bias to social threat cues among youth with LOC eating. Utilizing magnetoencephalography (MEG) can help to elucidate the neural bases of attention bias toward threat that may contribute to LOC eating. The current study examined the relationship between attention bias to social threat cues and neural activation implicated in social anxiety and subsequent energy intake at a laboratory test meal in youth with overweight, with and without LOC eating. All participants (N = 55; M_{age} = 15.2 ± 1.7y; BMI-z = 1.8 ± 0.4; 29% with LOC eating) were female, between the ages of 12-17 years, and had overweight or obesity (BMI ≥ 85th percentile). Results were largely null, with a few notable findings that should be interpreted with

caution. There was a significant relationship for % energy consumed from protein, such that greater amygdala activation during top-down attention deployment was associated with lower % energy consumed from protein (p = .01). Further, there was a marginally significant relationship for % energy consumed from carbohydrates, such that greater amygdala activation during top-down attention deployment was associated with greater % energy consumed from carbohydrates (p = .03). These findings suggest that a potential mechanism for maladaptive eating patterns may be heightened activation in anxiety processing regions due to sustained attentional deployment toward social threat. A better understanding of the neural underpinnings involved in the links between LOC eating and anxiety may aid in the development of novel targets for reducing excess intake that leads to exacerbated disordered eating and adult obesity.

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CHAPTER 1: INTRODUCTION

Loss of control (LOC) eating, a key feature of binge eating disorder (BED), is commonly reported by youth with higher weight (261) and adolescent girls of all weight strata (2). Data indicate that LOC eating in childhood may be a prospective marker for adverse outcomes. Of concern, LOC eating is a precursor to partial- or full-syndrome BED as well as increases in depressive and anxiety symptoms, higher risk for excess weight and fat gain, and worsening of metabolic syndrome components (118; 254). LOC eating in youth is highly comorbid with anxiety (104; 173; 223; 254), and is predictive of increases in anxiety symptoms over time (118; 254), potentially suggesting shared neural underpinnings and/or etiologies. Indeed, neuroimaging data shows that girls with overweight or obesity who reported LOC eating demonstrated a neural response to social distress similar to the response of youth with anxiety (125). These data suggest youth with LOC eating may have an attention bias (preferential allocation of attention to highly salient stimuli) to socially threatening stimuli. This attention bias may be explained by the interpersonal model of disordered eating. According to interpersonal theory (Figure 1), LOC eating may develop as a result of maladaptive coping with negative affective states, such as anxiety, that arise from socially distressing situations (30; 164; 244; 290). Food consumption is triggered as an attempt to cope with the uncomfortable affective state. This maladaptive strategy may be due, in part, to heightened sensitivity to incoming social cues and abnormalities in anxiety processing socio-emotional neural circuits (125; 190). Notably, there are data to suggest that anxiety, specifically, plays a role in the relationship between social cues and consumption of overeating highly palatable foods in youth with reported LOC eating (125; 218; 256). This further bolsters the notion that the interpersonal model may help to elucidate a mechanism for LOC eating in some youth. However, the interpersonal model has not been directly tested making use of a task to assess attention bias to social threat cues among youth with LOC eating.

Further, there are no data to indicate whether LOC eating impacts the relationship between attention bias to social threat and neural aspects of anxiety processing and subsequent eating behaviors. The temporal nature of attention bias to social threat and activity in neural circuits involved in anxiety processing is ideally suited for measurement by magnetoencephalography (MEG), which has both excellent temporal and acceptable spatial resolution (66; 67; 111). Thus, utilizing MEG may elucidate the neural bases of attention bias toward threat that may contribute to LOC eating. The current study examined the relationships between attention bias to social threat cues, neural activation implicated in social anxiety, and subsequent energy intake at a laboratory test meal in youth with overweight, with and without LOC eating. A better understanding of the neural underpinnings involved in the links between LOC eating and anxiety may aid in the development of targets for reducing excess intake that leads to exacerbated disordered eating and adult obesity.

At the outset of this dissertation, a broad overview of the literature on primarily pediatric obesity and BED will lay the foundation for the importance of research in this area. Given youth are less likely to experience full-syndrome BED, LOC eating will be defined and delineated in relation to its physiological and psychosocial contributors and consequences. Included within the discussion of physiological factors related to LOC eating will be a description of the physiological bases of appetite. Chronic stress in youth and the physiological influence of psychosocial stress on appetite and eating will be described, in addition to the underlying neurobiology of these relationships. Subsequently, a review of the research on anxiety, and its close links to LOC eating, as a driver of excess consumption will follow. Interpersonal theory will be outlined to describe the relationships among these variables. The review of the literature and the theoretical basis of the interpersonal model will lay the framework for the current study,

which aims to integrate prior research in the field and fill the gaps in the literature on underlying neurobiology of LOC eating and anxiety in youth. Lastly, aims and hypotheses will be delineated, methods to test specified aims will be outlined, and results will be discussed.

OVERWEIGHT AND OBESITY

Adult Overweight/Obesity

The prevalence of overweight (body mass index, BMI, ≥85th percentile for age and sex) in the United States has more than tripled in the past four decades (89; 179). Further, when considering rates of overweight (BMI ≥ 25 kg/m²) in adults, well over half of the population meets classification, with recent prevalence of adult overweight estimated at 68% (89; 179). Current estimates indicate that 35% of men and 40% of women in the U.S. have obesity (BMI ≥ 30 kg/m²). Class 3 obesity, defined as BMI ≥ 40 kg/m², is estimated to be present in almost 6% of men and 10% of women in the U.S. Overweight and obesity are associated with a range of adverse medical comorbidities (97). Among adults, obesity is associated with a number of medical comorbidities including type 2 diabetes mellitus, coronary heart disease, gall bladder disease, an increased incidence of certain forms of cancer, respiratory complications such as obstructive sleep apnea, hyperlipidemia, hypertension, depression, and osteoarthritis (145; 183), as well as all-cause mortality (21; 88). Common psychological comorbidities of overweight and obesity include internalizing disorders such as depression and anxiety (33; 38; 207). The economic consequences of obesity are concerning as well; conservative estimates of weight-related disease costs and health care expenditures in the United States are roughly $78.5 billion each year (87; 271).

Pediatric Overweight/Obesity

Prevalence of Pediatric Obesity

The current prevalence of pediatric obesity is at a peak level in U.S. history. Approximately one-third of U.S. children between the ages of 2-19 years old are overweight, and 17% are classified as having obesity, while rates of extreme obesity are roughly 6% in youth (95; 149; 177; 179). For children and adolescents, overweight is defined as at or above the 85th percentile and obesity is defined as at or above the 95th percentile, adjusted for age and sex (149; 177; 178). Given the shift of those on the highest end of the obesity spectrum, most recently, an additional "extreme" or "severe" obesity category has been described as BMI ≥120% of the 95th percentile for age and sex (72; 92-94). Pediatric overweight is highly problematic given children and adolescents with higher weight are more likely to develop into adults with obesity (227).

Course of Pediatric Obesity

Pediatric obesity is highly persistent and tends to track into adulthood (15; 226; 227; 288). Weight trajectories have been studied in pediatric samples from infancy to adulthood. Increased risk for obesity can start as early as infancy, with the most rapid period of incremental weight gain occurring roughly between the ages of 2 and 6 years old (99). Although the majority of infants with obesity revert to overweight or non-overweight in childhood, a large proportion of infants with excess weight tend to remain so into childhood (293), which in turn, tends to continue to obesity in adolescence (99; 157). Once in childhood, only one-third of young children with obesity will experience persistent remission when followed from kindergarten through eighth grade (157). Generally, about 55% of children with obesity and 80% of adolescents with obesity maintain their weight status into adulthood (226), underscoring adolescence as a particularly vulnerable time for intervention and prevention of excess weight

gain. Additionally, while there is considerable genetic and familial impact on pediatric obesity (76; 167; 215; 281), the natural course of adiposity gain suggests psychological and behavioral influences during development may play equally as important of a role in the progression of obesity.

Correlates and Outcomes of Pediatric Obesity

Pediatric overweight is related to serious medical risks such as elevated blood pressure and dyslipidemia (74), as well as certain types of cancer later in life, including breast, colon, kidney, and esophageal cancer (123). Obesity is considered a primary contributor to metabolic syndrome (MetS), defined as a cluster of adverse physiological health abnormalities including abdominal obesity as well as abnormal cholesterol, blood sugar, and triglyceride concentrations that increase one's risk for heart disease and type 2 diabetes (296). Given the serious medical consequences associated with obesity, development of obesity during childhood and adolescence is considered a major public health concern. Additionally, pediatric obesity generates considerable financial burden in both direct healthcare and indirect productivity costs across the lifetime (110), making it a significant economic concern as well. As such, a focus on intervention and prevention efforts for pediatric obesity are critical in order to minimize adverse medical and economic consequences.

Obesity Intervention and Treatment

Results of several recent meta-analyses suggest that interventions designed to reduce or prevent obesity are generally statistically efficacious as compared to outcomes from control groups, but usually do not induce clinically-relevant reductions in body weight expected to impact on comorbid conditions or long-term outcomes (144; 272). Currently, the recommended approach to pediatric obesity is behavioral weight loss or maintenance treatment. Response rate

for treatment of childhood obesity is variable, and there may be individual differences in youths' responsiveness to behavioral modification therapy. Some studies have shown that younger children tend to respond better than adolescents to behavioral treatments (143), identifying adolescents as a group in need of further and more specified intervention research. Further, efficacy of behavioral weight loss or maintenance treatments are seen regardless of treatment dose, intensity, or duration of treatment (117; 272), meaning there is insufficient research to provide specific recommendations for development of future interventions. Individual differences may explain the mixed findings regarding efficacy of behavioral weight loss treatments in youth. Given obesity treatment effects in both adulthood and childhood are often transient and are eventually followed by weight regain (294), obesity prevention among youth has become a vital target of researchers (193).

BINGE EATING DISORDER

A well-researched, modifiable contributor to obesity is binge eating, defined as the consumption of a large amount of food accompanied by a perceived inability to stop eating that causes distress. According the current Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), binge eating disorder (BED) is characterized by the consumption of a large amount of food and the experience of loss of control (LOC) over eating (7). Full-syndrome BED is characterized by recurrent, objectively large binge episodes, the absence of regular compensatory behaviors, and significant distress surrounding binge episodes (7). DSM-5 criteria for BED are listed in Table 1. Personal and familial history of obesity is a prominent risk factor for binge-type eating disorders (137), and twin studies reveal that additive genetic factors account for approximately 40% to 60% of liability for BED (270). The transition from late

adolescence to early young adulthood may be a time of particularly increased risk for disordered eating, given binge eating and BED symptoms tend to persist or worsen during this time (107).

PEDIATRIC LOSS OF CONTROL EATING

Overview of LOC Eating

Background and Definition of LOC Eating

Full-syndrome diagnosis of BED (see Table 1) is uncommon in childhood (251; 261). Several criteria of DSM-5 BED likely contribute to the decreased likelihood of diagnosis in childhood. First, while binge eating involves consuming an objectively large amount of food, it can be difficult to determine what constitutes a large amount among growing boys and girls at different developmental stages (159; 224). Additionally, younger children tend to have less autonomy over food decisions compared to older adolescents or adults, and as such may not have access to objectively large amounts of food. Although children are less likely to meet criteria for a diagnosis of BED, many youths report they experience a subjective sense of loss of control over eating without necessarily consuming an objectively large amount of food. As a result, this has prompted most researchers studying children and adolescents to examine LOC eating as opposed to, or in addition to, binge eating episodes. Thus, LOC eating, regardless of the amount of food consumed, is typically a key target when studying pediatric samples. Defined empirically, LOC over eating involves the subjective experience of being unable to control what or how much is being eaten (263; 292), and is a key feature of BED (7).

Prevalence of LOC Eating

LOC eating is highly prevalent in children and adolescents (116; 251), particularly in those with overweight or obesity. A meta-analysis estimated that across studies, approximately 31% of youth with overweight or obesity report LOC eating (116). Roughly 23% of youth of

across weight strata report LOC eating in the past month, with almost 10% reporting recurrent episodes (211). Adolescence, in particular, is a critical stage of development (54; 284) during which LOC eating patterns and related psychological and medical problems are exacerbated. Prevalence of disordered eating increases substantially in adolescence (63; 141), and the likelihood of engaging in LOC eating increases with stage of pubertal development and age for girls (73). Greater severity and prevalence of LOC eating is observed among girls, with prevalence rates of LOC eating typically twice as high in adolescent girls compared to their male peers (2; 263). Girls with LOC eating exhibit differences in impairment of psychological (269) and social functioning (199) compared to boys with LOC or girls without LOC eating.

The criteria used to estimate prevalence of LOC eating are inconsistent across studies. For example, some studies classify LOC eating in youth as "at least one episode of LOC eating in the past month," (211; 254) while others use "one episode in the past three months," (100; 106) "one episode in the past year," (229; 230) or "ever reported LOC eating" (249). As a result, the reported estimates of LOC eating, particularly among youth, may not be precise. However, data indicate that youth who report ever experiencing LOC eating appear to be distinguishable from those who have never experienced LOC, with these youth displaying higher levels of anxiety and eating disorder cognitions (100). Thus, it is likely that *any* reported LOC eating may represent a meaningful marker in distinguishing vulnerable youth, despite the categorical criteria.

Course of LOC Eating

LOC eating can manifest early in life (44), typically emerging during adolescence (247), but can be reported as early as middle childhood (249; 261). By contrast, full-syndrome BED does not typically manifest until later adolescence or adulthood, with a peak age of onset occurring between 18-20 years old (235). LOC eating can exhibit a variable course; while some

research has shown persistence prospectively (185), other studies suggest that LOC eating generally tends to remit in about 50% of youth over time, even in the absence of intervention (107; 118; 254). Regardless, it appears that at least half of youth who report LOC eating will persist, identifying LOC as a key risk factor for development of partial or full-syndrome BED (118; 254). The early onset and persistent course of LOC eating in some youth suggest it may be a particularly salient target for early intervention in vulnerable youth (44).

Assessment of LOC Eating

Several methods are commonly used to assess LOC eating. Most studies have utilized single-item surveys, self-report questionnaires, parent reports of their child's eating behaviors, or clinical interview methodology. While questionnaire methods have the advantage of convenience and ease of administration, responses typically vary based on the method used and the respondent. For example, parent reports of LOC eating behaviors have poor concordance with information gathered from child interviews in identifying presence of LOC episodes or objective overeating (262). Similarly, child self-reports of LOC eating are inconsistent with parent reports (234) and even child interview methods (70; 85; 253). These inconsistencies in assessment methods likely contribute to the discrepancies in prevalence rates, correlates, and outcomes of LOC eating among youth.

Clinical interview methods are typically considered a more optimal method of assessment of LOC eating, as opposed to child self-report or parent-report. The interactive nature of interview-based assessment methods allows for questions to be explained so they are understood by each individual. Age-related developmental differences can be addressed on an individual level as well. In the case that a concept such as LOC eating is not well understood by a child, specific examples can be provided until understanding is achieved (261). Of the available interviews, the

Eating Disorder Examination (EDE) (81), has been used most frequently and has been adapted specifically for youth prone to obesity and who may report LOC (249; 250). The EDE captures the frequency of LOC eating episodes in the past 28 days. A drawback of the EDE and other interview methods is that they require time-intensive training and ongoing supervision.

As LOC eating episodes are typically characterized by the consumption of snacks and desserts high in sugar and fat (252; 267), an alternate method used to assess pediatric LOC eating is through direct examination of energy intake at a laboratory test meal. This method typically consists of a calorically standardized buffet-style meal, which includes a broad variety of foods that range in macronutrient composition and are commonly consumed by youth. Participants are given instructions prior to the meal such as "Let yourself go and eat and much as you want." (252). Several studies have used this assessment method effectively. Laboratory studies using a test meal have effectively demonstrated differences between youth with LOC eating and those without in terms of amount (120; 168), macronutrient composition (120; 252), and type of energy consumed (252). In these studies, LOC eating was typically either categorically predetermined by self-report questionnaires (168), semi-structured interview (252), or self-rated immediately after the experimental test meal (120). This method of assessing pediatric LOC eating allows for more specific behavioral observations and is not reliant on errors in memory recall, difficulty describing, or lack of awareness of eating patterns.

In addition to the laboratory test meal paradigm, there are several other commonly utilized methodologies to capture LOC eating among youth. Most studies have utilized single-item surveys, self-report questionnaires, parent reports of their child's eating behaviors, or clinical interview methodology. While questionnaire methods have the advantage of convenience and ease of administration, responses typically vary based on the method used and the respondent.

For example, parent reports of LOC eating behaviors, which are typically identical to child version except the questions are referenced to the child, have poor concordance with information gathered from child interviews in identifying presence of LOC episodes or objective overeating (262). While parent and self-report questionnaires may be useful as screening tools, a clinical interview is likely necessary to identify LOC and eating disorders in children (70). The interactive nature of interview-based assessment methods allows for questions to be explained so they are understood by each individual. The Eating Disorder Examination (EDE) (81) has been used most frequently and has been adapted specifically for youth prone to obesity and who may report LOC eating (249; 250). However, the convenience of the EDE is limited in that it requires training and is more time consuming to administer than self-report questionnaires. Finally, to assess LOC eating in the natural environment and on a momentary level, ecological momentary assessment (EMA) is an ideal methodology. In EMA protocols, participants are given an electronic device, such as a smartphone, on which they complete recordings or brief self-assessments, reporting on level of control over eating, throughout the day for a given time period (e.g. a two-week protocol). The EMA device may include randomly distributed signals to prompt recording or assessment completion or allow for self-initiated assessments to ensure a comprehensive sampling of the LOC eating behavior. Limited studies have made use of EMA methodology to assess pediatric LOC eating. Therefore, more data are required to determine the suitability of EMA for effective capturing LOC eating behaviors, correlates, and outcomes. Studies that have used this method with youth have had compliance rates around 70% (105; 119; 200), which is approximately 20% lower than EMA studies of adults with binge eating (233) and may reflect a limitation of this method with youth given their lack of control over schedules. For example, school hours and restrictions may prohibit youth from having the EMA device with

them during the day. Indeed, youth showed better compliance with event-contingent recordings during the summer, holidays, and weekends (200). Although EMA is an ideal method for momentary assessment of eating in the natural environment, the various limitations to compliance among youth may pose barriers to effective use of this method with adolescents. Given the various strengths and limitations of methods, when possible, multiple assessment methods and respondents, including child and parent report, interview, test meals, and EMA should be used to evaluate the presence or absence of LOC eating in youth (44).

Physiological Bases of Appetite and LOC Eating

Relationships between LOC eating and markers of obesity-related health issues indicate youth with LOC eating may be at particular risk for adverse physiological outcomes. Given the link between LOC eating and excess body weight, data on the physiological correlates of LOC have typically focused on appetitive hormones and metabolic functioning.

Role of the Endocrine System

Endocrine System and Appetite

The endocrine system, working in conjunction with the central nervous system, helps to regulate vital activities such as metabolism, homeostasis, growth, development, and tissue function. The endocrine system consists of clusters of cells that secrete hormones into the bloodstream to target tissues throughout the body based on the distribution of each hormone's receptors. Appetite is influenced by several biological systems within the body, primarily as a result of communication between the endocrine and central nervous systems. Appetitive hormones responsible for hunger and feeding include, among the many implicated in meal regulation (266), ghrelin, which is released by the stomach and intestines and may have a role in initiating eating; leptin, a peptide hormone released from fat cells that signals overall adipocyte

triglyceride accumulation as well as acute challenges to adipose tissue accumulation (such as fasting) to the brain; and cholecystokinin, which reduces feeding following intake of fat into the duodenum (3; 53). Low levels of amino and fatty acids and blood glucose can stimulate hunger due to the body's desire to regulate concentrations of blood metabolites (53; 266).

Endocrine System and LOC Eating

Several appetitive hormones have been studied directly in relation to LOC eating in youth. Pediatric LOC eating is associated with higher fasting serum leptin (45; 166), an adipose-tissue derived hormone that promotes hunger, food intake, and body weight regulation (3), above and beyond the contribution of adiposity. Insulin, an appetitive hormone that serves as an "adiposity signal" and links feeding behavior with the size of adipose stores (191), has been associated with LOC eating cross-sectionally in youth across the weight strata (46). Though the direction of the causal arrow is unclear, these relationships may signify that LOC eating is linked to worsened leptin or insulin resistance, which can promote further hunger, food intake, weight gain, and worsened metabolic characteristics (130; 142). Given youth reporting LOC eating experience dysregulation in appetitive hormones, targeting LOC eating may serve as an important potential point of early intervention in youth.

Hormones may also influence the development of LOC eating in children and adolescents prospectively. Estradiol, a hormone involved in the expression of genes linked to negative valence system functioning, has been shown to mediate the relationship between genetic risk and binge eating behaviors (140; 274). Androgens may also be potential moderators for the development of binge eating behaviors. Females with an opposite-sex twin have decreased risk for disordered eating in late puberty compared to females with a same-sex twin (62), which

suggests prenatal exposure to testosterone may minimize risk for development of binge eating during puberty.

Role of the Central Nervous System

Central Nervous System and Appetite

In conjunction with the endocrine system, appetite is primarily controlled by the central nervous system. Underlying neural factors may put youth at higher risk for dysregulation in appetite and, subsequently, development of pediatric obesity. The hypothalamus, in particular, regulates hunger and satiety. Within the hypothalamus, damage to, or suppression of the ventromedial nucleus, which provide a sense of satiety, triggers insatiable eating and can contribute to obesity (3; 52). Additionally, the lateral hypothalamus, the paraventricular, dorsomedial, and arcuate nuclei of the hypothalamus, the amygdala, hindbrain, and prefrontal cortex are all implicated in appetitive and feeding behaviors. When food is ingested, glucagon-like peptide-1 (GLP-1) is released from gastrointestinal (GI) cells as well as hindbrain neurons, namely the nucleus tractus solitarius (NTS), which contributes to the control of food intake (122). Neural impulses facilitate communication between the brain and the gastrointestinal tract in order to signal to the brain whether there is enough food in the stomach, and whether the blood has sufficient amounts of circulating glucose, amino acids, fatty acids, and appetite hormones (3; 52; 266).

Upon exposure to palatable food cues, dopaminergic reward systems in the brain show high levels of activation, which can trigger sudden, strong food cravings (19; 91). Following palatable food cue exposure, hyperactivation in the dorsal striatum may be uniquely associated with increases in food craving (186). Associative learning processes are partially responsible for the relationship between palatable food-related cues and increased craving (86; 91). When food

cues have a heightened incentive value, such as when they are highly palatable or particularly rewarding foods, attention is captured more readily due to a sensitized dopaminergic reward system (50; 155; 175; 286). Various brain regions central to food cue processing and reward value encoding overlap with areas that are implicated in attention circuitry, including the insula, medial prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex (98; 208; 237; 238; 240). These overlapping regions may account for the relationship between heightened food cue incentive salience and automatic attentional biases to palatable food cues.

Central Nervous System and LOC Eating

Among individuals with overweight and obesity, and particularly among those with LOC eating, there may be unique underlying neural differences influencing appetite and overeating. Neural projections from the nucleus accumbens to the hypothalamus and ventral pallidum, brain areas central to food reward and regulation of food intake, are likely involved in the increases in the reinforcing value of palatable foods and aberrant eating seen among individuals with overweight (19). Regions implicated in hedonically motivated behavior and dopaminergic functioning are more responsive to palatable, high-sugar foods in adolescents of parents with greater weight status compared to adolescents at lower risk for development of obesity (221). These findings further support evidence for underlying heritable obesity risk factors that contribute to overeating in adolescents.

LOC eating has been proposed in addiction theoretical models to occur as a result of anticipated food reward in an attempt to alleviate cravings (91). Compared to those without LOC eating, children with LOC eating exhibit increased neural activation in the cerebellum, which is involved in satiety signaling, in response to highly palatable food cues (79). A recent pilot study found group differences in neural activity among youth with overweight and LOC eating

compared to controls, showing increased neural activation in areas implicated in attentional processes, inhibitory control, emotion regulation, and response inhibition (102). These preliminary findings suggest youth with LOC eating and overweight may need to expend greater cognitive effort relative to their peers in order to regulate energy consumption (102), potentially identifying a high-risk phenotype for aberrant eating behaviors. Taken together, the central nervous system plays a substantial role in the manifestation of LOC eating behaviors.

Correlates and Outcomes of LOC Eating

Physiological Correlates and Outcomes of LOC Eating

Overweight/ Obesity

Physiologically, LOC eating is strongly associated with overweight and obesity, as well as greater adiposity (41; 207; 261) in youth. Youth who engage in LOC eating behaviors are uniquely at risk for subsequent excess weight gain and obesity across studies (230), particularly in conjunction with emotional eating behaviors (242). Prospectively, LOC eating has been associated with excessive weight gain (83; 230; 260) and greater risk for gains in adiposity (248), as well as a higher medical risk including worsening metabolic dysfunction (255). As such, LOC eating is a well-documented risk factor for excess weight and adiposity gain and development of overweight or obesity.

Metabolic Syndrome

In addition to risk for overweight and obesity, LOC eating is associated with obesity-related markers of health, such as components of the metabolic syndrome (MetS) (198), and is predictive of adverse metabolic outcomes (255). More specifically, youth reporting LOC eating episodes show greater dysfunction in components of metabolic syndrome, such as higher systolic blood pressure, high low-density lipoprotein cholesterol (LDL-C) (198), higher fasting insulin,

and greater insulin resistance (46), even after adjusting for adiposity. Thus, pediatric LOC eating not only puts youth at higher risk for development of obesity, but increases risk for comorbid obesity-related health problems as well. Data suggest dietary intake and macronutrient consumption may be partially responsible for the association between LOC eating and metabolic dysfunction. Youth with LOC eating typically consume a greater amount of carbohydrates, including snack and dessert-type foods (252; 267), which could potentially contribute to worsened MetS-related measures (198; 255).

Psychological and Behavioral Correlates and Outcomes of LOC Eating

LOC eating has been thoroughly studied in relation to psychological and behavioral correlates and outcomes, including eating-disordered cognitions (254), and symptoms of depression and anxiety (118; 254). Prospectively, LOC eating may predict the onset of anxiety disorders, depression, and more severe eating psychopathology later in life. LOC eating is a known predictor of partial- or full-syndrome BED as well as worsening of eating disorder psychopathology (118; 254). Several notable areas of research studied in relation to risk for worsening psychopathology among those with LOC eating are negative affect, cognitive dysfunction, and social concerns.

Affective Factors

Emotion dysregulation has been found to be independently associated with eating pathology (39; 150). According to a recent meta-analysis, emotion regulation plays a key role across the eating pathology spectrum (194). In particular, however, emotion dysregulation may be especially important in the consideration of eating disorders involving binge eating behaviors. Compared to restrictive-type eating disorders, binge-type eating disorders are associated with greater difficulties in emotion regulation dimensions, including impulsivity and goal-directed

behavior in adolescence (283). Youth with LOC eating tend to have maladaptive emotion regulation strategies compared to their counterparts without LOC eating (133). Data support emotion dysregulation as a moderator between LOC eating and weight-related variables (133), such that only among youth who reported LOC eating, fat mass and BMI*z* are positively associated with emotion dysregulation.

In line with affect dysregulation, negative affect may play a critical role in the risk for LOC eating among youth. One laboratory study among youth at high risk for obesity and with reported LOC eating found that premeal state negative affect was related to increased intake of energy-dense foods, including greater consumption of carbohydrates, dessert, and snack-type foods (201). Further, various negative mood states were examined among girls in relation to eating patterns utilizing a laboratory test meal paradigm. Results found that only state anxiety, but no other mood state including depression, anger, fatigue, or confusion, mediated the relationship between recent social stress and energy intake during a laboratory test meal (218). Additionally, a study utilizing ecological momentary assessment found that interpersonal stressors predicted increases in negative affect and even more importantly the occurrence of momentary LOC eating episodes (200). Similarly, in response to negative affect associated specifically with social distress, another study showed that girls with LOC eating and overweight or obesity failed to engage prefrontal cortex regions implicated in emotion regulation, and subsequently engaged in increased food intake (125). Two other small neuroimaging studies found that state negative affect was associated with increased orbitofrontal cortex and reward system activation upon exposure to palatable, energy-dense food cues (27; 138), particularly among those reporting disinhibited eating (27). Taken together, these findings further support the notion that LOC eating may be a response to negative affective states.

Cognitive Factors

Cognitive factors may also play a role in development of LOC eating in youth. One such cognitive factor is attentional bias to food cues, or a biased cognitive processing of food-related stimuli. Facets of attention and reward intersect, in that individuals tend to allocate more attention to stimuli that are more rewarding and salient. An underlying theoretical mechanism for attentional bias to food cues is described by incentive-sensitization theory, which posits that repeated exposure to a rewarding stimulus produces an exacerbated reward response in vulnerable individuals, resulting in increased salience and strong motivational properties for the stimulus (206). Attentional bias to palatable food cues has been proposed to promote or maintain obesity through increased exposure to food cues in the current obesogenic environment, and thus, increased vulnerability to rewarding cues that motivate eating (50; 175; 176). Over time, reward value from *consuming* palatable food (i.e. consummatory reward) decreases, while reward value derived from *cues* associated with consumption (i.e. anticipatory reward) increases, potentially exacerbating overeating episodes in vulnerable individuals (24; 239). Prior research has supported this seeming paradox, finding that individuals who engage in binge eating show decreased activation in areas implicated in reward-based learning and taste processing when given food (26; 34). This reduced activation of reward in response to consumption of food may underlie a need for overconsumption in order to experience the desired rewarding effect of food.

The literature has shown mixed results on the relationships between attentional bias to food and obesity in youth, which may reflect the heterogenous etiology of obesity and highlights the importance of identifying specific phenotypes of those prone to obesity (84). It is possible that youth who already meet threshold criteria for a diagnosis of BED differ substantially in degree of emotional and cognitive factors compared to their counterparts who do not meet that

threshold. Further, there are various facets of attentional bias that capture somewhat opposing constructs, which may contribute to mixed findings in the literature. Assessment techniques commonly used to capture attention bias include visual dot-probe tasks and eye tracking measurements (172; 286). Reaction-time based measures, such as visual probe tasks, are generally conceptualized as a measure of initial, unconscious processing of stimuli (219), while eye-tracking measures, such as fixation or duration, assess overt, conscious experiences of attention (210).

One study found that, only among youth with LOC eating, attentional bias toward highly palatable foods measured via reaction time was positively associated with BMI*z* (219). Another smaller study observed a positive association between attentional detection bias for food targets and greater reward sensitivity (212), but a negative association between gaze duration bias for food and BMI among youth with BED (212). Shorter gaze duration potentially suggests an avoidant visual attention pattern in individuals with higher BMI, as a maladaptive attempt to reduce motivation for eating by avoiding visual awareness of food cues. This approach-avoidance pattern of initial detection and avoidant sustained attention may reflect competing influences of enhanced salience to food cues and attempts to control behavioral responses (176), potentially accounting for a portion of the mixed results seen in the literature on attention bias and obesity or binge eating. However, this avoidant gaze pattern approach may be dysfunctional in that visual avoidance interferes with habituation to food cues and may predispose individuals to binge eating behaviors over time (80; 212). Overall, preliminary research suggests that the combination of attentional bias to eating disorder-specific cues, such as food and weight/shape cues, as well as attentional bias toward social threat cues may contribute to LOC eating in youth, underscoring the importance of the role of negative affect on LOC eating behaviors (241).

Executive function impairments, such as poorer global processing and set shifting (6) as well as inhibitory control (42; 47), may be another cognitive component contributing to development of LOC eating among youth with overweight and obesity. Poorer executive functioning has been shown to predict weight gain in adolescents, and LOC eating behaviors may mediate this relationship (103). Children who report LOC eating may be more susceptible to the impact of increased portion sizes on intake, also known as the portion size effect (79), as evidenced in a trial examining children's intake of energy-dense foods across laboratory test meals. This suggests that individuals with LOC eating may be more impulsive, resulting in an impaired ability to regulate their intake of energy-dense foods when presented with larger portions.

Further, problems with self-regulation, a facet of executive function, are more often reported by adolescents with LOC eating compared to those without LOC eating (273). Greater activation in the ventromedial prefrontal cortex, an area implicated in emotion regulation and reward responsivity, has been associated with binge eating in adolescents, suggesting that subjective appraisal of reward may influence overeating behaviors in youth (24). A randomized controlled trial examined the effects of a three-week pilot program designed to enhance self-regulation, and more specifically, inhibitory control, in preschool-aged children, with the aim of reducing intake of energy-dense foods (203). A group by weight interaction was observed, such that children with overweight or obesity in the treatment group exhibited similar energy intake to children with healthy weight, while in the control group, those with overweight/obesity consumed more energy than children with healthy weight (203). Given the relationship between LOC eating and aspects of cognitive regulation, training of emotion- and self-regulation skills from an early age may prove promising to limit excessive energy intake.

Social Factors

Socioenvironmental factors, such as weight-based teasing and dieting, are consistently related to LOC eating in youth, independent of weight. Dieting (174), maladaptive family environments (151), and weight-based teasing (132), have been shown to be cross-sectionally and prospectively associated with LOC eating. Factors within the family environment, such as insecure attachment style, have been associated with child reports of LOC eating and may impact the development of eating disorder symptoms in youth (265). Thin-ideal internalization promoted by the media predicts self-objectification, which in turn further predicts negative emotional experiences related to one's body and appearance. Indeed, these negative emotional experiences impact subsequent dietary restraint and binge eating, and each of these core features of eating disorders may influence each other (65). Taken together, social pressures from peers and family, including unrealistic standards of beauty, unhealthy weight control behaviors, and weight-based teasing, impact youth's risk for developing LOC eating.

Interpersonal Theory of Loss of Control Eating

According to interpersonal theory, LOC eating is conceptualized as a response to negative affect specifically associated with psychosocial stress, which can occur as a result of poor communication in relationships or social isolation (164; 244; 258). LOC eating may develop as a result of maladaptive coping with negative affective states that arise from socially distressing situations, and food consumption is thought to be triggered as an attempt to cope with uncomfortable affective states (258). The interpersonal model of binge eating has been supported over the course of treatment for reductions in binge eating and eating disorder symptomatology among adults (128).

Adolescents (96), and girls in particular (209; 243), exhibit heightened vulnerability to social stressors, identifying adolescent girls as a particularly vulnerable population. Regardless of disordered eating status, individuals with obesity across the lifespan report greater interpersonal stress, poorer quality of social life, and more frequent experiences of teasing and bullying compared to individuals of healthy weight (4). Taken together, interpersonal theory implicates social stress, particularly as a consequence of maladaptive psychosocial functioning, as a potentially key driver of LOC eating among adolescent girls with overweight and obesity. A more in depth exploration of facets of psychosocial stress is warranted in order to gain a better understanding of the mechanisms for LOC eating among this high-risk group.

PSYCHOSOCIAL STRESS AND LOC EATING

Psychosocial stress may play an important role in the onset and maintenance LOC eating episodes and risk for excess weight gain (154; 295). In general, stress can have both direct and indirect effects on the endocrine system as well as the autonomic nervous system, cardiovascular system, and other bodily systems (53). Theoretical models propose LOC eating occurs as a means of coping with acute or chronic stress in addition to negative emotion (3). Additionally, aspects of LOC eating episodes such as increases in appetite, energy intake, and the occurrence of "stress-induced food intake" can be triggered by stress (3). Individuals with binge eating symptoms are more likely to interpret difficult situations as more stressful and to have greater difficulty with emotion regulation in response to stress (189). As such, individuals who struggle with binge eating behaviors may be a particularly vulnerable population to the effects of psychosocial stress and subsequent increases in appetite and body fat.

Psychosocial Stress in Adolescence

There may be critical developmental windows for exposure to psychosocial stress. Psychosocial stress can be operationalized in many ways, but has typically been considered as stress related to life events such as relationship stress, work stress, financial hardship, or family problems (22; 23; 268). Early life exposure to stress is related to later increases in stress reactivity and cognitive deficits in adulthood, suggesting the effects of psychosocial stress may have a detrimental impact on various brain structures at different stages of life (158). Given the frontal cortex is not yet fully developed during adolescence, this neural region may be particularly vulnerable to psychosocial stress during this stage of development (158). These data suggest psychosocial stress may have lasting impacts on various brain structures throughout development, with adolescence being a potentially critical stage. The increased prevalence of psychopathology, such as anxiety disorders, during adolescence suggests youth may be particularly sensitive to the effects of elevated stress levels during this developmental period (188). As such, adolescence may be a sensitive period of development for the effects of psychosocial stressors due to unique cognitive and social vulnerabilities.

Anxiety and LOC Eating

One facet of psychosocial stress that has been prominently linked to disordered eating is anxiety. Anxiety disorders are highly relevant to the study of eating disorders given they are commonly observed prior to the onset of disordered eating behaviors and clinical eating disorders (18; 131). Heritable factors such as emotion regulation difficulties may maintain the underlying relationship between anxiety and disordered eating (228). Anxiety sensitivity, a trait construct involving anxiety-congruent cognitions and components of physical and social anxiety-related concerns, is a risk factor for eating disorders (11) and shares genetic underpinnings with disordered eating behaviors (82). Together, genetic and non-shared environmental factors

originating from anxiety sensitivity contribute to approximately one-quarter of the explained variance in disordered eating behaviors in an adolescent twin cohort (82).

In adults, the comorbidity between anxiety and BED is well-defined in the literature (14; 101; 124; 182; 246). Moreover, adolescents with overweight at high risk for the development of eating disorders display elevated levels of anxiety and negative affect (73). More specifically, LOC eating in youth has been closely linked to pediatric anxiety symptoms (100; 165; 218), and LOC eating during childhood has been shown to predict increases in anxiety symptoms prospectively (254). Notably, links between anxiety and LOC eating have been found above and beyond the contribution of excess body weight or fat (223).

Anxiety symptoms may play a role in elevated BMI as well. While anxiety alone is not a predictor of excessive weight gain in youth, a meta-analysis supports a significant positive relationship between weight status and anxiety in youth (38). Further, youth with high anxiety who have overweight or obesity endorse greater psychosocial distress compared to their counterparts with low anxiety (153). Adolescent obesity has also been shown to predict later onset of anxiety disorder diagnosis in girls (10).

Intervention data in youth reinforces the importance of anxiety in relation to LOC eating and weight outcomes. In a randomized control trial of an intervention for prevention of excess weight gain, girls with higher trait anxiety at baseline showed the greatest improvements in weight and adiposity three years following an intervention, compared to girls with low baseline trait anxiety in the intervention condition and those in the standard of care treatment (256). Conversely, there were no relationships between baseline depressive symptoms and BMI*z* outcomes in either of the intervention groups (256), further bolstering the importance of anxiety over and above other facets of negative affect. The high overlap between LOC eating and anxiety

in youth, particularly among those with overweight, suggests a shared etiology and requires more in-depth exploration.

Social Anxiety and LOC Eating

While any form of anxiety might induce LOC eating, the combination of pediatric LOC eating and social anxiety, in particular, may even further exacerbate overeating and adverse outcomes. According to interpersonal theory, LOC eating may develop as a result of maladaptive coping with negative affective states, such as anxiety, that arise from socially distressing situations, and food consumption is triggered as an attempt to cope with the uncomfortable affective state (258). Youth with LOC eating report greater social stress and social problems compared to those without LOC eating (64; 77; 108; 114; 199). Self-reported perceived social threats have been shown to predict LOC eating behaviors in children and adolescents (114), potentially implicating social anxiety in the promotion of excess energy intake and weight gain. Indeed, social anxiety has been shown to be positively associated with binge eating behaviors, and adults meeting criteria for BED reported higher social anxiety than adults without BED (180). Further, adults who report first becoming overweight in childhood or adolescence display higher levels of social anxiety compared to individuals who first exhibited overweight in adulthood (180). Taken together, higher levels of social anxiety may be a particularly important early risk factor for binge eating behaviors and subsequent excess weight gain.

Neurocognitive Factors Implicated in Social Anxiety and LOC Eating

Individuals with LOC eating show hyperactivation in brain regions central to social threat processing and initial attention capture, including the amygdala, anterior cingulate cortex, and orbitofrontal cortex (78; 90; 217), when exposed to social threat cues. One neuroimaging study of 22 adolescent girls with overweight and obesity found that girls with overweight or obesity

and reported LOC eating demonstrated a similar neural response to social distress as youth with anxiety (125). Specifically, those with LOC showed reduced engagement of the ventromedial prefrontal cortex, an area of executive function implicated in interpreting social intentions and affect regulation, relative to their counterparts without LOC, who experienced increased activation (125). Additionally, adolescent girls with overweight and LOC eating experienced greater activity in the fusiform face area, which is implicated in the processing of emotions, during the negative peer feedback task, and immediately following this task consumed more energy at a laboratory test meal (125). As such, the literature suggests social anxiety may be a potentially important facet to consider in better understanding mechanisms driving LOC eating, particularly among adolescents. Perceived social threat may trigger LOC eating, above and beyond resulting increases in anxiety, due to alterations in the direct connections between circuitry implicated in social threat and the hypothalamus (68; 264). Together, these findings lend support to social-anxiety models of LOC eating. Youth with manifestations of LOC eating and social anxiety may be identified as a particular phenotype for those who are prone to weight-related health issues.

Attention Bias to Social Threat

One potential mechanism for the interpersonal model of LOC eating, and more specifically, the relationship between social anxiety and overeating, may be attention bias to social threat, or an automatic allocation of attention to highly salient stimuli. Attention bias is a propensity to focus on particular environmental stimuli, and has been thought to contribute to risk or maintenance of psychopathological issues, such as anxiety (222). Within the attentional bias framework, there are two key processes: automatic or "bottom-up" attention, and voluntary or "top-down" attention. Initial unconscious attention capture occurs first and evokes the

"bottom-up" processes in response to salient stimuli. Subsequently, voluntary continued attention deployment towards or away from the stimuli characterizes "top-down" processes (13; 57; 58; 192).

During automatic "bottom-up" unconscious attention capture, ventral prefrontal neural networks involved in attention orienting and emotional processing are implicated, including the insula, ventral anterior cingulate cortex, medial prefrontal cortex, and the inferior frontal gyrus (57; 58; 192). Involuntary activation of these neural areas occurs shortly after exposure to the salient stimulus, typically within 150 milliseconds (ms). Implicit attention biases result from hyperactivation in these stimulus-driven, "bottom-up" neural regions upon exposure to salient cues (170; 190). This early and rapid orientation of "bottom-up" automatic attention is often shortly followed by an attentional shift away from the salient stimuli, referred to as inhibition of return, which typically occurs within 500 ms (139). During voluntary "top-down" continued attention deployment, activation of dorsal prefrontal neural regions, such as the dorsolateral prefrontal cortex, dorsal anterior cingulate, and superior parietal cortex, are implicated in conscious allocation of attention toward or away from salient cues (57; 58; 192). Hypo-activation in these "top-down" attentional control neural regions may result in persistent attention deployment and impact attentional bias and anxiety.

In the eating disorders field, individuals with attention biases to disliked body parts or palatable foods are at greater risk for disordered eating attitudes (13), and overeating behaviors (19; 20). In relation to anxiety, it has been proposed that those with anxiety disorders may have a vigilance-avoidance pattern of attention, such that anxiety symptoms are associated with stimulus-driven automatic orientation of attention to threatening stimuli (55; 222), alternately followed by a slower, goal-directed voluntary shift of attention in line with goal-oriented

behavior such as avoidance of threatening stimuli. Some evidence suggests the avoidance phase during voluntary attention deployment is a goal-directed, but maladaptive process in an attempt to minimize distress in individuals with anxiety (71; 156), which may ultimately impair habituation to distressing cues and result in a perpetuation of anxiety over time.

Attention bias models of anxiety and disordered eating propose that socially stressful situations trigger an increased attendance to potential socially threatening cues (13) in those with LOC eating. Adult studies have supported the link between attention bias to socially threatening stimuli and increased risk for disordered eating attitudes and behaviors (112; 113). Compared to happy or neutral facial expressions, individuals with high anxiety show enhanced vigilance and attention bias toward threatening faces (31). More specifically, attentional bias to social threat cues is positively related to pediatric anxiety symptoms (1). Given the well-established relationship between pediatric anxiety and LOC eating (100; 165), it is possible youth with LOC eating have an attention bias to socially threatening stimuli (112) similar to that of youth with anxiety. Attention bias to social threat cues may be a potential mechanism for the relationship between social anxiety and overeating behaviors in youth with LOC eating, and given the dearth of literature exploring the impact of attention bias to social threat on LOC eating, this mechanism warrants further investigation.

CURRENT RESEARCH GAPS

There are currently several important research gaps in the literature: 1) The role of attention bias to social threat cues and neurobiological mechanisms of anxiety have not been previously considered in relation to LOC eating, which may elucidate mechanisms for LOC eating and provide a clearer understanding of drivers of the construct to elucidate early treatment targets; 2) No model has tested the impact of attention bias to social threat and neural activation of anxiety

processing regions on LOC eating in vivo in the laboratory. This study helps to characterize distinctive subtypes of LOC eating and mechanisms that contribute to disordered eating and subsequent weight gain in youth, providing a pathway for novel prevention and intervention efforts.

STUDY MODEL

Given LOC eating in youth is highly comorbid with anxiety (14; 100; 101; 124; 165; 182; 246), and is predictive of increases in anxiety symptoms over time (254), there may be shared neural underpinnings and/or etiologies between LOC eating and anxiety in youth. According to interpersonal theory, LOC eating may develop as a result of maladaptive coping with negative affective states, such as anxiety, that arise from socially distressing situations. Food consumption is triggered as an attempt to escape from the uncomfortable affective state. This maladaptive coping strategy may be due, in part, to heightened sensitivity to incoming social cues and abnormalities in anxiety processing socio-emotional neural circuits. The physiological mechanisms of psychosocial stress may elucidate the impact of anxiety on appetite, satiety, and weight gain in those with disordered eating. The current study theorizes that attention bias to social threat elicits hyperactivation in "bottom-up" brain regions implicated in unconscious attention capture and social anxiety, and blunted activation in "top-down" attention deployment and affect regulation regions, and individuals will seek to reduce negative affect through LOC eating behaviors. See Figure 2 for the current study's theoretical model of neural underpinnings of social anxiety and LOC eating. A better understanding of the neural underpinnings involved in the links between LOC eating and anxiety may aid in the development of novel targets for reducing excess intake that leads to obesity and obesity-related health comorbidities.

THE PRESENT STUDY

Study Objective

The objective of the current study was to determine the relationships between attention bias to social threat cues and neural activation implicated in social anxiety and subsequent energy intake at a laboratory test meal in girls with overweight or obesity, with and without LOC eating. Further, this investigation examined if LOC eating moderated the relationships between attention bias to social threat and neural activation of anxiety-processing and emotion regulation regions and subsequent energy intake at a laboratory test meal.

AIMS AND HYPOTHESES

No model has been previously tested for the impact of attention bias to social threat and neural activation of anxiety-processing and emotion regulation regions on LOC eating in vivo in the laboratory. The current study aimed to determine the relationships between attention bias to social threat cues and neural activation implicated in social anxiety and subsequent energy intake at a laboratory test meal in girls with overweight or obesity, with and without LOC eating. It was hypothesized that attention bias to social threat cues would elicit hyperactivation in "bottom-up" brain regions implicated in unconscious attention capture and social anxiety, and blunted activation in "top-down" attention deployment and affect regulation regions, which would interact with LOC eating in order to reduce the negative affective feelings of anxiety through overeating behaviors.

Aim 1

To examine relationships between attention bias to social threat cues and neural activity in anxiety-processing and emotion regulation regions among youth, and differences between youth with and without LOC eating.

Hypothesis 1a: Greater attention bias to social threat (i.e. shorter reaction times to angry faces than happy or neutral faces) will be associated with increased activation in "bottom-up" unconscious attention capture areas and areas involved in anxiety processing, and blunted activation of "top-down" attention deployment and affect regulation regions in response to social threat cues.

Hypothesis 1b: Youth with LOC eating will exhibit greater attention bias to social threat cues, but not to non-threatening cues, compared to youth without LOC eating.

Aim 2

To examine if differences in attention bias to social threat and neural activation in response to social threat cues are related to energy intake at a laboratory test meal.

Hypothesis 2a: Greater attention bias to social threat cues, but not non-threating cues, will be associated with greater energy intake.

Hypothesis 2b: Increased activation of "bottom-up" unconscious attention capture and anxiety processing regions, and blunted activation of "top-down" attention deployment and affect regulation regions in response to social threat cues will be associated with greater energy intake.

Aim 3

To examine if LOC eating moderates the relationship between attention bias to social threat and neural activation and differences in intake at a laboratory test meal.

Hypothesis 3a: The presence of LOC eating will moderate the relationship between attention bias to social threat and energy intake, such that among youth with LOC eating, attention bias to social threat will be more robustly related with energy intake.

Hypothesis 3b: The presence of LOC eating will moderate the relationship between increased activation of "bottom-up" unconscious attention capture and anxiety processing regions, and blunted engagement of "top-down" attention deployment and affect regulation regions in response to social threat cues and energy intake, such that among youth with LOC eating, increased activation of "bottom-up" unconscious attention capture and anxiety processing regions, and blunted activation of "top-down" attention deployment and affect regulation regions will be more robustly associated with energy intake.

Exploratory Aim 4

To examine whether state anxiety mediates the relationship between increased activation of "bottom-up" unconscious attention capture and anxiety processing regions, and blunted activation of "top-down" attention deployment and affect regulation regions in response to social threat cues and energy intake.

Hypothesis 4: State anxiety will partially mediate the relationship between increased activation of "bottom-up" unconscious attention capture and anxiety processing regions, and blunted activation of "top-down" attention deployment and affect regulation regions and energy intake, such that increased activation of "bottom-up" unconscious attention capture and anxiety processing regions, and blunted activation of "top-down" attention deployment and affect regulation regions in response to social threat cues will partially explain increases in state anxiety, which will partially explain increases energy intake.

Exploratory Aim 5

To examine whether anxiety sensitivity moderates the relationship between attention bias to social threat and increased activation of "bottom-up" unconscious attention capture and anxiety processing regions.

Hypothesis 5: Anxiety sensitivity will moderate the relationship between attention bias to social threat and increased activation of "bottom-up" unconscious attention capture and anxiety processing regions, such that among those with greater anxiety sensitivity, attention bias to social threat will be more robustly associated with activation of "bottom-up" unconscious attention capture and anxiety processing regions.

CHAPTER 2: METHODS

RESEARCH DESIGN

This study was one component of the Mobile Attention Retraining in Overweight Female Adolescents protocol (ClinicalTrials.gov ID: NCT02977403). Only the procedures and measures relevant to this dissertation are presented in the Methods section. Adolescent girls with overweight or obesity participated in a screening visit and a laboratory visit. Girls underwent a physical examination and participated in two semi-structured psycho-diagnostic interviews during the screening visit in order to determine eligibility. Girls then returned for the laboratory visit, during which they completed an anatomical MRI scan, a social threat attention bias paradigm while undergoing a magnetoencephalography neuroimaging scan, and then finally a laboratory test meal. The study used a cross-sectional design to examine differences in attentional bias to a laboratory social threat paradigm among adolescent girls with and without LOC eating.

PARTICIPANTS AND RECRUITMENT

Participant Eligibility

Inclusion criteria was female sex, 12-17 years old at the start of the study, overweight or obesity (BMI at or above the 85th percentile for age and sex according to the Centers for Disease Control US standards) (148), English-speaking, and right handedness. Inclusion in the LOC group was defined by the presence of one or more episodes of LOC eating during the past month prior to assessment, as assessed using a clinical diagnostic interview for eating disorders. Inclusion in the No LOC group was defined by no episodes of LOC eating during the past month.

Girls were excluded if they met any of the following criteria: an obesity-related health comorbidity requiring medical treatment, such as hypertension or fasting hyperglycemia

consistent with diabetes; presence of other major medical illnesses including renal, hepatic, gastrointestinal, endocrinologic, hematological problems or pulmonary disorders; regular use of any medication known to affect body weight or eating behavior (e.g., stimulants prescribed for attention deficit hyperactivity disorder); current pregnancy or a history of pregnancy; a significant reduction in weight during the past three months, for any reason, exceeding 5% of body weight; presence of a significant, full-threshold psychiatric disorder based on DSM criteria that may impede competence or compliance or possibly hinder completion of the study; a history of significant or recent brain injury that may considerably influence performance; current involvement in a weight loss program, participating in psychotherapy aimed at weight loss or treatment of eating behavior; or a condition under which MEG participation would be contradicted (e.g., metal in the body, pregnancy, claustrophobia, history of significant neurological insult or injury). Girls who reported allergies to gluten, nuts, dairy, fruit, or any other item in the test meal array were excluded from the test meal portion of the study. See Table 2 for full eligibility criteria.

Recruitment

Participant recruitment methods included mailings to families in the greater Washington, D.C. metropolitan area. This recruitment method has been used successfully for prior community-based studies of youth with and without LOC eating (252; 254; 260). Participants called the phone number associated with the study and were pre-screened on the phone before attending an in-person assessment visit.

Participant Compensation

All participants received $70 for the screening visit and $75 for the MEG scan and test meal visit, for a total compensation of $145.

STUDY PROCEDURES

Participants completed a screening visit that involved consent/assent, physical examination, dual energy x-ray absorptiometry (DXA) scan, and two semi-structured interviews. Youth then completed a laboratory visit during which they underwent an anatomical MRI scan, MEG recording, social threat task, completed psychological questionnaires, and a laboratory test meal. All participant visits took place at the NIH Hatfield Clinical Research Center.

Screening Visit

Potentially eligible families were seen at the NIH Clinical Center. The screening visit involved:

Consent/assent

The study's purposes, testing procedures, and possible study risks were reviewed in detail with families. Interested parents and daughters signed IRB-approved consent and assent forms.

History and Physical Examination

Height and fasting weight, medical history, physical examination, and assessment of current medical and psychiatric illness were assessed by trained NIH staff.

Dual Energy X-ray Absorptiometry (DXA) Scan

Total mass (kg), lean mass/fat-free mass (kg), fat mass (kg), and fat mass percentage (%) were assessed by dual-energy X-ray absorptiometry (DXA) (GE Lunar iDXA, GE Healthcare, Madison WI; software GE encore 15), a validated measure of body composition in youth (231).

Semi-Structured Interviews

Youth participated in several semi-structured clinical interviews during the screening visit, conducted by trained and supervised staff:

Eating Disorder Examination (EDE)

The overeating section of the EDE was administered to determine LOC eating presence (see Appendix 1). Girls who reported at least one episode of LOC eating in the past 28 days on the EDE were categorized to the LOC eating group.

Schedule for Affective Disorders and Schizophrenia for School-Age Children (KSADS)

Sections of the KSADS were used to assess psychiatric functioning and exclude participants with significant psychiatric co-morbidities that may have impeded competence or compliance, or possibly hindered completion of the study (see Appendix 2). The KSADS was only administered to participants who positively endorsed depression, suicidal ideation, mania, psychosis, or substance use disorder on a screening measure. Participants were administered only relevant portions of the KSADS in order to identify any current psychiatric issues that warranted study exclusion or would have impeded study adherence.

Self-Report Questionnaires

Participants completed a series of self-report questionnaires at the screening visit, primarily assessing specific facets of negative affect including anxiety and depression. Further details on self-report questionnaires are described in the Measures section.

State-Trait Anxiety Inventory for Children– State subscale (STAIC)

The STAIC-State subscale (232) is a 20-item self-report measure of state anxiety with very good psychometric properties. Further details are described in the Measures section.

Anxiety Sensitivity Index – Revised (ASI-R)

Anxiety sensitivity is a trait defined by fear of anxiety-related physical sensations (60; 202). Prior research suggests that anxiety sensitivity is a distinct construct from state or trait anxiety and may contribute to the development or maintenance of a variety of psychological

disorders, including social anxiety (5; 163). Specifically, the ASI-R was initially planned to be administered in conjunction with the social threat visual probe task to explore the potential relationship between ASI-R and attentional biases toward threatening social stimuli. Barriers to this administration are discussed elsewhere.

Children's Depression Inventory (CDI)

The CDI (146; 147) is a widely used measure that assesses the presence and degree of childhood depressive symptoms over the past two weeks, such as worthlessness, negative mood, and fatigue.

Laboratory Visit: MEG Scan Social Threat Task and Test Meal

After determining eligibility at the screening visit, adolescents returned for a second visit to participate in the MEG scan social threat task and test meal. Participants began fasting at 10:00 pm the night before this visit.

Anatomical MRI Scan

An MRI scan was conducted on a Siemens MAGNETOM Verio 3T scanner equipped with a 16-channel head/neck coil for co-registration with MEG. Standard imaging parameters were used including acquisition of T1 weighted structural images for co-registration.

Magnetoencephalography

Facets of attentional bias, such as "bottom-up" initial attention capture and "top-down" maintained attention deployment, involve neural processes that occur over short periods of time, and thus must be measured by temporally sensitive methods (57). The temporal nature of attention bias to social threat and activity in neural circuits involved in anxiety processing is ideally suited for measurement by magnetoencephalography (MEG), which has both excellent temporal and acceptable spatial resolution (66; 67; 111). Utility of MEG has been supported for

differentiating between neural components of attention bias to social threat (32). Previous research on attention bias has utilized functional MRI to provide high spatial resolution for key brain regions of interest, however this method is limited in its capacity to elucidate temporal sequences of neural activity. As such, utilizing MEG can help to elucidate the neural bases of attention bias toward threat that may contribute to LOC eating behaviors.

Neural magnetic fields were recorded via MEG with the 275-channel OMEGA system. Head position was also measured during the recording. Participants sat in the magnetically shielded recording room while wearing a helmet covered with 275 SQUID sensors. Head position within the magnetometer was 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 defined the coordinate system for the signals and allowed for post-hoc correction of head movement artifacts. MEG data was sampled at 600 Hz (bandwidth 0-150 Hz) and 7mm voxels. "Bottom-up" initial attention capture was analyzed between 0-150 ms after each stimulus onset, and "top-down" maintained attention deployment was analyzed between 150-500 ms after stimulus onset. The MEG session lasted for approximately 60 minutes.

Social Threat Task

The social threat attention bias task examined participants' reaction times and neural response during a dot-probe paradigm (See Figure 3). The paradigm involved two picture pairs of angry, happy, or neutral faces, presented side-by-side on a computer screen, followed by a probe appearing behind one of the images, prompting a response. The task consisted of three face pair types: neutral-neutral, happy-neutral, and angry-neutral. Each pair type consisted of 15 face pairs, presented four times each. The order of pair types was randomized across all participants, but the specific pairs remained consistent. The location of each stimuli and probe

was counterbalanced across participants. Importantly, the probe replaced the neutral images (i.e. neutral faces) and the salient images (i.e. happy or angry faces) with equal frequency. Trials were excluded from analyses if the participant did not respond with the time window or responded incorrectly.

Following a practice sessions, the dot-probe task consisted of 180 trials, divided into four segments with 45 trials each. Each pair of images appeared on the computer screen for 500ms. After 500ms, the image pair disappeared and a probe (horizontal or vertical dots) appeared in one of the previously occupied photo locations for 200ms. Participants responded with a right or left sided button-press to indicate the orientation of the dots. A central fixation cross appeared for 500ms before each face pair presentation, and the blank inter-trial interval lasted for 1300ms. Trials consisted of a mixture of incongruent trials, in which the probe replaced the neutral face image, and congruent trials, in which the probe replaced the angry or happy face image. Sixty pairs of each combination (neutral-neutral, angry-neutral, happy-neutral) were presented in randomized order. The spatial location of images and probes were counter-balanced.

Attentional bias was calculated by subtracting the mean reaction times in responding to probes replacing a salient stimulus (i.e. angry or happy faces) from mean reaction times to probes replacing a neutral stimulus (i.e. neutral faces). Bias scores were calculated separately for both "angry bias" and "happy bias." Angry bias was calculated by subtracting mean reaction times to angry faces from mean reaction times to neutral faces. Happy bias was calculated by subtracting mean reaction times to happy faces from mean reaction times to neutral faces. Theoretically, reaction times are expected to be faster (i.e. shorter) when the probe replaces a stimulus the participant was currently orienting toward at the time of the probe presentation onset. A score of 0 indicates no attentional bias to either cue, while a negative score (<0)

indicates a bias away from the more salient cue (i.e. angry or happy faces), and a positive score (>0) indicates a bias toward the more salient cue.

This social threat task has been used extensively in pediatric samples with anxiety symptoms and has been repeatedly shown to stimulate neural responsivity linked to regions associated with anxiety (57; 171; 172; 190). It has also been shown to stimulate similar neurocircuitry to that of other social anxiety laboratory paradigms (32; 125; 172), and, in particular, circuits linked to our preliminary data using fMRI (125). Split-half reliability of mean reaction time and attentional bias on similar platforms has shown to be good in prior research (161; 282).

Laboratory Test Meal

Immediately prior to and following the MEG session, girls completed rating scales for hunger, fullness, social anxiety, and food craving (see Appendix 3). Participants then were introduced to the multi-array test meal (~11,000 kcal) (See Figure 4) with tape-recorded instructions to "Let yourself go and eat as much as you want." Consumption was calculated by weighing each item before and after the meal. Rating scales for hunger, fullness, social anxiety, and food craving were repeated post-meal. The primary outcome variable of interest was total energy intake (kcal). The nature of the laboratory buffet test meal also allows for exploratory analyses of more specific macronutrient variables (i.e. percentage of energy consumed from protein, fats, and carbohydrates). Energy content and macronutrient composition for each food item was determined according to standards from the U.S.D.A. Nutrient Database for Standard Reference and information supplied by food manufacturers (See Table 3 for meal contents). This LOC eating paradigm is well-validated and has been successfully used in pediatric (252) and

adult studies (279). Figure 5 outlines all study procedures for both the screening and laboratory visits.

MEASURES AND MATERIALS

Measures

Eating Disorder Examination (EDE)

The EDE (81) is a semi-structured psycho-diagnostic interview of eating disorder psychopathology. The EDE contains 21 items that assess disordered attitudes and behaviors related to eating, body-shape and weight, and 13 items designed and adapted to diagnose specific DSM-5 eating disorders. The EDE has demonstrated sound psychometric properties in adolescents, and is reliable and valid in adolescent samples (51; 261).

Schedule for Affective Disorders and Schizophrenia for School-Age Children (KSADS)

The KSADS (129) is a reliable and valid semi-structured diagnostic interview to assesses DSM psychiatric diagnoses.

State-Trait Anxiety Inventory for Children– State subscale (STAIC)

The STAIC-State subscale (232) is a 20-item self-report measure of state anxiety with good psychometric properties, including good reliability and construct validity (184). The STAIC-State total score is calculated by a sum of all items rated on a 3-point Likert scale. Higher scores indicate greater state anxiety, with total scores ranging from 20-60.

Anxiety Sensitivity Index – Revised (ASI-R)

The ASI-R is a 36-item self-report measure assessing anxiety sensitivity and is a revised and expanded version of the original 16-item Anxiety Sensitivity Index (12). 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 anxiety sensitivity, with total 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 (69).

Children’s Depression Inventory (CDI)

The CDI (146; 147) is a 27-item self-report measure that assesses the presence and degree of childhood depressive symptoms over the past two weeks. Items are scored on a Likert scale ranging from 0 to 2, with total scores ranging from 0 to 54. Greater scores indicate greater depressive symptoms. The CDI has shown high internal consistency in pediatric samples (109; 146).

Materials

All computers, psychological questionnaires, and psychological interviews required for the current study were already purchased for prior research or were publicly available. Data analysis software and the materials required for the laboratory session were also previously purchased.

Dual Energy X-ray Absorptiometry (DXA) Scan

Total mass (kg), lean mass/fat-free mass (kg), fat mass (kg), and fat mass percentage (%) were assessed by dual-energy X-ray absorptiometry (DXA) (GE Lunar iDXA, GE Healthcare, Madison WI; software GE encore 15), a validated measure of body composition in youth (231).

Stadiometer and digital scales

The NIH Clinical Research Center pediatric clinics were equipped with stadiometers and calibrated digital scales available for use.

Magnetoencephalography (MEG) Instruments

The NIMH MEG Core Facility's main instrument is a CTF MEG™ brain imaging system, a whole-head SQUID magnetometer with 275 channels, capable of recording the magnetic field of the brain at very high spatial and excellent temporal resolution. The system is housed in a magnetically shielded room for enhanced passive noise reduction. In addition, the CTF MEG system is equipped with synthetic 3rd gradient balancing, an active noise cancellation technique that uses a set of reference channels to subtract background interference. There is currently no standard reliability index for MEG. The MEG Core Facility is located at the NIH Clinical Center.

HUMAN SUBJECTS PROTECTIONS

The National Institutes of Health (NIH) and USU IRBs approved all study procedures. All information provided by the participant has been kept confidential and is protected to the fullest extent provided by law. Parents and participants provided written consent and assent, respectively, for study participation. Hard copies of consent, assent, and data are stored in the Section on Growth and Obesity laboratory in filing cabinets in a locked office. Electronic copies of data are stored using the NIH-Sponsored Clinical Trials Data Base or on NIH-secured and password-protected computers in the Section on Growth and Obesity's locked office space, accessible only by authorized study personnel. All identifiable data for the project was processed and stored by the study team. Confidentiality of discussions during the participant visits were honored, and only study staff has access to identifiable information.

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 were screened for these contraindications before having any scan. If they had any risk for injury, they did not receive an MRI scan. In addition, all magnetic objects (for example, watches, coins, jewelry, and credit cards) were removed before entering the MRI scan room. Since it is unclear whether MRI is completely safe during pregnancy, all participants, as females, had a pregnancy test performed no more than 24 hours before the structural MRI scan, and the scan was not conducted if the pregnancy test was positive. 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 were fitted with hearing protection. There are no known long-term risks of MRI scans.

The current study involved minimal risk and no direct benefit to the participants. However, data from the study will help to examine the relationship between attention bias to social threat cues, neural activation implicated in anxiety, and subsequent energy intake at a laboratory test meal in youth with overweight or obesity, with and without LOC eating. Information gained from this study may be beneficial to adolescents who experience disinhibited eating. Data from this project may also be used to inform the development of prevention programs that can prevent adverse health outcomes in youth at high risk for overweight and obesity.

DATA ANALYTIC APPROACH

Data Management

Anatomical MRI data preprocessing was conducted using AFNI software, which included removing the skull and normalizing to standard Talairach space. Raw MEG data was filtered using third gradient reference coils with fixed weights. Primary analyses used a broad

frequency band (1-30 Hz), in line with procedures from prior MEG studies in new populations (32; 59; 204). Fixed frequency smoothing and transformation were applied to obtain oscillatory power estimates. Oscillatory power activity was calculated through subtraction of the baseline activity (500ms immediately prior to stimulus onset) (32) from the activity evoked during the unconscious attention capture (0-150ms after stimulus onset) and continued attention deployment periods (150-500ms after stimulus onset), respectively. A relative power activity was calculated using a log(a/b) ratio, with a = activity evoked during the unconscious attention capture period, and b = activity evoked during the continued attention deployment period. This was designed in line with the hypotheses of relative *hype*ractivity during attention capture and relative *hypo*activity during attention deployment, and was designed with reduction of excessive number of tests in mind. I was trained in the synthetic aperture magnetometry (SAM) beamformer technique (276) 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 was co-registered and transformed into Talairach space with use of AFNI software. A priori brain regions were selected for examination based on the hypotheses.

Statistical Analyses

All non-MEG analyses were performed with IBM SPSS Statistics (version 25). All MEG-related data analyses were performed with Analysis of Functional NeuroImages (AFNI) software (61) and co-registered to the high-resolution structural MRI scan. Arcsine square-root transformations were conducted for percentage intake from carbohydrates, fats, and protein. As appropriate, covariates included commonly included demographics, such as age and race (48); anthropomorphic variables, such as adiposity (248), height, fat mass percentage, lean mass, and pubertal status in order to account for body size, metabolic activity, and hormonal influences on

outcomes (73; 140); and psychological variables, such as pre-task anxiety (173), in order to account for baseline level of anxiety that may have impacted outcomes related to any anxiety fluctuations in response to exposure to social threat cues during the MEG task. False discovery rate control was applied to MEG analyses in order to adjust for multiple comparisons within large 3D volumes and determine statistical significance of brain activity. A whole-brain-derived false discovery rate threshold of approximately $p < .01$ was applied. Given the predetermined voxel size (7 mm) in the MEG analyses, only regions-of-interest that survived a $p < .01$ uncorrected threshold in a priori brain regions-of-interest were interpreted.

Aim 1

To examine relationships between attention bias to social threat cues and neural activity in anxiety-processing and emotion regulation regions among youth, and differences between youth with and without LOC eating.

Hypothesis 1a: Greater attention bias to social threat (i.e. shorter reaction times to angry faces than happy or neutral faces) will be associated with increased activation in "bottom-up" unconscious attention capture areas and areas involved in anxiety processing, and blunted activation of "top-down" attention deployment and affect regulation regions in response to social threat cues. A multiple linear regression model was used with attention bias (i.e. angry bias or happy bias) as the IV, engagement of unconscious attention capture and anxiety processing regions (i.e. greater activation in the insula, striatum, amygdala), and engagement of attention deployment and affect regulation regions (i.e. less activation in the anterior cingulate cortex, dorsolateral prefrontal cortex, medial prefrontal cortex, ventrolateral prefrontal cortex) as the DV, and age, race, adiposity, height, and pre-task anxiety as covariates. Depressive symptoms were considered as a covariate in a secondary analysis.

Hypothesis 1b: Youth with LOC eating will exhibit greater attention bias to social threat cues (i.e. greater angry bias), but not to non-threatening cues (i.e. happy bias), compared to youth without LOC eating. A one-way analysis of covariance (ANCOVA) was used with LOC eating (presence/absence) as the independent variable (IV), attentional bias scores (i.e. angry bias, happy bias) as the continuous dependent variable (DV), and age, race, adiposity, height, and pre-task anxiety as covariates. Depressive symptoms were considered as a covariate in a secondary analysis.

Aim 2

To examine if differences in attention bias to social threat and neural activation are related to energy intake at a laboratory meal.

Hypothesis 2a: Greater attention bias to social threat cues (i.e. angry bias), but not non-threating cues (i.e. happy bias), will be associated with greater energy intake. A multiple linear regression model was used with attentional bias scores (i.e. angry bias, happy bias) as the IV, energy intake as the DV, and age, race, pubertal status, height, fat mass percentage, and lean mass as covariates. Depressive symptoms were considered as a covariate in a secondary analysis.

Hypothesis 2b: Increased activation of "bottom-up" unconscious attention capture and anxiety processing regions (i.e. insula, striatum, amygdala), and blunted activation of "top-down" attention deployment and affect regulation regions (i.e. anterior cingulate cortex, dorsolateral prefrontal cortex, medial prefrontal cortex, ventrolateral prefrontal cortex) in response to social threat cues will be associated with greater energy intake. Multiple linear regression models were used, with engagement of unconscious attention capture and anxiety processing regions (i.e. activation in the insula, striatum, amygdala), and engagement of attention deployment and affect regulation regions (i.e. activation in the anterior cingulate cortex,

dorsolateral prefrontal cortex, medial prefrontal cortex, ventrolateral prefrontal cortex) as the IV, energy intake (kcal) as the DV, and age, race, pubertal status, height, fat mass percentage, and lean mass as covariates. Depressive symptoms were considered as a covariate in a secondary analysis.

Aim 3

To examine if LOC eating moderates the relationship between attention bias to social threat and neural activation and differences in intake at a laboratory test meal.

Hypothesis 3a: The presence of LOC eating will moderate the relationship between attention bias to social threat (i.e. angry bias) and energy intake, such that among youth with LOC eating, attention bias to social threat will be more robustly related with energy intake. General linear models (GLMs) were used with attentional bias scores as the IV, LOC eating (presence/absence) as the moderator, energy intake (kcal) as the DV, and age, race, pubertal status, height, fat mass percentage, and lean mass as covariates. Depressive symptoms were considered as a covariate in a secondary analysis.

Hypothesis 3b: The presence of LOC eating will moderate the relationship between increased activation of "bottom-up" unconscious attention capture and anxiety processing regions, and blunted engagement of "top-down" attention deployment and affect regulation regions in response to social threat cues and energy intake, such that among youth with LOC eating, increased activation of "bottom-up" regions and blunted activation of "top-down" regions will be more robustly associated with energy intake. GLMs were conducted with engagement of unconscious attention capture and anxiety processing regions (i.e. activation in the insula, striatum, amygdala), and engagement of attention deployment and affect regulation regions (i.e. activation in the anterior cingulate cortex, dorsolateral prefrontal cortex, medial prefrontal

cortex, ventrolateral prefrontal cortex) as the IV, LOC eating (presence/absence) as the moderator, energy intake (kcal) as the DV, and age, race, pubertal status, height, fat mass percentage, and lean mass as covariates. Depressive symptoms were considered as a covariate in a secondary analysis.

Exploratory Aim 4

To examine whether state anxiety mediates the relationship between increased activation of "bottom-up" unconscious attention capture and anxiety processing regions, and blunted activation of "top-down" attention deployment and affect regulation regions in response to social threat cues and energy intake.

Hypothesis 4: State anxiety will partially mediate the relationship between increased activation of "bottom-up" regions and blunted activation of "top-down" regions in response to social threat cues and energy intake, such that increased activation of "bottom-up" regions and decreased activation of "top-down" regions in response to social threat cues will partially explain increases in state anxiety, which will partially explain increases energy intake. A cross-sectional mediation model was conducted with "bottom-up" and "top-down" neural activation as the IV, state anxiety as the mediator, energy intake (kcal) as the DV, and age, race, pubertal status, height, fat mass percentage, and lean mass as covariates. Depressive symptoms were considered as a covariate in a secondary analysis. The significance of the mediation effect was tested using SPSS PROCESS macro (115).

Exploratory Aim 5

To examine whether anxiety sensitivity moderates the relationship between attention bias to social threat and increased activation of "bottom-up" unconscious attention capture and anxiety-processing regions.

Hypothesis 5: Anxiety sensitivity will moderate the relationship between attention bias to social threat and increased activation of "bottom-up" unconscious attention capture and anxiety processing regions, such that among those with greater anxiety sensitivity, attention bias to social threat will be more robustly associated with activation of "bottom-up" regions. A GLM was conducted with attentional bias scores as the IV, anxiety sensitivity as the moderator, activation of "bottom-up" regions as the DV, and age, race, pubertal status, height, and fat mass as covariates. Depressive symptoms were considered as a covariate in a secondary analysis.

Power Analysis

A sample size of 80 adolescent girls was proposed based on a power analysis to detect small to medium effects sizes across all hypotheses involving MEG analyses. This calculation was based on recommended equations for estimating sample size when using general linear models (56; 121), and assuming 35% attrition rate in unusable MEG data based on prior MEG studies in youth (32; 205). Recruitment of 80 youth would have provided at least 80% power to detect small to medium effect sizes (Cohen's d = 0.2-0.5) with 52-53 youth included in MEG analyses after expected attrition. Given attrition rate due to unusable data was expected to be lower for the cognitive attentional bias task, power was expected to be greater than 80% for those analyses.

Updated Power Analysis due to COVID-19-related Dissertation Recruitment Barriers

Due to the COVID-19 global pandemic, project recruitment was stalled as of March 13, 2020. Recruitment was originally planned to be ongoing through 2020, however due to the pandemic, it was truncated halfway through the original timeline, and additional participants were not able to be accumulated due to the stay-at-home and social distancing orders and to closure of the MEG Core Facility at NIH.

Prior to the pandemic-related recruitment barriers, a total of 55 participants completed the two required visits, with approximately 38 participants having usable MEG imaging data. For at least 80% power to detect small-to-medium effect sizes, the original proposal planned for recruitment of 80 participants, and assumed 35% attrition in unusable MEG data, for a final sample of 52 participants to be included in analyses. Over two-thirds of the expected sample size (n = 80) was enrolled in the reduced recruitment window, and the expected data attrition rate of 35% was aligned with the currently enrolled reduced sample. As such, I have included an updated power analysis for each of the three primary aims below:

Updated Power Analyses for Aim 1

To examine relationships between attention bias to social threat cues and neural activity in anxiety-processing and emotion regulation regions among youth, and differences between youth with and without LOC eating.

Hypothesis 1a: Greater attention bias to social threat (i.e. shorter reaction times to angry faces than happy or neutral faces) will be associated with increased activation in "bottom-up" unconscious attention capture areas and areas involved in anxiety processing, and blunted activation of "top-down" attention deployment and affect regulation regions in response to social threat cues. A multiple linear regression model was used with attention bias (i.e. angry bias or happy bias) as the IV, engagement of unconscious attention capture and anxiety processing regions (i.e. greater activation in the insula, striatum, amygdala), and engagement of attention deployment and affect regulation regions (i.e. less activation in the anterior cingulate cortex, dorsolateral prefrontal cortex, medial prefrontal cortex, ventrolateral prefrontal cortex) as the DV, and age, race, adiposity, height, and pre-task anxiety as covariates. Depressive symptoms were considered as a covariate in a secondary analysis.

The new power analysis for Aim 1a assumes an alpha = 0.05; power = 0.8; total sample size = 38; and an effect size f = 0.46 (large).

The post-hoc power analysis for Aim 1a assumes two-tailed; an alpha = 0.05; power = 0.8; an effect size ϕ = 0.3 (medium); with the required sample size = 82.

Hypothesis 1b: Youth with LOC eating will exhibit greater attention bias to social threat cues (i.e. angry bias), but not to non-threatening cues (i.e. happy bias), compared to youth without LOC eating. A one-way analysis of covariance (ANCOVA) was used with LOC eating (presence/absence) as the independent variable (IV), attentional bias scores (i.e. angry bias, happy bias) as the continuous dependent variable (DV), and age, race, adiposity, height, and pre-task anxiety as covariates. Depressive symptoms were considered as a covariate in a secondary analysis.

The new power analysis for Aim 1b assumes an alpha = 0.05; groups = 2; power = 0.8; total sample size = 55; and an effect size f = 0.39 (medium-to-large).

The post-hoc power analysis for Aim 1b assumes two-tailed; an alpha = 0.05; power = 0.8; an effect size d = 0.01 (small); with the required sample size = 394.

Updated Power Analyses for Aim 2

To examine if differences in attention bias to social threat and neural activation are related to energy intake at a laboratory meal.

Hypothesis 2a: Greater attention bias to social threat cues (i.e. angry bias), but not non-threating cues (i.e. happy bias), will be associated with greater energy intake. A multiple linear regression model was used with attentional bias scores (i.e. angry bias, happy bias) as the IV, energy intake as the DV, and age, race, pubertal status, height, fat mass percentage, and lean mass as covariates. Depressive symptoms were considered as a covariate in a secondary analysis.

The new power analysis for Aim 2a assumes an alpha = 0.05; power = 0.8; total sample size = 55; and an effect size f = 0.28 (medium-to-large).

The post-hoc power analysis for Aim 2a assumes two-tailed; an alpha = 0.05; power = 0.8; an effect size ϕ = 0.3 (medium); with the required sample size = 82.

Hypothesis 2b: Increased activation of "bottom-up" unconscious attention capture and anxiety processing regions (i.e. insula, striatum, amygdala), and blunted activation of "top-down" attention deployment and affect regulation regions (i.e. anterior cingulate cortex, dorsolateral prefrontal cortex, medial prefrontal cortex, ventrolateral prefrontal cortex) in response to social threat cues will be associated with greater energy intake. General linear models (GLM) were used, with engagement of unconscious attention capture and anxiety processing regions (i.e. activation in the insula, striatum, amygdala), and engagement of attention deployment and affect regulation regions (i.e. activation in the anterior cingulate cortex, dorsolateral prefrontal cortex, medial prefrontal cortex, ventrolateral prefrontal cortex) as the IV, energy intake (kcal) as the DV, and age, race, pubertal status, height, fat mass percentage, and lean mass as covariates. Depressive symptoms were considered as a covariate in a secondary analysis.

The new power analysis for Aim 2b assumes an alpha = 0.05; power = 0.8; total sample size = 38; and an effect size f = 0.46 (large).

The post-hoc power analysis for Aim 2b assumes two-tailed; an alpha = 0.05; power = 0.8; an effect size ϕ = 0.3 (medium); with the required sample size = 82.

Updated Power Analyses for Aim 3

To examine if LOC eating moderates the relationship between attention bias to social threat and neural activation and differences in intake at a laboratory test meal.

Hypothesis 3a: The presence of LOC eating will moderate the relationship between attention bias to social threat (i.e. angry bias) and energy intake, such that among youth with LOC eating, attention bias to social threat will be more robustly related with energy intake. GLMs were used with attentional bias scores as the IV, LOC eating (presence/absence) as the moderator, energy intake (kcal) as the DV, and age, race, pubertal status, height, fat mass percentage, and lean mass as covariates. Depressive symptoms were considered as a covariate in a secondary analysis.

The new power analysis for Aim 3a assumes an alpha = 0.05; groups = 2; power = 0.8; total sample size = 55; and an effect size f = 0.38 (medium-to-large).

The post-hoc power analysis for Aim 3a assumes two-tailed; an alpha = 0.05; power = 0.8; an effect size f = 0.25 (medium); with the required sample size = 229.

Hypothesis 3b: The presence of LOC eating will moderate the relationship between increased activation of "bottom-up" unconscious attention capture and anxiety processing regions, and blunted engagement of "top-down" attention deployment and affect regulation regions in response to social threat cues and energy intake, such that among youth with LOC eating, increased activation of "bottom-up" regions and blunted activation of "top-down" regions will be more robustly associated with energy intake. GLMs were conducted with engagement of unconscious attention capture and anxiety processing regions (i.e. activation in the insula, striatum, amygdala), and engagement of attention deployment and affect regulation regions (i.e. activation in the anterior cingulate cortex, dorsolateral prefrontal cortex, medial prefrontal cortex, ventrolateral prefrontal cortex) as the IV, LOC eating (presence/absence) as the moderator, energy intake (kcal) as the DV, and age, race, pubertal status, height, fat mass percentage, and lean mass as covariates. Depressive symptoms were considered as a covariate in a secondary analysis.

The new power analysis for Aim 3b assumes an alpha = 0.05; groups = 2; power = 0.8; total sample size = 38; and an effect size f = 0.48 (large).

The post-hoc power analysis for Aim 3b assumes two-tailed; an alpha = 0.05; power = 0.8; an effect size f = 0.25 (medium); with the required sample size = 229.

Despite the smaller than expected sample, all members of the present dissertation committee provided written approval to move forward with data analysis and interpretation. The signed memo outlining this explicit approval by all committee members and the dissertation committee chair is included in the Supplement.

CHAPTER 3: RESULTS

Participant Characteristics

Fifty-five adolescent girls were recruited. All participants ($N = 55$) were female and had overweight or obesity (BMI $\geq 85^{th}$ percentile). The average age of the participants was 15.2 ± 1.7 years. Twenty-six participants were non-Hispanic Black (47.3%), fifteen were non-Hispanic White (27.3%), and five participants were of multiple races (9.1%). Five participants identified as Hispanic or Latino (9.1%), and four participants did not report their ethnicity (7.3%). The average BMI-*z* of participants was 1.8 ± 0.4. The majority of participants had obesity (60%), while 40% of participants did not meet criteria for obesity but met criteria for overweight. Sixteen participants (29.1%) reported the presence of at least one episode of LOC eating within the past month. The average trait anxiety score was 34.6 ± 6.2. Regarding state anxiety prior to the MEG scan, the range of scores was 20-41, with a mean of 30.3 ± 4.5. Chi-square and *t*-tests revealed there were no significant differences between groups of girls with and without LOC eating on age, race, ethnicity, BMI-*z*, or state and trait anxiety (*p*s > .05). Participant characteristics are outlined in Table 4.

Missing Data

As stated in the previous power analysis section, due to the limitations of social distancing and stay-at-home orders during the COVID-19 pandemic, recruitment was truncated, resulting in less data collected than expected. There were participants with missing data, particularly for the Anxiety Sensitivity Index (ASI) referenced in Exploratory Aim 5, for which data collection began after the initiation of the original protocol. Forty-five of the 55 participants were missing ASI data, and of the ten participants with valid data, listwise there were only five

participants with both ASI data and other outcome variables of interest, which precluded analyses for this exploratory aim.

Regarding missing data for other primary outcome variables of interest, there were $n = 16$ participants with missing attention bias task data, due to reasons including excessive errors >80 ($n = 10$), technical button box issues ($n = 3$), or failure to administer the task due to visit timing issues ($n = 3$). There were $n = 17$ participants with missing MEG data during the attention bias task, due to reasons including excessive task errors >80 ($n = 10$), technical computer software issues ($n = 4$), or failure to administer the task due to visit timing issues ($n = 3$). Finally, there were $n = 3$ participants with missing test meal data, due to reasons including allergies ($n = 1$), not liking enough of the test meal foods on a Food Preferences Questionnaire ($n = 1$), and feeling nauseated during the visit ($n = 1$).

Overall there were $N = 38$ participants with complete and usable data. Participant characteristics for those with usable data are outlined in Table 5. Of these participants, there were $n = 14$ (36.8%) with LOC eating, 52.6% with obesity, and 47.4% with overweight. Chi-square and *t*-tests were conducted to determine whether the missingness of primary outcome variables differed by race, ethnicity, LOC status, age, BMI, or trait anxiety level. There were no differences between missing and non-missing data on race, ethnicity, LOC status, age, BMI, or trait anxiety level (ps > .06). Of the participants included in the final sample with usable data, the average number of errors on the dot-probe task was 33.5 (range 6-74). For participants who were not included in the final sample due to non-usable MEG data, excessive dot-probe errors, or missing test meals, the average number of errors on the dot-probe task was 133.9 (range 33-278).

Results of Aim 1

Aim 1

To examine relationships between attention bias to social threat cues and neural activity in anxiety-processing and emotion regulation regions among youth, and differences between youth with and without LOC eating.

Hypothesis 1a: Greater attention bias to social threat (i.e. shorter reaction times to angry faces than happy or neutral faces) will be associated with increased activation in "bottom-up" unconscious attention capture areas and areas involved in anxiety processing, and blunted activation of "top-down" attention deployment and affect regulation regions in response to social threat cues.

Results of Hypothesis 1a: When adjusting for age, race, height, fat mass (kg), and pre-task anxiety, attention bias to social threat was not significantly related to increased engagement in "bottom-up" unconscious attention capture areas and areas involved in anxiety processing, including the amygdala [($F(1, 29) = .34$, β=-.11, p=.56)], insula [($F(1, 29) = .09$, β=.06, p=.77)], or striatum [($F(1, 29) = .12$, β=-.07, p=.73)]. Attention bias to angry faces was not significantly related to lower activation of attention deployment and affect regulation regions, including the anterior cingulate cortex [($F(1, 29) = .25$, β=-.09, p=.62)], dorsolateral prefrontal cortex [($F(1, 29) = .11$, β=.06, p=.74)], medial prefrontal cortex [($F(1, 29) = .19$, β=-.08, p=.67)], or ventrolateral prefrontal cortex [($F(1, 29) = .03$, β=-.03, p=.87)]. See Table 6 for summarized results.

Further, except for a marginally significant relationship with amygdala activation that did not survive the correction threshold [($F(1, 29) = 1.82$, β=.36, p=.05)], attention bias to happy faces (i.e. shorter reaction time to happy faces compared to neutral faces) was not significantly related to activation in any of the regions of interest (ps>.07). Finally, when considered as an additional covariate, depressive symptoms were not a significant predictor in any of the models

with attention bias to angry faces (*p*s>.36) or attention bias to happy faces (*p*s>.16), nor did it significantly change any of the model results for either attention bias to angry or happy faces.

Hypothesis 1b: Youth with LOC eating will exhibit greater attention bias to social threat cues (i.e. angry bias), but not to non-threatening cues (i.e. happy bias), compared to youth without LOC eating.

Results of Hypothesis 1b: A total of thirty-seven youth had completed listwise data of attention bias scores that did not exceed the error cut-off. Compared to youth without LOC eating (*n*=23), youth with LOC eating (*n*=14) did not display significantly greater attention bias to angry social threat cues [$F(1, 30) = .05$, $p = .82$] when adjusting for age, race, height, fat mass (kg), and pre-task anxiety. Similarly, youth with LOC eating did not differ in attention bias to non-threatening happy cues compared to youth without LOC eating [$F(1, 30) = .02$, $p = .90$] when covarying for age, race, height, fat mass (kg), and pre-task anxiety. When considered as an additional covariate, depressive symptoms were not significant in either the model with angry bias (*p*=.96) or happy bias (*p*=.80). See Table 7 for fully summarized results.

Results of Aim 2

Aim 2

To examine if differences in attention bias to social threat and neural activation are related to energy intake at a laboratory meal.

Hypothesis 2a: Greater attention bias to social threat cues (i.e. angry bias), but not non-threating cues (i.e. happy bias), will be associated with greater energy intake.

Results of Hypothesis 2a: The overall model for total energy intake, with attentional threat bias scores (i.e. angry bias) as the IV, total energy (kcal) intake as the DV, and age, race, pubertal status, height, fat mass percentage, and lean mass as covariates, was not significant

[$F(7, 28) = 2.08$, p=.08, R^2_{adj} =.18], and attention bias to angry threat-cues was not significantly related to greater total energy intake (β=-0.18, p=.27). Attention bias for angry threat-cues was also not significantly related to any percentage macronutrient variables, including percentage of energy consumed from protein (β=-0.23, p=.21), fats (β=-0.23, p=.21), or carbohydrates (β=0.27, p=.14). Similarly, attention bias for happy face cues was not significantly related to total energy intake (β=-0.06, p=.73), or to any percentage macronutrient variables, including percentage of energy consumed from protein (β=0.12, p=.51), fats (β=-0.15, p=.40), or carbohydrates (β=0.09, p=.65). When considered as an additional covariate, depressive symptoms were not a significant predictor in any Aim 2a models (ps>.21). See Table 8 for fully summarized results.

Hypothesis 2b: Increased activation of "bottom-up" unconscious attention capture and anxiety processing regions (i.e. insula, striatum, amygdala), and blunted activation of "top-down" attention deployment and affect regulation regions (i.e. anterior cingulate cortex, dorsolateral prefrontal cortex, medial prefrontal cortex, ventrolateral prefrontal cortex) in response to social threat cues will be associated with greater energy intake.

Results of Hypothesis 2b: When controlling for age, race, height, percentage fat mass, lean mass (kg), and pubertal status, engagement in "bottom-up" unconscious attention capture areas and areas involved in anxiety processing was not significantly related to total energy intake (kcal), which included the amygdala [($F(1, 27) = .02$, β=.03, p=.88)], insula [($F(1, 27) = 1.00$, β=.18, p=.33)], or striatum [($F(1, 27) = 1.14$, β=.19, p=.30)]. Similarly, activation of "top-down" attention deployment and affect regulation regions was not significantly related to total energy intake, which included the anterior cingulate cortex [($F(1, 27) = 1.53$, β=.21, p=.23)], dorsolateral prefrontal cortex [($F(1, 27) = .65$, β=.14, p=.43)], medial prefrontal cortex [($F(1, 27)$

= 2.61, β=.27, p=.12)], or ventrolateral prefrontal cortex [(F(1, 27) = .25, β=.09, p=.62)]. See Table 9 for fully summarized results.

With regard to percentage of energy consumed from protein, there was a negative significant relationship with amygdala activation during attention-deployment [(F(1, 27) = 7.79, β=.51, p=.01)], which did survive the correction threshold of p = .01. There were no other significant relationships between engagement in areas involved in anxiety processing and percentage of energy consumed from protein, including the insula [(F(1, 27) = .24, β=-.10, p=.63)] or striatum [(F(1, 27) = .38, β=-.13, p=.54)]. Similarly, activation of affect regulation regions was not significantly related to percentage of energy consumed from protein, which included the anterior cingulate cortex [(F(1, 27) = .15, β=-.28, p=.15)], dorsolateral prefrontal cortex [(F(1, 27) = .78, β=-.18, p=.39)], medial prefrontal cortex [(F(1, 27) = .11, β=-.31, p=.11)], or ventrolateral prefrontal cortex [(F(1, 27) = .01, β=-.02, p=.91)].

Engagement in areas and areas involved in anxiety processing was not significantly related to percentage of energy consumed from fats, which included the amygdala [(F(1, 27) = 2.88, β=.33, p=.10)], insula [(F(1, 27) = .14, β=.08, p=.71)], or striatum [(F(1, 27) = .58, β=.-15, p=.45)]. Similarly, activation of affect regulation regions was not significantly related to percentage of energy consumed from fats, which included the anterior cingulate cortex [(F(1, 27) = 1.04, β=-.19, p=.32)], dorsolateral prefrontal cortex [(F(1, 27) = .91, β=-.19, p=.35)], medial prefrontal cortex [(F(1, 27) = 1.57, β=-.24, p=.22)], or ventrolateral prefrontal cortex [(F(1, 27) = .002, β=-.01, p=.96)].

In the examination of percentage of energy consumed from carbohydrates, there was a positive marginally significant relationship with amygdala activation during attention-deployment [(F(1, 27) = 5.33, β=-.44, p=.03)], although it did not survive the correction

threshold of $p = .01$. There were no other significant relationships between areas involved in anxiety processing and percentage of energy consumed from carbohydrates, including insula [($F(1, 27) = .02$, β=-.03, p=.90)], or striatum [($F(1, 27) = .66$, β=.17, p=.43)]. Similarly, affect regulation regions were not significantly related to percentage of energy consumed from carbohydrates, including the anterior cingulate cortex [($F(1, 27) = 1.71$, β=.25, p=.20)], dorsolateral prefrontal cortex [($F(1, 27) = 1.08$, β=.21, p=.31)], medial prefrontal cortex [($F(1, 27) = 2.44$, β=.30, p=.13)], or ventrolateral prefrontal cortex [($F(1, 27) = .002$, β=.01, p=.96)].

When considered as an additional covariate, depressive symptoms were not significant in any of the Aim 2b models (ps>.35).

Results of Aim 3

Aim 3

To examine if LOC eating moderates the relationship between attention bias to social threat and neural activation of anxiety regions and differences in intake at a laboratory test meal.

Hypothesis 3a: The presence of LOC eating will moderate the relationship between attention bias to social threat (i.e. angry bias) and energy intake, such that among youth with LOC eating, attention bias to social threat will be more robustly related with energy intake.

Results of Hypothesis 3a: In a generalized linear model adjusting for age, race, height, pubertal status, percentage fat mass, and lean mass, attention bias to social threat was not significantly related to total energy intake (kcal) [$F(1, 26) = 1.76$, $p = .20$, $\eta_p^2 = .06$]. The main effect of LOC eating was marginally significantly related to total energy intake [$F(1, 26) = 4.19$, $p = .05$, $\eta_p^2 = .14$]. The interaction of LOC eating and attention bias to social threat was not significantly related to total energy intake [$F(1, 26) = .62$, $p = .44$, $\eta_p^2 = .02$]. See Table 10 for fully summarized results.

For percentage of energy consumed from protein, the was no significant relationship with attention bias to social threat [$F(1, 26) = 1.61$, $p = .22$, $\eta_p^2 = .06$], or LOC eating [$F(1, 26) = .81$, $p = .38$, $\eta_p^2 = .03$]. The interaction of LOC eating and attention bias to social threat was not significantly related to percentage of energy consumed from protein [$F(1, 26) = .06$, $p = .82$, $\eta_p^2 < .01$].

For percentage of energy consumed from fats, the was no significant relationship with attention bias to social threat [$F(1, 26) = .98$, $p = .33$, $\eta_p^2 = .04$], or LOC eating [$F(1, 26) = .43$, $p = .52$, $\eta_p^2 = .02$]. The interaction of LOC eating and attention bias to social threat was not significantly related to percentage of energy consumed from protein [$F(1, 26) = 2.43$, $p = .13$, $\eta_p^2 = .09$].

For percentage of energy consumed from carbohydrates, the was no significant relationship with attention bias to social threat [$F(1, 26) = 1.59$, $p = .22$, $\eta_p^2 = .06$], or LOC eating [$F(1, 26) = .68$, $p = .42$, $\eta_p^2 = .03$]. The interaction of LOC eating and attention bias to social threat was not significantly related to percentage of energy consumed from protein [$F(1, 26) = 1.34$, $p = .26$, $\eta_p^2 = .05$].

Similarly, the interaction between LOC eating and attention bias to happy faces was not significant for total energy intake [$F(1, 26) = 1.07$, $p = .31$, $\eta_p^2 = .04$], or for any of the macronutrient variables, including percentage of energy consumed from protein [$F(1, 26) = .57$, $p = .46$, $\eta_p^2 = .02$], fats [$F(1, 26) = 1.54$, $p = .23$, $\eta_p^2 = .06$], or carbohydrates [$F(1, 26) = 1.49$, $p = .23$, $\eta_p^2 = .05$]. When considered as an additional covariate in secondary analyses, depressive symptoms did not significantly contribute in any of the models (ps > .26).

Hypothesis 3b: The presence of LOC eating will moderate the relationship between increased activation of anxiety processing regions, and blunted engagement of affect regulation

regions in response to social threat cues and energy intake, such that among youth with LOC eating, increased activation of anxiety processing regions and blunted activation of affect regulation regions will be more robustly associated with energy intake.

Results of Hypothesis 3b: In the generalized linear models for total energy intake (kcal) adjusting for age, race, height, pubertal status, percentage fat mass, and lean mass, the interaction of LOC eating and activation of anxiety processing regions was not significant, which included the interaction of LOC eating with the amygdala [$F(1, 25) = .09$, $p = .77$, $\eta_p^2 < .01$], insula [$F(1, 25) = .57$, $p = .46$, $\eta_p^2 = .02$], and striatum [$F(1, 25) = 1.05$, $p = .32$, $\eta_p^2 = .04$]. The interaction of LOC eating and engagement of affect regulation regions in response to social threat cues was not significant for total energy intake, which included the interaction of LOC eating and the anterior cingulate cortex [$F(1, 25) = .48$, $p = .49$, $\eta_p^2 = .02$], dorsolateral prefrontal cortex [$F(1, 25) = .43$, $p = .52$, $\eta_p^2 = .02$], medial prefrontal cortex [$F(1, 25) = 1.16$, $p = .29$, $\eta_p^2 = .04$], and ventrolateral prefrontal cortex [$F(1, 25) = 1.00$, $p = .33$, $\eta_p^2 = .04$]. See Table 11 for fully summarized results.

For percentage of energy consumed from protein, there was no significant interaction of LOC eating and activation of anxiety processing regions, which included the interaction of LOC eating with the amygdala [$F(1, 25) = 2.42$, $p = .13$, $\eta_p^2 = .09$], insula [$F(1, 25) = .24$, $p = .63$, $\eta_p^2 = .01$], and striatum [$F(1, 25) = .13$, $p = .72$, $\eta_p^2 = .01$]. The interaction of LOC eating and engagement of affect regulation regions in response to social threat cues was not significant for percentage of energy consumed from protein, which included the interaction of LOC eating and the anterior cingulate cortex [$F(1, 25) = .66$, $p = .42$, $\eta_p^2 = .03$], dorsolateral prefrontal cortex [$F(1, 25) = 1.15$, $p = .29$, $\eta_p^2 = .04$], medial prefrontal cortex [$F(1, 25) < .01$, $p = .99$, $\eta_p^2 < .001$], and ventrolateral prefrontal cortex [$F(1, 25) = .01$, $p = .94$, $\eta_p^2 < .001$].

For percentage of energy consumed from fats, there was no significant interaction of LOC eating and activation of anxiety processing regions, which included the interaction of LOC eating with the amygdala [$F(1, 25) = 1.47$, $p = .24$, $\eta_p^2 = .06$], insula [$F(1, 25) < .01$, $p = .98$, $\eta_p^2 < .001$], and striatum [$F(1, 25) = .12$, $p = .74$, $\eta_p^2 = .01$]. The interaction of LOC eating and engagement of affect regulation regions in response to social threat cues was not significant for percentage of energy consumed from fats, which included the interaction of LOC eating and the anterior cingulate cortex [$F(1, 25) = 1.41$, $p = .25$, $\eta_p^2 = .05$], dorsolateral prefrontal cortex [$F(1, 25) = 1.21$, $p = .28$, $\eta_p^2 = .05$], medial prefrontal cortex [$F(1, 25) = .01$, $p = .94$, $\eta_p^2 < .001$], and ventrolateral prefrontal cortex [$F(1, 25) = .51$, $p = .48$, $\eta_p^2 = .02$].

For percentage of energy consumed from carbohydrates, there was no significant interaction of LOC eating and activation of anxiety processing regions, which included the interaction of LOC eating with the amygdala [$F(1, 25) = 2.12$, $p = .16$, $\eta_p^2 = .08$], insula [$F(1, 25) = .03$, $p = .86$, $\eta_p^2 < .01$], and striatum [$F(1, 25) = .15$, $p = .70$, $\eta_p^2 = .01$]. The interaction of LOC eating and engagement of affect regulation regions in response to social threat cues was not significant for percentage of energy consumed from carbohydrates, which included the interaction of LOC eating and the anterior cingulate cortex [$F(1, 25) = 1.60$, $p = .22$, $\eta_p^2 = .06$], dorsolateral prefrontal cortex [$F(1, 25) = 1.52$, $p = .23$, $\eta_p^2 = .06$], medial prefrontal cortex [$F(1, 25) = .01$, $p = .92$, $\eta_p^2 < .001$], and ventrolateral prefrontal cortex [$F(1, 25) = .38$, $p = .54$, $\eta_p^2 = .02$].

When considered as an additional covariate in secondary analyses, depressive symptoms did not significantly contribute in any of the models (ps > .29).

Exploratory Aim 4

To examine whether state anxiety mediates the relationship between increased activation of "bottom-up" unconscious attention capture and anxiety processing regions, and blunted activation of "top-down" attention deployment and affect regulation regions in response to social threat cues and energy intake.

Hypothesis 4: State anxiety will partially mediate the relationship between increased activation of anxiety processing regions and blunted activation of affect regulation regions in response to social threat cues and energy intake, such that increased activation of anxiety processing regions and decreased activation of affect regulation regions in response to social threat cues will partially explain increases in state anxiety, which will partially explain increases energy intake.

Results of Exploratory Aim 4: Mediation findings are summarized in Table 12. Neural activity was not significantly associated with state anxiety for any of the regions of interest, including the following: amygdala (a = -1.30, SE = 2.91, p = .66); insula (a = -2.55, SE = 3.00, p = .40); striatum (a = -1.00, SE = 4.08, p = .81); anterior cingulate cortex (a = 2.23, SE = 2.50, p = .38); dorsolateral prefrontal cortex (a = 0.89, SE = 3.88, p = .82); medial prefrontal cortex (a = 1.48, SE = 3.15, p = .64); ventrolateral prefrontal cortex (a = 0.39, SE = 4.73, p = .94). State anxiety was not significantly associated with total energy intake in any of the mediation models (b path ps > .78).

State anxiety did not significantly mediate the relationship between neural activity and total energy intake for any of the regions of interest, including the following: amygdala (ab = 1.44, SE = 48.45, 95% bias-corrected confidence interval (CI) = [-70.32, 133.85]); insula (ab = -2.75, SE = 61.20, 95% CI = [-166.00, 98.50]); striatum (ab = 0.55, SE = 81.92, 95% CI = [-

122.29, 222.86]); anterior cingulate cortex (ab = -7.62, SE = 44.17, 95% CI = [-114.92, 67.91]); dorsolateral prefrontal cortex (ab = -1.74, SE = 73.29, 95% CI = [-156.93, 145.53]); medial prefrontal cortex (ab = -4.41, SE = 48.27, 95% CI = [-117.42, 83.40]); ventrolateral prefrontal cortex (ab = -0.49, SE = 63.42, 95% CI = [-88.19, 167.04]).

Exploratory Aim 5

To examine whether anxiety sensitivity moderates the relationship between attention bias to social threat and increased activation of "bottom-up" unconscious attention capture and anxiety processing regions.

Hypothesis 5: Anxiety sensitivity will moderate the relationship between attention bias to social threat and increased activation of "bottom-up" unconscious attention capture and anxiety processing regions, such that among those with greater anxiety sensitivity, attention bias to social threat will be more robustly associated with activation of "bottom-up" anxiety processing regions.

Results of Exploratory Aim 5: As stated in the previous power analysis section, due to the limitations of social distancing and stay-at-home orders during the COVID-19 pandemic, recruitment was truncated, resulting in less data collected than expected, particularly for the Anxiety Sensitivity Index (ASI), for which data collection began after the initiation of the original protocol. Forty-five of the 55 participants were missing ASI data, and of the ten participants with valid data, listwise there were only five participants with both ASI data and other outcome variables of interest. As a result, the general linear model was not able to yield results as expected due to the small *n*. No results can be reported or interpreted related to Exploratory Aim 5.

CHAPTER 4: DISCUSSION

The objective of the current study was to determine the relationships between attention bias to social threat cues and neural activation implicated in social anxiety and subsequent energy intake at a laboratory test meal in youth with overweight or obesity, with and without loss-of-control (LOC) eating. Further, this investigation examined whether LOC eating moderated the relationships between attention bias to social threat and neural activation of anxiety regions and subsequent energy intake at a laboratory test meal. Given that loss-of-control (LOC) eating in youth is highly comorbid with anxiety (14; 100; 101; 124; 165; 182; 246), a better understanding of the neural underpinnings involved in the links between LOC eating and anxiety could aid in the development of novel targets for reducing excess intake that leads to obesity and obesity-related health comorbidities. The following sections will highlight the results and interpretation of findings for each of the primary study aims.

SAMPLE CHARACTERISTICS

The study sample ($N = 55$) consisted entirely of adolescent females, all of whom had overweight or obesity. The subsample of participants with usable data ($N = 38$) did not significantly differ on any sample characteristics. Individuals who identified as non-Hispanic Black were overrepresented in this study, comprising almost half of the study sample versus approximately 13% of the U.S. population, while individuals who were non-Hispanic White were markedly underrepresented, comprising 27.3% of the study sample versus approximately 60% of the U.S. population. However, among U.S. youth between the ages of 2 and 19 years old, the odds of obesity are higher among non-Hispanic Black children and adolescents compared to non-Hispanic White children and adolescents (177), which may account for the demographic breakdown of the current study sample that was recruited for the BMI range constituting

overweight or obesity. Taken together, the study sample represents a racially and ethnically diverse subset of adolescent girls with overweight or obesity.

Almost one-third (29.1%) of the current sample of youth reported the presence of at least one episode of LOC eating within the past month, which is consistent with population estimates finding that, across studies, approximately 31% of youth with overweight or obesity report LOC eating (116). There were no significant differences between groups of girls with and without LOC eating on racial or ethnic demographic characteristics. This finding is consistent with past research (48; 100; 220), which has demonstrated a similar prevalence of LOC eating or binge eating between African-American and Caucasian youth. Although some measures to assess LOC eating have been validated among minority groups (17) (most notably, the EDE, which was utilized in the current study), some pediatric studies have utilized assessments for disordered or binge eating that have been validated in primarily Caucasian samples (126). It is important for future research to continue to rigorously validate assessment methodology for LOC eating among minority samples of youth.

There were no significant differences between those with and without LOC eating on reported anxiety, which contradicts past literature finding that youth with LOC eating have significantly elevated trait anxiety symptoms above and beyond the contribution of excess body weight or fat (223). However, this discrepancy may be a result of the smaller than anticipated sample size in the current study, compared to larger sample sizes used in past research for similar analyses (223). Anxiety disorders are commonly observed prior to the onset of disordered eating behaviors and clinical eating disorders (18; 131). It is possible that, given study criteria excluded any youth with presence of a significant, full-threshold psychiatric disorder that may have impeded completion of the study, the current sample was not clinically severe enough for these

relationships to emerge. Given the small sample size, these comparisons between groups with and without LOC eating should be interpreted with caution and should be replicated among larger samples in future studies.

Aim 1: Attention Bias To Social Threat And Neural Activity Among Youth With And Without LOC Eating

Aim 1 examined the relationships between attention bias to social threat cues and neural activity in anxiety processing regions among youth, as well as differences in these constructs between youth with and without LOC eating. Results from Aim 1 revealed that dot-probe attention bias score to social threat was not significantly related to engagement in "bottom-up" unconscious attention capture in areas involved in anxiety processing, or activation of "top-down" attention deployment in affect regulation regions. Similarly, attention bias to happy faces was not significantly related to neural activation in any of the regions of interest. These results did not support the hypothesis that greater attention bias to social threat would be associated with increased activation of "bottom-up" unconscious attention capture in areas involved in anxiety processing, and blunted activation of "top-down" attention deployment in affect regulation regions in response to social threat cues. Further, results of Aim 1 revealed that youth with LOC eating did not exhibit significantly greater attention bias to angry social threat cues compared to youth without LOC eating. Youth with LOC eating also did not display differences in attention bias to non-threatening happy cues compared to youth without LOC eating. These findings did not support the hypothesis that youth with LOC eating would exhibit greater attention bias to social threat cues, but not to non-threatening cues, compared to youth without LOC eating.

Within the attentional bias framework, implicit attention biases are thought to be a result of hyperactivation in stimulus-driven "bottom-up" neural regions upon exposure to salient cues

(170; 190), while hypoactivation in implicated neural regions during voluntary "top-down" attentional deployment may result in persistent attention deployment and impact attentional bias (57; 58; 192). In line with this framework, the current study proposed that attention bias to social threat cues would relate to hyperactivation in "bottom-up" regions implicated in unconscious attention capture and social anxiety processing, and blunted activation in "top-down" attention deployment and affect regulation regions, which would in turn influence LOC eating in order to reduce the neural underpinnings of anxiety through overeating behaviors. This theoretical framework was not supported by the results of Aim 1, which may be due in part to several study limitations. Not only was the sample size reduced due to the pandemic-related social-distancing and stay-at-home orders, but there were also missing attention bias task data for a number of participants due to excessive task errors. These excessive errors may indicate that some participants might not have understood the dot-probe task instructions or perhaps found the task boring and had difficulty focusing for sustained periods. Individual differences in task engagement and motivation have been shown to moderate the efficacy of dot-probe tasks (162; 225). The further diminished sample size for analyses involving the dot-probe task due to issues involving excessive errors may have impacted the results. Future research should examine the relationships between dot-probe task attention bias to threat and neural activation related to anxiety among a larger sample of adolescents or using potentially more engaging and motivating approaches, such as incorporation of game-like elements (25; 187).

Attention bias to social threat cues has been shown to be positively related to pediatric anxiety symptoms (1), and given the well-established relationship between pediatric anxiety and LOC eating (100; 165), it was hypothesized that youth with LOC eating would have an increased attention bias to socially threatening stimuli (112), similar to that of youth with anxiety.

However, this hypothesis was also not supported by the results of Aim 1. These findings may have differed from the prior literature due to methodological discrepancies in the approach to capture attention bias to threat. Prior studies examining attention bias to threat among adult women with eating disorders have primarily utilized an emotional Stroop attention bias task (112; 113), rather than a dot-probe task as in the current study. The emotional Stroop task, although widely used, has been criticized for its lack of specificity in determining which processes are attributable to the increased reaction times for salient stimuli, and the task does not allow for investigation into specific mechanisms of hypervigilance versus avoidance patterns to threat-based stimuli (13). Further, the emotional Stroop task has lacked consistency in its use of control stimuli across studies, and similar effects have been found across both clinical and non-clinical samples (152), suggesting a lack of discriminant validity. These task limitations may partially account for the discrepancies observed between prior literature and the current findings on attention bias to socially threatening cues among youth with and without LOC eating. It is also possible that a different pattern of findings may have emerged with recruitment of a larger sample of adolescents with and without LOC eating. However, the current data suggest that attention bias to social threat is not more pronounced among youth with LOC eating compared to those without.

Dot-Probe Reliability

In addition to sample size limitations, the current findings regarding attention bias scores on the dot-probe task and neural activation in implicated brain regions may have differed if other approaches to capture attention bias had been utilized. Although widely used and supported by the literature for its discriminant validity in distinguishing between clinical and non-clinical groups (e.g. anxious and non-anxious youth) (16), the test-retest reliability of the dot-probe task

has been called into question (195; 213; 278). The design of the dot-probe attentional bias task assumes a stable, trait-like bias underlies attention towards salient stimuli, and that this bias can be accurately summarized with a single calculated score. However, some research has found that contextual factors, such as mood state (16), have been shown to influence performance on the dot-probe task, suggesting it may be dynamic rather than trait-like. Attention may also diminish over the course of the task, due to factors such as habituation or boredom, which could contribute to variations in attentional bias score within and between trials (9; 195). Attention bias scores that are captured using button-press reaction times, as in dot-probe tasks, have several inherent technical limitations that could contribute to errors that diminish reliability. Speed of button-pressing can be influenced by a variety of factors that do not pertain to the underlying attentional bias cognitive construct, such as response selection latency or technical equipment failures (195).

Given the reliability concerns raised in relation to the dot-probe task, a post-hoc exploratory reliability analysis was conducted with data collected from the current sample. First, the internal consistency, or Cronbach's α, was analyzed for the total raw reaction times across all face-cue trial types, as well as the correlation between the averaged raw reaction times for each face-cue category. Subsequently, the split-half reliability of the derived dot-probe bias scores was analyzed by splitting the raw trial reaction times into even and odd trials and re-calculating separate bias scores. The correlation between the newly derived even and odd trial bias scores were correlated; with the expectation that a highly reliable bias score would yield high correlations.

The results of the reliability analysis showed that the internal consistency of the raw reaction times was high (Cronbach's $\alpha > .95$), and the correlation of averaged reaction times was also high (pearson's $r > .85$). The high internal consistency results for the raw trial data suggests

that those who responded quickly on the task consistently responded quickly, and those who had slow button-presses were consistently slow. This indicator that the *task* itself is highly reliable is positive for interpretation of the MEG-related aims and results that utilized trial-level derived measurements of neural activity. The results of the split-half reliability analysis of the even and odd trial-derived bias scores, however, was poor to moderate (Pearson's *rs* range = -.03 - .31). This result is an indicator that the formula used to calculate the bias score is unreliable, and that the project aims and results involving the attention bias score should be interpreted with caution.

The underlying problem related to the formula for calculating bias scores is a mathematical consequence of the logic of derived difference scores. When using a linear composite score that relies on the difference of two highly correlated components, the composite score's resulting reliability is a function of the reliability of each component score and the magnitude of the correlation between these components. The magnitude of the correlation between the components either increases or decreases the reliability of the composite, depending on whether you add or subtract the components. When one adds highly correlated components together, the resulting composite score is even higher in reliability. When one subtracts highly correlated components, however, as is the case for dot-probe bias scores, the reliability of the resulting composite score decreases, resulting in much weaker reliability than either component alone. Given these mathematical reliability concerns of the dot-probe bias score, alternate methodologies to capture attention bias should be considered in future research.

Dot-probe tasks were originally designed within the cognitive psychology domain to make inferences about cognition (i.e. attention bias) based on overt behaviors (i.e. reaction times); however, more recently developed methodologies may better capture the underlying cognitive construct. One such methodology is eye-tracking. While eye-tracking methodology has

shown convergent validity with dot-probe attention bias tasks (169), it has been shown to outperform dot-probe tasks in reliability indices (195; 278). Intuitively, eye-tracking can better encapsulate the visual component involved in cognitive processing of attentional allocation to threat cues. Unlike motor-response button presses, eye-tracking techniques can provide a more direct measurement of participant's gaze patterns as an indicator of overt visual attention bias to threat, which makes it a more appealing option for future studies. Although the larger protocol for the current study did include eye-tracking methods, unfortunately this data was subject to excessive technical equipment failures; and in combination with pandemic-related barriers, eye-tracking data was even further severely underpowered than data collected for the current aims. Future research should re-examine the relationships between attention bias to threat and bottom-up and top-down neural activation patterns using alternate, optimally reliable methodologies, such as eye-tracking techniques, in order to determine the underlying neurocognitive mechanism of attentional bias and how it may contribute to psychopathology.

Given the dearth of literature exploring the relationship between attention bias to social threat and LOC eating, future research should replicate this study using a larger sample and optimally reliable methodologies to determine whether attention bias to social threat may be a potential mechanism for the relationship between social anxiety and overeating behaviors in youth with LOC eating.

AIM 2: ATTENTION BIAS TO SOCIAL THREAT, NEURAL ACTIVITY, AND ENERGY INTAKE

Results from Aim 2 revealed that dot-probe attention bias to social threat was not significantly related to greater total energy intake, nor was it significantly related to any percentage of macronutrient variables, including percentage of energy consumed from protein, fats, or carbohydrates. Similarly, dot-probe attention bias for non-threatening happy face cues

was not significantly related to total energy intake, nor to any percentage of macronutrient variables. These results did not support the hypothesis that greater scores of attention bias to social threat cues, but not non-threating cues, would be associated with greater energy intake. It is possible that a significant relationship between dot-probe attention bias and total energy intake may have emerged with recruitment of a larger sample of adolescents, as the current sample was underpowered to detect small-to-medium effects. As discussed for Aim 1, the dot-probe task reliability limitations (195; 213; 278) may have impacted the findings between attention bias to socially threatening cues and energy intake, and it is possible that different results may have emerged with use of a more optimally reliable measurement of attention bias, such as eye tracking methodologies (195; 278).

Regarding neural activation patterns in Aim 2, neural activation during "bottom-up" unconscious attention capture in areas involved in anxiety processing was not significantly related to total energy intake. Similarly, activation during "top-down" attention deployment in affect regulation regions did not show a significant relationship with total energy intake. Overall, the results of Aim 2 did not support the primary hypothesis that increased activation during "bottom-up" unconscious attention capture in anxiety processing regions, and blunted activation during "top-down" attention deployment in affect regulation regions in response to social threat cues would relate to greater total energy intake. It is possible that using the visual dot-probe task design as a marker of exposure to social threat may have accounted for the lack of significant findings related to total energy intake. One small fMRI study examining the role of anxiety in the interpersonal model of LOC eating utilized an alternate social threat design, referred to as a 'chatroom social threat paradigm' (125). This study had several similarities to the current project, in that its' sample consisted of adolescent girls with overweight or obesity, and the girls

participated in an objective laboratory buffet lunch test meal immediately following the neuroimaging session, however the social threat chatroom paradigm differed in design. Prior to the fMRI scan, participants were told prior to the task that they would be "chatting online with peers," and they were asked to select peers with whom they were and were not interested in chatting based on online "profiles." Then, while participants were in the scanner, it was revealed who was and was not interested in chatting with them. This reveal of rejection from their peers was intended to simulate the stress involved in peer interactions (125). It may be that actual simulated rejection from peers of a similar age to the participants, as opposed to simple exposure to angry adult face cues, could have elicited a more salient response in the current study as it relates to total energy intake. These task design considerations will be important to take into account for future studies exploring the role of social threat in relation to anxiety and overeating.

The nature of the laboratory buffet test meal allowed for exploratory analyses of more specific macronutrient variables in relation to neural activation patterns (i.e. percentage of energy consumed from protein, fats, and carbohydrates). There was a significant relationship showing that greater amygdala activation during top-down attention deployment related to a lower percentage of energy consumed from protein. There was also a marginally significant relationship showing that greater amygdala activation during top-down attention deployment related to greater percentage of energy consumed from carbohydrates. There were no other notable relationships between bottom-up or top-down neural activation in regions of interest and macronutrient content. These analyses examining macronutrient variables in relation to neural activation patterns were exploratory, thus no specific hypotheses were formulated a priori regarding the directionality of relationships between neural activation and percentage of energy consumed from protein, carbohydrates, or fats. As such, these findings should be interpreted with

caution. Further, the sample size was limited given the pandemic-related recruitment barriers, which lends additional reason to interpret the following findings with caution.

Greater amygdala activation during top-down attention deployment related to a lower percentage of energy consumed from protein and a marginally significant greater percentage of energy consumed from carbohydrates. This pattern of eating is consistent with prior LOC eating literature examining laboratory eating behaviors among those at high risk for overeating and excess weight gain. Youth with LOC eating tend to display eating patterns involving lower protein consumption and greater consumption of highly palatable foods, such as carbohydrates (252), during laboratory meal studies. Further, lower protein consumption and greater consumption of carbohydrates has been shown to relate to facets of negative affect, such as anxiety, among youth with LOC eating (43; 201) such that greater negative affect predicts lower percentage of intake from protein and greater percentage of intake from carbohydrates in the laboratory. This prior literature is consistent with the current neural activation pattern findings in the amygdala, which is a prominent anxiety processing region and may provide insights into an underlying neural mechanism for the relationship between negative affect and a maladaptive eating pattern that could contribute to excess weight gain. Lower protein consumption has been shown to be associated with lower satiety following a meal, which may conceivably contribute to subsequent overeating behaviors and increased overall energy intake as youth fail to become fully satiated (181; 214; 287). Alternately, highly palatable dessert-type foods, which are typically high in carbohydrates and/or fats, are often referred to as “comfort foods”; and according to affect theory of binge eating (136), individuals seek “comfort” and reduction of negative affect through overeating behaviors and consumption of these highly palatable foods. Prospectively, this pattern of consumption of lower protein and greater amounts of highly

palatable foods may serve as a mechanism for excess weight gain or development of full-syndrome binge-eating disorder (252). Notably, percentage of energy consumed from fats was not significantly related to greater amygdala activation during attention deployment, nor any other neural activation patterns. Some prior studies in the pediatric disinhibited eating literature have also seen this similar pattern, finding that consumption of less protein and greater carbohydrates, but not fats, relates to LOC eating (252; 267). It is possible the lack of findings related to fat intake may be due in part to the composition of the laboratory buffet test meal used in the current study. The test meal array included some dessert-type foods that were high in carbohydrate but low in fat, such as jelly beans, as opposed to highly palatable dessert-type foods that are high in both carbohydrates and fats, such as ice cream (252). Although the laboratory buffet test meal used in the current study included foods typically considered palatable by youth (252), it is possible that the nature of a single laboratory test meal may not reflect youths' patterns of eating in the natural environment, thus potentially limiting the ecological validity of this paradigm. In isolation, however, results suggested that greater amygdala activation during attention deployment related to lower percentage of energy consumed from protein, and higher percentage of energy consumed from carbohydrates. Although findings should be interpreted with caution for the reasons discussed, these cross-sectional data are a first step in supporting this potential mechanism.

While findings regarding the macronutrient intake pattern of lower protein and higher carbohydrate consumption were theoretically consistent with prior literature, the timing of the attention capture versus attention deployment neural activation pattern was somewhat unexpected. In line with Aim 1, it was hypothesized that neural activity-related results would reflect a "vigilance-avoidance pattern" of attentional bias, such that youth would display a

stimulus-driven automatic orientation of attention ("bottom-up") toward threatening stimuli (55), which would align with immediate hyperactivation in anxiety processing regions, and alternately would be followed by hypoactivation in affect regulation regions and a deployed attentional shift ("top-down") away from threatening stimuli as an avoidance behavior. This theoretical vigilance-avoidance framework has been observed among youth with anxiety disorders, such that anxiety symptoms are associated with stimulus-driven automatic orientation of attention to threatening stimuli (55) alternately followed by a shift of attention in line with goal-oriented behavior such as avoidance of threatening stimuli. The "avoidance phase" during attention deployment has been theorized to serve as an attempt to minimize distress (71; 156), but could ultimately prove maladaptive in that avoidance can impair habituation to distressing cues and result in a perpetuation of anxiety over time. In Aim 2, this particular neural activation pattern was hypothesized to relate to greater overall energy intake, which could potentially be extended to maladaptive eating patterns of greater carbohydrate and lesser protein intake that would reflect risk for excess weight gain. More specifically, it was expected that anxiety processing regions, such as the amygdala, would exhibit hyperactivation during the attention capture period, not the attention deployment period, and that this activation would relate to maladaptive eating patterns. However, this pattern was not supported by data from the current study, and instead, amygdala hyperactivation during the attention *deployment* period related to the observed maladaptive intake patterns. Further, none of the affect regulation regions of interest (i.e. anterior cingulate cortex, dorsolateral prefrontal cortex, medial prefrontal cortex, ventrolateral prefrontal cortex), which were expected to exhibit *hypo*activation during attention deployment, were significant in any of the models. This may suggest that difficulties in affect regulation in response to social threat is not a prominent underlying mechanism for the relationship between social anxiety and

LOC eating behaviors. Overall, the amygdala activation pattern during the attention deployment period, as opposed to the attention capture period, indicates that there was no "avoidance" per se as suggested in the vigilance-avoidance framework, and instead there may have been a sustained attentional deployment *toward* threat. Thus, current findings may suggest that hyperactivation in a prominent anxiety processing region, the amygdala, during sustained attention deployment toward socially threatening cues may contribute to maladaptive eating patterns.

Although these results should be interpreted with caution due to their exploratory nature and the sample size limitations of the current study, the findings are in line with the interpersonal theory of binge eating. Increased prolonged attendance toward socially distressing stimuli may contribute to heightened social distress, and subsequently maladaptive overeating patterns and LOC eating may serve as an attempt to cope with the uncomfortable resulting negative affective states (258). Adolescents (96), and girls in particular (209; 243), as well as individuals with obesity across the lifespan (4), experience exacerbated vulnerability to social stressors, which may make the composition of the current sample uniquely susceptible to this potential interpersonal mechanism for overeating. Taken together, in line with interpersonal theory and the attentional bias literature, the current findings indicate that a potential mechanism for maladaptive eating patterns among girls with overweight may be heightened activation in anxiety processing neural regions due to sustained attentional deployment toward socially threatening cues. A more rigorous exploration of this potential mechanism is warranted given the dearth of literature on the relationship between social anxiety and overeating behaviors. If this mechanistic pattern continues to be supported by future studies, these findings could potentially inform clinical approaches to reduce hyper-attendance to social threat that could contribute to overeating and excess weight gain among youth with symptoms of social anxiety.

Aim 3: LOC Eating Moderation Of Attention Bias To Social Threat, Neural Activity, And Energy Intake

Results from Aim 3 revealed that the main effect of LOC eating was marginally significantly related to total energy intake. However, in relation to the primary analysis of Aim 3, the interaction of LOC eating and attention bias to social threat was not significantly related to total energy intake, contrary to hypotheses. Similarly, there was no significant interaction between attention bias to threat and LOC eating on any of the macronutrient variables. These findings did not support the hypothesis that the presence of LOC eating would moderate the relationship between attention bias to social threat and energy intake, such that among youth with LOC eating, attention bias to social threat would be more robustly related with energy intake. Additionally, the interaction of LOC eating and neural activation in regions of interest was not significant for total energy intake or any macronutrient variables. These findings did not support the hypothesis that the presence of LOC eating would moderate the relationship between increased activation of anxiety processing regions, and blunted engagement of affect regulation regions in response to social threat cues and energy intake, such that among youth with LOC eating, increased activation of anxiety processing regions and blunted activation of affect regulation regions would be more robustly associated with energy intake.

Among this sample of adolescent girls with overweight or obesity, the main effect of LOC eating was marginally significant in relation to total energy intake. This finding is in line with a robust literature linking LOC eating with maladaptive food intake patterns. Compared to their counterparts without LOC eating, youth with LOC eating have been shown to consume more energy (120) and more highly-palatable foods (106; 252). Moreover, an independent but similar sample among only girls with overweight or obesity also found a significant relationship

between LOC eating and increased energy consumption at a laboratory test meal designed to elicit binge eating (252). If analyzed among a larger sample, the results from the current study could suggest a trend toward a more robustly significant relationship between LOC eating and greater total energy intake among adolescent girls with overweight or obesity. While full-syndrome BED does not typically manifest until later adolescence or adulthood (235), LOC eating behaviors typically emerge during adolescence (247). At least half of youth who report LOC eating will persist in engaging in the behavior over time, identifying LOC eating as a key risk factor for later development of partial or full-syndrome BED (118; 254). Further, LOC eating has been prospectively associated with excessive weight gain (83; 230; 260) and greater risk for gains in adiposity (248) among youth. The early onset and persistent course of LOC eating suggest it may be a particularly salient target for early intervention in youth who are vulnerable for excess weight gain and associated adverse health comorbidities.

Neither attention bias to threat nor neural activation in regions of interest significantly interacted with LOC eating for total energy intake or any macronutrient variable. As discussed previously, results of Aim 1 suggested that youth with LOC eating did not, in fact, exhibit significantly greater attention bias to angry social threat cues compared to youth without LOC eating. Attention bias models have proposed that socially stressful situations trigger an increased attendance to potential socially threatening cues (13), particularly among those with LOC eating. As such, it was thought that attention bias to threat may be a potential mechanism for the relationship between social anxiety and overeating behaviors among youth with LOC eating in particular. Prior studies in adult samples have supported the link between attention bias to socially threatening stimuli and increased risk for disordered eating attitudes and behaviors (112; 113); however, these studies also utilized an emotional Stroop task to capture attentional bias,

which has several limitations as discussed previously. It is possible the relationship between attention bias to threat and LOC eating behaviors may not emerge until later in adulthood, which could account for the lack of findings in the current sample of adolescents. It is also possible that recruitment of a larger sample of adolescents with and without LOC eating may have resulted in different findings. Outcomes of the current study should be interpreted with caution, and future research should replicate this question among a larger, adequately powered sample.

Although beyond the scope of the current study, which focused on anxiety processing neural pathways, reward-related neural pathways may be a potential mechanism relevant to the relationship between intake and social anxiety among youth with LOC eating (24; 27; 91; 138). The theoretical framework that posits disturbances in reward processing may be implicated in the etiology of LOC eating behaviors is incentive sensitization theory (239; 289). This theory suggests that, among individuals with LOC eating, anticipatory neural reward for food increases over time, but neural reward responsivity to *consumption* of palatable foods decreases with repeated exposure (24). The incentive sensitization framework has been supported by past literature. For example, in an fMRI study it was found that among women with bulimia nervosa who were presented with various foods, neural regions implicated in reward-based learning and taste processing exhibited decreased activation (26), which may underlie compulsive overconsumption of food intake in order to experience the desired level of reward from eating. Moreover, individuals with obesity exhibit reduced dopamine receptors in the dorsal striatum (275; 280), which are involved in consummatory reward processing, and tend to have hypoactivation in the dorsal striatum in response to food intake that predicts gains in adiposity (236). Therefore, youth with LOC eating or excess weight may be chronically hypo-responsive to neural reward derived from consumption of food, potentially driving exponentially greater

amounts of food intake in order to reach similar levels of neural reward. While food intake generally activates neurological reward pathways that may reduce feelings of anxiety (3), a chronic hypo-responsivity to food reward may perpetuate overeating patterns as a maladaptive attempt to overcome a neurological reward deficit (36) that is exacerbated even further by heightened anxiety. Given results of the current study did not support the hypotheses that LOC eating would interact with neural activation patterns in line with attention bias to social threat to predict greater energy intake, alternate neural mechanisms, such as reward pathways, should be explored in relation to LOC eating in order to help better explain the link between social anxiety and LOC eating among vulnerable youth with excess weight.

Exploratory Aim 4: State Anxiety Mediation Of Neural Activity And Energy Intake

Results of Exploratory Aim 4 revealed that state anxiety did not significantly mediate the relationship between neural activity and total energy intake for any of the regions of interest. These results did not support the exploratory hypothesis that state anxiety would partially mediate the relationship between increased activation of anxiety processing regions and blunted activation of affect regulation regions in response to social threat cues and energy intake, such that increased activation of anxiety processing regions and decreased activation of affect regulation regions in response to social threat cues would partially explain increases in state anxiety, which would partially explain increases energy intake. The limited sample size in the current study likely impacted the findings, as the mediation analysis was underpowered to detect small to medium effects.

Facets of state negative affect, such as anxiety and depressive symptoms, have been shown to play a critical role in overeating behaviors among youth. Results of one study among

girls found that state anxiety, but no other mood state including depression, anger, fatigue, or confusion, mediated the relationship between recent social stress and energy intake during a laboratory test meal (218). Another laboratory study among youth at high risk for obesity and with reported LOC eating found that premeal state negative affect was related to increased intake of energy-dense foods, including greater consumption of carbohydrates, dessert, and snack-type foods (201). With regard to neural activation, two studies found that state negative affect was associated with increased orbitofrontal cortex and reward system activation upon exposure to palatable, energy-dense food cues (27; 138), particularly among those reporting disinhibited eating (27). Another neuroimaging study showed that girls with LOC eating and overweight or obesity failed to engage prefrontal cortex regions implicated in emotion regulation, and subsequently engaged in increased food intake (125). Although there is consistent support for the role of state anxiety in eating within a laboratory setting, some pediatric studies utilizing more naturalistic approaches such as ecological momentary assessment have not found a direct relationship between state negative affect and LOC eating (105; 119; 200). These inconsistencies observed in the pediatric literature may be due to key differences in emotion regulation across the developmental spectrum (245). Results may have differed with a younger sample of youth as opposed to the current sample of adolescent girls. Alternately, it is possible that greater trait negative affect masks state anxiety, particularly among healthy youth who do not meet criteria for clinical levels of anxiety or depression. Among the sample in the current study, the average trait anxiety score was 34.6, which is above what some have suggested as a clinical cut-off of 32 for the State-Trait Anxiety Inventory for Children – Trait Subscale (232). Thus, youth in the current sample may experience consistent elevated trait negative affect, and as a result might be less likely to endorse increased levels of momentary state anxiety (43). Future research should

carefully distinguish between the role of state and trait anxiety on eating. Further, studies should examine the potential mediating role of state anxiety on neural engagement in regions implicated in emotion regulation and LOC eating behaviors among a larger sample of youth across the weight and developmental spectrum. However, in isolation, the results of Exploratory Aim 4 did not support the hypothesis that increased activation of anxiety processing regions and decreased activation of affect regulation regions in response to social threat cues would partially explain increases in state anxiety, which would explain increases energy intake.

STUDY STRENGTHS

The current study has several strengths. First, the sample consisted of a racially and ethnically diverse subset of adolescent girls with overweight or obesity, which improves the representativeness and generalizability of results. A well-validated semi-structured interview, the Eating Disorder Examination, was used to assess LOC eating, and is considered an optimal method for assessment of disordered eating in youth (35; 81; 261). Further, use of MEG, which has both excellent temporal and acceptable spatial resolution, was considered a strength for the current study given it is ideally suited for the temporal nature of attention bias to social threat and short-occurring activity in neural circuits involved in anxiety processing (66; 67; 111). Body composition covariates were objectively measured by trained staff using calibrated scales and stadiometers for height and weight, and DXA techniques for fat mass. Finally, the laboratory test meal is a well-validated and controlled paradigm designed to elicit a disinhibited eating episode (201; 252). This test meal design allowed for specific analysis of objective energy intake among youth with and without LOC eating in a highly controlled environment.

STUDY LIMITATIONS

This study has several notable limitations. First, due to the limitations of social distancing and stay-at-home orders during the COVID-19 pandemic, recruitment was truncated, resulting in less data collected than expected and an underpowered sample for most analyses. This recruitment barrier limits interpretation of the current findings, and thus all results were interpreted with caution. Further, there were a number of participants with missing or unusable data. An *a priori* power analysis estimated 35% attrition due to excessive movement during MRI/MEG, based on prior studies involving fMRI and MEG in youth (32; 205), which is consistent with the attrition rate due to missing data in the collected sample. Importantly, there were no differences between race, ethnicity, LOC status, age, BMI, or trait anxiety level for missing and non-missing task data; although the degree of missing data still warrants caution in interpretation of results. Additionally, the sample was restricted to only female adolescents with overweight and obesity, which limits the ability to generalize results to boys, younger children, adults, or children of healthy weight. Lack of a control group consisting of girls without overweight or obesity limits the ability to determine whether results may have differed among individuals with and without overweight and obesity, and whether the proposed mechanisms may be differentially associated in individuals with and without overweight and obesity. Additionally, given the attention bias task includes angry faces, but not other salient threat stimuli, and is specific to *social* threat, ability to determine associations between attention bias to other types of threats or phobias and food intake is limited. It is also possible the laboratory buffet test meal may have not accurately reflected eating in the natural environment, thus potentially limiting the ecological validity of the findings. Additional limitations include the use of cross-sectional data, which limits the ability to examine relationships between attention bias to

social threat and overeating behaviors over time, and as such, no causal conclusions can be drawn from any of the findings.

CLINICAL IMPLICATIONS

Should the current findings be supported within a larger sample, these results may have a range of potential implications for providers who treat adolescent girls with LOC eating, anxiety, or overweight. First, this study adds to the growing literature on the interpersonal theory of eating disorders, which supports the role of social distress as a driver of LOC eating behaviors and a contributor to the development of excess weight gain. According to interpersonal theory (164; 244), LOC eating may develop as a result of maladaptive coping with negative affective states, such as anxiety (218), that arise from socially distressing situations. Food consumption is then triggered as an attempt to escape from the uncomfortable affective state. This maladaptive coping strategy may be due, in part, to heightened sensitivity to incoming social cues and abnormalities in anxiety processing socio-emotional neural circuits (125; 190). Informed by the interpersonal theory framework, findings from the current study indicate that a potential mechanism for maladaptive eating patterns among girls with overweight or obesity may be heightened activation in anxiety processing neural regions due to sustained attentional deployment toward socially threatening cues. If this mechanistic pattern continues to be supported by future studies with larger samples, these findings could potentially inform clinical approaches to reduce hyper-attendance to social threat that could contribute to overeating and excess weight gain among youth with symptoms of social anxiety.

Interpersonal Psychotherapy

Interpersonal psychotherapy (IPT) is an evidence-based therapy founded in interpersonal theory that has demonstrated extensive empirical support for the treatment of eating disorders

involving bingeing behaviors. IPT is a time-limited treatment, conducted in either an individual or group format, that emphasizes the role of interpersonal factors in the onset and maintenance of binge eating behaviors. IPT operates under an assumption that interpersonal functioning is critical to psychological adjustment and social well-being (40). IPT has been adapted as a treatment for the prevention of excess weight gain for adolescents who report LOC eating (259). In this adaptation, IPT aims to link LOC eating to interpersonal concerns in order to target symptoms. Prospective three-year follow-up data for a randomized control trial of this IPT adaptation revealed that the greatest improvements in adiposity were seen among adolescent girls with high anxiety and social adjustment problems (256). Given IPT directly focuses on improving interpersonal relationships and negative mood states, assigning girls with these specific vulnerabilities to IPT for the prevention of excess weight gain may result in optimally beneficial outcomes. These important findings lend support to the relevance of social-anxiety models of LOC eating, as discussed throughout this dissertation, and thus IPT may be a highly pertinent treatment modality for the discussion of clinical implications for the current study.

IPT for the prevention of excess weight gain was specifically designed to target the needs of adolescent girls between the ages of 12 and 17 years old who are at high risk for adult obesity due to high BMI and reports of LOC eating. This target population exactly aligns with the characteristics recruited for the current sample. Moreover, given IPT centers on improving familial and peer relationships, it has been suggested that this treatment modality may be particularly salient among racial or ethnic minority groups (291). Indeed, a longitudinal randomized controlled trial comparing IPT to a general health education control found that girls belonging to ethnic and racial minority groups (primarily African-American) who were randomly assigned to IPT showed significantly greater reductions in LOC eating episodes one

year following treatment (257) compared to minority girls who were assigned to health education. These significant reductions in reported LOC eating among non-White girls persisted when girls were re-examined at three years following treatment (37). In a study in which IPT was adapted for the prevention of excess weight gain among African-American girls, it was found to be acceptable among this population (49), which is highly relevant to the current study sample which consisted of a large proportion of girls who identify as non-Hispanic Black. While IPT has shown to be particularly well-suited for populations aligned with the characteristics unique to the current sample of adolescent girls with overweight or obesity, it is also time-intensive and requires highly trained personnel, and thus may benefit from supplemental intervention approaches.

Attention Bias Modification Training Supplemental Approaches

Among individuals with binge eating behaviors, attention bias modification training, a method designed to reduced unwanted attention biases, has targeted attention bias to highly palatable foods, and has been shown to effectively reduce intake of chocolate (135; 285), or to increase biases for and intake of healthy foods (127). In practice, attention bias modification training involves a similar structure to the visual dot-probe task, with the exception of the probe replacing the neutral cue 100% of the time, as opposed to equally replacing the neutral and salient or threatening cue. Over time, this retraining should result in the individual learning how to attend away from social threat cues. As few as five attention retraining sessions have exhibited a lasting effect on reduction of attention bias to food (134). Another small study among adults with overweight or obesity and BED found that reduction in attentional bias to food was effective in reducing LOC eating episodes, eating disorder symptoms, and BMI at a follow-up three months following an attention retraining intervention (29). Notably, among youth with

overweight or obesity, decreased attention bias following just one session of attention retraining has been shown to be related to a reduction in food intake (28). In relation to anxiety disorders, and in line with the aims of current study, attention bias modification retraining has been widely utilized and has shown to be effective at reducing maladaptive attentional biases related to pediatric anxiety (75). Compared to controls, attention retraining away from threat has been shown to reduce stress reactivity (160), as well as anxiety symptoms among individuals with both social and generalized anxiety disorders (8; 9). Taken together, it is plausible that attention retraining to reduce bias to social threat could readily supplement established psychotherapies such as IPT for youth with overweight or obesity and LOC eating. As a supplemental neurocognitive intervention, attention retraining could be utilized in between weekly IPT sessions or following a 12-week IPT treatment program to bolster or prolong the positive effects of treatment and help youth continue to reduce LOC eating episodes and prevent excess weight gain. Alternately, treatment matching approaches, which involve the selection of specific therapeutic approaches that are most appropriate for a patient's needs and characteristics, may prove to be a clinically relevant alternative approach for use of attention bias modification retraining. Results from past literature are highly promising, in that just a single session of attention retraining could effectively reduce attentional bias among youth (28), making it a highly implementable and relatively undemanding supplement to more intensive clinical approaches. Additionally, attention retraining would conceivably require less time, personnel, and could offer increased accessibility compared to individual or group psychotherapeutic clinical approaches. Given the current study suggested that neural underpinnings implicated in prolonged attention bias to social threat may increase anxiety that contributes to maladaptive eating patterns, attention retraining approaches to reduce bias to social threat may be relevant to

the treatment of LOC eating and excess weight gain. Reducing attention bias to social threat may help some youth with overweight reduce their consumption of energy-dense, highly palatable foods. A better understanding of the neural underpinnings involved in the links between LOC eating and anxiety is needed in order to support these findings, and could aid in the development of more comprehensive intervention approaches for reducing excess intake that leads to obesity and related health comorbidities.

FUTURE DIRECTIONS

First, as discussed previously, future studies on pediatric LOC eating and anxiety should continue to rigorously validate assessment methodology for LOC eating among minority samples of youth, particularly given the odds of obesity are higher among non-Hispanic Black children and adolescents compared to non-Hispanic White youth (177), indicating a particularly vulnerable population for adverse health outcomes that is in need of further study. Most notably, recruitment for the current study was truncated due to pandemic-related research limitations, resulting in less data collected than expected and an underpowered sample. As such, future research should replicate all models in the current study among a larger, more adequately powered sample of youth. It would also be pertinent for future research to examine several comparison groups that were not included in the current study in order to improve the generalizability, or specificity, of results. For example, future studies should include a comparison group of adolescent girls without overweight or obesity in order to determine whether findings may be unique to those who meet criteria for high weight, and whether the proposed mechanisms may be differentially associated among individuals without overweight and obesity. A comparison group of adolescent boys or younger, pre-pubertal children would

also be helpful in future studies for generalizability purposes, given the vast differences between boys and girls in nutritional needs across the various stages of the developmental spectrum (159).

More specifically to the primary aims of the current study, there are some concerns related to the test-retest reliability of dot-probe tasks (195; 213; 278), which was the task design utilized in the current study to capture attentional bias to social threat. Future research should re-examine the relationships between attention bias to threat and neural bottom-up and top-down attention activation patterns using alternate, optimally reliable methodologies in order to determine the underlying neurocognitive mechanism of attentional bias and how it may contribute to psychopathology. Eye-tracking techniques, which have shown convergent validity with dot-probe attention bias tasks (169), have outperformed dot-probe tasks in reliability indices (195; 278) and would be an optimal methodology for future related studies. Although the larger protocol for the current study did include eye-tracking methods, the technology was subject to excessive technical failures and as such was even further underpowered than the data included in the primary aims. Eye-tracking methodology is highly conducive to the unique advantages of MEG in terms of the temporally sensitive nature of the analyses, and would allow for continuous analysis of short-term neural activity as participants' eye gaze shifts toward or away from threatening cues.

The dot-probe attention bias task only included face cues as a social threat stimuli. However, it may provide further insights into the fear-based relationship between social anxiety and LOC eating for future research to explore relationships between attentional bias to other threat- or phobia-stimuli and food intake. It would be interesting to determine whether the amygdala, a pertinent fear-based and anxiety processing neural region, displays similar levels of hyperactivation that related to food intake in response to alternate threat stimuli. Finally, it is

possible that the laboratory buffet test meal utilized in the current study may have not accurately reflected girls' eating behaviors in the natural environment. Future research would benefit from harnessing more naturalistic eating assessment methodologies, such as ecological momentary assessment, in determining whether natural daily intake patterns differ in relation to neural facets of attention bias to social threat among youth with and without LOC eating. Examination of LOC eating behaviors in the natural environment may be particularly important given the toxic food environment (277), which could exacerbate LOC eating due to increased exposure to highly salient palatable food cues. Alternately, youths' natural *social* environments, which could be much richer in terms of highly salient social threat cues due to weight-based teasing and bullying (196; 197; 216), may provide further insights into the relationship between neural underpinnings of social anxiety and LOC eating behaviors among girls with overweight or obesity.

CONCLUSION

In conclusion, the current dissertation aimed to indicate whether LOC eating impacts the relationship between attention bias to social threat and neural aspects of anxiety processing and subsequent eating behaviors. More specifically, the study was designed to closely examine the relationship between attention bias to social threat cues and neural activation implicated in social anxiety and subsequent energy intake at a laboratory test meal among girls with overweight, with and without LOC eating. Findings were largely non-significant and should be interpreted with caution. However, a significant exploratory relationship emerged suggesting that greater amygdala activation during top-down attention deployment related to a lower percentage of energy consumed from protein and greater percentage of energy consumed from carbohydrates. If these results are replicated in future hypothesis-driven, rather than exploratory, studies, these findings could indicate that a potential mechanism for maladaptive eating patterns may be

heightened activation in anxiety processing neural regions due to sustained attentional deployment toward socially threatening cues. Given the relatively limited literature on the neural underpinnings of anxiety and attention bias to social threat among youth with overweight, the largely null findings in the current study may still be informative for future studies if replicated within a larger sample. Future research is still needed for a better understanding of the neural underpinnings involved in the links between LOC eating and anxiety. Elucidating neurocognitive mechanisms to explain the link between LOC eating and anxiety could help to aid in the development of novel targets for reducing excess food intake that contributes to the development of pediatric disordered eating and obesity-related health outcomes.

Figure 1: Interpersonal Model of LOC Eating. The Interpersonal Model is a well-supported theory in the eating disorders literature that proposes LOC eating may develop as a result of maladaptive coping with negative affect that arises from psychosocial stress.

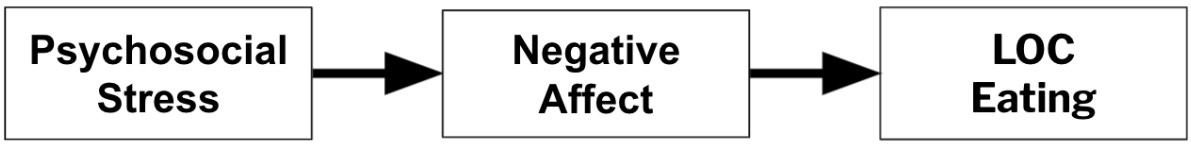
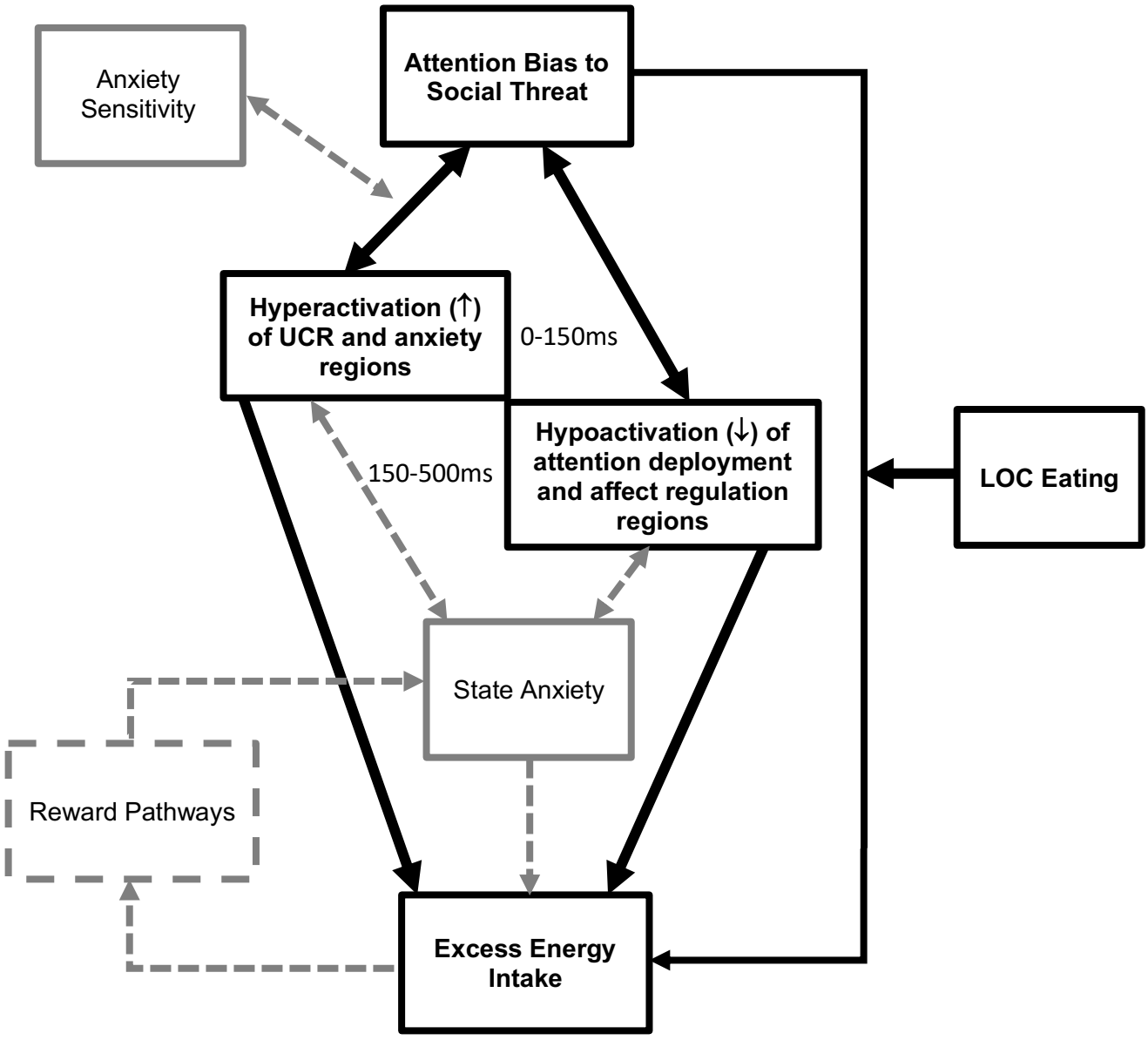


Figure 2: Model of Neural Underpinnings of Social Anxiety and LOC Eating. The current conceptual model proposes that exposure to social threat will elicit hyperactivation in anxiety processing neural regions during bottom-up attention capture, and blunted activation in affect regulation regions during top-down attention deployment; further, in line with the interpersonal model (Figure 1), youth will be driven to reduce anxiety through overeating behaviors. The presence of LOC eating is conceptualized as a moderator of these relationships to result in excess energy intake.



Note: Dotted boxes indicate constructs that were not formally tested in the current study; dotted lines with solid gray boxes indicate exploratory moderators or mediators.

Figure 3. Social Threat Visual Dot Probe Task. The Social Threat Visual Dot Probe Task includes two side by side picture pairs of angry, happy, or neutral faces projected on a computer screen. After 500ms, the face pairs disappear and a set of horizontal or vertical dots appears in one of the locations previously occupied by the faces, prompting a left or right button press response.

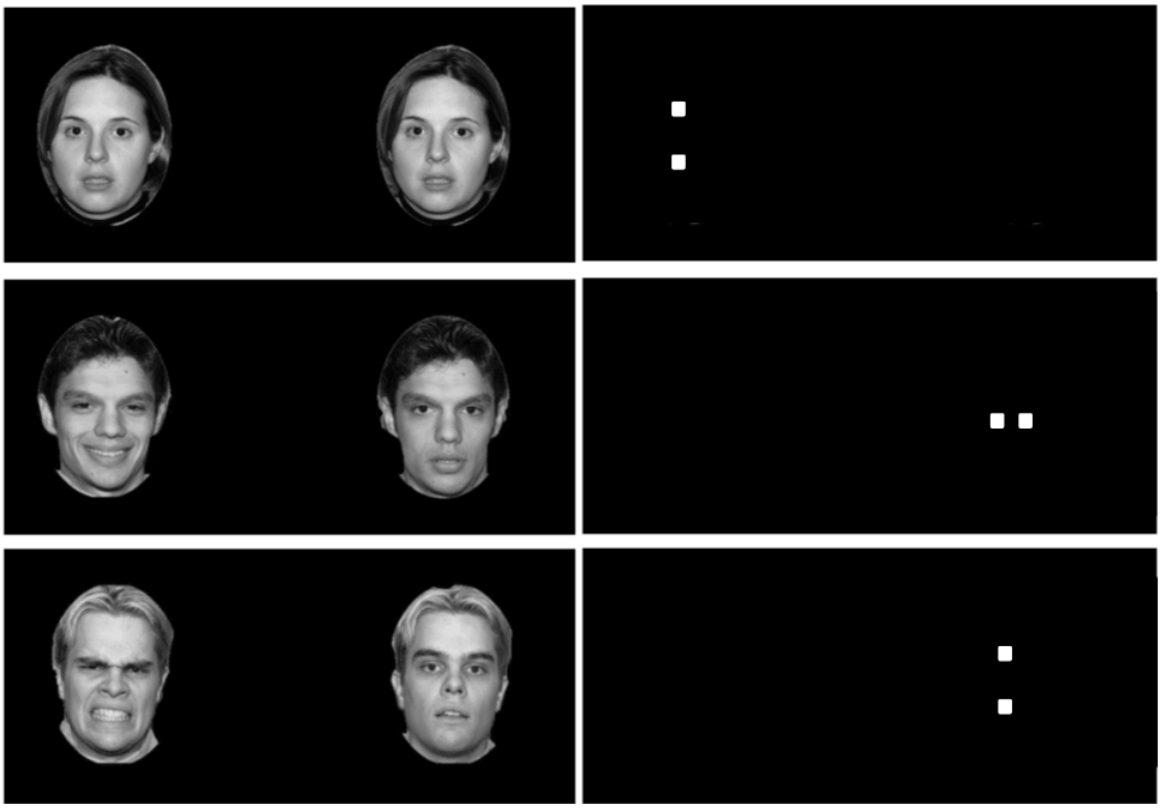


Figure 4. Laboratory Buffet Lunch Test Meal. Participants ate from a >10,000 kcal laboratory buffet lunch test meal consisting of a variety of macronutrients. All participants received tape recorded binge instructions before the meal to “Let yourself go and eat as much as you want”.

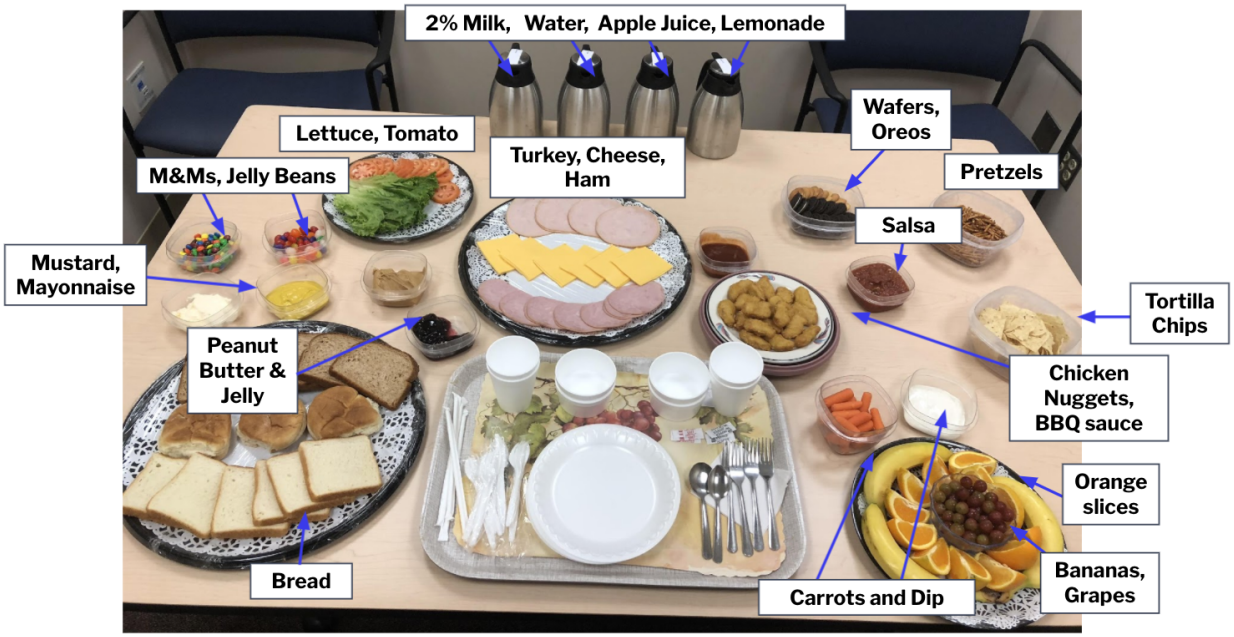


Figure 5: Timeline of Study Procedures. Following a phone screen, individuals completed two study visits. During a screening visit they completed consent/assent procedures, a physical examination and DXA scan, a series of self-report questionnaires, and participated in semi-structured clinical interviews. If participants were determined to be eligible after the screening visit, they returned for a second laboratory visit where they completed an structural MRI scan, a series of questionnaires, a social threat task during a MEG session, and lastly a laboratory test meal.

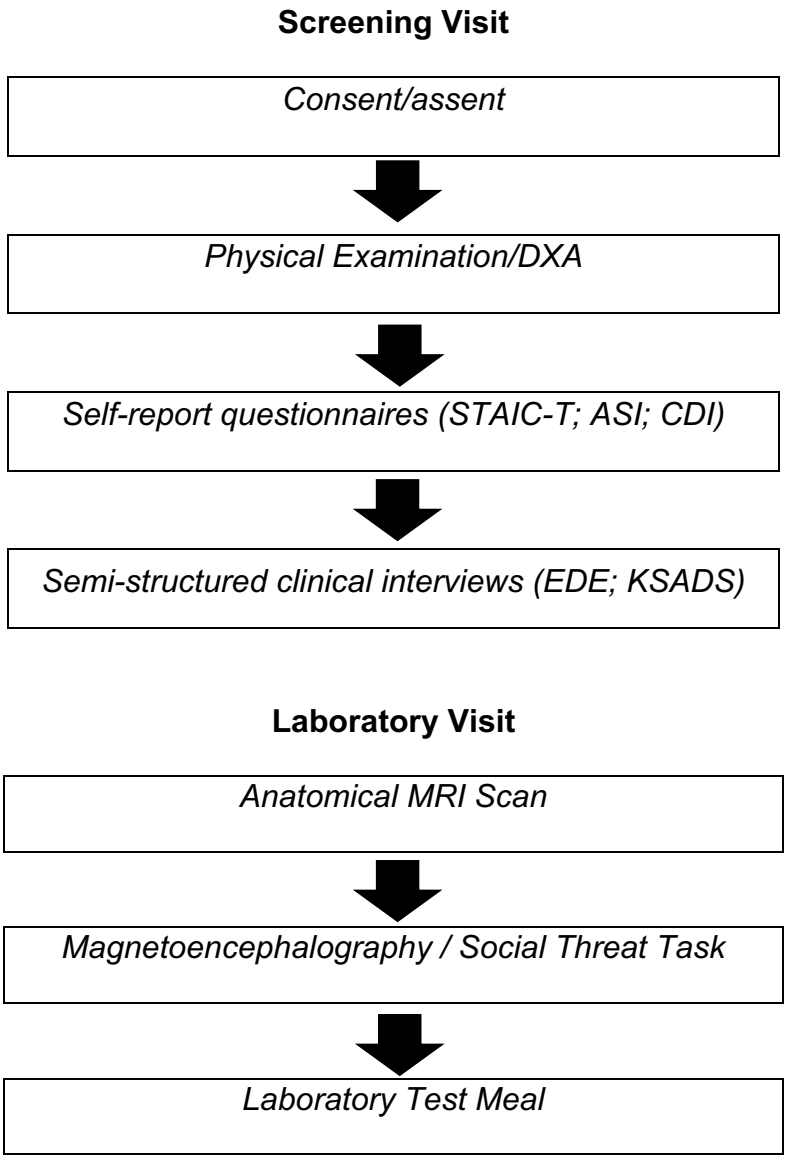
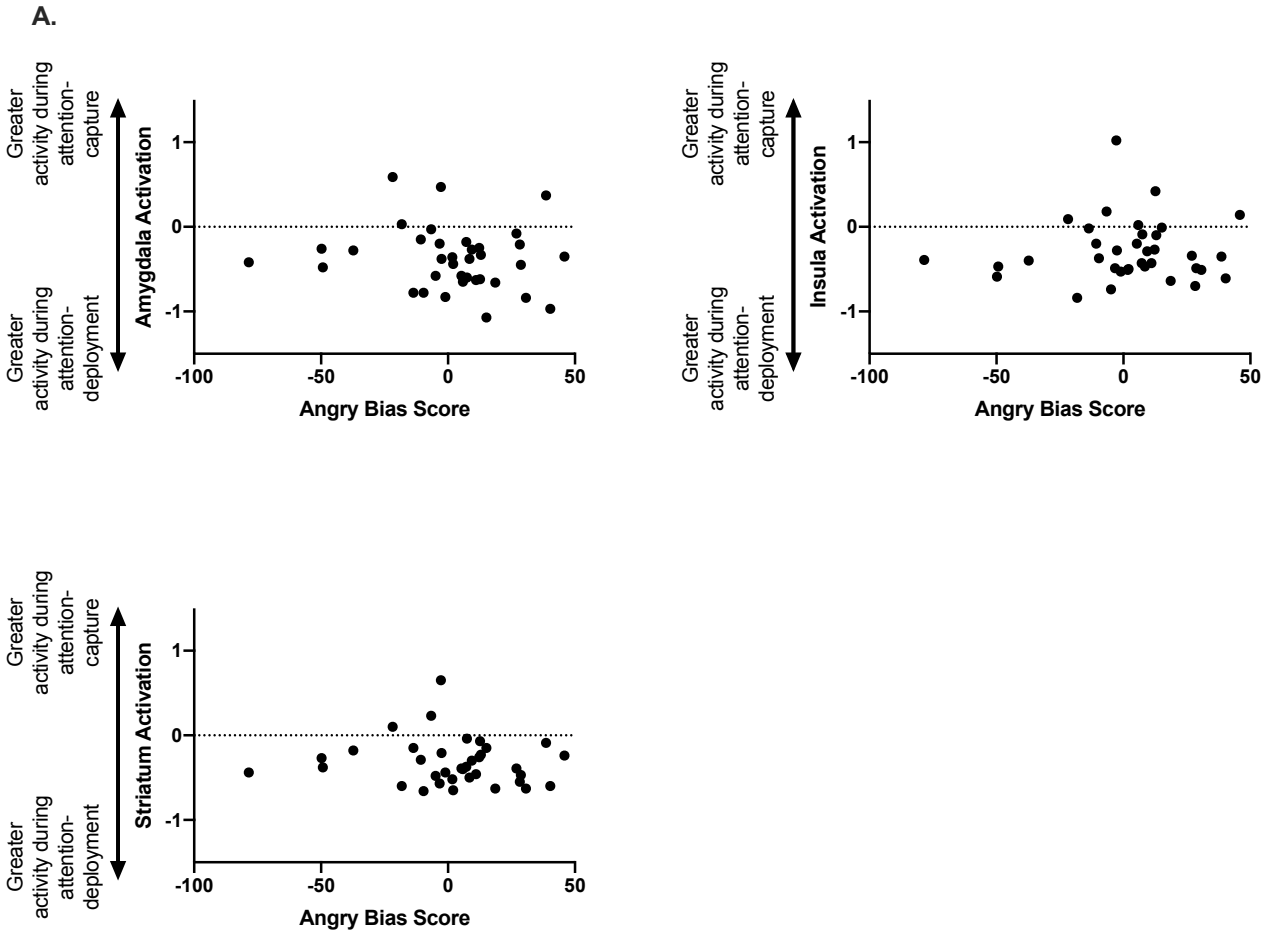
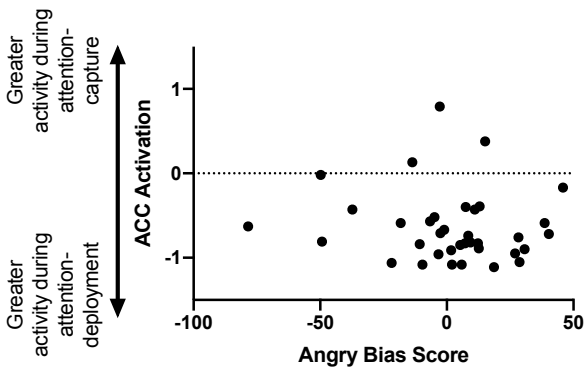


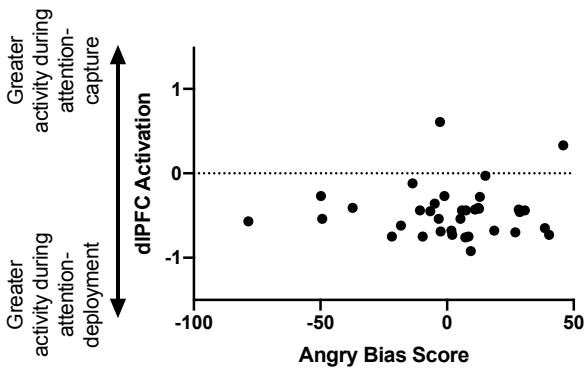
Figure 6. Aim 1a Linear Regression Analyses for Attention Bias to Social Threat and Neural Activation. Panel A = anxiety-processing regions (amygdala, insula, striatum); Panel B = affect regulating regions (anterior cingulate cortex, dorsolateral prefrontal cortex, medial prefrontal cortex, ventrolateral prefrontal cortex). Attention bias score to social threat was not significantly related to activation in areas involved in anxiety processing (*p*s > .56). Attention bias score to social threat was not significantly related to activation of affect regulation regions (*p*s > .62).

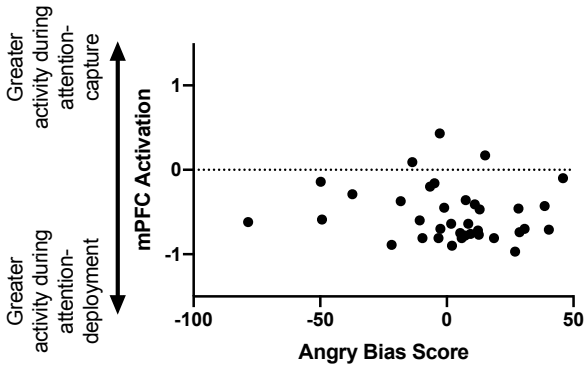
Note: The y-axis represents a ratio of relative region-of-interest (ROI) activation during attention capture vs. attention deployment; more positive numbers indicate greater activation in the ROI during the bottom-up attention capture time period, and more negative numbers indicate greater activation in the ROI during the attention deployment period.



B.


Greater activity during attention-capture
Greater activity during attention-deployment
ACC Activation
1
0
-1
-100
-50
0
50
Angry Bias Score


Greater activity during attention-capture
Greater activity during attention-deployment
dlPFC Activation
1
0
-1
-100
-50
0
50
Angry Bias Score


Greater activity during attention-capture
Greater activity during attention-deployment
mPFC Activation
1
0
-1
-100
-50
0
50
Angry Bias Score

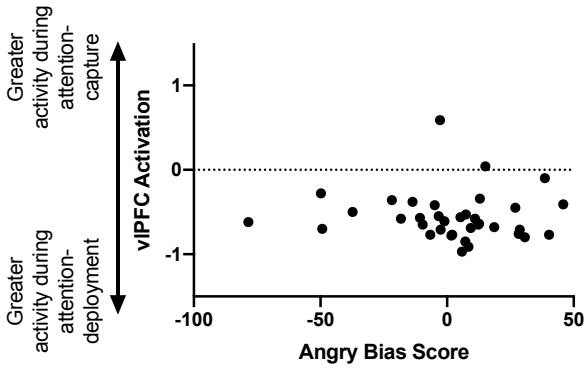

Greater activity during attention-capture
Greater activity during attention-deployment
vlPFC Activation
1
0
-1
-100
-50
0
50
Angry Bias Score

Figure 7. Aim 1b Analysis of Covariance for Loss-of-Control Eating Presence and Attentional Bias. Compared to youth without LOC eating, youth with LOC eating did not display significantly greater attention bias score to angry social threat cues (p = .82). Similarly, youth with LOC eating did not differ in attention bias score to non-threatening happy cues compared to youth without LOC eating (p = .90).

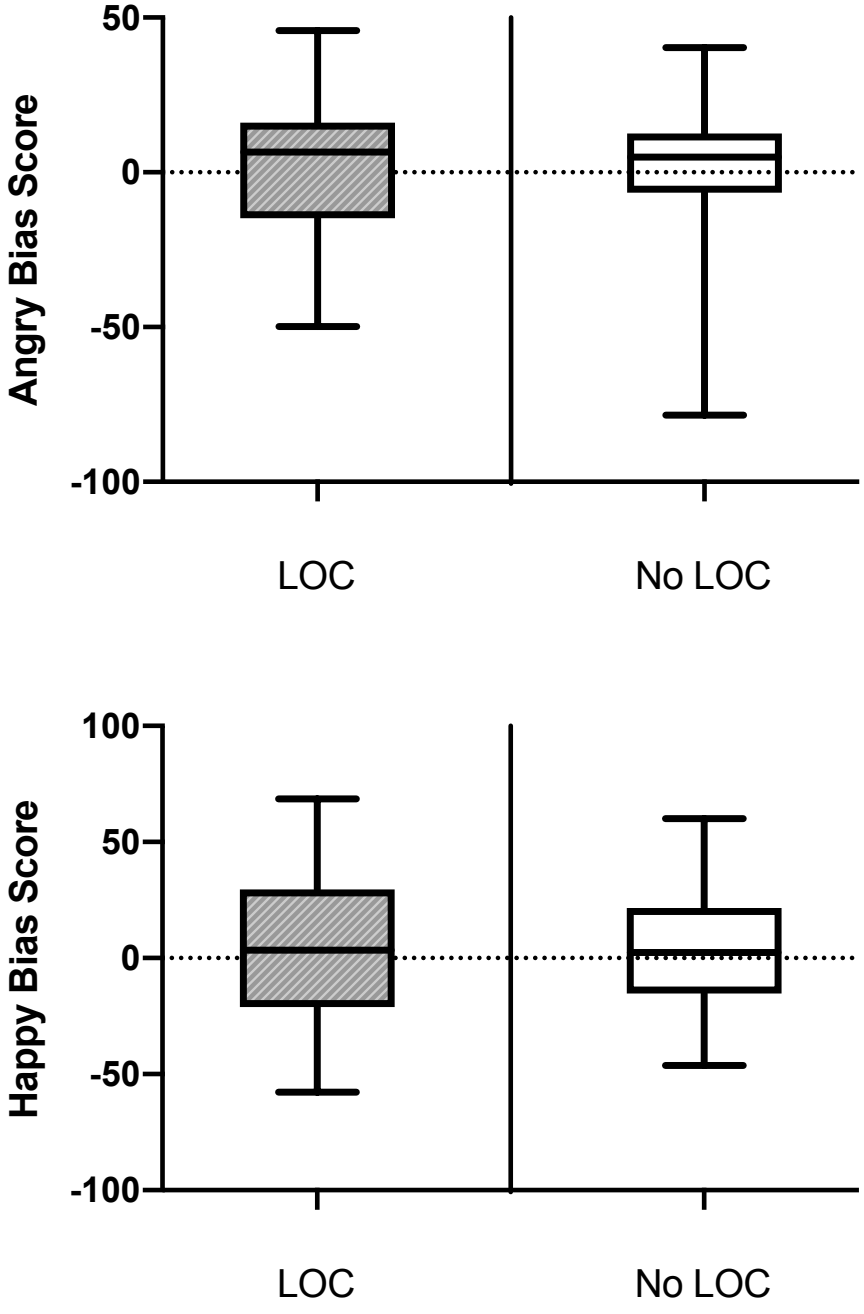


Figure 8. Aim 2a Linear Regression Analyses for Attention Bias to Social Threat and Test Meal Intake. Attention bias score to social threat was not significantly related to greater total energy intake (p = .27), or to any percentage macronutrient variables (ps > .14).

Note: For percentage macronutrient variable graphs, the y-axis is arsin square root transformed for analyses.

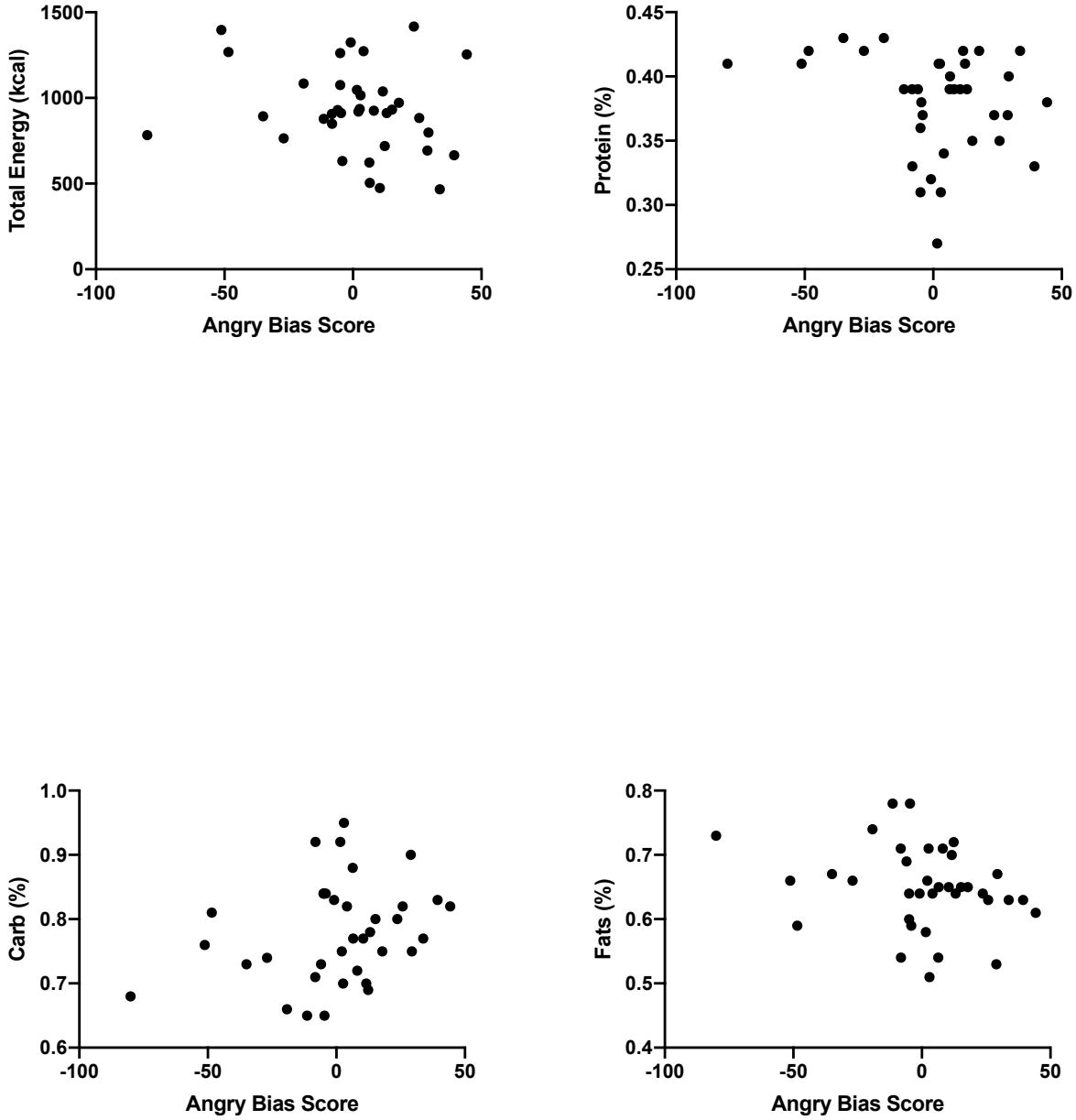
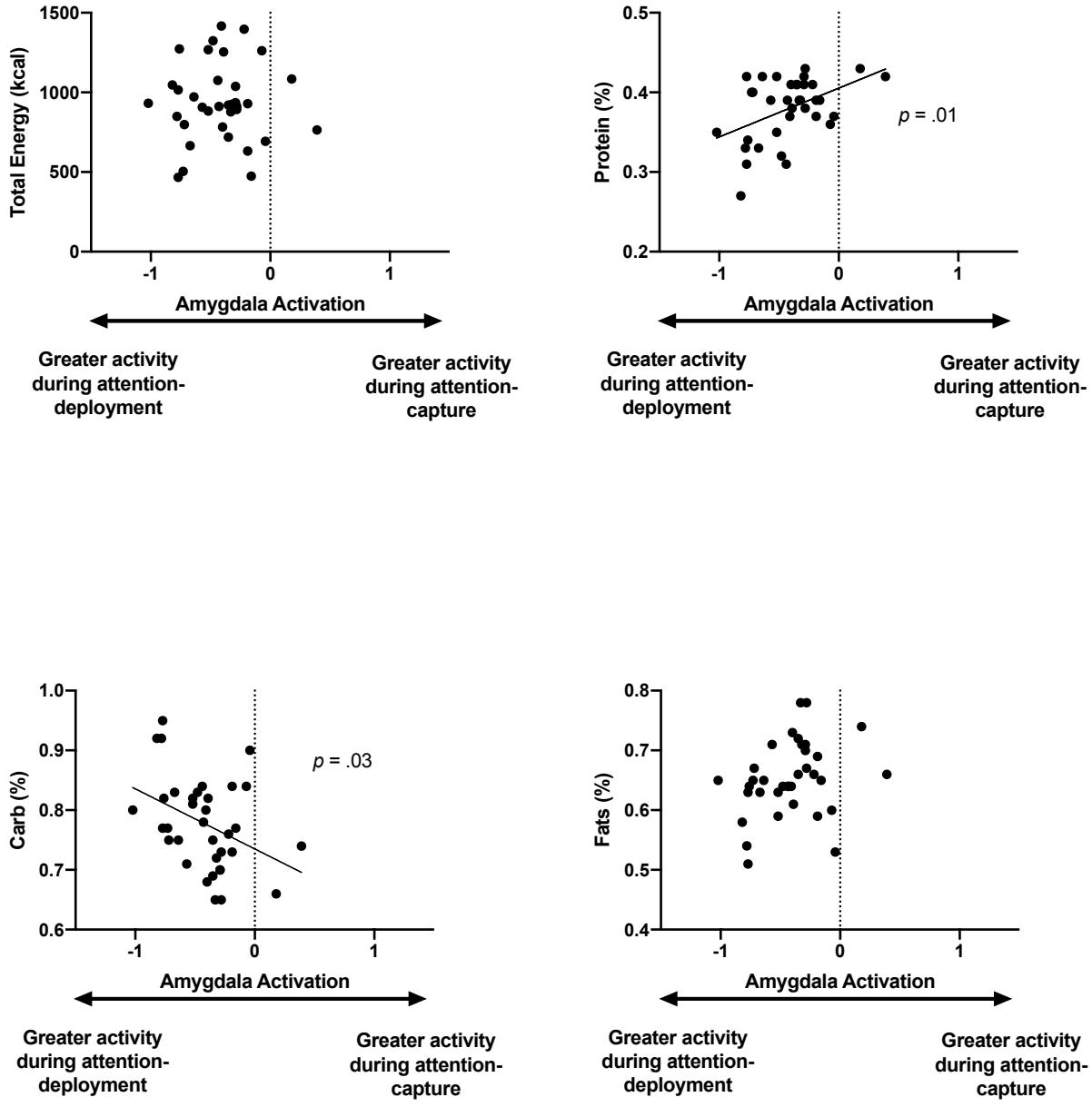


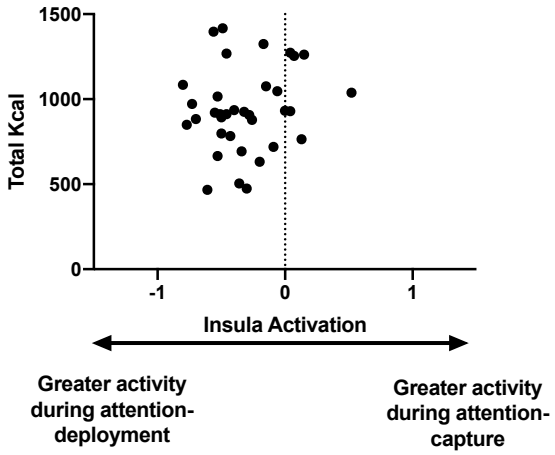
Figure 9. Aim 2b Linear Regression Analyses for Neural Activity and Test Meal Intake. Intake in relation to neural activity in A) Amygdala; B) Insula; C) Striatum; D) Anterior Cingulate Cortex; E) Dorsolateral Prefrontal Cortex; F) Medial Prefrontal Cortex; G) Ventrolateral Prefrontal Cortex. Activation in areas involved in anxiety processing was not significantly related to total energy intake (*p*s > .30), or percentage of energy consumed from protein. Activation of affect regulation regions was not significantly related to total energy intake (*p*s > .12) or percentage of energy consumed from protein. Greater amygdala activation during top-down attention deployment was significantly associated with lower % energy consumed from protein ($p = .01$). Greater amygdala activation during top-down attention deployment was marginally significantly associated with great energy consumed from carbohydrates ($p = .03$).

Note: For all graphs, the x-axis represents a ratio of relative region-of-interest (ROI) activation during attention capture vs. attention deployment; more positive numbers indicate greater activation in the ROI during the bottom-up attention capture time period, and more negative numbers indicate greater activation in the ROI during the attention deployment period. For percentage macronutrient variable graphs, the y-axis is arsin square root transformed for analyses.

A.


Total Energy (kcal)
1500
1000
500
0
-1
0
1
Amygdala Activation
Greater activity during attention-deployment
Greater activity during attention-capture
Protein (%)
0.5
0.4
0.3
0.2
p = .01
Carb (%)
1.0
0.9
0.8
0.7
0.6
p = .03
Fats (%)
0.8
0.7
0.6
0.5
0.4

B.


1500
1000
500
0
Total Kcal
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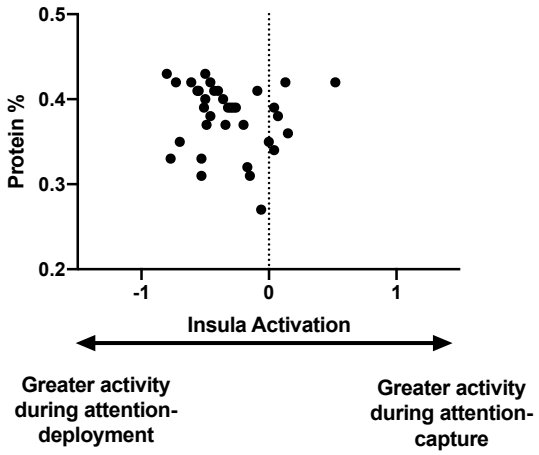
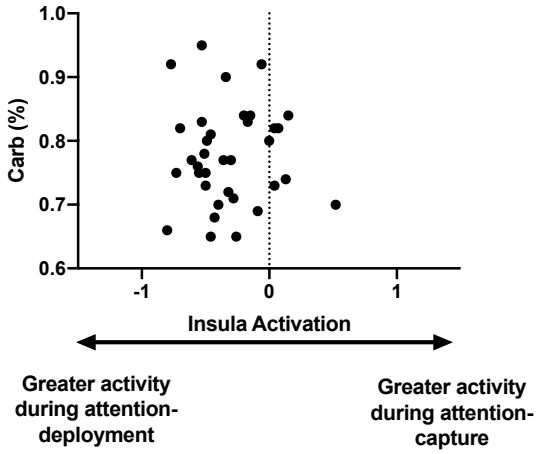
0
1
Insula Activation
Greater activity during attention-deployment
Greater activity during attention-capture


0.5
0.4
0.3
0.2
Protein %
-1
0
1
Insula Activation
Greater activity during attention-deployment
Greater activity during attention-capture


1.0
0.9
0.8
0.7
0.6
Carb (%)
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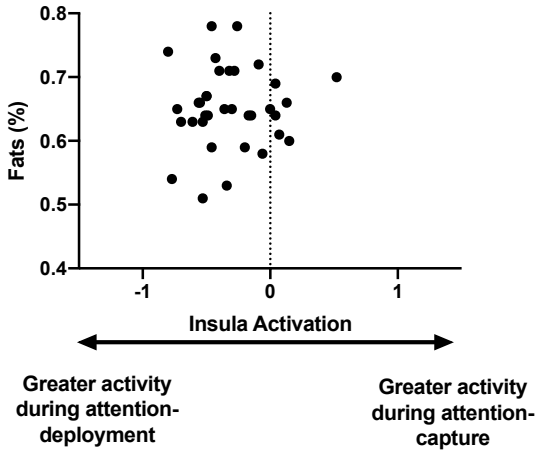
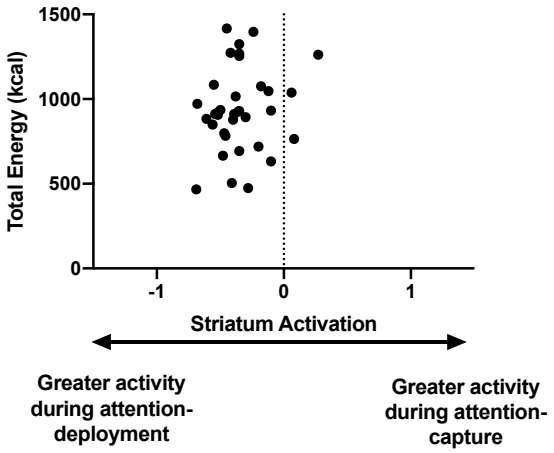
0
1
Insula Activation
Greater activity during attention-deployment
Greater activity during attention-capture


0.8
0.7
0.6
0.5
0.4
Fats (%)
-1
0
1
Insula Activation
Greater activity during attention-deployment
Greater activity during attention-capture

C.


Total Energy (kcal)
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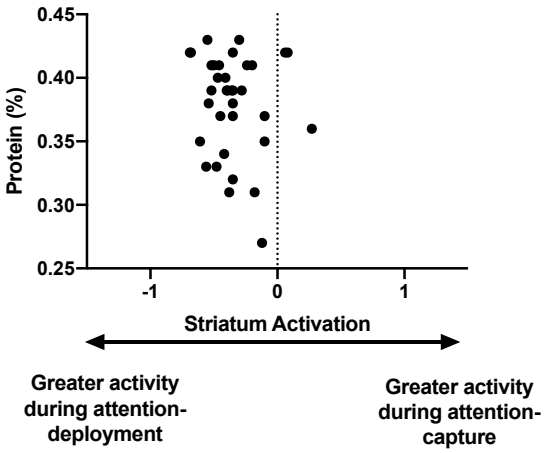
1000
500
0
-1
0
1
Striatum Activation
Greater activity during attention-deployment
Greater activity during attention-capture


Protein (%)
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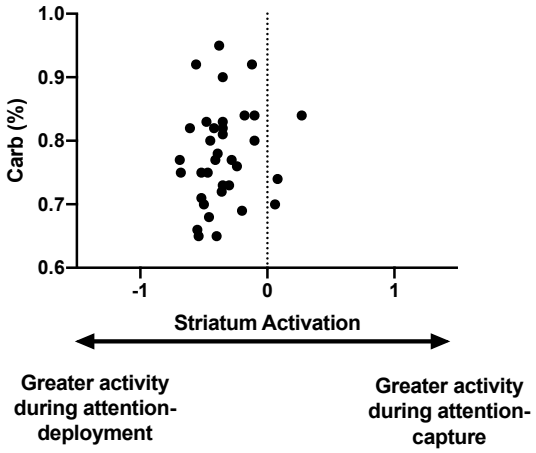
0
1
Striatum Activation
Greater activity during attention-deployment
Greater activity during attention-capture


Carb (%)
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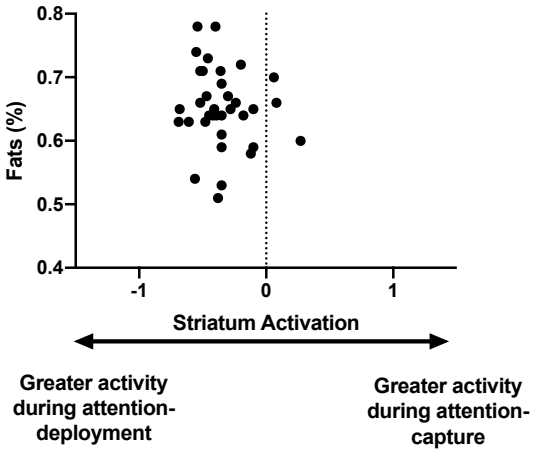
0.7
0.6
-1
0
1
Striatum Activation
Greater activity during attention-deployment
Greater activity during attention-capture


Fats (%)
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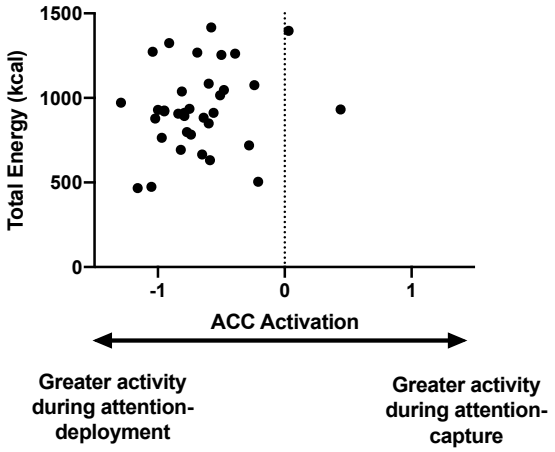
0.6
0.5
0.4
-1
0
1
Striatum Activation
Greater activity during attention-deployment
Greater activity during attention-capture

D.


Total Energy (kcal)
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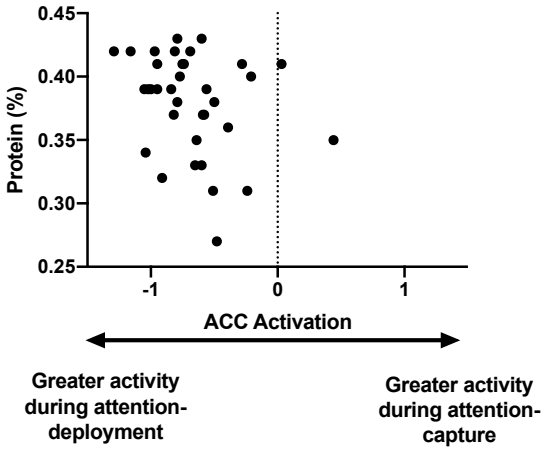
1000
500
0
-1
0
1
ACC Activation
Greater activity during attention-deployment
Greater activity during attention-capture


Protein (%)
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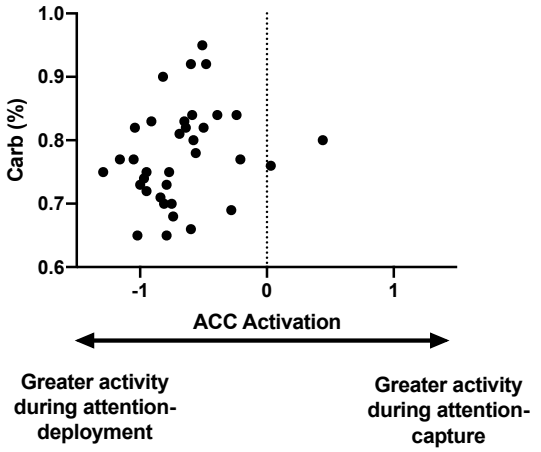
0.40
0.35
0.30
0.25
-1
0
1
ACC Activation
Greater activity during attention-deployment
Greater activity during attention-capture


Carb (%)
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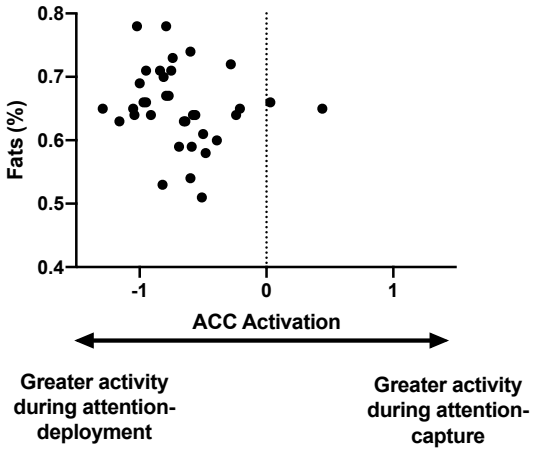
0.8
0.7
0.6
-1
0
1
ACC Activation
Greater activity during attention-deployment
Greater activity during attention-capture


Fats (%)
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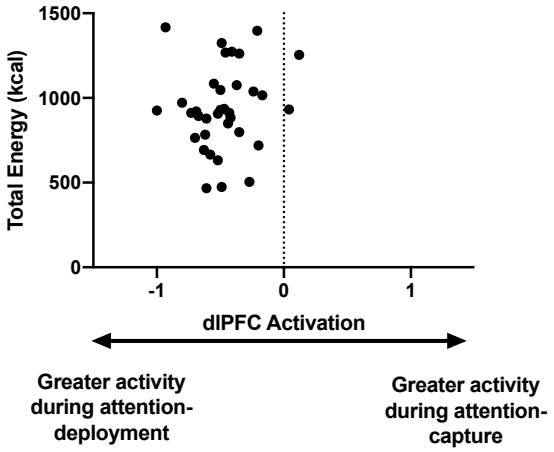
0.7
0.6
0.5
0.4
-1
0
1
ACC Activation
Greater activity during attention-deployment
Greater activity during attention-capture

E.


Total Energy (kcal)
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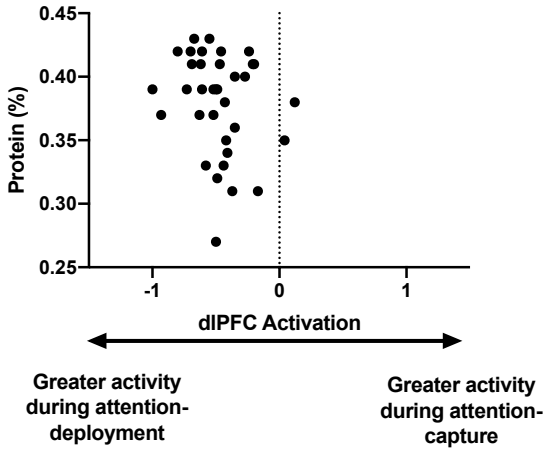
1000
500
0
-1
0
1
dlPFC Activation
Greater activity during attention-deployment
Greater activity during attention-capture


Protein (%)
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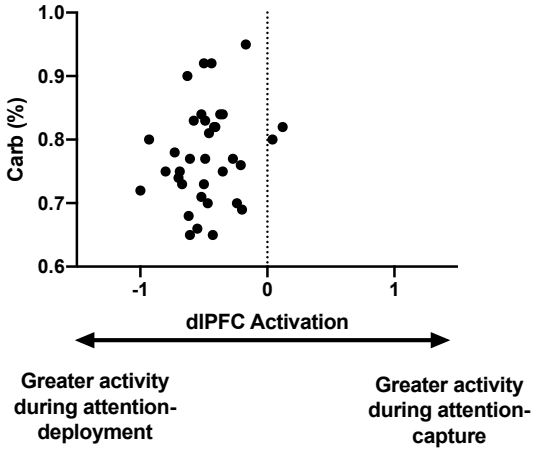
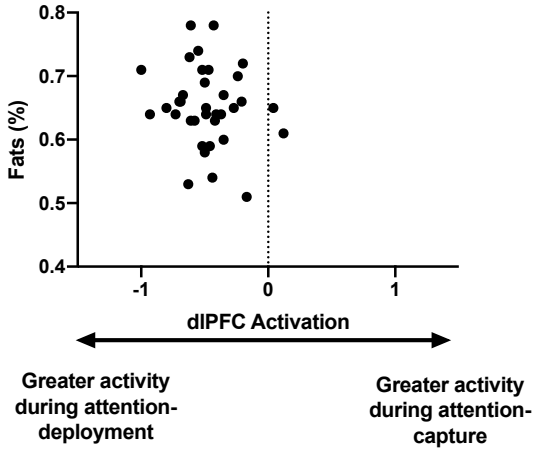
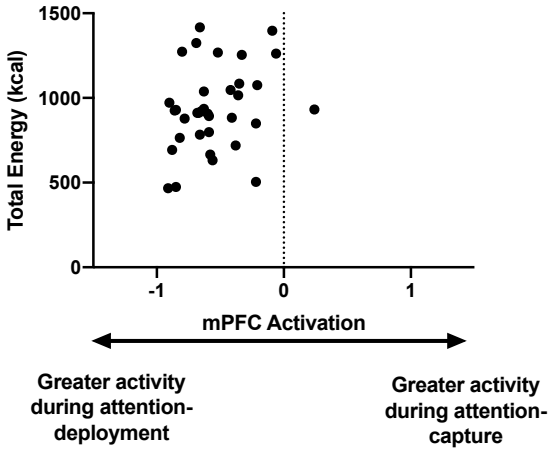
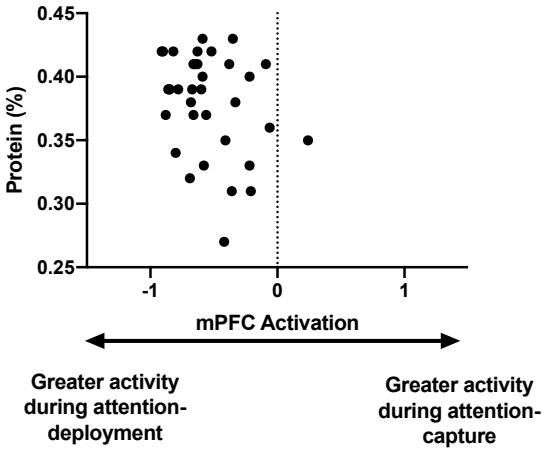
0.40
0.35
0.30
0.25
-1
0
1
dlPFC Activation
Greater activity during attention-deployment
Greater activity during attention-capture

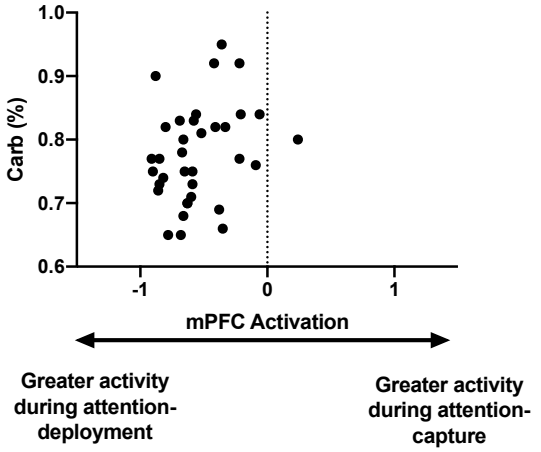

Carb (%)
1.0
0.9
0.8
0.7
0.6
-1
0
1
dlPFC Activation
Greater activity during attention-deployment
Greater activity during attention-capture

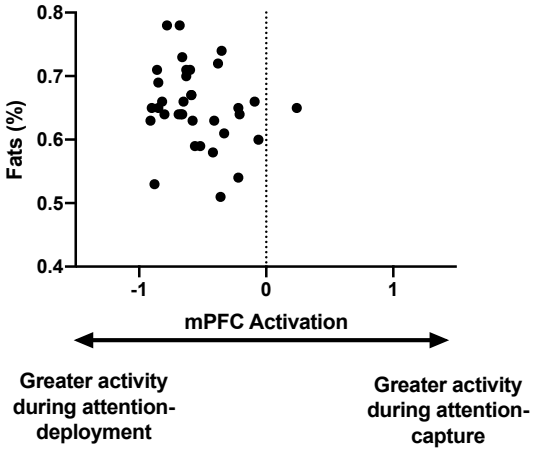

Fats (%)
0.8
0.7
0.6
0.5
0.4
-1
0
1
dlPFC Activation
Greater activity during attention-deployment
Greater activity during attention-capture

F.

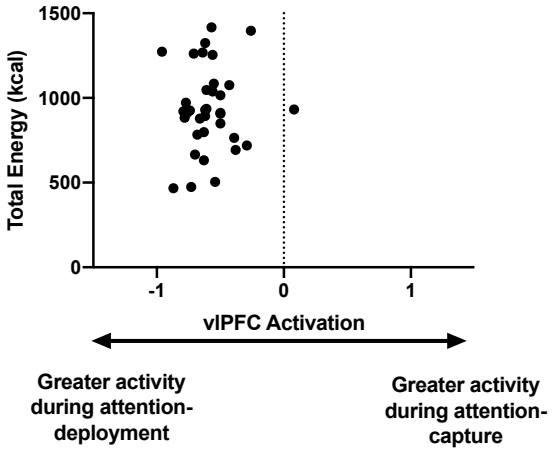

Total Energy (kcal)
1500
1000
500
0
-1
0
1
mPFC Activation
Greater activity during attention-deployment
Greater activity during attention-capture

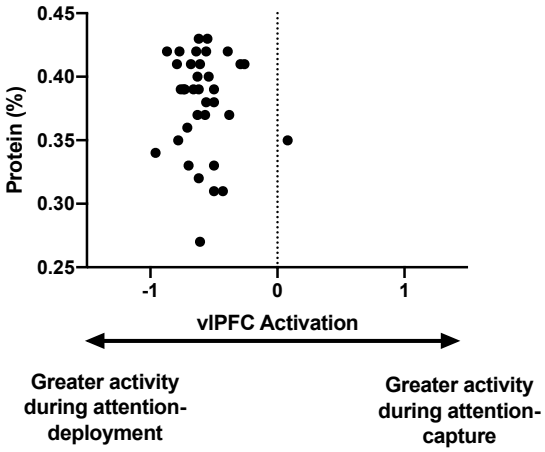

Protein (%)
0.45
0.40
0.35
0.30
0.25
-1
0
1
mPFC Activation
Greater activity during attention-deployment
Greater activity during attention-capture

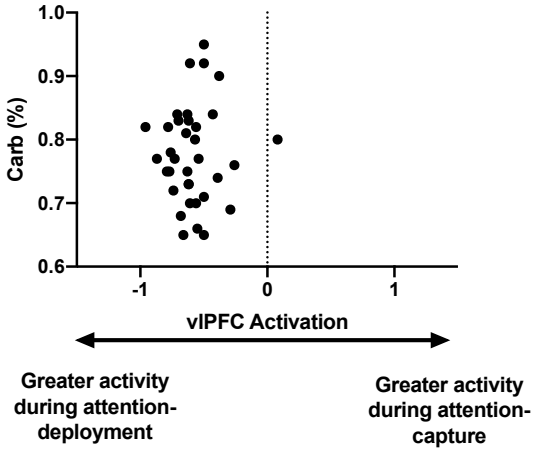

Carb (%)
1.0
0.9
0.8
0.7
0.6
-1
0
1
mPFC Activation
Greater activity during attention-deployment
Greater activity during attention-capture


Fats (%)
0.8
0.7
0.6
0.5
0.4
-1
0
1
mPFC Activation
Greater activity during attention-deployment
Greater activity during attention-capture

G.


Total Energy (kcal)
1500
1000
500
0
-1
0
1
vlPFC Activation
Greater activity during attention-deployment
Greater activity during attention-capture


Protein (%)
0.45
0.40
0.35
0.30
0.25
-1
0
1
vlPFC Activation
Greater activity during attention-deployment
Greater activity during attention-capture


Carb (%)
1.0
0.9
0.8
0.7
0.6
-1
0
1
vlPFC Activation
Greater activity during attention-deployment
Greater activity during attention-capture

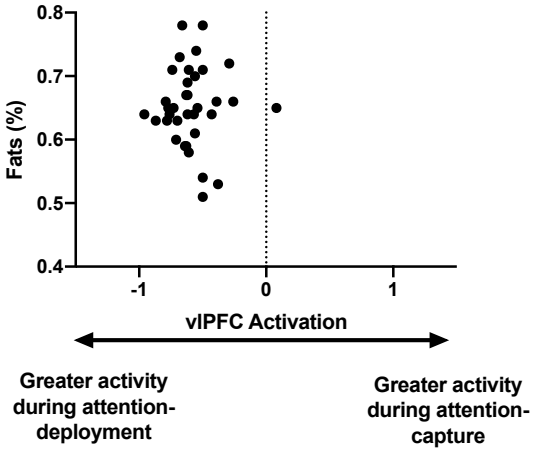

Fats (%)
0.8
0.7
0.6
0.5
0.4
-1
0
1
vlPFC Activation
Greater activity during attention-deployment
Greater activity during attention-capture

Table 1. Binge-Eating Disorder DSM-5 Criteria

DSM-5 Binge-Eating Disorder
1. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following: a. Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances b. The sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating)
2. Binge-eating episodes are associated with three (or more) of the following: a. Eating much more rapidly than normal b. Eating until feeling uncomfortably full c. Eating large amounts of food when not feeling physically hungry d. Eating alone because of being embarrassed by how much one is eating e. Feeling disgusted with oneself, depressed, or very guilty after overeating
3. Marked distress regarding binge eating is present
4. The binge occurs, on average at least 1 day a week for 3 months
5. The binge eating is not associated with the regular use of inappropriate compensatory behavior (e.g., purging, fasting, excessive exercise) and does not occur exclusively during the course of anorexia nervosa or bulimia nervosa.

Table 2: Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
Age between 12 and 17 years	Obesity-related health comorbidity requiring medical treatment or other major illness
Female sex	Regular use of any medication known to affect body weight or eating behavior
BMI ≥ 85th percentile for age and sex	Current pregnancy or a history of pregnancy
Right handedness	A significant reduction in weight during the past three months exceeding 5% of body weight
English-speaking	Presence of full-threshold psychiatric disorder
	Current and regular substance use
	A history of significant or recent brain injury
	Current involvement in a weight loss program
	A condition under which MEG is contradicted

Table 3. Contents Included in Laboratory Buffet Lunch Test Meal

Food Item	**Kcal**	**Food Item**	**Kcal**	**Food Item**	**Kcal**
2% Milk	468.22	White Bread	512.57	Bananas	355.64
Water	0	Wheat Bread	631.63	Grapes	167.5
Apple Juice	425	Turkey	152.54	Carrots	70
Lemonade	455.36	American Cheese	757.89	Ranch Dip	268.66
Lettuce	7.5	Ham	221.05	BBQ Sauce	119.12
Tomato	36	Vanilla Wafers	210.26	Orange Slices	276.97
M&M’s	600	Oreos	580.26	Peanut Butter	675
Jelly Beans	428.57	Pretzels	535.71	Grape Jelly	300
Mustard	90	Tortilla Chips	600	Chicken Nuggets	629.05
Mayonnaise	586.96	Salsa	117.19	Kaiser Rolls	529.68

Table 4. Participant Characteristics

	Total Sample ($N = 55$)	LOC + ($N = 16$)	No LOC ($N = 39$)
Age (years)	15.2 ± 1.7	15.6 ± 1.3	15.0 ± 1.8
Race (%)			
Non-Hispanic White	27.3	37.5	35.9
Non-Hispanic Black	47.3	62.5	43.6
Multiple Races	9.1	0.0	17.9
Ethnicity (%)			
Hispanic or Latino	9.1	0.0	14.3
Non-Hispanic or Latino	83.6	100.0	85.7
Not Reported	7.3	12.5	5.1
BMI-*z*	1.8 ± 0.4	1.7 ± 0.4	1.8 ± 0.5
Overweight (%)	40.0	43.8	38.5
Obesity (%)	60.0	56.3	61.5
Trait Anxiety	34.6 ± 6.2	33.4 ± 4.9	35.1 ± 6.6
State Anxiety	30.3 ± 4.5	31.4 ± 4.8	29.8 ± 4.3

Note: LOC = Loss-of-control eating; BMI-*z* = body mass index *z*-score

Table 5. Participant Characteristics with Usable MEG Data

	Total Sample ($N = 38$)	LOC + ($N = 14$)	No LOC ($N = 24$)
Age (years)	15.4 ± 1.5	15.8 ± 1.2	15.2 ± 1.6
Race (%)			
Non-Hispanic White	35.1	42.9	37.5
Non-Hispanic Black	43.2	57.1	33.3
Multiple Races	10.8	0.0	25.0
Ethnicity (%)			
Hispanic or Latino	10.8	0.0	17.4
Non-Hispanic or Latino	89.2	100.0	82.6
BMI-*z*	1.7 ± 0.4	1.7 ± 0.5	1.7 ± 0.4
Overweight (%)	47.4	42.9	50.0
Obesity (%)	52.6	57.1	50.0
Trait Anxiety	33.7 ± 5.7	33.7 ± 4.5	33.7 ± 6.4
State Anxiety	30.3 ± 4.6	31.5 ± 5.0	29.6 ± 4.2

Table 6. Summary of Aim 1a Linear Regression Analyses for Attention Bias to Social Threat and Neural Activation

Dependent Variable	Independent Variables	*b*	*SE(b)*	*β*	*t*	*p*-value
Amygdala	AB to social threat	0.00	0.00	-0.11	-0.59	0.56
	Age	0.02	0.05	0.07	0.34	0.74
	Race	0.00	0.15	-0.01	-0.03	0.98
	Height	0.00	0.01	0.03	0.14	0.89
	Fat mass	0.13	0.59	0.04	0.21	0.83
	State anxiety	0.00	0.02	-0.03	-0.17	0.87
Insula	AB to social threat	0.00	0.00	0.06	0.30	0.77
	Age	-0.03	0.05	-0.14	-0.67	0.51
	Race	-0.22	0.14	-0.29	-1.53	0.14
	Height	0.01	0.01	0.16	0.87	0.39
	Fat mass	0.10	0.57	0.03	0.17	0.87
	State anxiety	0.00	0.02	-0.01	-0.03	0.98
Striatum	AB to social threat	0.00	0.00	-0.07	-0.40	0.69
	Age	-0.05	0.03	-0.31	-1.56	0.13
	Race	-0.12	0.08	-0.25	-1.42	0.17
	Height	0.01	0.01	0.37	2.07	0.05
	Fat mass	0.13	0.34	0.07	0.39	0.70
	State anxiety	0.00	0.01	-0.01	-0.05	0.96
ACC	AB to social threat	0.00	0.00	-0.09	-0.50	0.62
	Age	-0.02	0.06	-0.05	-0.26	0.79
	Race	0.03	0.17	0.04	0.19	0.85
	Height	0.01	0.01	0.10	0.52	0.60

	Fat mass	0.15	0.68	0.04	0.22	0.83
	State anxiety	0.03	0.02	0.26	1.42	0.17
dlPFC	AB to social threat	0.00	0.00	0.06	0.33	0.74
	Age	-0.04	0.04	-0.21	-1.00	0.32
	Race	0.00	0.12	0.00	0.02	0.98
	Height	0.00	0.01	0.03	0.17	0.87
	Fat mass	0.31	0.48	0.13	0.65	0.52
	State anxiety	0.01	0.01	0.15	0.80	0.43
mPFC	AB to social threat	0.00	0.00	-0.08	-0.44	0.67
	Age	-0.04	0.05	-0.19	-0.89	0.38
	Race	0.04	0.13	0.05	0.28	0.79
	Height	0.01	0.01	0.13	0.69	0.50
	Fat mass	0.16	0.52	0.06	0.31	0.76
	State anxiety	0.01	0.01	0.18	0.95	0.35
vlPFC	AB to social threat	0.00	0.00	-0.03	-0.17	0.87
	Age	-0.01	0.03	-0.03	-0.16	0.88
	Race	-0.13	0.08	-0.30	-1.62	0.12
	Height	0.01	0.01	0.28	1.56	0.13
	Fat mass	-0.12	0.33	-0.07	-0.35	0.73
	State anxiety	0.01	0.01	0.12	0.64	0.53

Note: AB = attention bias; ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; mPFC = medial prefrontal cortex; vlPFC = ventrolateral prefrontal cortex

Table 7. Summary of Aim 1b Analysis of Covariance for Loss-of-Control Eating Presence and Attentional Bias

Dependent Variable	Independent Variables	*F*	*p*-value	Partial eta squared
Angry AB	LOC Presence	0.05	0.82	0.00
	Age	2.86	0.10	0.09
	Race	0.08	0.78	0.00
	Height	0.17	0.68	0.01
	Fat mass	0.05	0.83	0.00
	State Anxiety	0.24	0.63	0.01
Happy AB	LOC Presence	0.02	0.90	0.00
	Age	0.16	0.69	0.01
	Race	0.02	0.90	0.00
	Height	0.00	0.96	0.00
	Fat mass	1.79	0.19	0.06
	State Anxiety	0.92	0.35	0.03

Note: AB = Attention bias; LOC = Loss-of-control eating

Table 8. Summary of Aim 2a Linear Regression Analyses for Attention Bias to Social Threat and Test Meal Intake

Dependent Variable	Independent Variables	*b*	*SE(b)*	*β*	*t*	*p*-value
Total energy (kcal)	AB to social threat	-2.02	1.79	-0.18	-1.13	0.27
	Age	-34.25	37.28	-0.18	-0.92	0.37
	Race	132.13	112.64	0.22	1.17	0.25
	Height	15.82	9.21	0.40	1.72	0.10
	% Fat Mass	1.84	9.52	0.04	0.19	0.85
	Lean mass	7.70	11.51	0.16	0.67	0.51
	Pubertal status	-189.35	92.70	-0.42	-2.04	0.05
% Protein	AB to social threat	0.00	0.00	-0.23	-1.28	0.21
	Age	0.00	0.01	-0.12	-0.55	0.59
	Race	-0.03	0.02	-0.38	-1.77	0.09
	Height	0.00	0.00	-0.01	-0.05	0.96
	% Fat Mass	0.00	0.00	-0.10	-0.48	0.64
	Lean mass	0.00	0.00	0.05	0.17	0.87
	Pubertal status	0.02	0.01	0.29	1.26	0.22
% Fats	AB to social threat	0.00	0.00	-0.23	-1.29	0.21
	Age	-0.01	0.01	-0.23	-1.10	0.28
	Race	0.01	0.03	0.10	0.48	0.64
	Height	0.00	0.00	-0.04	-0.16	0.87
	% Fat Mass	0.00	0.00	0.11	0.54	0.59
	Lean mass	0.00	0.00	-0.13	-0.50	0.62
	Pubertal status	0.04	0.02	0.40	1.78	0.09
% Carbs	AB to social threat	0.00	0.00	0.27	1.51	0.14

Age	0.01	0.01	0.24	1.10	0.28
Race	0.01	0.03	0.06	0.26	0.80
Height	0.00	0.00	0.03	0.13	0.90
% Fat Mass	0.00	0.00	-0.05	-0.25	0.80
Lean mass	0.00	0.00	0.10	0.37	0.71
Pubertal status	-0.05	0.03	-0.42	-1.84	0.08

Note: AB = attentional bias

Table 9. Summary of Aim 2b Linear Regression Analyses for Neural Activity and Test Meal Intake

Dependent Variable	Neural Predictor	*b*	*SE(b)*	*β*	*t*	*p*-value
Total energy (kcal)	Amygdala	24.75	163.26	0.03	0.15	0.88
	Insula	160.83	161.19	0.18	1.00	0.33
	Striatum	241.72	226.76	0.19	1.07	0.30
	ACC	171.73	138.88	0.21	1.24	0.23
	dlPFC	165.59	205.38	0.14	0.81	0.43
	mPFC	272.88	168.95	0.27	1.62	0.12
	vlPFC	132.34	266.47	0.09	0.50	0.62
% Protein	Amygdala	0.06	0.02	0.51	2.79	0.01*
	Insula	-0.01	0.03	-0.10	-0.49	0.63
	Striatum	-0.02	0.04	-0.13	-0.62	0.54
	ACC	-0.03	0.02	-0.28	-1.47	0.15
	dlPFC	-0.03	0.03	-0.18	-0.88	0.39
	mPFC	-0.04	0.03	-0.31	-1.65	0.11
	vlPFC	-0.01	0.04	-0.02	-0.12	0.91

% Fats	Amygdala	0.07	0.04	0.33	1.70	0.10
	Insula	0.02	0.04	0.08	0.37	0.71
	Striatum	-0.04	0.06	-0.15	-0.76	0.45
	ACC	-0.04	0.04	-0.19	-1.02	0.32
	dlPFC	-0.05	0.05	-0.19	-0.96	0.35
	mPFC	-0.05	0.04	-0.24	-1.25	0.22
	vlPFC	0.00	0.07	-0.01	-0.05	0.96
% Carbs	Amygdala	-0.11	0.05	-0.44	-2.31	0.03†
	Insula	-0.01	0.05	-0.03	-0.12	0.90
	Striatum	0.06	0.07	0.17	0.81	0.43
	ACC	0.06	0.04	0.25	1.31	0.20
	dlPFC	0.07	0.06	0.21	1.04	0.31
	mPFC	0.08	0.05	0.30	1.56	0.13
	vlPFC	0.00	0.08	0.01	0.05	0.96

Note: ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; mPFC = medial prefrontal cortex; vlPFC = ventrolateral prefrontal cortex

*$p < .01$

†$p < .05$

Table 10. Summary of Aim 3a General Linear Model Analysis for Interaction between Loss-of-Control Eating and Attention Bias to Social Threat on Energy Intake

Dependent Variable	Independent Variables	*F*	*p*-value	Partial eta squared
Total energy (kcal)	LOC Presence	4.19	0.05	0.14
	AB to Social Threat	1.76	0.20	0.06
	LOC × Threat AB	0.62	0.44	0.02
	Age	2.06	0.16	0.07
	Race	0.83	0.37	0.03
	Height	2.71	0.11	0.09
	Pubertal Status	3.05	0.09	0.11
	% Fat Mass	0.13	0.73	0.01
	Lean Mass	0.27	0.61	0.01
% Protein	LOC Presence	0.81	0.38	0.03
	AB to Social Threat	1.61	0.22	0.06
	LOC × Threat AB	0.06	0.82	0.00
	Age	0.09	0.77	0.00
	Race	2.64	0.12	0.09
	Height	0.00	0.97	0.00
	Pubertal Status	0.87	0.36	0.03
	% Fat Mass	0.26	0.61	0.01
	Lean Mass	0.13	0.72	0.01
% Fats	LOC Presence	0.43	0.52	0.02
	AB to Social Threat	0.98	0.33	0.04

	LOC × Threat AB	2.43	0.13	0.09
	Age	0.89	0.36	0.03
	Race	0.46	0.50	0.02
	Height	0.00	0.98	0.00
	Pubertal Status	3.53	0.07	0.12
	% Fat Mass	0.20	0.66	0.01
	Lean Mass	0.56	0.46	0.02
% Carbs	LOC Presence	1.59	0.22	0.06
	AB to Social Threat	1.34	0.26	0.05
	LOC × Threat AB	0.76	0.39	0.03
	Age	0.01	0.95	0.00
	Race	0.00	0.98	0.00
	Height	3.23	0.08	0.11
	Pubertal Status	0.02	0.88	0.00
	% Fat Mass	0.24	0.63	0.01
	Lean Mass	1.59	0.22	0.06

Note: AB = Attention bias; LOC = Loss-of-control eating

Table 11. Summary of Aim 3b General Linear Model Analysis for Interaction between Loss-of-Control Eating and Neural Activity on Energy Intake

Dependent Variable	Neural Interaction Terms	*F*	*p*-value	Partial eta squared
Total energy (kcal)	LOC × Amygdala	0.09	0.77	0.00
	LOC × Insula	0.57	0.46	0.02
	LOC × Striatum	1.05	0.32	0.04
	LOC × ACC	0.48	0.49	0.02
	LOC × dlPFC	0.43	0.52	0.02
	LOC × mPFC	1.16	0.29	0.04
	LOC × vlPFC	1.00	0.33	0.04
% Protein	LOC × Amygdala	2.42	0.13	0.09
	LOC × Insula	0.24	0.63	0.01
	LOC × Striatum	0.13	0.73	0.01
	LOC × ACC	0.66	0.42	0.03
	LOC × dlPFC	1.16	0.29	0.04
	LOC × mPFC	0.00	0.99	0.00
	LOC × vlPFC	0.01	0.94	0.00
% Fats	LOC × Amygdala	1.47	0.24	0.06
	LOC × Insula	0.00	0.98	0.00
	LOC × Striatum	0.12	0.74	0.01
	LOC × ACC	1.41	0.25	0.05
	LOC × dlPFC	1.21	0.28	0.05
	LOC × mPFC	0.01	0.94	0.00
	LOC × vlPFC	0.51	0.48	0.02
% Carbs	LOC × Amygdala	2.12	0.16	0.08
	LOC × Insula	0.03	0.86	0.00
	LOC × Striatum	0.15	0.70	0.01

LOC × ACC	1.60	0.22	0.06
LOC × dlPFC	1.52	0.23	0.06
LOC × mPFC	0.01	0.92	0.00
LOC × vlPFC	0.38	0.54	0.02

Note: LOC = Loss-of-control eating; ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; mPFC = medial prefrontal cortex; vlPFC = ventrolateral prefrontal cortex

Table 12. Summary of Exploratory Aim 4 Mediation Analyses for the Mediating Role of State Anxiety between Neural Activity and Total Energy Intake

Independent Variable	*a (SE)*	*b (SE)*	*c (SE)*	*c' (SE)*	*ab (SE)*	*95% CI (ab)*
Amygdala	-1.30 (2.91)	-1.11 (11.37)	14.35 (162.27)	12.91 (166.24)	1.44 (48.45)	-70.32, 133.85
Insula	-2.55 (3.00)	1.08 (11.15)	203.32 (163.88)	206.07 (169.62)	-2.75 (61.20)	-166.00, 98.50
Striatum	-1.00 (4.08)	-0.55 (11.02)	266.26 (220.42)	265.71 (225.22)	0.55 (81.92)	-122.29, 222.86
ACC	2.23 (2.50)	-3.42 (11.21)	153.51 (137.32)	161.13 (142.09)	-7.62 (44.17)	-114.92, 67.91
dlPFC	0.89 (3.88)	-1.96 (10.80)	326.47 (205.34)	328.20 (209.65)	-1.74 (73.29)	-156.93, 145.53
mPFC	1.48 (3.15)	-2.98 (10.69)	297.17 (164.95)	301.57 (168.82)	-4.41 (48.27)	-117.42, 83.40
vlPFC	0.39 (4.73)	-1.25 (11.30)	97.58 (261.84)	98.06 (267.21)	-0.49 (63.42)	-88.19, 167.04

Note: SE = standard error; ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; mPFC = medial prefrontal cortex; vlPFC = ventrolateral prefrontal cortex

APPENDIX 1: EATING DISORDER EXAMINATION (EDE)

EATING DISORDERS EXAMINATION CODING FORM
v.12 with edits from v. 14 and v. 15
DSM-5 BED and LOC Severity version
Revised March 2017

Name: _____ Age: _____

Date: _____ Sex: _____

Interviewer:_____
Time of Interview:_____

Severity Ratings

0= absence of feature
1= feature almost, but not quite, absent
2=
3= severity midway between 0 - 6
4=
5= feature present to a degree not quite severe enough to justify a rating of a 6
6= feature present to an extreme degree

Frequency Ratings

0= absence of feature
1= 1-5 days
2= 6-12 days
3= 13-15 days
4= 16-22 days
5= 23-27 days
6= feature present every day

1. **PATTERN OF EATING**...
(p. 7)

"I would like to ask about your pattern of eating. Over the past four weeks, which of these meals and snacks have you eaten on a regular basis?"

a. breakfast _____

b. mid-morning snack _____

c. lunch _____

d. mid-afternoon snack _____

e. evening meal _____

f. evening snack _____

g. nocturnal snack _____

APPENDIX 2: KIDDIE SCHEDULE FOR AFFECTIVE DISORDERS AND SCHIZOPHRENIA FOR SCHOOL-AGED CHILDREN (KSADS)

MIR Study #: _____ Cohort: _____

MR#: __ __ - __ __ - __ __ -__ Interval: _____

K-SADS SUMMARY SHEET

Interviewer: _____

Date: __ __ / __ __ / __ __ __ __

Disorder	Current (past 1 month)		Lifetime			
	0 NO	1 YES	0 NO	1 YES	If yes, age (y)?	If yes, past 6 mos?
1. Major Depression	☐	☐	☐	☐		
2. Mania	☐	☐	☐	☐		
3. Hypomania	☐	☐	☐	☐		
4. Psychosis	☐	☐	☐	☐		
5. Panic Disorder	☐	☐	☐	☐		
6. Separation Anxiety Disorder	☐	☐	☐	☐		
7. Avoidant Disorder/ Social Phobia	☐	☐	☐	☐		
8. Agoraphobia/ Specific Phobia	☐	☐	☐	☐		
9. Overanxious/ Generalized Anxiety	☐	☐	☐	☐		
10. Obsessive Compulsive Disorder	☐	☐	☐	☐		
11. Anorexia Nervosa	☐	☐	☐	☐		
12. ADHD	☐	☐	☐	☐		
13. Oppositional Defiant Disorder	☐	☐	☐	☐		
14. Conduct Disorder	☐	☐	☐	☐		
15. Cigarette Use	☐	☐	☐	☐		
16. Alcohol Abuse	☐	☐	☐	☐		
17. Substance Abuse	☐	☐	☐	☐		

Psychiatric History	Current (past 1 month)		Lifetime			
	0 NO	1 YES	0 NO	1 YES	If yes, age (y)?	Describe
1. Therapy	☐	☐	☐	☐		
2. Psychotropic Medication	☐	☐	☐	☐		
3. Psychiatric Hospitalization	☐	☐	☐	☐		

K-SADS Summary 1

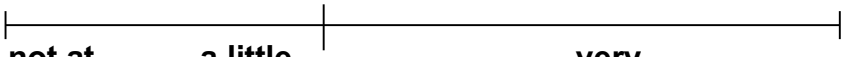
APPENDIX 3: HUNGER AND FULLNESS RATING SCALES

FEELINGS QUESTIONNAIRE

Please rate the following statements according to your appetite and how you are feeling **RIGHT NOW**.

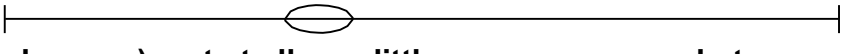
For each one, draw a vertical line on the scale at the spot that represents your answer.

For example: **CORRECT** marking:
How hungry do you feel right now? (If slightly, but more than a little, hungry.)

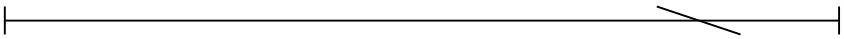


not at a little very

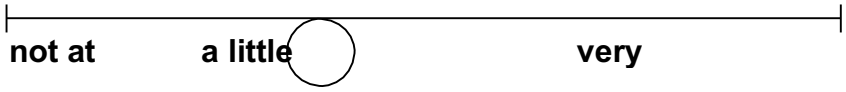
For example: **INCORRECT** markings:
How hungry do you feel right now? (If slightly, but more than a little,



hungry.) not at all a little somewhat very extremely



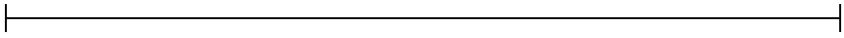
not at a little very



not at a little very

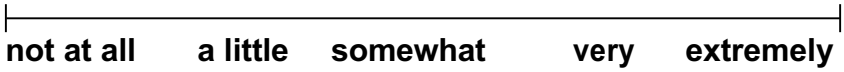
PLEASE PROCEED TO THE NEXT PAGE.

1. How hungry do you feel right now?



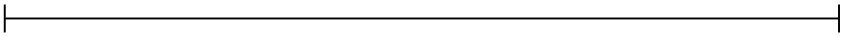
not at all a little somewhat very extremely

2. How full do you feel right now?



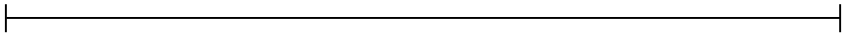
not at all a little somewhat very extremely

3. How much food do you think you could eat right now?



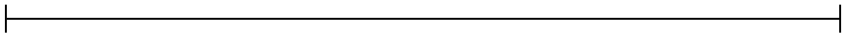
not at all a little somewhat very extremely

4. I feel anxious.



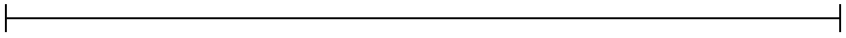
not at all a little somewhat very extremely

5. I feel sleepy.



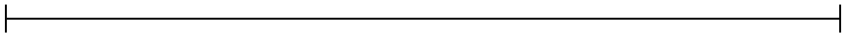
not at all a little somewhat very extremely

6. I feel sick.



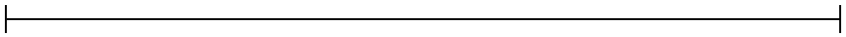
not at all a little somewhat very extremely

7. I feel dizzy.



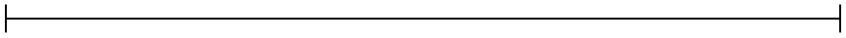
not at all a little somewhat very extremely

8. My tummy is rumbling.



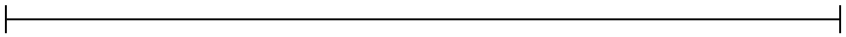
not at all a little somewhat very extremely

9. My tummy feels upset.



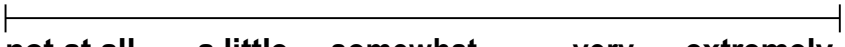
not at all a little somewhat very extremely

10. My head hurts. (I have a headache.)



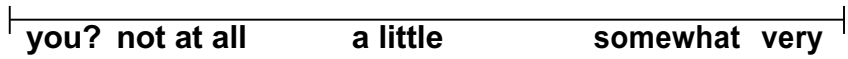
not at all a little somewhat very extremely

11. I feel thirsty.

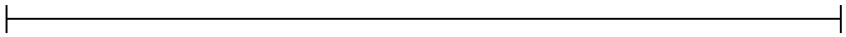


not at all a little somewhat very extremely

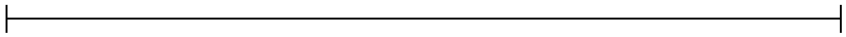
12. How worried do you feel right now about what others think of



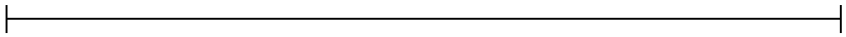
13. How worried are you right now about what others might be saying about you?



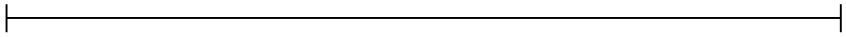
14. How nervous right now about being teased or other people making fun of you?



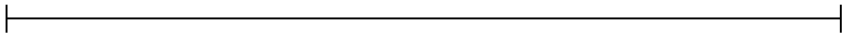
15. How nervous are you feeling right now about talking to certain people?



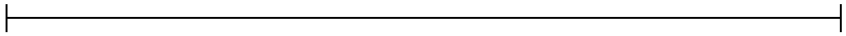
16. How intensely do you desire (want) to eat one or more specific foods?



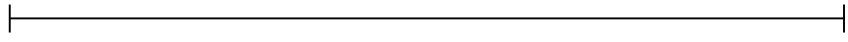
17. How much are you craving one or more specific foods?



18. How great is your urge for one or more specific foods?



19. How hard is it to stop thinking about one or more specific foods right



SUPPLEMENT: COMMITTEE COVID MEMO

Uniformed Services University

Date: November 11, 2020

To: Tracy Sbrocco, PhD
Jack Yanovski, MD, PhD
Andrew Waters, PhD
Marian Tanofsky-Kraff, PhD

From: Meghan Byrne, M.S., Doctoral Candidate in Medical & Clinical Psychology, Uniformed Services University

Subject: Dissertation Recruitment Barriers due to COVID-19

Status of dissertation recruitment and roadblocks due to COVID-19

Due to COVID-19, recruitment for my dissertation project, "Neural Underpinnings of Anxiety in Relation to Eating Behaviors in Adolescence," which received approval from this committee on May 22, 2019, has been stalled since March 13, 2020. Recruitment was originally planned to be ongoing through 2020, however it is now uncertain whether any additional participants will be able to be accumulated due to the global pandemic-related stay-at-home and social distancing orders.

To provide an update on my enrollment to date, a total of 55 participants have completed the two required visits for my study, and 36 participants have usable MEG imaging data. For at least 80% power to detect small-to-medium effect sizes, I had originally planned for recruitment of 80 participants, and assumed 35% attrition in unusable MEG data, for a final sample of 52 participants to be included in my analyses. Thus, to date I have enrolled over two-thirds of my expected sample size, and the expected data attrition rate of 35% is in line with my currently enrolled sample. I have included an updated power analysis for each of my primary proposed Aims below:

Aim 1
To examine relationships between attention bias to social threat cues and neural activity in anxiety processing regions among youth, and differences between youth with and without LOC eating.
Hypothesis 1a: Youth with greater attention bias to social threat (i.e. shorter reaction times to angry faces than happy or neutral faces) will exhibit increased activation in "bottom-up" unconscious attention capture areas and areas involved in anxiety processing, and blunted activation of "top-down" attention deployment and affect regulation regions in response to social threat cues. I will use a multiple linear regression model with attention bias (i.e. angry bias or happy bias) as the IV, engagement of unconscious attention capture and anxiety processing regions (i.e. greater activation in the insula, striatum, amygdala), and engagement of attention deployment and affect regulation regions (i.e. less activation in the anterior cingulate cortex, dorsolateral prefrontal cortex, medial prefrontal cortex, ventrolateral prefrontal cortex) as the DV, and age, race, adiposity, height, and pre-task anxiety as covariates. Depressive symptoms will be considered as a covariate in a secondary analysis.

- *New power analysis: alpha = 0.05, power = 0.8; total sample size = 36; effect size f = 0.46 (large)*

Hypothesis 1b: Youth with LOC eating will exhibit greater attention bias to social threat cues (i.e. greater angry bias), but not to non-threatening cues (i.e. happy bias), compared to youth without LOC eating. A one-way analysis of covariance (ANCOVA) will be used with LOC eating (presence/absence) as the independent variable (IV), attentional bias scores (i.e. angry bias, happy bias) as the continuous dependent variable (DV), and age, race, adiposity, height, and pre-task anxiety as covariates. Depressive symptoms will be considered as a covariate in a secondary analysis.

- *New power analysis: alpha = 0.05, groups = 2, power = 0.8, total sample size = 55; effect size f = 0.39 (medium-to-large)*

Aim 2
To examine if differences in attention bias to social threat and neural activation are related to energy intake at a laboratory meal.
Hypothesis 2a: Greater attention bias to social threat cues (i.e. greater angry bias), but not non-threating cues (i.e. happy bias), will be associated with greater energy intake. I will use a multiple linear regression model with attentional bias scores (i.e. angry bias, happy bias) as the IV, energy intake as the DV, and age, race, pubertal status, height, fat mass percentage, and lean mass as covariates. Depressive symptoms will be considered as a covariate in a secondary analysis.

- *New power analysis: alpha = 0.05, power = 0.8; total sample size = 55; effect size f = 0.28 (medium-to-large)*

Hypothesis 2b: Increased activation of "bottom-up" unconscious attention capture and anxiety processing regions (i.e. insula, striatum, amygdala), and blunted activation of "top-down" attention deployment and affect regulation regions (i.e. anterior cingulate cortex, dorsolateral prefrontal cortex, medial prefrontal cortex, ventrolateral prefrontal cortex) in response to social threat cues will be associated with greater energy intake. General linear models (GLM) with engagement of unconscious attention capture and anxiety processing regions (i.e. activation in the insula, striatum, amygdala), and engagement of attention deployment and affect regulation regions (i.e. activation in the anterior cingulate cortex, dorsolateral prefrontal cortex, medial prefrontal cortex, ventrolateral prefrontal cortex) as the IV, energy intake (kcal) as the DV, and age, race, pubertal status, height, fat mass percentage, and lean mass as covariates will be used. Depressive symptoms will be considered as a covariate in a secondary analysis.

- *New power analysis: alpha = 0.05, power = 0.8; total sample size = 36; effect size f = 0.46 (large)*

Exploratory Aim 3
To examine if LOC eating moderates the relationship between attention bias to social threat and neural activation of anxiety regions and differences in intake at a laboratory test meal.
Hypothesis 3a: The presence of LOC eating will moderate the relationship between attention bias to social threat (i.e. angry bias) and energy intake, such that among youth with LOC eating, attention bias to social threat will more robustly related with energy intake. GLMs will be used with attentional bias scores as the IV, LOC eating (presence/absence) as the moderator, energy intake (kcal) as the DV, and age, race, pubertal status, height, fat mass percentage, and lean mass as covariates. Depressive symptoms will be considered as a covariate in a secondary analysis.

- *New power analysis: alpha = 0.05, groups = 2, power = 0.8, total sample size = 55; effect size f = 0.38 (medium-to-large)*

Hypothesis 3b: The presence of LOC eating will moderate the relationship between increased activation of "bottom-up" unconscious attention capture and anxiety processing regions, and blunted engagement of "top-down" attention deployment and affect regulation regions in response to social threat cues and energy intake, such that among youth with LOC eating, increased activation of "bottom-up" regions and blunted activation of "top-down" regions will be more robustly associated with energy intake. GLM will be conducted with engagement of unconscious attention capture and anxiety processing regions (i.e. activation in the insula, striatum, amygdala), and engagement of attention deployment and affect regulation regions (i.e. activation in the anterior cingulate cortex, dorsolateral prefrontal cortex, medial prefrontal cortex, ventrolateral prefrontal cortex) as the IV, LOC eating (presence/absence) as the moderator, energy intake (kcal) as the DV, and age, race, pubertal status, height, fat mass percentage, and lean mass as covariates. Depressive symptoms will be considered as a covariate in a secondary analysis.

- *New power analysis: alpha = 0.05, groups = 2, power = 0.8, total sample size = 36; effect size f = 0.48 (large)*

Unfortunately, all of my proposed aims will be affected by the recruitment halt. However, in light of the vast uncertainty around COVID-19, I would like to request to continue with data analysis and defense of my dissertation as planned, despite the smaller than expected sample. If approval by all members of my committee is obtained, I will plan to move forward with the data analysis and interpretation phase, and will subsequently schedule a defense date with the collected sample.

If committee members grant their approval for this proposed plan moving forward, please provide your signature and date below:

APPROVALS:

1. Committee Chair:

Tracy Sbrocco, PhD Signature [redacted] ***12 Nov 2020*** **Date**

2. Major Advisor:

Marian Tanofsky-Kraff, PhD Signature: Marian Tanofsky Kraff [redacted] **Date**

3. Co-Advisor: USU Faculty Member (in Graduate Program awarding degree):

Andrew Waters, PhD Signature: [redacted] **Date** 11.20.20

USU
Uniformed Services University

4. Additional members as required by Program and/or requested by student and advisor:

Jack Yanovski, MD, PhD Signature: Jack A. Yanovski -S Digitally signed by Jack A. Yanovski -S Date: 2020.11.12 09:59:17 -05'00' **Date** 11/12/2020

Institution (if not USU): **National Institute of Child Health and Human Development**

Student:

Name: **Meghan Byrne** Signature [redacted] **Date** 11/11/2020

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