Reward Systems and Food Avoidance in Adolescents with Low Weight Eating Disorders
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Mount Sinai	Protocol Title:	Reward Systems and Food Avoidance in Adolescents with Low Weight Eating Disorders
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MSSM Protocol Template HRP-503a

Brief Summary of Research (250-400 words):

Anorexia nervosa (AN), a characteristically relentless pursuit of thinness with an intense fear of weight gain despite significantly low body weight , is a serious psychiatric disorder with high rates of morbidity and mortality. Low weight eating disorders (LW-ED), the broader category of eating pathology that includes AN and similar variants, are characterized by a chronic course, poor response to treatment, and food avoidance. Emerging neuroimaging evidence suggests that deficits in insula-amygdala-ventral striatum (IAVS) neurocircuitry contribute to individual variability in aversive and reward learning, and that these brain regions demonstrate abnormal responses to food/eating stimuli. Our pilot data suggest that patients with LW-ED experience difficulty extinguishing food-cue associations in a reversal learning paradigm compared to healthy controls, a difficulty that is related to psychophysiological measures of aversive disgust (not fear). We have also successfully piloted an interoceptive exposure intervention for this population that targets visceral sensitivity and seeks to increase 'top-down' regulation of the IAVS neurocircuit. The proposed project will (a) use novel fMRI-EMG to test the relationship between effective connectivity within amygdala-insula-ventral striatum network and its relationship to psychophysiological and behavioral measures of acute threat and reward learning in 60 adolescents with LWEDs and 30 healthy controls, (b) test the sensitivity of this network to an experimental interoceptive exposure paradigm relative to patients receiving family based therapy for weight restoration using dynamic causal modeling of fMRI-EMG data pre-post experimental conditions, (c) validate this model against objective measures of laboratory and real world eating behavior. The results of this study will help us better understand the core neurocircuitry that underlies both threat processing and reward/aversive learning and how this circuit relates to objective behavior. Further, we will determine the modifiability of this neurocircuitry via two distinct behavioral interventions chosen to target different aspects of affective processing and reward learning. These data will be used to inform future clinical interventions targeting aversive/reward learning within this population and dysregulation in insula-amygdala-ventral striatum subcircuits.

1) Objectives:

Our primary objectives are to test our disgust-conditioning model of food avoidance adolescent patients with low-weight eating disorders. We aim to do this by investigating the underlying neurocircuitry involved in food-cue learning and its reversal (i.e., updated learning through reversal of cue-absence vs. cue-target). Our aims are:

Aim 1: Delineate neurocircuitry through which aversive-disgust responses to palatable food hijack the *acquisition* of food-cue associations in adolescents with LW-EDs versus health controls.

Aim 2: Characterize the impairments in neurocircuitry that underlies resistance to food-cue *extinction* in adolescents with LW-EDs versus controls.

Aim 3: Determine the effect of 6-sessions of interoceptive-exposure (IE) and family based therapy for weight regain on neurocircuitry for aversive food-cue *acquisition* and *exposure* in adolescents with LW-EDs.

Aim 4: Assess the relationship between eating behavior and neurocircuitry for food-cue acquisition and extinction at baseline and following intervention.

Research Question:

We have two primary research questions to be investigated in this proposal. First, we are testing for group differences in the underlying neurocircuitry of aversive learning among adolescents with low weight eating disorders and healthy controls and validating this neurocircuitry across multiple domains (psychophysiology of emotion, symptom expression, and objective and real world eating behavior). Our second primary research question is whether interoceptive exposure can modify the connectivity within the neuro-network that underlies food-cue learning in patients with low-weight eating disorders. We will validate these changes through psychophysiology measures of emotion, symptom change, and measures of objective and real-world eating behavior.

The proposed project will

(a) use novel fMRI-EMG to test the relationship between effective connectivity within amygdala-insula-ventral striatum network and its relationship to psychophysiological and behavioral measures of acute threat and reward learning in 60 adolescents with LW-EDs and 30 healthy controls.

(b) test the sensitivity of this network to an experimental interoceptive exposure paradigm relative to patients receiving family based therapy for weight restoration using dynamic causal modeling of fMRI-EMG data pre-post experimental conditions. IE, a behavioral intervention hypothesized to work via altering prefrontal regulation of the insula response to aversive stimuli by decreasing visceral sensitivity, will be compared to a contingency

management driven family-based weight gain control (FB-WGC) intervention hypothesized to modify the striatal response to food by changing incentive value of food.

(c) validate this model against objective measures of laboratory and real world eating behavior.

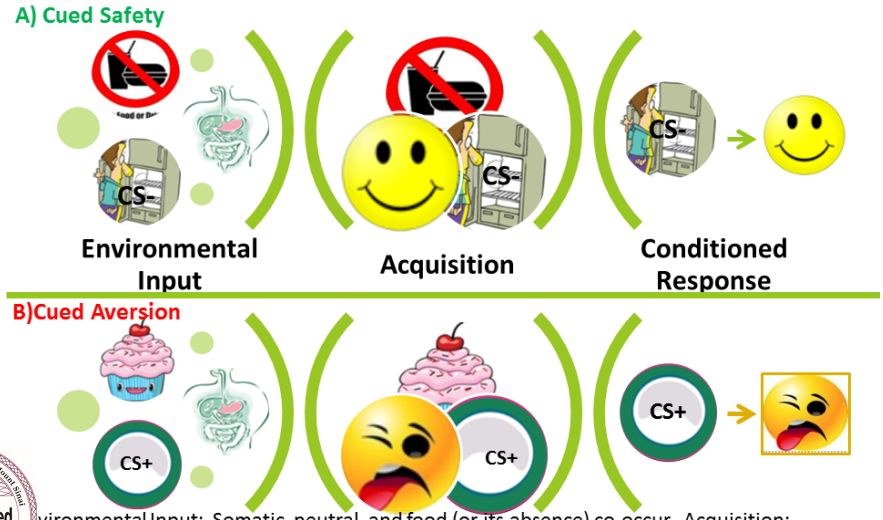
2) Background

Low-Weight Eating Disorders

Significance of Low Weight Eating Disorders and the IAVS Sub-Network. Anorexia nervosa (AN) is a serious psychiatric disorder with high rates of morbidity and mortality(1-6). To date, DSM-variants of AN are most commonly examined in research studies; however, the characteristic features of this disorder remain unchanged regardless of nosological system, namely a relentless pursuit of thinness with an intense fear of weight gain despite significantly low body weight(7). In this broader dimension of low weight eating disorder (LW-ED), we posit that food-cue learning relies on an interconnected network of the insula, anterior cingulate cortex, amygdala, and ventral striatum. This IAVS sub-network assigns valence and feeds forward salient sensory information to prefrontal regions involved in decision making and choice, and contains key nodes known to be dysregulated among LW-ED adolescents(8). IE, a behavioral intervention that theoretically targets the IAVS sub-network to extinguish learned associations characterized by visceral sensitivity, offers the best test of this theory. Studying a model of impaired food-cue (i.e., stimulus-response) learning and affective processing in LW-ED will help advance recent theories of impaired habit formation(7) and emotion regulation(9) in AN, and is a natural extension of our clinical expertise with LW-ED(10) and experience developing exposure therapies with this population(11).

Reversal Learning and Low Weight Eating Disorders

Figure 1. Summary of Conditioned Safety and Aversion to Food



vironmental Input: Somatic, neutral, and food (or its absence) co-occur. Acquisition: peated co-occurence leads to emotional salience directed by interoceptive input related to od (e.g., bloating) or food absence (e.g., empty stomach). Conditioned Response: Emotional response influences behavioral decisions about food and its avoidance.

A.1.1 Reversal Learning and Food Avoidance. **Figure 1** highlights the basic conditioning processes we theorize cause persistent food avoidance among patients with LW-ED. Aversive conditioning and extinction models are broadly implicated in mental illness(12) and have a well-defined neurocircuitry translated from pre-clinical

to human studies(13-15). Our theory builds on seminal work by Co-I Shiller(16), which extends classic conditioning models to reversal learning. The latter offers a measure of the ability to extinguish learned associations in the context where the original threat remains present in the environment, despite the extinction of the conditioned stimulus (CS)+UCS association. Consequently, reversal learning may better generalize to human experience where the predictability of threat changes, but the threat remains(17). Among patients with LW-EDs, impaired reversal of food associations could be why dieting (i.e., associations of calorie dense food with an aversive threat state) becomes a chronic, pathological pattern of food avoidance. In our model (see **Figure 1**), stimuli that signal information about food (e.g., eating environments) and eating itself become associated with an aversive state (i.e., feeling fat, gross, etc.) and other stimuli (e.g., dieting tips, exercise cues, etc.) are paired with 'safety' or the absence of this aversive state (e.g., empty stomach). These relationships form in the context of a typical diet and motivate food avoidance, resulting in weight loss. However, when weight loss becomes unhealthy, it should be possible to reverse these associations to promote consumption of higher density food and avoid the reversed cue associated with the threat of malnutrition. Individuals with LW-ED fail to reverse these associations, which contributes to food avoidance.

Development of Interoceptive Exposure for Food Avoidance and Visceral Sensitivity

Our interoceptive exposure (IE) was developed to reduce visceral sensitivity by altering interoceptive conditioning similar to interventions for irritable bowl syndrome(18-22), consequently increasing tolerance for insula-driven interoception. IE specifically reduces the threshold for visceral sensitivity in anxiety(22, 23) and somatic disorders(24). IE mediates psychotherapy outcomes via specific reductions in visceral sensitivity(25-27) indicating that IE works by changing the influence of interoceptive information on affect and associated behavior (e.g., avoidance). We have developed and pilot tested a 6-Session IE module for LW-ED(11, 28). Details regarding the IE intervention are provided in multiple other sections of the application. Visceral sensitivity plays a primary role in food choice and consumption, and increased tolerance of these sensations should reduce the use of food avoidance. As the insula is integral to almost all salient aspects of food/eating, including somatic symptoms (e.g., stomach distention in the absence of food(29)), we theorize IE targets the effective role of the insula in processing food-cue associations characterized by visceral sensitivity (e.g., bloating, etc.).

Eating and AN

Although some research has attempted to measure the pathology of eating behavior, most of the measures are subjective and rely heavily on patient report. Currently, there is a limited amount of studies that have objectively examined the food intake of patients

with low weight eating disorders. An examination of the eating behavior among adult women with anorexia nervosa in an inpatient setting showed that despite improvements in psychological symptoms, eating disturbances persisted after patients achieved weight restoration(30). The level of anxiety is modifiable via traditional exposure therapy(31, 32), however, these changes have almost no measurable impact on eating behavior. Consequently, adaptations to interventions that may improve eating behavior have significant value in developing treatments for this population.

3) Setting of the Human Research

Research will take place at the Mount Sinai Eating and Weight Disorders Program (EWDP) (for consenting, intakes, and behavioral/psychological assessment) and Translational and Molecular Imaging Institute (TMII) at the Icahn School of Medicine at Mount Sinai to conduct fMRI tasks and EMG readings.

Potential subjects will be identified through our clinic, and through other referrals from their treatment providers, as well as through flyers distributed throughout Mount Sinai and the surrounding areas. As per Mount Sinai Resource, we will be also recruiting via MSSM Update Weekly Newsletter, MSSM psychiatry list-serv and MSSM post-doc list-serv.

4) Resources Available to Conduct the Human Research

The Mount Sinai EDWP sees a high volume of clients, many of whom fall within the age and eligibility guidelines for this study. Therefore, we expect no difficulty recruiting all participants within the planned time schedule.

Prior to commencing this study, all persons assisting with this research will be trained on the protocol instructions detailing their trial-related duties and functions will be provided in a clear and concise manner. In addition, all persons assisting with this research will have completed the IRB education requirements for Human Subjects research prior to their involvement in the study.

Principal Investigator:
The PI will be responsible for monitoring and directing the overall progress of all aspects of the study proposed in this application. Specifically, the PI will screen potential research participants, oversee training of the research assistants, supervise database creation and entry, and serve as the secondary statistician on data analyses (ensuring data quality, management, and interpretation of statistical models). He will also lead weekly staff meetings and be responsible for submitting grant related materials (IRB, Progress

Report, etc.) and lead efforts in manuscript preparation and publication from the study. Further, the PI will be one of the providers of the experimental 6-week behavioral challenge.

Co-Investigators:
Co-Investigators will be responsible for reviewing data collected during the single and multi-item test meals (e.g., amount and types of food consumed) and will assure the quality of the laboratory meal assessments. They will work closely to offer expertise related to the measurement of eating behavior and assist with the interpretation of data, the presentation of results, and preparation of study reports. The Co-Investigators will examine scans to check for medical abnormalities, aid in the interpretation of neurobiological data and results overall, and review labs for medical clearance to participate in the study. Additionally, Co-I's will aid in the collection and analysis of EMG data, oversee the data processing and the statistical analysis of imaging data. They will also be responsible for ensuring the integrity of the scans and behavioral data collected from the reversal learning task.
Co-I's will also contribute to data analysis by co-registering the facial EMG findings with the neuroimaging data and using dynamic causal modeling to examine connectivity within the regions of interest.
Another Co-I role will be analyzing data obtained from the FaceReader emotional detection software. FaceReader output is of a high density, with 20 recordings made every second. Furthermore, many of the recordings will be obtained while the participant is eating, adding to the amount of noise present in the data (i.e., the act of chewing can be mistaken for emotional reactions). The Co-I will oversee the data processing and analysis of these data after data has been collected, fitting the best models while removing as many of the extraneous recordings as possible. They will work closely to estimate and calibrate DCMs and advise on issues related to data interpretation.

Non-Key Personnel:
Clinical Psychologist
The Clinical Psychologist will be primarily responsible for diagnostic interviewing and for providing the behavioral challenge. They will oversee coordination between the post-doctoral fellow and research assistant to generate integrity ratings for interviews and will have immediate oversight of the clinical status of participants with low weight eating disorders.

Nutritionist
The nutritionist will aid the Co-I in the preparation and coding of the test-meal replacement shake and standardized multi-item meal. Specifically, the nutritionist will assist with the execution and analysis of laboratory test meals (e.g., measuring food residue), and will help with the interpretation of eating behavior data.

Post-Doctoral Fellow

The post-doctoral fellow will be responsible for diagnostic interviewing and for providing the behavioral challenge. The post-doctoral fellow will also coordinate with the research assistant to generate integrity ratings for interviews and will have immediate oversight of the study's process.

Clinic Research Coordinators

Our coordinators will work closely with the PI, and will attend to the administrative components of the project. These responsibilities include, but are not limited to, recruitment of subjects; coordinating and scheduling clinical assessments; ensuring that all rating scales and clinical reports are completed in a timely fashion; ensuring that checks are generated to reimburse subjects for their participation in the protocol as well as other fiscal aspects of the study (e.g., purchasing supplies). In addition, this person will be responsible for preparing all IRB documentation and will make sure that all consenting of subjects is appropriately completed.

Volunteers

Our volunteer interns will work closely with the PI and the Clinical Research Coordinators on this project. Responsibilities include, but are not limited to, recruitment of subjects, escorting participants to other areas at Mount Sinai and inputting data.

5) Study Design

a) Recruitment Methods

Adolescent female participants with AN and healthy comparison controls will be recruited for this study. Participants will be recruited via phone calls to the Project Coordinator at the Mount Sinai Eating and Weight Disorders Program, and through advertisements and emails to listservs of school counseling centers, and hospitals. In addition, the study will be publicized on the Mount Sinai Clinical Trials and Eating and Weight Disorders Program websites, as well as in the local media via IRB-approved flyers. Staff will recruit healthy comparison controls predominantly through posting flyers at local schools and community centers. All potential advertising tools will be submitted to the IRB for approval prior to their use. Participants will be instructed to contact the Project Coordinator at 212-659-8724 and will be invited for a consultation in which the study will be thoroughly explained to them in verbal and written form by the principal investigator or by another member of the research team (i.e. project coordinator, research assistant, or extern therapists). Individuals that call the Mount Sinai Eating and Weight Disorder Program looking for treatment will be informed of the study. Interested participants and/or parent(s) will be informed that at

least one parent or legal guardian will be expected to attend the initial in-person screening visit with the adolescent participants and provide informed consent at that time.

b) Inclusion and Exclusion Criteria

Low Weight ED Patients

Inclusion criteria:

- Females,
- Adolescents ages 12-18,
- Speak English,
- Seeking treatment
- Refusal to maintain greater than minimally low body weight based on BMI for age percentiles and growth trajectories,
- Clinically significant restriction of food intake on the dietary restraint subscale of the EDE or evidence of persistent food avoidance as reported by patient or guardians.
- Given medical clearance from pediatrician or equivalent.

Exclusion criteria:

- Current psychotropic medication that would have an effect on performance on behavioral tasks (i.e., anti-anxiety medication),
- Comorbid psychotic or bipolar disorder,
- Active suicidal ideation,
- Major medical illness known to influence eating or weight,
- Current substance dependence,
- Previous exposure therapy for LW-ED.
- Physical limitation that would prevent participation (e.g., allergic to chocolate),
- For patients with current or a history of sexual or physical abuse by parents, siblings, or guardians, perpetrators of the abuse will be excluded from treatment; if physical or sexual abuse by a family member occurs during the course of treatment, perpetrators will be excluded from ongoing treatment

Healthy Comparison Adolescents

Inclusion criteria:

- Females,
- Adolescents ages 12-18,
- Speak English.

Exclusion criteria:

- Current psychotropic medication that would have an effect on performance on behavioral tasks (i.e., stimulant medication),
- Current or lifetime history of any psychiatric disorder, including eating disorders by K-SADS,
- Current or lifetime history of learning disorder or developmental disability
- Active suicidal ideation,
- Major medical illness,
- Other physical limitation that would prevent participation (e.g., allergic to chocolate).

c) Number of Subjects

A total of 118 female adolescents will be recruited to obtain complete assessments on 60 female adolescents with a low weight ED and 30 healthy comparison adolescents between the ages of 12-18.

d) Study Timelines

Participants' participation will include 10 visits over approximately 8-week period for AN participants and 4 visits for healthy comparison controls. During the 6 weeks separating the testing, adolescents with low weight EDs will receive an intervention (please see below), whereas healthy comparison adolescents will not have additional contact with study staff during this time.

Visit 1 will consist of screening procedures to determine eligibility, completion of self-report questionnaires, and a laboratory based eating measure.

In Visit 2, all participants will complete a reversal learning computerized task while undergoing an fMRI scan with EMG, computerized task also using EMG, and lastly the completion of a multi-item meal task in which we will analyze eating behavior via video recording and facial recognition software.

The next 6 visits will only apply for **LW-ED participants and not healthy controls** and will consist of the exposure-based intervention, across a span of 6 weeks. Participants will be randomized into one of two intervention groups, a weight gain control group and an interoceptive exposure group.

In Visit 9, all participants will complete self-report measures, single item meal task, and height and weight.

In Visit 10, all participants will complete the same self-report questionnaires, concurrent fMRI--EMG, and computerized learning task, and the multi-item meal task.

After the 10 visits, LW-ED participants are offered 20 sessions of free open-label family-based treatment.

The duration anticipated to enroll all study subjects is 42 months [~1.5 LW-ED patients per month with 60 enrolled by ~month 40 (2 months start-up)], leaving 6 months to analyze the data.

The anticipated duration of the study is 4 years.

The study is estimated to be completed 4 years from the date of initial IRB approval.

e) Study Endpoints

The study is estimated to be completed 4 years from the date of initial IRB approval including months 43-48 for data analysis.

f) Procedures Involved in the Human Research

All tests and procedures being performed are completely research-related and are not part of clinical care. LW-ED participants will complete Visits 1-10 while healthy comparison adolescents will only complete the Baseline Assessments (Visits 1 and 2) and the final two visits (Visit 9, and 10). The total timeline for participation is approximately 9 weeks.

The study will be described to interested participants (or parents) and the first of two baseline assessment sessions will be scheduled. **Participants with low weight EDs will not be enrolled into the study until clearance to receive outpatient therapy has been received from her pediatrician**. **We will provide a medical clearance form with guidelines for the necessary tests to determine if participants can be seen on an outpatient basis. If necessary, participants may be further medically evaluated by a psychiatrist on staff. The psychiatrist will provide feedback and facilitate the coordination of care if medical evaluation reveals abnormalities.**

Table 1: Summary of Visits and Measures Associated with Each Measure

Baseline		**Session 1 of IE or FBT**	**Session 2 of IE or FBT**	**Session 3 of IE or FBT**	**Session 4 of IE or FBT**	**Session 5 of IE or FBT**	**Session 6 of IE or FBT**	**Post-Treatment**	
Visit 1 (Day 0)	**Visit 2** (Day 1-7)	**Visit 3** (Day 14)	**Visit 4** (Day 21)	**Visit 5** (Day 28)	**Visit 6** (Day 35)	**Visit 7** (Day 42)	**Visit 8** (Day 49)	**Visit 9** (Day 50-57)	**Visit 10** (Day 57-80)
		2 hours	1 hour	1 hour	1 hour	1 hour	1 hour		
Eligibility **1) Consent/ Assent 2) K-SADS 3) EDA-5** 4) C-SSRS	**fMRI-EMG** 1) reversal food-cue learning 2)disgust conditioning task	Video Coding	Video Coding	Video Coding	Video Coding	Video Coding	Video Coding		**fMRI-EMG** 1) reversal food-cue learning 2)disgust conditioning task
Self-Report Measures **(6):** 1) CIA 2) DSR 3) ASI-III 4) BAQ 5)CES-DC 6) YEDE-Q	**EMG-behavior** reversal $$-cue learning							**Self-Report** Measures (6): 1) CIA 2) DSR 3) ASI-III 4) BAQ 5)CES-DC 6) YEDE-Q	**EMG-behavior** reversal $$-cue learning
Lab eating paradigm (meal replacement shake)	**Lab eating** paradigm (multi-item meal)							**Lab eating** paradigm (meal replacement shake)	**Lab eating** paradigm (multi-item meal)
Height/ Weight								**Height/ Weight**	
	Real World Eating Food records collected								**Real World Eating** Food records collected

****Healthy controls will complete only Visits 1,2, 9,10.**
**Timeline is approximate; however, intervention sessions would occur 7 days apart.

The Baseline Assessment includes Visits 1-2:

Visit 1 (2 hours total)
This is an in-person screening visit to determine eligibility.

Consent/Assent Process:

- Conducted with a trained member of the research team (project coordinator or study therapist). In order for the adolescent to participate in the study, at least one parent or guardian must participate in intervention sessions. Any parent(s) who will be involved in the intervention will sign an informed consent document and written assent will be obtained from all adolescents.

Assessments:

- *EDA-5* for eating disorder diagnoses and psychopathology.
- Relevant sections of the *K-SADS* (mania, psychosis, alcohol and substance abuse) to determine any lifetime psychiatric disorder to determine eligibility.
- Columbia-Suicide Severity Rating Scale (C-SSRS) to assess for suicidal ideation.

Self-Report

- Clinical Impairment Assessment (CIA)
- Disgust Scale-Revised (DSR)
- Anxiety Sensitivity Index-III (ASI-III)
- Body Awareness Questionnaire (BAQ)
- Center for Epidemiological Studies Depression Scale for Children (CES-DC)Youth Eating Disorder Examination-Questionnaire (YEDE-Q)

We will have a trained study coordinator review medical clearance from the participant's physician, consistent with our clinic's procedures for outpatient care.

If found eligible after these assessments, the participant will complete the single-item meal and will be scheduled for Visit 2.

Single-Item Meal: A standardized laboratory test meal will be used as an objective assessment of food avoidance in adolescents with LW-EDs. The meal consists of a strawberry yogurt shake used previously in a study of AN by Dr. Sysko (Co-I)(30). Limited intake observed in this test meal before and after intensive inpatient treatment and subjective reports of anxiety by patients suggest the utility of this paradigm for LW-EDs. Procedures are based on those described by Sysko et al.(30, 31), and will be identical for experimental IE sessions. Participants will be presented with an 55 fluid ounce (1626.50-mL) covered opaque container containing approximately 1475 grams (1 kcal per gram, or 1475 kcal) of strawberry yogurt shake. Patients will be informed that the meal consists of a strawberry yogurt shake, but will not be told the amount provided in the container. The instructions will direct participants to consume as much of the shake as they would like and that the meal will serve as their lunch (or dinner) for the day and to avoid touching or manipulating the container in any way. The meal will be placed on a modified

version of an eating monitor, which measures intake (in g) every 5 s. During the meal, participants will also be observed through a closed-circuit video monitor to ensure that they are following instructions and to monitor behavior. Ratings will be made before and after the test meal of hunger, fullness, sickness, loss of control, urge to eat, preoccupation with thoughts of food, disgust, and fear of fatness on a 15-cm visual analog scales (VAS). Consumption of the shake in Kcal will be the primary outcome, with secondary outcomes of rate of eating in Kcal/min during the 30 min meal.

Visit 2 (3 hours total)
After Visit 1, all participants will complete fMRI and lab procedures, then patients with LW-EDs will be randomized to an intervention.

(1) **fMRI-EMG reversal food-cue learning task and disgust conditioning task**
(Total completion Time: 2hrs) Both tasks will take place within the scanner. Participants will first be given instructions for the two tasks and will do a short practice version in the mock scanner with the study coordinator to ensure they are comfortable. Participants will be in the fMRI scanner for a total of 1 hour.

a. **Reversal food-cue learning task**: During phase one of the Reversal Food Validation fMRI task, (i.e., Acquisition) participants will be presented with visual food or neutral stimuli on a computer screen. Some stimuli, conditioned stimuli, will sometimes be followed by a food or a no outcome (e.g., loss or gain of a food item, M&Ms or Hershey's kisses). Other stimuli will never be followed by an outcome and will be used for comparison. Phase two of the task, Reversal, is similar to Acquisition only the reinforcement contingencies will be reversed. That is, some of the previously non-paired stimuli will be now paired with the outcome while the previously paired stimuli will be now unpaired. A response pad will be placed around the participant's right arm and the participant will be instructed to make ratings. Participants will also have MRI safe EMG electrodes from BioPac systems attached in order to provide a physiological measure of learned contingencies. For this task, participants are instructed that afterwards they will be given the equivalent number of M&Ms (240) or Hershey's kisses (48) that they are presented in the task, regardless of their responses.

b. **Disgust choice conditioning task**: The conditioning procedure will test the ability to learn and extinguish disgust associations. The task includes distinct acquisition and extinction phases. In the acquisition phase, the conditioned stimuli (CS), consisting of blue and green squares, will be presented individually at fixation, followed 4 s later by the co-presentation of the unconditioned stimuli (UCS) to the left and right of the CS. The UCS will consist of two sets of pictures

depicting either intact fresh food or rotted versions of the same food items. Subjects will be instructed to attend to possible associations between the CS and UCS and to rate the "disgust" versus "desire" associated with the UCS on a Likert scale presented during the inter-trial interval using a 5-button fiber optic system on the right hand. In the extinction phase, the CS will be displayed again individually at fixation, but the UCS will not be presented alongside the CS and the ITI will not include the Likert scale. Subject awareness of the response contingencies will be assessed with a post-scan interview.

(2) **Reversal $$-cue learning** (completion time, 25 min): This paradigm mirrors that of the fMRI-EMG except that it is completed outside the scanner with stimuli delivered via laptop and keypad used for item response. The stimuli will be a small monetary rewards that correspond to 15 cent reinforcements as cued by pictures of either 15 pennies or 3 nickels. Participants are instructed that afterwards they will be given the equivalent amount of money that they are presented in the task, either 240 pennies or 48 nickels equating to $2.40, regardless of their responses.

The stimuli for the food-cue learning task and the $$-cue task are paired and counter-balanced for the pre- and post-scans. The 2 stimuli groups include M&Ms/pennies and Hershey's kisses/ nickels. Participants randomized to M&Ms/pennies in the pre-scan will receive Hershey's kisses/nickels in the post-scan, and vice versa.

(3) **Lab eating paradigm (Multi-Item Meal)**

Along with the fMRI scan, participants will also participate in an eating behavior task as a part of the study. Prior to beginning the study, participants will be instructed to eat all daily meals as usual, with no meal occurring within 4 hours prior to the eating behavior task. Participants will be given scripted instructions by a study coordinator and will be asked to "eat as much or as little as you'd like." They will be presented with a multi-item meal that will consist of a variety of foods (e.g., bread, chicken, apples, oranges, oreos, potato chips, etc.).

As part of the task, participants will also be asked to make ratings before and after the test meal using the VAS. . Participants will be instructed to ring a bell to indicate the end of the meal, and will be asked to complete questionnaires. Test meals will be observed via closed-circuit television by a member of the staff. Outcome measures will include amount consumed, macronutrient distribution, and duration of eating.

Since it is possible participants will be distressed following the multi-item meal, study coordinators will conduct a short debriefing interview with them after completion.

Treatment (Visits 3-8)

After the baseline assessment (Visits 1-2), patients with LW-EDs will be randomized to 6 weekly sessions of FBT-WG or IE. Randomization will occur after we have processed the baseline fMRI scans. If the study coordinators have determined the participant's scan is free of interference from motion in the scanner, the participant will be randomized within this group. If the study coordinators determine a participant's scan is unusable, the participant will be excluded from the study.

In both FBT-WG and IE, the first session lasts two hours and the remaining 5 sessions last one hour.

FBT-Weight Gain Control (FBT-WG): Participants and families randomized to FBT-WG will receive 6-weeks of FBT treatment for AN[111]. Sessions occur weekly, with the first session lasting two hours and the remaining 5 sessions one hour. FBT is atheoretical in terms of the etiology, but uses parent-enforced contingencies to increase value of eating and decrease the value of food avoidance. The six sessions of FBT focus primarily on disordered eating, using a functional analysis to facilitate parental use of positive/negative contingencies to motivate eating behavior. In session 2, a family meal provides the therapist with an opportunity for direct observation of the familial interaction patterns around eating. The therapist makes careful and persistent requests for united parental action toward re-feeding and/or regulating eating habits, the primary concern at this point of the treatment, and the therapist tries to create and reinforce a strong parental alliance around efforts at feeding the child, and align the patient with the sibling sub-system. Parents are taught to reinforce even minimal efforts at eating and creating clear consequences for food avoidance and successful eating. Weekly sessions offer an opportunity for therapist to reinforce/update the contingency plan and reinforce the parents for remaining consistent and persistent in their re-feeding of the adolescent.

IE-Paradigm: Participants randomized to this intervention are provided with a meal replacement shake of 'unknown' Kcal or macronutrient content and are asked to mindfully observe the sensations (aversive taste, texture, bloating, icky feeling, etc.) and associated emotional states (i.e., disgust) with the empathetic support of parents/therapist in session, without expectation of habituation. The IE 6-session paradigm builds on our proposed model of food avoidance in AN(10), which posits that a conditioned aversive response to food coupled with a pleasurable response to the absence of food accounts for maladaptive food avoidance. Sessions occur on a weekly basis with session one lasting 2 hrs. During the 1st hour, the therapist explains an aversive conditioning model of LW-ED, sensory components of eating, and the concept of IE. The therapist explains the goal of IE is to help patients learn to

tolerate their interoceptive experience (e.g., disgust), so that eating can become more flexible. At the end of the first session, the therapist and parent(s) review a manual, which provides clear instructions for structuring the re-feeding process (e.g., sitting with child during all mealtimes; guidelines for IE homework; planning meals). In the 2nd hour, participants are given a meal replacement shake and instructed to focus on internal bodily sensations and to continue eating while experiencing and labeling these sensations. This practice is then assigned for homework, charging parents with orchestrating IE in similar pattern using a visceral sensitivity hierarchy established in the first session and is continued through the end of the module. The therapist uses an empathetic active stance to encourage IE that will subsequently serve as an example for parents in IE homework assignments. Participants rate their level of distress 4 times in the session and physiological response is recorded using EMG and facial recognition software. The remaining 5 sessions last one hour, and participants eat a meal replacement shake over 30-minutes, identical to the first session. All sessions include debriefing and development of IE homework that includes daily practice of IE.

Visit 9 and 10: These visits will follow the same procedures as Visits 1 and 2 respectively.

The eating sessions in visits 1 and 2 and visits 3 and 4 (9 and 10 for adolescents with a low weight eating disorder) and the treatment sessions (visits 3-8) will be video recorded to be decoded via software to analyze participants' emotional responses to eating. Treatment integrity will also be evaluated from the recording of the intervention sessions. The video recordings will be stored securely for the duration of the study in a password protected file that only the study staff can access.

g) Specimen Banking

Not applicable.

h) Data Management and Confidentiality

DATA SHARING PLAN

We will share the primary outcome data from this project with the National Data Archive managed by the National Institutes of Mental Health. The data archive contains anonymized raw data from NIH sponsored programs and research for use in testing reliability of findings from these studies and allowing for future discovery from these data by other investigators or in combination with data collected from other investigators.

Our plan will be to upload our primary outcomes which include neuroimaging data (structural scan, BOLD sequence, and task behavioral data) as well as participant weight, eating, and self-report questionnaire data. No identifying information will be shared (e.g., video data, names, address, date of birth). All data will be stored via a unique ID, generated by the data archive that is independent of the unique ID by which data at Mount Sinai is stored. These two IDs will only be stored by the Mount Sinai investigators.

a) Data Management and Confidentiality

All data stored in the computer database will be anonymized when entered into the database. Data will be stripped of all personal identifiers and each subject will be referred to by a unique research code. The file that contains the link between identifying information and the research code will be kept in a locked file cabinet in the Mount Sinai EWDP in a different location from where the data stored with the research code is maintained. Only authorized members of the research staff will have access to this link.

National Database for Autism Research (NDAR) Data-Sharing –With parental consent, this study will collect and provide research data and related findings to the National Database Archive (NDA). NDA is a biomedical informatics system and data repository created by the National Institutes of Health – part of the U.S. Department of Health and Human Services (DHHS), an agency of the U.S. Government – to assist biomedical researchers working to develop a better understanding of mental health and/or to develop more effective methods to diagnosis, treat and prevent mental health conditions. Data entered into NDA will be kept confidential, with NDA being designed for access by researchers only. Data provided to NDA as part of participation in this research study can not be linked to your identifying information. Once data are uploaded, they will not have a direct link back to identifying information held at Mount Sinai. If parents consent to sharing data with NDA, they mat at any time request that their data or their child's data be removed from NDAR, but they must do so in writing to the Principal Investigator at the address on the first page. If they do not want to consent to sharing their data, they will still be eligible for participation in this study.

b)

Raw data will be stored in locked filing cabinets in the project coordinators' office in the EWDP at The Mount Sinai Medical Center. The data to be stored will include de-identified information pertaining to consented participants will receive individualized identifier codes that will be generated in advance of any data acquisition. These codes will be used on all future documents instead of names. An Excel file of the key to the codes (that links names of participants to assigned codes) will be password protected on an encrypted personal network drive that only Mount Sinai EDWP staff can access. Additionally, only designated study staff will have access to the locked password key containing the password to this file. The de-identified data to be stored will include information pertaining to demographic and psychiatric status obtained from the questionnaires and clinical interview. Data will be stored for a minimum of 7 years, with the exception of the video recordings that will only be stored for the duration of the study. All questionnaire and interview data and video recordings will use study identification numbers and electronically stored data will be coded and password protected in a secure database (with a password protected back-up device in a locked office).. Contact information for participants' parents will also be stored on a password protected file and will only be used for scheduling purposes. Only the coordinator and the Principal Investigator will have direct access to this information. The Primary Investigator, Dr. Thomas Hildebrandt, will provide intermittent review of procedures employed to ensure proper data management that protects participant confidentiality. The research data file will be kept on an encrypted personal network drive on the Academic Computing file server located in the medical center's secure data center.

c) Provisions to Monitor the Data to Ensure the Safety of subjects

Only the primary investigator and the research assistants within his laboratory have access to file cabinet keys and computer passwords.

MSSM Principal Monitor: Indicate whether this person is the PI, a Team Member, or is Independent:

PI:
Last Name: Hildebrandt
First Name: Thomas
Academic Title: Senior Faculty Member
Department: Psychiatry
Mailing Address: One Gustave L. Levy Place, Box #1230
Phone: 212-659-8673
Fax: 212- 849-2561

E-mail: tom.hildebrandt@mssm.edu

The research team will have methods in place for dealing with any adverse events that may arise during study procedures. The PI will ensure that any adverse events that occur are recorded and reported within 24 hours of discovery to the ISMMS IRB; this includes both expected and unexpected adverse events.

All prospective participants will also be screened for psychotic symptoms using the KSADs. Any endorsement of psychotic symptoms will exclude the participant from the study; however, referrals will be made for the treatment of these symptoms.

In the case of active suicidal or homicidal plans or intent revealed during the course of evaluation, a licensed psychologist/psychiatrist will evaluate the patient. If necessary, the participant will be taken to the emergency room or admitted to the inpatient facility. In the discovery of a previously unknown psychiatric disorder during evaluation, if safety is compromised or could potentially be compromised, the procedure above will be followed. If not (e.g., the discovery of a Major Depressive Disorder with no psychotic features and no suicidality), the participant will be notified and encouraged to seek help in a sequenced fashion following treatment. The patient's primary clinician will also be notified assuming a written release is signed by the participant.

In the event of a medical emergency during study procedures, emergency services will be notified to take the patient to the hospital.

In the case of clinically significant worsening of eating disordered symptoms identified during study participation, a clinician will determine whether the patient needs to be referred to a higher level of care based on the clinical standards for adolescents utilized within the Eating and Weight Disorders Program. The clinician and PI will subsequently determine whether the patient needs to be withdrawn from the study (e.g., in the case of a referral for psychiatric medication), or if continued participation is possible (e.g., brief medical hospitalization with a new medical clearance to receive outpatient treatment from the treatment team). We will not interfere with any recommendations about the decision to receive or discontinue outpatient treatment made by the providers providing additional care to study participnts.

d) Withdrawal of Subjects

Patients are free to end their participation in the study at any point. In addition, patients may be discharged involuntarily if they meet any exclusion criteria during the

course of their participation (i.e. if a patient becomes pregnant). If a patient is withdrawn from the study, the research team will explain the reasons for the withdrawal. Withdrawal from this study will not affect a patient's clinical care or access to any care or other opportunities to which they are otherwise entitled. Subjects may also withdraw permission for the use and disclosure of any protected information for research, but must do so in writing to the Principal Investigator at the address listed in the consent document.

Participants with low weight EDs will be informed that not participating in the study will not change or restrict their eligibility for treatment in the Eating and Weight Disorders Program and will not jeopardize their relationship with their pediatric subspecialist, if they were referred from Pediatric Associates or the Adolescent Health Center.

6) Risks to Subjects

Risks to patients in the study would be no more than those that exist as a result of the illness and no more than are usual in clinical practice and management.

From a psychological standpoint, there is the potential for participants to become upset or anxious during the tests or interviews. Participants may also experience fatigue when completing the tasks in the assessments. All evaluations will be conducted by trained clinicians and the fMRI scans will be conducted by trained imaging staff. If a participant becomes upset or anxious, a member of the study team will ask the patient if she wishes to continue their participation. The protocol will be discontinued if a participant experiences a level of emotional discomfort such that she wishes to end her participation in the protocol. She may end her participation in this study at any time, with no consequence to her ability to access services at Mount Sinai in the future. If the participant experiences emotional discomfort as a result of her participation in the study, the research team member administering the protocol will attempt to provide comfort to the participant, will contact the Principle Investigator, and will discuss with the participant the need for a referral for further mental health services. To minimize fatigue, if the participant states feeling tired during testing or if the examiner notices this, the participant will be encouraged to take a break.

In the case of active suicidal or homicidal plans or intent revealed during the course of evaluation, a licensed psychologist or psychiatrist will evaluate the patient. If necessary, the participant will be taken to the emergency room or admitted to the inpatient facility. If safety is compromised or could potentially be compromised by the discovery of a previously unknown psychiatric disorder during evaluation, the procedure above will be followed. If not (e.g., the discovery of a Major Depressive Disorder with no psychotic features and no suicidality), the participant will be

notified and encouraged to seek help in a sequenced fashion following treatment. The patient's primary pediatrician clinician will also be notified assuming a written release is signed by the participant.

Psychophysiology: There is limited risk to the electrophysiological recording procedures. There is potential for slight irritation at the site of electrode application. There is no discomfort or physical risk associated with the recording of skin conductance and facial EMG.

Lastly, there are no known risks of the fMRI procedure. Some people may find it difficult to lie perfectly still in the scanner for one hour. The scanning is also noisy, and some might find that noise and confinement uncomfortable. The technician will remain with participants until they are comfortable inside the scanner. If the participant feels uncomfortable inside the scanner at any time, the test will be stopped immediately and the participant will have the option to withdraw from the study. Rarely, people react strongly to being enclosed in a small space and may become extremely anxious. Every precaution will be implemented to ensure such instances do not occur.

In this study, patients may overeat or binge eat. There are minimal physical risks associated with this behavior among patients with a LW-ED who regularly engage in this behavior and who show no physical deterioration as a result. We are not asking patients to do anything differently from what happens in the course of their illness. Psychologically, participants may be upset after overeating and feel depressed or guilty afterward. A member of the staff is present during both meal sessions, and will be available to speak with the participant if he or she becomes upset. With asking more than 100 patients to eat in the laboratory in a series of similar studies, we have not encountered any significant adverse physical or psychological events.

7) Provisions for Research Related Injury

We do not expect any research related harm or injury to occur to participants during their participation in this study. However, if a patient is harmed during the course of their participation in the study, the research team will respond to any immediate emergencies, and then make referrals for follow-up care, as appropriate.

8) Potential Benefits to Subjects

Potential benefits to the patients in this proposed study include the possibility of a reduction of symptoms associated with low weight eating disorders. Healthy comparison adolescents are not expected to derive benefits from participation.

Indirect benefits: Benefits to future patients, researchers, clinicians, and health care planners could include valuable information about ways to improve treatment for low weight eating disorders and a greater understanding of the neurocircuitry that underlies different types of learning.

9) Provisions to Protect the Privacy Interests of Subjects

During the consent process, the member of the research team will thoroughly explain the provisions made to ensure data confidentiality. As part of this process, the acting member of the research team will explain that these provisions are in place to ensure that information deemed sensitive or private is protected. If, during the clinical interview, the administering clinician senses that a participant is uncomfortable with the nature of the interview, the clinician will stop the interview and review the guidelines in place for the protection of participant privacy. If the participant continues to exhibit distress or states that he/she is uncomfortable with the information being asked, the clinician will cease that line of inquiry.

10) Economic Impact on Subjects

Patients will not incur any costs associated with the study evaluations or interventions. Any potential costs of EWDP treatment not included in the protocol (or at external treatment centers or with non-EWDP treatment providers) will be the patients' responsibility, as this is not part of the study protocol. Any eating-disorder related care outside of the EWDP but intersecting with its standard approach (e.g., DXA, physician costs to obtain medical clearance or ongoing medial management; management of psychotropic medication by an outside psychiatrist) will also be the responsibility of the patient.

11) Payment to Subjects

All participants will be paid $275 for the pre and post-intervention assessments. Specifically, participants will be paid $50 for visit 1, $65 for visit 2, $70 for visit 3 (visit 9 for adolescents with eating disorders), and $90 for visit 4 (visit 10 for adolescents with eating disorders).

Follow-up Treatment: LW-ED participants will also be offered 20 free sessions of open label psychotherapy for their eating low weight eating disorderover a maximum of six months in the EWDP as compensation for participation. If participants wish to attend these sessions, the first session will continue approximately one week after

Visit 10 and all 20 sessions would be completed within 6-months following Visit 10. When deciding to participate in this study, all participants will be made aware of the full range of treatment option offered by the EWDP, including that our program routinely offers free treatment for eating disorders through our student extern therapists. Therefore, participants should feel no obligation to participate in this study only to receive free treatment for their eating disorder.

12) Consent Process

Voluntary written informed assent/consent will be obtained from all participants and parents prior to study entry in accordance with the Institutional Review Board of Mount Sinai. Assent/consent will be obtained at the Icahn School of Medicine at Mount Sinai in a closed office with only members of the research group present. The initial assent/consent forms describe the nature of the procedures and time requirements, potential risks, the confidentiality of information, and the rights of research subjects. This will include an explanation of the protocol, of its risks and benefits, and of alternatives to participation. Participants will be made aware that if they choose to participate, they must give consent to be video recorded as needed in the protocol.

Consent forms of parents of adolescents with low weight EDs will indicate procedures that parents need to complete as part of the intervention to which they are randomized. Participants with low weight EDs will be informed that not participating in the study will not change or restrict their eligibility for treatment in the Eating and Weight Disorders Program and will not jeopardize their relationship with their pediatric subspecialist, if they were referred from Pediatric Associates or the Adolescent Health Center. Participants' understanding of the protocol will be examined by direct questioning prior to their signing the assent/consent forms.

A standard, formal assent procedure (as mandated by the Icahn School of Medicine Institutional Review Board) will be conducted for all children. This will include explanation of the protocol in a developmentally appropriate way, discussing alternatives to participation in the project with the individual, providing the opportunity to ask questions, and certification of assent of a minor that will be witnessed by a nurse or a clinician that is not related to the child and is not a part of the research team.

If a participant is under the age of 18 and completes the assent procedure at the beginning of her participation then turns 18 during the course of her participation, she will be required to complete formal adult consent procedures in order to continue her

participation. Children will be reconsented when they turn 18 years old to have their data stored in the National Data Archive. If a child is lost to follow up when they turn 18, their data will be removed from the archive and destroyed.

Consistent with Federal and State guidelines, all participants will be informed that if an unreported case of child abuse is discovered during the course of the study it will be reported. The assent/consent forms will specifically read: "An exception to confidentiality is a *previously unreported* incident of child abuse and neglect that is obtained during research. The investigator will report this information to the appropriate local (e.g., Administration for Children's Services) or state agency in accordance with New York State law." A copy of the assent/consent form is provided to all participants. If the individual decides not to participate in this study, a project staff member provides reasonable and timely assistance in obtaining an alternative referral, if applicable and so desired. The decision not to participate does not affect eligibility to participate in future studies, to receive treatment at the participating institution, or to receive treatment on a private basis from a referring clinician.

13) Process to Document Consent in Writing

The standard PPHS consent template will be used.

14) Vulnerable Populations

Children: 1. Mount Sinai Medical Center Certification of Assent procedure will be used. The investigator will explain the protocol to the child in a developmentally appropriate manner. If the child agrees to participate she will be asked about the protocol by an independent clinician, who is not related to the child and is not involved in the study (e.g., non-study personnel). This clinician will need to certify in writing that the child indeed understands the protocol and is assenting to it. If assent is not obtained, evaluation will not commence even if the parent consents.

2. The clinicians involved in this study will be trained in the management and interviewing of children.

Financially disadvantaged persons: The study population is expected to include participants from all financial and social strata. We will not exclude a participant based on financial parameters nor will we ask for a payment for the evaluation. The reimbursement of free treatment for patients with low weight EDs is not coercive, in that it does not constitute an unreasonably high incentive for participation even for financially disadvantaged persons. The opportunity to receive free treatment allows for persons in this situation to receive at least the equivalent of standard care provided by specialists in ED treatment.

15) Multi-Site Human Research (Coordinating Center)

Not applicable.

16) Community-Based Participatory Research

Not applicable.

17) Sharing of Results with Subjects

Not applicable.

18) External IRB Review History

Not applicable.

19) Control of Drugs, Biologics, or Devices

Note: The IDS has its own forms that must be completed and a review process that must be followed before the IDS representative will sign off on Appendix B for submission to the PPHS.

Not applicable.

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