Published in final edited form as:

Contemp Clin Trials. 2015 January ; 40: 218–231. doi:10.1016/j.cct.2014.12.008.

Brain function predictors and outcome of weight loss and weight loss maintenance

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Abstract

Obesity rates are associated with public health consequences and rising health care costs. Weight loss interventions, while effective, do not work for everyone, and weight regain is a significant problem. Eating behavior is influenced by a convergence of processes in the brain, including homeostatic factors and motivational processing that are important contributors to overeating. Initial neuroimaging studies have identified brain regions that respond differently to visual food cues in obese and healthy weight individuals that are positively correlated with reports of hunger in obese participants. While these findings provide mechanisms of overeating, many important questions remain. It is not known whether brain activation patterns change after weight loss, or if they change differentially based on amount of weight lost. Also, little is understood regarding biological processes that contribute to long-term weight maintenance. This study will use neuroimaging in participants while viewing food and non-food images. Functional Magnetic Resonance Imaging will take place before and after completion of a twelve-week weight loss intervention. Obese participants will be followed through a 6-month maintenance period. The study will address three aims: 1. Characterize brain activation underlying food motivation and impulsive behaviors in obese individuals. 2. Identify brain activation changes and predictors of weight loss. 3. Identify brain activation predictors of weight loss maintenance. Findings from this study will

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have implications for understanding mechanisms of obesity, weight loss, and weight maintenance. Results will be significant to public health and could lead to a better understanding of how differences in brain activation relate to obesity.

Keywords

Weight loss; functional Magnetic Resonance Imaging; Obesity

1. Introduction

Overweight (Body Mass Index [BMI] of 25 to 29.9 kg/m²) and obese (BMI of 30 kg/m² or greater) individuals represent approximately 69.2% of adults in the United States [1]. Both overweight and obesity are characterized by the accumulation of excessive levels of body fat and contribute to heart disease, hypertension, diabetes, and some cancers, as well as psychosocial and economic difficulties [2-5]. The cost of treatment for weight reduction is now estimated to exceed 147 billion dollars annually [6]. Reduction in obesity prevalence remains a major aim of Healthy People 2020 [7].

Obesity is a complex medical and behavioral problem that can be impacted by energy balance interventions that reduce energy intake and increase energy expenditure. However, the factors underlying obesity are still poorly understood. On the energy intake side, eating behavior is influenced by a convergence of processes in the brain, including homeostatic factors and motivational processing. Motivational processes is an especially important contributor to overeating in humans [8]. Food is a highly salient reinforcer [9] and its presentation is associated with increased activity in limbic and paralimbic networks in the brain. Abnormal activity in these networks may lead to increased eating behavior. As such, overeating and obesity may be conceptualized as reflecting failures in impulse control that are associated with unique patterns of brain activation to food stimuli. Therefore, the increasing concern surrounding the dramatic rise of obesity has led to research aimed at understanding the neural mechanisms of appetitive function in humans [10-13].

Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies examining neural responses to food stimuli in healthy weight and obese adults have consistently demonstrated that the paralimbic cortical and prefrontal areas support motivation and cognitive control processes [14-16]. These activation studies have utilized two approaches to stimulating response in appetite control regions: 1) Participants are scanned while anticipating and then tasting liquid food after a prolonged fast [17]; or 2) Participants are scanned while viewing pictures of food, after a fasting period and soon after feeding [18-21]. Both approaches have produced similar findings, pointing to changes in activation in brain regions known to play a role in taste, reward, motivation, and regulation and control of behavior [14].

The most consistent findings include activations within healthy weight individuals in studies that compare food images relative to non-food images. Studies with healthy weight individuals implicate brain structures in the paralimbic cortex, including the orbitofrontal cortex (OFC), medial prefrontal cortex (MFC), anterior cingulate cortex (ACC), amygdala,

hippocampal formation, and insula [14, 16, 22-29]. The nucleus accumbens has also been found to be predictive of subsequent food consumption and subsequent weight gain [30, 31].

In obese individuals, as compared to healthy weight individuals, findings suggest that activation in the anterior insula, amygdala, striatum, and OFC occurs in response to the sight of food [14, 16, 32-41]. Increased connectivity between the OFC and accumbens has also been observed [42]. Functional connectivity studies have also suggested that the striatal network, including the occipital lobe and inferior parietal cortex, is engaged when obese individuals observe food stimuli as compared to non-food stimuli. Obese individuals have also displayed decreased functional connectivity between the OFC and the inferior occipital gyrus [43] and decreased activity in the amygdala, lateral and medial PFC, and anterior cingulate has been observed during passive viewing as compared to increased activation during the taste imagination [44]. Increased recruitment of the insula has also been observed when obese individuals passively view food as compared to reappraising food's reward value, which is associated with greater activity in the lateral PFC [39]. Taken together, findings from imaging studies examining brain response to food cues show that obesity is characterized by hyper-responsiveness in regions of the brain typically associated with reward, emotion, and taste processing.

Weight loss has been associated with differential patterns of brain activation in obese individuals [14, 16]. Rosenbaum and colleagues [19] examined the reward system activation in response to visual food cues in individuals that reported successfully losing and maintaining at least 10% of their initial body weight and found that individuals who maintained weight loss showed decreased activation in the ACC, amygdala, precentral gyrus, fusiform gyrus, and hypothalamus. To date, there are very few longitudinal studies that have compared pre- and post-weight loss changes in brain activation. Bruce and colleagues [45] found that, among individuals who lost weight following bariatric surgery, surgery, there was decreased activation in regions of the brain previously implicated in food motivation and reward (e.g., the parahippocampus, medial prefrontal cortex, insula, and inferior frontal gyrus) when viewing food vs non-food pictures following weight loss surgery. Increased activation to food vs nonfood pictures after weight loss was observed in the anterior prefrontal cortex, a region of the brain that has been implicated in cognitive control and inhibition. Murdaugh et al. [46] conducted a small study including 25 obese individuals and found greater pre-weight loss treatment activation to high-calorie food vs. control pictures in brain regions implicated in reward-system processes including the nucleus accumbens, anterior cingulate, and insula. Murdaugh et al also observed similar correlations with weight loss in brain regions implicated by other studies in vision and attention, such as superior occipital cortex, inferior and superior parietal lobule, and prefrontal cortex. Less successful weight maintenance at follow-up was predicted by greater post-treatment activation in insula, ventral tegmental area, putamen, and fusiform gyrus. Thus, successful weight loss has been associated with diminished activation in areas of the brain that process reward, motivation, and taste, as well as with increased activation in areas of the brain known to facilitate cognitive and behavioral control.

Although a variety of literature exists examining the relationship between food and the brain, there still are several limitations. First of all, no well controlled longitudinal trials

have been conducted to evaluate the influence weight loss changes the brain and its activation relative to food cues in overweight and obese adults. In addition, trials have not been conducted to determine if baseline brain activation can be used to predict weight loss post diet. Finally, very little research is available regarding weight maintenance and if brain activation can be used to predict those that will be able to maintain their weight loss as compared to those who do not. The study proposed herein is designed to address these limitations within the present research.

There are three primary aims associated with the proposed investigation. The first aim is to identify differences in brain activation to visual food cues in high and low food motivation states in obese and healthy weight groups. We hypothesize that obese, relative to healthy weight; individuals will show greater activation to food pictures in limbic and paralimbic brain regions, both before and after eating. We also plan to identify behavioral correlates of activation differences to visual food cues in high and low food motivation states in obese and healthy weight groups. We hypothesize that areas of increased activation in limbic and paralimbic brain regions will be significantly correlated with self-report measures of increased food motivation and unrestrained eating behavior in obese participants compared to healthy weight participants. The second aim of the present investigation is to identify activation changes from Baseline to Post Diet sessions in both obese and healthy weight control participants. We hypothesize that individuals who lose more weight will show greater reductions in activation, from the baseline to follow-up, in limbic and paralimbic brain regions in comparison to unsuccessful dieters and healthy weight controls. In addition, we also propose to identify activation patterns at baseline that predict greater weight loss at follow-up. We hypothesize that fMRI activation in limbic and paralimbic regions taken from the Baseline Session scans will be significantly correlated with subsequent weight loss in obese subjects. The third aim of this study is to identify fMRI activation differences from baseline to follow-up between successful weight maintainers (i.e., 7% weight loss) and healthy weight control participants. We hypothesize that individuals who successfully maintain weight loss will show reduced activation in limbic and paralimbic brain regions, in comparison to the other obese groups and healthy weight controls. Finally, we plan to identify activation patterns in follow-up that predict successful weight maintenance. We hypothesize that fMRI measures of activation in limbic and paralimbic regions taken from the follow-up scan will be correlated with weight maintenance and weight regain.

While initial imaging studies have illuminated potential neural mechanisms contributing to overeating, many important questions remain. The studies proposed herein are designed to address important translational issues related to changes in brain activation in weight loss success and what neurobiological processes contribute to the long-term maintenance of weight loss. In addition, it is not clear which brain regions are predictive of initial weight loss or long-term weight maintenance. Findings from this study will have significant implications for understanding mechanisms of obesity, weight loss, and weight maintenance, and may ultimately lead to more effective interventions. For instance, functional neuroimaging may provide “probes” for new interventions designed to specifically change activity in target areas of the brain.

2. Study Overview

We will conduct a 9-month study, 12-week diet followed by a 6-month maintenance period. Functional MRI scans will be completed on obese (baseline BMI 30 to 45 kg/m²) and healthy weight (BMI < 25 kg/m²) participants with a food motivation fMRI paradigm twice: once during a baseline state (baseline session), and once after obese participants have completed a 12-week weight loss intervention (follow-up session). We will then follow obese participants over the course of a six-month maintenance period. All healthy weight controls will be brought back in for the Follow-up Session scan. Healthy weight control participants will not participate in the diet, but weight will be obtained and participants will be excluded if they gain or lose more than 5% of their baseline body weight. Age, sex, and cognitive status (IQ) will be controlled for in all analyses either by including the variables as covariates or creating matched.

3. Materials and methods

3.1 Participants

3.1.1. Obese Group—We will recruit one hundred and two obese individuals that will be assigned to the weight loss group and 35 healthy weight individuals will be assigned the control group. The sample will include at least 50% women and 20% minorities. The following inclusion/exclusion criteria will be used for the obese group: **Inclusion.** 1) Age 21 to 55 years. We have restricted our sample to this age range because we believe that behavioral interventions for weight loss may be different for individuals who are younger or older than this proposed age range. Additionally, individuals above age 55 are likely to have a greater number of medical problems and medication use that could significantly impact the exercise protocol and outcomes. 2) BMI of 30.0 to 45.0 kg/m². We have restricted our sample to this BMI range because individuals with a BMI less than 30.0 kg/m² are not classified as obese and individuals with a BMI > 45.0 kg/m² may require more aggressive weight loss/prevention of weight regain interventions than we have proposed (e.g., surgery, medication, etc.). In addition, individuals with a BMI greater than 45.0 kg/m² may be uncomfortable due to the size limitations of the MRI scanner. 3) Clearance for participation from their primary care physician (PCP) will be obtained via a letter to the PCP that explains the research program and is returned to the investigators. **Exclusion.** 1) Participation in a research project involving weight loss or exercise in the previous 6 months, as these proximal experiences may impact the results of this study. 2) Participation in a regular exercise program (i.e., > 500 kcal/week. of planned activity as estimated by questionnaire [39]). 3) Not weight stable (± 4.5 kg) for 3 months prior to intake as determined from an online initial eligibility questionnaire. 4) Pregnant during the previous 6 months, lactating, or planned pregnancy in the following 15 months. 5) Serious medical risk such as type 1 diabetes, cancer or recent cardiac event (e.g., heart attack, angioplasty, etc.). Medical risk will be determined by a health history questionnaire and physician consent form. 6) Any history of psychiatric diagnosis, any psychoactive medications and history of neurological trauma (e.g., concussion, positive loss of consciousness). 7) Taking medications known to significantly affect weight (gain or loss) (e.g., thyroid, beta blockers). 8) Use medications that affect appetite or cannot exercise (e.g., walk). 9) Exhibit eating disorders (i.e., score >20

on the Eating Attitudes Test; [47]), restraint (i.e., score of >10 on the Eating Inventory Questionnaire [48]), depression (i.e., score >16 on the Center for Epidemiological Studies Depression Scale [49]) or drug addiction (medical history) as these individuals may need treatment beyond the scope of this study. 10) Metabolic disease that would affect energy balance (e.g., diabetes mellitus or hypothyroidism). 11) Adherence to specialized diet regimes, such as multiple food allergies, vegetarian, macrobiotic, etc. 12) Do not have access to grocery shopping and meal preparation (i.e. those in military, college with cafeteria plan, etc.). Approval for this study was obtained from the Human Subjects Committee at the University of Kansas Medical Center-Kansas City.

3.1.2. Healthy Weight Controls—We will recruit 35 healthy weight individuals will be assigned the control group. The sample will include at least 50% women and 20% minorities and the demographics will not significantly differ from the obese. The following inclusion/exclusion criteria will be used for the healthy weight control group: **Inclusion.** 1) Age 21 to 55 years. 2) BMI between 18 and 24.9 kg/m² to serve as controls. **Exclusion.** 1) Participation in a research project involving weight loss or exercise in the previous 6 months, as these proximal experiences may impact the results of this study. 2) Participation in a regular exercise program (i.e., > 500 kcal/week. of planned activity as estimated by questionnaire [39]. 3) Not weight stable (± 4.5 kg) for 3 months prior to intake as determined from an online initial eligibility questionnaire. 4) Pregnant during the previous 6 months, lactating, or planned pregnancy in the following 15 months. 5) Serious medical risk such as type 1 diabetes, cancer or recent cardiac event (e.g., heart attack, angioplasty, etc.). Medical risk will be determined by a health history questionnaire and physician consent form. 6) Any history of psychiatric diagnosis, any psychoactive medications and history of neurological trauma (e.g., concussion, positive loss of consciousness). 7) Taking medications known to significantly affect weight (gain or loss) (e.g., thyroid, beta blockers). 8) Use medications that affect appetite or cannot exercise (e.g., walk). 9) Exhibit eating disorders (i.e., score >20 on the Eating Attitudes Test; [47]), restraint (i.e., score of >27 on the Binge Eating Scale [50]), depression (i.e., score >16 on the Center for Epidemiological Studies Depression Scale [49]) or drug addiction (medical history) as these individuals may need treatment beyond the scope of this study. 10) Metabolic disease that would affect energy balance (e.g., diabetes mellitus or hypothyroidism). 11) Adherence to specialized diet regimes, such as multiple food allergies, vegetarian, macrobiotic, etc.

We have carefully considered the circumstances of the healthy weight controls with respect to diet, exercise and contact. We have chosen to have the healthy weight participants to act as true controls and not change their diet or exercise habits. The healthy weight controls will be free living sedentary individuals eating ad libitum diets but maintaining a normal weight compared to obese individuals who lose weight and attempt to maintain weight using a standard behaviorally based intervention. Therefore, we can determine differences in brain function for individuals who self-regulate their weight compared to individuals who attempt weight loss and maintenance using a standard clinical paradigm. In addition, these individuals will provide an estimate of the effects of paradigm repetition as we expect some effects of repetition when completing the fMRI tasks.

3.2. Intervention: Behavioral weight loss meetings

Sixty minute in-person behaviorally based meetings of 5-15 individuals will be conducted weekly during the 3 month weight loss period (0 to 3 months). During the first 3 months of the maintenance phase, meetings will be held twice per month, followed by once per month for the remaining 3 months of the maintenance phase. All meetings will use behavioral strategies based on Social Cognitive Theory (SCT) to promote change in both diet and exercise [51, 52]. The following components of SCT will be employed: goal setting, self-monitoring, self-efficacy, manipulation of the environment to promote behavioral change, and reflection on outcome expectations and outcome value. Meetings will begin with a check-in question designed to identify barriers to diet and exercise and to allow the group to work together to identify solutions which promotes group cohesion and social support. Weekly homework assignments are designed to increase self-efficacy for both diet and exercise and to provide practice of behavioral skills. For example, participants will be asked to identify items at the grocery store that meet calorie, fat, or fiber content consistent with a healthy diet. This learning experience improves confidence in the ability to identify food items to promote weight loss and prevent weight regain. A description of clinic topics that will be incorporated into the intervention is presented in Table 1.

3.2.1. Intervention: Weight loss diet (0-3 months)—Energy Intake will be reduced to ~1,200 to 1,500 kcal/day using a combination of commercially available portion controlled meals (PCM's), fruits and vegetables, low calorie shakes, and non-caloric beverages. Participants are provided with a list of selected PCM's provided by Health Management Resources, fruits and vegetables, shakes, and non-caloric beverages that are acceptable. Participants will consume a daily minimum of 2 entrees (180 to 270 kcals each), at least 5 servings of fruits and/or vegetables, and 3 shakes (~100 kcal each). Non-caloric beverages such as diet soda, coffee, etc. will be allowed ad libitum. When combined with a variety of fruits and vegetables, PCM's (entrees + shakes) provide a diet with all necessary nutrients specified by the Dietary Reference Intakes [53]. The weight loss and weight regain prevention diets for this study will be based on 25+ years of investigator experience with weight management [54-58]. Participants reaching a BMI of 22 kg/m² during weight loss will be transitioned to the prevention of weight regain diet described below; however, in our experience, this is an infrequent occurrence

3.2.2. Intervention: Weight maintenance diet (3 – 9 months)—We recognize there are numerous approaches to the prescription of energy intake for the prevention of weight regain. Following weight loss we will recommend a daily energy intake of estimated resting metabolic rate * 1.2 to account for activities of daily living [59]. This energy intake recommendation theoretically results in a negative energy balance in all groups when exercise energy expenditure is considered. However, we anticipate compensatory changes in components of energy balance such as increased energy intake and/or decreased daily PA (both of which are measured in this trial) as the literature indicates most individuals regain weight subsequent to weight loss [60-65]. Thus, we believe our approach will maximize the potential to prevent weight regain and provides a reasonable compromise between scientific rigor, practicality, and generalizability.

During the weight maintenance phase, participants will receive a meal plan with suggested servings of grains, proteins, fruits, vegetables, dairy, and fats, based on their energy requirements and the USDA's 2005 "My Pyramid" (www.mypyramid.gov). Participants will be encouraged (not required) to continue consuming a minimum of 14 PCM's (entrees or shakes) and a minimum of 35 servings of fruits and vegetables per week. They will be provided with a list of low calorie PCM's and shakes available at local supermarkets or may purchase the HMR PCM's and shakes provided during the weight loss phase from the study coordinator.

3.2.3. Use of portioned controlled meals (PCM's)—We are proposing to use PCM's to promote weight loss and to encourage weight maintenance for a number of reasons. PCM's are emerging as a state-of-the-art treatment and appear to promote greater weight loss and maintenance compared to meal plans of identical energy levels [66]. PCM's provide individuals with a fixed quantity of food with known energy content and have a number of potential advantages for individuals trying to manage their weight. They eliminate the need to weigh and measure foods, save time in planning and preparing meals, provide built-in portion control and energy reduction, and reduce contact with energy dense foods [67, 68]. PCM's are just as convenient as take-out or fast food as they are now widely available in grocery stores, convenience stores, delivery services, etc, and can be transported easily from home to work. PCM's come in a large variety of liquids and solid foods, many of which are shelf stable, and in most cases all can be enhanced with additional flavors, extracts, fruits and vegetables, etc., to create even more variety and volume in the diet. In addition, PCM's have the potential to be used indefinitely as part of a weight management strategy, as they are nothing more than prepackaged food and therefore carry no risk of adverse side effects. We provide extensive dietary counseling to the participants to help ensure meal plans incorporate all food groups and meet all nutrient requirements.

3.2.4. Intervention: Interventionist training—Health educators have backgrounds in nutrition, exercise physiology, or psychology with a minimum of two years of experience in weight management. Health educators receive ongoing training which includes weekly staff meetings where lessons are discussed and presentations are critiqued, monthly one-on-one training with program coordinators who observe and listen to ongoing classes and provide suggestions for improvement, and attendance at professional meetings and seminars throughout the year to improve teaching skills and to remain current with the latest weight management research.

3.4. Strategies for participant retention

We will obtain participant contact information to include name, address, telephone numbers, and email. Participants who miss class will be contacted by their health educator following the absence. Participants that miss more than 3 consecutive class sessions will be contacted by contact attempts, no further attempts will be made during the intervention period. However, participants will be contacted to encourage completion of the end-study outcome assessments. Staff training will focus on relationship building between participants and the intervention team. Weekly project meetings with the principal the study coordinator. After a maximum of 3 unsuccessful investigator and the intervention team will problem solve any

participant retention issues that may arise. We will use behavioral contracts during recruitment and after the intervention has begun to support our retention efforts and to determine the understanding of participants regarding the requirements for study participation. These strategies resulted in a loss to follow-up of 22% in our recently completed trial comparing the effectiveness of phone with face-to-face behavioral clinics for weight management [69].

3.5. Routine clinic data reports from group meetings

Groups will report the number of PCM's consumed, the number of fruits and vegetables consumed, minutes of PA completed, and number of steps as recorded on step counters according to their meeting schedule (weekly, biweekly, monthly). Participants will weigh on a scale at the clinic site at each clinic meeting. These weights are intended to monitor progress only and are not the weights we will use for outcome data. Changes in medications and adverse events will be reported privately to the health educator at clinic meetings. Between meetings, we will gather the same information except weight via toll free phone, fax, or email. The data gathered between meetings occurs at approximately the mid-point. For example, if we are meeting weekly, it will be mid-week, if bi-weekly it will be the non-meeting week, if monthly it will be at the 2 week interval, etc. This also provides contact between the participant and health educator between clinic meetings.

3.6. Physical activity

We plan to target 300 min/wk of moderately vigorous PA using a progressive protocol (see Table successful weight loss and maintenance 2). We will target 300 min/wk since it has been associated with [70, 71]. All exercise will be unsupervised. Participants will achieve the targeted amount of 300 min/wk within the first 6 weeks by beginning with a daily 15-minute session and then adding an additional 10 min/day each week for the next 5 weeks. For the proposed investigation, the targeted PA amount will then be held steady for the remainder of the study. In addition to minutes reported, physical activity will also be estimated by pedometer step counts and by written record provided by the participant at each clinic meeting and data collection period. Step counts are used to reinforce and measure lifestyle physical activity (unplanned or unstructured activity and/or activities of daily living).

3.7. Physiological outcome assessments

The fMRI appointment will be scheduled for 4 or 5 hours in length and counterbalanced so each participant has a long and a short session. During the appointment, participants' will complete a safety screening (including urine pregnancy test for females) an IQ estimate (WASI, ~30 mins), questionnaires (~30 mins), two 1-hour MRI scan, a meal (~30mins) and anthropometric assessments/blood pressure (~30 mins, See section 3.8.2.). During the short session participants will complete the first fMRI (pre-meal), eat a small meal, and complete the second fMRI (post-meal), and then complete all remaining testing. During the longer session, participants will eat a small meal, complete the post-meal fMRI, and then wait 4-hours before completing the fasted-fMRI (pre-meal); during the 4 hours all other testing will be completed.

3.7.1. Anthropometrics (Body weight, height, BMI, and waist circumference)—

Body weight will be recorded at baseline, 3, 6, and 9 months using a digital scale accurate to + 0.1 kg (Befour Inc Model #PS6600, Saukville, WI). All participants will be weighed after arriving for MRI appointments, at least 4-hours fasted. Participants will be weighed in standard hospital scrubs after attempting to void. Subsequently, height will be measured using a stadiometer (Model PE-WM-60-84, Perspective Enterprises, Portage MI) and body mass index (kg/m^2) will be calculated. Waist circumference, a surrogate measure for abdominal adiposity, will be obtained using the procedures of Lohman et al (1988).

3.7.2. Blood pressure—

Blood pressure will be measured at baseline, 3, 6, and 9 months. Blood pressure will be measured just after measurement of weight and height using an electronic sphygmomanometer (Magnitude 3150 MRI Vital Signs Monitor, Invivo Corporation, Gainesville, FL). The participant will be seated for a minimum of 5 min in an isolated room with the arm bared, supported, and positioned at the heart level. A cuff will be selected based on measurement of the length and circumference of the arm [72]. Systolic and diastolic pressures will be recorded [73]. Two measures will be averaged and additional measures will be obtained if the measures differ by more than 5 mmHG [74, 75]. The collection of both the anthropometric assessments and blood pressure will take approximately 20-30 minutes at each time point.

3.7.3. Energy intake—

Energy intake will be assessed by 3-day food records (2 week days/1 weekend day) at baseline, 3, 6, and 9 months, prior to reporting to the laboratory for anthropometric assessments. Participants will be given verbal instructions and provided with written instructions titled “How to complete your food record” to improve record keeping. Food records will be reviewed by a registered dietitian during the laboratory visit to clarify any ambiguities. Data from the 3-day food records will be entered in the Nutrition Data System for Research (NDSR, version 2012, University of Minnesota) for calculation of energy and macronutrient content.

3.7.4. Dietary staff training and quality control—

All staff will complete standardized training for 3-day food records and NDS-R coding, prior to the beginning of data collection. After initial training, all dietary assessment staff will be required to complete ten 3-day food records obtained from non-study subjects and enter this data directly into NDS-R. The recalls will be evaluated according to a published dietary recall documentation checklist [76]. An error rate of less than 5% on this checklist and on NDS-R coding will be required before interviewers will be allowed to collect and process dietary recall data. During the study, all dietary recalls will be evaluated by our study dietitian using the recall documentation checklist before entry into the study database. Any recall with greater than 5% error will be eliminated and another recall obtained. Study staff demonstrating an error rate of 5% or greater for either energy intake or macronutrient composition will be required to obtain further training and repeat assessment of accuracy described previously. Staff not meeting our criteria for accuracy at any time during the study following 3 attempts will not be permitted to collect or process dietary data.

3.7.5 Process measures: Diet and physical activity—Process data will be collected to assess the fidelity of both the dietary and exercise components of the intervention. Health educators will track the number of PCM's consumed, fruit and vegetable intake, minutes of PA and steps taken per week, attendance at clinic meetings, and the number of reported midweek checks completed.

3.7.6. Medical management—Signed clearance from a licensed physician will be required prior to participation for all overweight and obese participants only. Additionally, all individuals must qualify based on their health history reported at baseline.

3.7.7. Outcome Measures for healthy weight Individuals—Outcomes for weight, height, BMI, waist circumference, blood pressure, and estimation of energy intake will be obtained in identical fashion as obese participants. Additionally, routine physical activity will be obtained at baseline, 3, 6, and 9 months using the Stanford Physical Activity Recall. Other process measures outlined above for the obese participants, such as steps or weekly records of physical activity, that are collected at clinic meetings will not be collected for the healthy weight group as they do not participate in these aspects of the study.

3.8. fMRI outcome assessments

3.8.1 Image acquisition—Scanning will be performed on a 3 Tesla head-only Siemens Allegra scanner (Siemens, Erlangen, Germany) fitted with a quadrature head coil. Participants' heads will be immobilized with cushions. Following automated scout image acquisition and shimming procedures performed to optimize field homogeneity, a structural scan will be completed. T1-weighted anatomic images will be acquired with a 3D MPRAGE sequence (TR/TE = 2300/3.06 ms, flip angle = 8°, FOV = 192 × 100 mm, matrix = 192 × 192, slice thickness = 1 mm). This scan will be used for slice localization for the functional scans, Talairach transformation, and co-registration with fMRI data. Following structural scans, three gradient echo blood oxygen level dependent (BOLD) scans will be acquired in 43 contiguous oblique axial slices at a 40° angle (repetition time/echo time [TR/TE] = 3000/30 ms, flip angle = 90°, field of view [FOV] = 220 mm, matrix = 64 × 64, slice thickness = 3 mm, 0.5 mm skip, in-plane resolution = 3 × 3 mm, 130 data points). To ensure head positioning is similar for healthy weight and OB participants, and to optimize BOLD signal in the ventral and medial portions of the frontal cortex, participants will be positioned in the scanner so that the angle of the anterior commissure-posterior commissure (AC-PC) plane is between 17° and 22° in scanner coordinate space, verified with a localization scan.

3.8.2. fMRI food motivation paradigm—Participants will view pictures of food, animals, and blurred low-level baseline images during two scanning sessions: 1) after fasting for four hours (pre-meal) and 2) immediately following a small uniform meal (post-meal) that is standardized for energy [Kcal = 500] and macronutrient content (e.g., a weighed lean meat [turkey, ham, roast beef or tuna] sandwich, carrot or celery sticks, ranch dressing, a piece of fruit, and skim milk). Previous studies examining the effect of satiation on brain activity have included a longer fasting period, typically 8 hours, and utilized meals designed to fully sate participants [18, 77]. For the purpose of this study, our goal was to design a paradigm that accurately reflects typical daily hunger and eating cycles. Accordingly, our

paradigm implements a 4-hour fast and a standardized meal to provide approximately 500 Kcal. The order of sessions (pre-meal, post-meal) is counterbalanced across subjects so that approximately half the group starts with the pre-meal session and half starts with the post-meal session. All participants will complete the fMRI task during the late morning through late afternoon; all meals will be consumed between 10:20 AM and 3:15 PM.

Food and animal images were obtained from professional stock photography and matched on brightness, resolution, and size. Our paradigm uses pictures of live animals as control stimuli, rather than tools, as used by LaBar et al.[18], in order to control for general interest and visual richness. In a pilot study of separate subjects ($n = 35$), 300 food and 300 animal images were rated for how appetizing, exciting (arousal), and pleasant (valence) they were using Lang et al. [78] methodology. The food and animal images did not differ with regard to valence ($F = 0.351$, $p = 0.55$) or arousal ($F = 0.002$, $p = 0.96$). The food images were rated significantly more appetizing than the animal images ($F = 9604.06$, $p < 0.001$). In addition, the food and animal images were blurred, so that the objects are not identifiable, by applying the fast Fourier transformation (FFT), removing the phase information, and then applying the inverse FFT in MATLAB (The MathWorks Inc., Natick, MA) program. Blurred objects are included as a low-level baseline comparison. All images are presented one time only to each subject. The paradigm is illustrated in Figure 1.

Participants will passively view the images during the first two BOLD sequences of each session. Each functional scan involves three repetitions of each block of each stimulus condition type (i.e., food, animal), alternated between blocks of blurred images. Within each of the two functional scans, 13 blocks of stimuli are presented; each block consists of 10 images. Visual stimuli will be presented via a back-projection system. Stimulus presentation time is 2.5 seconds, with an interstimulus interval (ISI) of 0.5 seconds. The order of category presentation will be counterbalanced across subjects. Participants will be instructed to remember as many food and animal images as they can while in the scanner.

Memory will be tested following the scanning session. From each of the food and animal groups, 50% of the images used in the scanning session (30 images) will be presented for recall (old) and interspersed with 15 novel distracter images from the same category (new). Participants will complete the computerized recognition memory task outside the scanner, immediately following each scanning session.

3.8.3. Resting state image acquisition—Following the functional paradigm, all participants will complete a resting state scan (third BOLD sequence). During this time, participants will be asked to close their eyes and keep their head still. The purpose of this scan is to examine resting state, default mode network functional connectivity in obese and healthy weight participants, as well as changes in functional connectivity associated with the diet intervention. Image acquisition will occur under the same parameters as the food motivation task.

3.9. Self-report scales

In addition to the physiological assessments and fMRI outcomes, we will also collect several self-report and behavioral measures of eating behavior, depression, hunger, impulsiveness,

self-efficacy, conscientiousness, emotional regulation, mood intelligence, sleep, IQ, and executive control. All self-report and behavioral measures will be completed at baseline and 3 months; the order of the measures was counterbalanced between subjects. For the testing sessions where subjects scanned pre-meal, ate, then scanned post-meal the scales were given following the post-meal scan. During testing sessions where subjects ate, had a post-meal scan then waited 4hrs for a pre-meal scan the scales were administered between scans. The testing session were counterbalanced between subjects, so each subject would have each format once.

3.9.1. Three-factor eating inventory—The Three-Factor Eating Inventory is the most commonly used measure of eating behavior and measures dietary restraint (conscious effort to restrict food intake; 20 items), disinhibition (degree of interference with controlled eating from emotional and situational influences; 16 items), and hunger (perceptions of hunger and its relationship to overeating; 15 items). These three factors are known to change with successful weight loss treatment, i.e. restraint increases and disinhibition and hunger decrease [48, 79]. In addition, these 3 factors of eating behavior predict weight loss maintenance, and they prospectively distinguish those who regain previously lost weight versus those who maintain weight over a 12-month period [80].

3.9.2. Eating behavior inventory—The Eating Behavior Inventory (EBI) measures frequency (5-point scale from ‘never’ to ‘always’) of 26 eating and self-regulation behaviors that are implicated in behavioral weight control treatment. It includes behaviors that are both adaptive (“If I’m served too much, I leave food on my plate” and “I weigh myself daily”) and maladaptive (“I snack after supper” and “I shop when I’m hungry”). The Eating Behavior inventory scores have been shown to significantly improve with behavioral weight loss treatment [81, 82].

3.9.3. Center for epidemiologic studies – Depression scale—The Center for Epidemiologic Studies – Depression Scale (CES-D; [49]) is a 20-item self-report measure assessment of depressive symptoms in the general population. Responses are on a 4-point scale ranging from 0=‘rarely or none of the time (<1 day)’ to 3=‘most or all of the time (5-7 days)’.

3.9.4. Visual analog hunger scale—Visual Analog Scales will be administered based on the methods of Burley et al [83] immediately prior to each MRI scan (pre-meal and post-meal scans). Visual analog scales are a 100 mm scale with the words “Not at all” anchored to the left-hand side and “Extremely” anchored to the right-hand side. Each scale includes one of the following questions, “How hungry do you feel right now?”, “How thirsty do you feel right now?”, “How full do you feel right now?”, “How nauseated do you feel right now?”, “How much stomach discomfort do you feel right now?”, “How sick do you feel right now?”, “How appetizing did you find your meal?” (post-meal condition only), and “What is your energy level right now?”. Participants placed a vertical line along the scale continuum that best described their perceived feelings. The 100 mm VAS is similar to a Likert-type scale in that each 10 mm is equivalent to an index of 1, thus each question is scored on a range from 1 to 10 for a total score ranging from 1 to 100.

3.9.5. Barratt impulsiveness scale—The Barratt Impulsiveness Scale (BIS-11; [84]) is a 30-item self-report questionnaire measuring general impulsiveness. Participants respond to possible ways of thinking and acting in different situations, using a 4-point scale from ‘rarely/never’ to ‘almost always/always.’

3.9.6. Delay discounting—The delay discounting task asks participants to choose between hypothetical immediate smaller and delayed larger rewards. Immediate reward values range from \$0.10 to \$105 and delayed rewards of \$100 are available after a delay of 0, 7, 30, 90, 180, 365, or 1825 days. All immediate reward values will be paired with all delay periods and randomized [85-87]. This task is administered via E-Prime (Psychology Software Tools, Inc., Sharpsburg, PA) and takes approximately 20 minutes to complete.

3.9.7. Exercise self-efficacy—The Exercise Self-Efficacy Questionnaire is a 5-item questionnaire used to assess an individual's confidence (‘not at all confident’ to ‘very confident’) in his or her ability to participate in regular exercise [88].

3.9.8. Weight efficacy life-style questionnaire—The Weight Efficacy Life-style Questionnaire (WEL; [89]) is a 20-item self-report questionnaire used to assess an individual's confidence (‘not at all confident’ to ‘very confident’) in his or her ability to control eating behavior in various situations.

3.9.9. Conscientiousness scale—The Conscientiousness Scale [90] is a self-report questionnaire used to measure an individual's conscientiousness based on multiple factors. We will use a 12-item, three-factor (self-control, industriousness, and responsibility) version. Responses are on a 4-point scale (‘disagree’ to ‘agree’).

3.9.11. Emotion amplification and reduction scales—The Emotion Amplification and Reduction Scales (TEARS; [91]) is an 18-item self-report index of an individual's emotion regulation ability through amplification and/or reduction of emotions. This valence-ambiguous measure has demonstrated high internal consistency and criterion validity in preliminary studies. Responses are on a 4-point rating scale (1=‘not at all true of me’ to 4=‘very true for me’).

3.9.12. Behavioral inhibition scale/behavioral activation scale—The Behavioral Inhibition Scale/Behavioral Activation Scale (BIS/BAS; [92]) is a 24-item self-report questionnaire measuring individual differences in the tendency to move toward something desired and/or move away from something unpleasant. Responses are on a 4-point scale from ‘very true for me’ to ‘very false for me’.

3.9.13. Affect intensity measure—The Affect Intensity Measure (AIM; [93]) is a 40-item self-report questionnaire designed to measure the depth and intensity of an individual's emotional experience. Items are rated on a scale (1=‘never’ to 6=‘always’) based on the frequency of which a behavior or experience occurs.

3.9.14. Pittsburgh sleep quality index—The Pittsburgh Sleep Quality Index (PSQI; [94]) is a 24-item self-report questionnaire designed to measure subjective sleep quality,

sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The first 23 items are rated on a 4-point scale (0='not during the past month' to 3='three or more times a week'). The last item, related to sleep quality, is rated on a 4-point scale from 0='very good' to 3='very bad.'

3.9.15. Response styles questionnaire—The Response Styles Questionnaire (RSQ; [95]) is a 32-item self-report assessment of people's cognitive and behavioral responses to sad or depressed mood. Participants are instructed to select from a list of thoughts and behaviors the ones that generally apply to them when they are in a sad or depressed mood.

3.9.16. Wechsler abbreviated scale of intelligence (WASI) vocabulary and matrix reasoning—The Wechsler Abbreviated Scale of Intelligence (WASI) Vocabulary and Matrix Reasoning subtests will be administered to verify that analyses can control for general intelligence [96].

Wechsler Test of Adult Reading (WTAR) is a measure of reading ability that can be used to estimate intellectual abilities. Participants are asked to read a series of increasingly difficulty words. It takes approximately 2 minutes to complete the test [96].

3.9.17. Stroop test—The Stroop Test is a measure of speed information processing and response inhibition [97]. A series of colored XXX and color words printed in black are presented on a computer screen. Participants are asked to either say the color or read the word as quickly as possible; in the final task the color words are printed in different colors and subjects are instructed to say the color of the text, not read the word. It takes approximately 4 minutes to complete this test.

3.10. Data management

Data will be categorized and entered into separate tables within a secure Access or Excel database. This trial is a multisite trial and at this time the two sites do not support the same data support systems (i.e., PC vs Mac iOS). For example, process variables will be kept in one table, while body weights will be in another table, blood pressure another table, etc., all linked by participant number. In addition, subjects' fMRI data will be identified only by number. Ten percent of the data will be double entered utilizing two separate databases and separate data entry personnel. At logical time points, the data will be checked for outliers and normalcy. Questionable data (e.g. >3 standard deviations from the mean) will be re-checked for accuracy and re-entered if necessary.

4. Analysis plan and power

The planned data analyses are built around the study aims. The first aim is to further characterize brain activation underlying increased food motivation and impulsive eating in obese individuals.

4.1.1. Aim 1.1

The goal of Aim 1.1 is to identify differences in brain activation to visual food cues in high and low food motivation states in obese and healthy weight groups. We hypothesize that the

obese group will show greater activation, compared to the healthy weight group, to food pictures in limbic and paralimbic brain regions, both before and after eating. Hypotheses will be tested in Group (Obese, healthy weight) x Stimulus (Food, Non-food) repeated measures ANOVA, separately in the Pre-Meal and Post-Meal condition. We expect to find a significant Group x Stimulus interaction in both conditions, as described in our preliminary study. *A priori* regions include the amygdala, hippocampal formation, OFC, MFC, ACC, and insular cortex.

4.1.2. Aim 1.2

In Aim 1.2 we plan to identify behavioral correlates of activation differences to visual food cues in high and low food motivation states in obese and healthy weight groups. We hypothesize that areas of increased activation in limbic and paralimbic brain regions will be significantly correlated with self-report measures of increased food motivation and unrestrained eating behavior in obese participants compared to healthy weight participants. We will compute Spearman's correlations between % signal change (Food vs. Baseline) in the maximum voxel of the six *a priori* ROIs, bilaterally, and EI, Hunger, Disinhibition, and Restraint scores, total score of the EBI, and visual analog ratings of hunger and satiation.

4.2.1. Aim 2.1

In Aim 2.1 we plan to identify activation changes from baseline to follow-up sessions in obese and healthy weight control participants. We hypothesize that greater % weight loss will be associated with greater reductions in activation, from the baseline to follow-up sessions, in limbic and paralimbic brain regions in comparison to those who lose less weight and the healthy weight controls. Hypotheses will be tested in Session (Baseline, Follow-Up) x Stimulus (Food, Non-food) repeated measures ANOVA, separately in the three groups (individuals that lose less than 7%, greater than 7% and healthy weight). We will first inspect activation maps with thresholds set at $p < .01$ (corrected for multiple comparisons). We will follow-up with ROI analyses in the six *a priori* regions, bilaterally by calculating % signal change (Food vs. Baseline Images), for each group and session, in the maximum voxel and computing the reductions in activation (% signal change at follow-up session minus % signal change at Baseline). The reductions in activation of the 2 obese and 1 healthy control groups will be compared by ANOVA for each ROI. We expect to find significantly greater reductions in activation among successful dieters than those in the other two groups. In addition to ROI analysis, we will also perform whole brain analysis. Considering potential outliers in measures of % weight loss and/or brain activation, we perform whole brain voxelwise robust regression, with Huber's weight function, using % weight loss as the dependent variable and brain activation as the predictor variable. Standard errors are determined by nonparametric bootstrap with 500 samples. Results are masked to *a priori* limbic and paralimbic regions of interest. In order to address the issue of multiple comparisons, significance is determined by a minimum cluster threshold of 8 voxels (216 mm³), uncorrected $p < 0.0001$.

4.2.2. Aim 2.2

The goal of Aim 2.2 is to identify activation patterns in the baseline session that predict successful weight loss. We hypothesize that fMRI measures of activation in limbic and paralimbic regions taken from the baseline session scans will be significantly correlated with subsequent weight loss in obese subjects. The primary outcome measure (dependent variable) for this specific aim is % weight loss between study entry and exit from the 12-week diet, across all obese participants in the Baseline Session. Brain regions with baseline brain activation correlated with weight loss will be identified by robust regression as described in Section 4.2.1, Aim 2.1.

4.3.1. Aim 3.1

In Aim 3.1 we plan to identify fMRI activation differences from baseline to follow-up between successful weight maintainers and healthy weight control participants. We hypothesize that individuals who successfully maintain weight loss will show reduced activation in limbic and paralimbic brain regions, in comparison to those who regain and with healthy weight controls. Hypotheses will be tested in Session (Baseline, Post-Diet) x Stimulus (Food, Non-food) repeated measures ANOVA, separately in the 3 groups. We will first inspect activation maps with thresholds set at corrected $p < .01$ to identify group differences. We will follow-up with ROI analyses in six bilateral *a priori* regions by computing the reductions in activation (% signal change at Post-Diet session minus % signal change at Baseline session) and comparing the reductions in activation of the 2 obese and 1 healthy control groups by ANOVA for each ROI. We expect to find significantly greater reductions in activation among successful dieters who maintain weight loss than those in the other two obese and the healthy weight groups. As in Aim 2.1, we will also perform whole brain analysis using robust regression analysis as detailed in 4.2.1, Aim 2.1.

4.3.2: Aim 3.2

In Aim 3.2 we plan to identify activation patterns in the Post-Diet Session that predict successful weight maintenance. We hypothesize that fMRI measures of activation in limbic and paralimbic regions taken from the Post-Diet Scan will be correlated with weight maintenance and weight regain. The primary outcome measure (dependent variable) for this specific aim is % weight regain between diet completion and the end of the 6 month follow-up, across all obese participants in the Post-Diet session. Again, robust regression as described in Section 4.2.1, Aim 2.1 will be applied to identify activation patterns in the Post-Diet Session that correlate with weight maintenance.

4.4 Secondary data analyses

The primary data analyses focus on the imaging data. However, clinical data are also collected (described above). Body weight will be used to form the primary outcome variables in the obese group of % weight loss and % weight regain. Other outcome measures, including BMI and waist circumference, will be examined as potential covariates in secondary data analyses. Measures of treatment compliance, such as PA, dietary intake, estimated energy expenditure, and steps counted may also be used in secondary analyses. We will also use the visual analog scales for the same purpose. Other questionnaire data will

be used to aid in exploratory analyses as well as analyses to determine mediators and moderators associated with weight loss, weight management and brain function. Resting state data will be collected and retained for exploratory analyses.

4.5. Power analysis

The study is designed to ensure at least 20 subjects in each cell at the final time point, based on a conservative attrition allowance of 25%. Effect sizes are difficult to measure in whole brain analyses using standard imaging software. However, published estimates of sample size for fMRI experiments with a conservative random effect model, indicate that 80% power can be achieved using a threshold of .05 with approximately 10 subjects, or .002 with approximately 20 subjects [98]. Based on Savage and colleagues [99] random effects analysis, we were able to conduct a power analysis for the ROI analyses in Aims 2.1 and 3.1. For Aim 2.1, the target total of 80 participants (40 successful dieters, 20 unsuccessful dieters, and 20 healthy controls) will provide 80% power to detect an effect size (defined as the ratio of between- to within-group variances) of 0.125; for Aim 3.1, 20 participants for each of the four groups will provide 80% power to detect an effect size of 0.143. Considering a conservative 25% attrition rate, we propose to recruit 80 obese and 27 healthy weighted subjects to achieve 60 and 20 subjects in the obese and healthy weight groups, respectively, at the final outcome points.

4.6. Anticipated problems/challenges and limitations

We have considered several potential problems and challenges.

Potential negative results for longitudinal arm of the study—We do not have longitudinal fMRI data to establish the outcome of diet and weight maintenance on brain function. However, the outcome of the post-diet analyses will be of interest regardless of outcome, whether brain function changes or not. Either outcome answers an important scientific question and we have adequate statistical power ($n=60$) to prove a negative result.

Other potential diet interventions—There are many potential choices that might result in significant weight loss. We chose a diet plan with which we have a history of success and necessary data to generate realistic expected outcomes. Additionally, it is a diet that is frequently used in other studies and, thus, provides comparisons.

Limitations—There are several limitations to the current study design that should be noted. 1) Lack of a third and final fMRI scan. Although this scan would be useful as part of the study design, the budget provided will only support two. In addition, the goal of the study is to examine brain changes during the diet intervention and how these changes were related to weight change/maintenance up to 9 months. Therefore a third scan was deemed unnecessary, but would improve the study design. 2) Resting data will be collected with eyes closed. This is being recognized as a limitation as data using both eyes open and it is currently unclear which approach is the “best”. 3) Due to the design of this study (i.e., fMRI), the exclusion criteria for the study was very broad and did exclude many patients that could benefit from weight loss. The primary reason for this was participant safety as

contradictory conditions, medications, metal implants, etc. could cause problems in the MRI.

5. Conclusion

Dietary interventions, while generally effective, do not work for everyone, and weight regain is a significant problem. The goals of the present investigation are to address the issue that there are currently no well controlled longitudinal trials to evaluate how weight loss changes the brain and its activation relative to food cues in obese adults. This proposed study will also be used to determine if baseline brain activation can be used to predict weight loss post diet and if brain activation can be used to predict those that will be able to maintain their weight loss as compared to those who do not. Findings from this study will have significant implications for understanding mechanisms of obesity, weight loss, and weight maintenance, and may ultimately lead to more effective interventions. Results of this work are highly significant for public health and could lead to a better understanding of how differences in brain activation relate to obesity.

Acknowledgements

The Hoglund Brain Imaging Center is supported by a generous gift from Forrest and Sally Hoglund and funding from the National Institutes of Health (UL1 TR000001). The authors would also like to thank Health Management Resources for their continued support. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

Funding: National Institutes of Health (R01-DK080090)

NCT registration: NCT02031848

Abbreviations

ACC	Anterior cingulate cortex
BMI	Body Mass Index
EBL	Energy Balance Laboratory
EBI	Eating Behavior Inventory
fMRI	Functional magnetic resonance imaging
MFC	Medial prefrontal cortex
NDS-R	Nutrition Data Systems for Research
OFC	Orbitofrontal cortex
PA	Physical activity
PET	Positron emission tomography
PCM's	Portion controlled meals
PWS	Prader-Willi Syndrome
rCBF	Regional Cerebral Blood Flow

ROI	Region of Interest
SCT	Social Cognitive Theory

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Figure 1.
Illustration of the blocked design fMRI paradigm, with a sample image for each condition.

Table 1

Behavioral Strategies: Incorporation of social cognitive constructs into the proposed intervention.

Behavioral Strategy	Operationalizing the Behavioral Strategy within the Intervention
Behavior Shaping	Participants will be taught to gradually modify their eating and physical activity behaviors according to the recommendations presented to them. Progressive plans for physical activity will be provided as well as structured meal plans that participants develop on their own with the guidance of their health educator.
Goal-Setting	Participants will be given weight loss goals of 5% of baseline body weight at month 3 and maintenance of the lost weight at months 9. Health educators and lesson materials focus on helping participants set and achieve appropriate behavioral goals (e.g., eating and physical activity) that ultimately affect weight loss and weight maintenance. Since weight maintenance is a dynamic, ever-changing process, it is expected that behavior goals will be updated and modified throughout the process in order to sustain weight maintenance.
Self-Monitoring	Self-monitoring is a quintessential skill in self-regulation. Participants will monitor eating (by reporting weekly consumption of fruits/vegetables and completing 3-day dietary records), physical activity (by reporting weekly exercise minutes, calories expended through exercise, and pedometer steps) and weight (by weekly weigh-ins and reporting weight change to the class). Self-monitoring will also be used as a tool to identify barriers.
Feedback and Reinforcement	Participants receive weekly feedback related to achievement of weight loss, physical activity, and eating behavior goals. Feedback includes reinforcement and concrete strategies for overcoming barriers.
Social/Peer Support	The in-person sessions will provide opportunities for social/peer support and modeling, as much of the discussion is designed so participants can share strategies and “teach” each other. Participants are also allowed to exchange email addresses and phone numbers for outside class correspondence.
Stimulus Control	Behavioral strategies are provided to decrease environmental cues for less desirable behaviors and to increase the environmental cues for healthy eating and physical activity.
Cognitive Strategies	Cognitive strategies recognizing and countering negative thoughts with role-playing opportunities to build skills. Examples include dealing with social relationships affected by weight, identifying/confronting self-sabotage attempts, and responding to stress with non-food techniques.
Relapse Prevention Strategies	Based on Marlatt and Gordon's relapse prevention model, participants are taught to recognize precursors and consequences of lapses, and develop a plan for addressing high risk situations.

Table 2

Physical Activity Progressive Protocol

WEEK	DURATION	INTENSITY	FREQ.	Total min/wk	Step Goal using Step Counter
Week 1	15 min	Moderate	5 day/wk	75 min/wk	10,000 Steps
Week 2	25 min	Moderate	5 day/wk	125min/wk	10,000 + Steps
Week 3	35 min	Moderate	5 day/wk	175 min/wk	10,000 + Steps
Week 4	45 min	Moderate	5 day/wk	225 min/wk	10,000 + Steps
Week 5	55 min	Moderate	5 day/wk	275 min/wk	10,000 + Steps
Week 6	60 min	Moderate	5 day/wk	300 min/wk	10,000 + Steps
Week 7	60 min +	Moderate to Vigorous	5 – 7 day/wk	300 min/wk +	10,000 + Steps
Week 8	60 min +	Moderate to Vigorous	5 – 7 day/wk	300 min/wk +	10,000 + Steps
Week 9	60 min +	Moderate to Vigorous	5 – 7 day/wk	300 min/wk +	10,000 + Steps
Week 10	60 min +	Moderate to Vigorous	5 – 7 day/wk	300 min/wk +	10,000 + Steps
Week 11	60 min +	Moderate to Vigorous	5 – 7 day/wk	300 min/wk +	10,000 + Steps
Week 12	60 min +	Moderate to Vigorous	5 – 7 day/wk	300 min/wk +	10,000 + Steps

Participants are taught that duration, frequency and intensity are inversely related and can be manipulated in order to achieve 300 min/wk goal on a schedule that fits their lifestyle and personal preference.

Table 3

Outcome assessment schedule

	Time Points			
Variable	0 months	3 months	6 months	9 months
Anthropometrics				
Weight	X	X	X	X
Height	X	X	X	X
Waist Circumference	X	X	X	X
Blood Pressure	X	X	X	X
Energy Intake (3-day food records)	X	X	X	X
fMRI	X	X		
Self-report scales	X	X		