A Randomized Controlled Trial Examining the Neurocognitive Benefits of a Nationally Available Weight Management Program

Principal Investigator: Ariana M. Chao, Ph.D., CRNP
University of Pennsylvania School of Nursing, Dept. of Biobehavioral Health Sciences
University of Pennsylvania School of Medicine, Dept. of Psychiatry
418 Curie Blvd, Room 323
Philadelphia, PA 19104
215-746-7183
arichao@upenn.edu

Co- Investigators: Thomas A. Wadden, Ph.D.
Ruben C. Gur, PhD

IRB Number: 834404

ClinicalTrials.gov Number NCT04202133

Study Site: Hospital of the University of Pennsylvania;
Center for Weight and Eating Disorders
University of Pennsylvania

Initial Version: October 10, 2019, version 1.0

Amended: February 5, 2020, version 2.0
February 24, 2020, version 2.1
May 11, 2020, version 3.0
July 6, 2020, version 4.0

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Study Summary

Title	A Randomized Controlled Trial Examining the Neurocognitive Benefits of a Nationally Available Weight Management Program
Short Title	Neurocognitive Benefits of WW
IRB Number	834404
Phase	Phase 4
Methodology	Randomized, wait-list controlled, open label
Study Duration	1.5 years
Study Center(s)	Single-center
Objectives	To assess the effects of a commercially available weight loss program (WW, formerly Weight Watchers) on neural response to food cues and memory tasks, as well as on structural brain morphology.
Number of Subjects	60
Main Inclusion and Exclusion Criteria	Key Inclusion: BMI$\geq$30 kg/m^2; female; ages 18-60 Key Exclusion: Weight > 158.8 kg; pregnancy or lactation; current psychiatric disorder that significantly interferes with daily living; active suicidal ideation; presence of conditions that may interfere with magnetic resonance imaging; use of weight loss medications or other agents known to affect body weight or blood glucose in the past 3 months; type 1 or 2 diabetes mellitus; visual, auditory, or other impairment affecting task performance
Reference therapy	Wait-list control group
Statistical Methodology	Mixed-effects linear models
Safety Evaluations	Adverse events
Data and Safety Monitoring Plan	Drs. Chao and the co-investigators will be responsible for monitoring the data quality and the ongoing safety of subjects. A data safety monitoring board will also monitor the data quality and ongoing safety of subjects.

BACKGROUND AND STUDY RATIONALE

Introduction

This study will be one of the first randomized controlled trials to assess whether weight loss induced through diet and physical activity can change neural responses to high- and low-calorie food images. In addition, it will evaluate whether weight loss can improve neural function when performing the N-back task, a measure of working memory. Findings will address notable gaps in the literature by testing whether a scalable weight loss intervention can help protect and improve neurocognitive functioning and brain health in individuals with obesity. This study will also provide important information about the effects of weight loss on neuroplasticity in brain regions crucial for memory and cognitive functioning, which will help to inform future interventions aimed at promoting brain health.

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

1.1 Background and Relevant Literature

Obesity, characterized by a body mass index (BMI)$\geq$30 kg/m^2, is caused by overconsumption of calories relative to energy expenditure.[1] The modern obesogenic environment, filled with cues to consume highly-palatable and energy-dense foods, is a major driver of overweight and obesity.[2] Obesity greatly increases the burden of chronic illnesses including Alzheimer's disease and dementia.[3-8] Even before the onset of these conditions, elevated body mass is linked with worse neurocognitive functioning such as poor inhibitory control, attention, and memory.[9] The purpose of this proposal is to evaluate the potential benefits of weight loss on two neural processes that have been shown to be impaired among people with obesity: food cue responsiveness and memory.

People with obesity have altered neural responses to environmental food cues, including when seeing pictures of food.[10] The majority of studies have shown that people with obesity, relative to those without, have greater responsiveness to high-calorie food images in regions of the brain associated with reward (e.g., striatum, amygdala, insula, orbitofrontal cortex), attention (anterior cingulate cortex), and motor processes (precentral gyrus, cerebellum).[10,11] Elevated reward-region responses to high-calorie food images and cues are associated with higher food cravings, more snack consumption, and future weight gain.[10,12-16] This increase in neural responsiveness has been hypothesized to be due to learning processes, as well as changes in energy-balance hormones, such as ghrelin, leptin, insulin, amylin, and peptide YY, which can modulate the brain networks associated with food reward and control.[17-19]

Another area of research has shown that individuals with obesity, relative to those of normal weight, have reduced performance on behavioral measures of memory,[20] as well as worse brain health in neural structures and functions associated with memory.[21] For example, relative to participants with normal weight, those with obesity have lower performance on measures of working memory (i.e., the ability to store and manage information on a transient basis) as assessed by tasks in which participants are asked to recall sequences of numbers.[20] Compared to participants with normal weight, those with obesity have decreased global brain volume, and decreased volumes in the temporal lobe, dorsolateral prefrontal cortex, orbitofrontal cortex, and

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hippocampus.[21,22] Reduced hippocampal volume among people with obesity is evident as early as childhood.[23] Relative to participants with normal weight, those with obesity have lower neural activation of the parietal cortex (an area associated with memory retrieval) during working memory tasks.[24] These brain structures and functions are crucial for memory, as well as general executive functioning and self-regulatory processes necessary to achieve long-term goals.[25,26]

Weight loss through diet, physical activity, and behavior modification is recommended for individuals with obesity. Benefits of weight loss include improvements in glycemia, triglycerides, high-density lipoprotein cholesterol, blood pressure, inflammation, and health-related quality of life.[27-29] After weight loss, individuals report improvements in appetite including decreased hunger,[30,31] food cravings,[32,33] and preoccupation with food, and increased fullness.[34] In addition, there is evidence that low-fat diets can help to decrease cravings for high-fat foods and to shift preferences to low-carbohydrate/high-protein foods.[35] However, the effects of weight loss on neural processes related to food cue reactivity and memory are not clear.

Acute caloric restriction appears to increase neural responses to food cues, especially high-calorie foods. Food, especially high-calorie and energy-dense food, is more attractive and palatable when people are hungry.[36] Compared to satiated conditions, *acute caloric deprivation* (typically fasting 8-24 hours) increases activation in neural regions that have been implicated in attention (anterior cingulate cortex), reward valuation (amygdala), memory (hippocampus), and homeostatic feeding (hypothalamus) in response to pictures of palatable foods versus non-food control images.[37,38] Further, acute caloric deprivation selectively increases responsiveness in brain reward systems (i.e., the ventral striatum, amygdala, anterior insula, and medial and lateral orbitofrontal cortex) to highly palatable foods relative to low-calorie food images.[39-41]

In contrast to acute caloric deprivation, moderate caloric restriction (i.e., a diet of 800-1500 kcals/day) for 3 weeks to several months alters neural responsiveness to food, but in the opposite direction of acute restriction. Longer-term moderate caloric restriction, with weight loss of approximately 3.5-10% of initial weight, has been associated with decreased food-cue reactivity to high-calorie foods in brain regions regulating energy balance (e.g., hypothalamus)[42], some regions of the dopaminergic reward system (e.g. orbitofrontal cortex[42,43], anterior cingulate cortex[42], amygdala[42], caudate[44,45]), and regions that execute appetitive behavior (e.g. precentral gyrus).[42,46] A small pilot trial also demonstrated that weight loss increased responsiveness to low-calorie foods (e.g., apple, grilled chicken, salmon; mean of 2.1 kcals/gram) in reward regions of the brain (dorsal and ventral striatum).[47]

Another body of research indicates that weight loss improves attention, executive functioning, and memory.[48] A recent meta-analysis of six studies demonstrated that weight loss induced through dietary changes, caloric restriction, and physical activity, significantly improved behavioral indices of memory compared to control groups.[48] Yet, few studies have assessed whether behavioral findings of memory changes with weight loss correspond with improved brain structure and function. Relative to control conditions, aerobic exercise increased left hippocampal volume,[49] possibly through prevention of decreased neurogenesis and improved angiogenesis. In rodents, switching from a high-fat diet to a low-fat diet helped to reverse impairments in memory.[50] Few studies have assessed the effects of lifestyle interventions consisting of dietary, physical activity, and behavioral modification on memory-related neural changes. Of the studies that have been conducted, compared to control groups, lifestyle interventions demonstrated improvements in hippocampal function,[51-53] as well as increased hippocampal volumes.[51,52] However, many of these studies are limited by pre-posttest designs and small sample sizes. Little is known about

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the impact of weight loss induced through lifestyle modification interventions (that include dietary and physical activity changes) on memory-related neural processes.

Thus, current evidence suggests that weight loss programs that encourage moderate caloric restriction and increased physical activity may improve neural responses to food cues. Furthermore, decreased neural reward responsiveness to high-calorie food cues and increased responsiveness to low-calorie food cues may underlie improvements seen in self-reported and behavioral measures of appetite. Behavioral weight loss studies also suggest that weight loss induced through diet, physical activity, and lifestyle changes can improve brain structures and function associated with memory. However, this literature is limited by small sample sizes and the lack of randomized trials that have directly assessed these questions. The present study is significant because it will help to improve our understanding of neuronal correlates of weight loss interventions. A better understanding of brain mechanisms underlying weight loss can improve the efficacy of obesity prevention and treatment interventions.

2 Study Objectives

The purpose of the present study is to conduct a randomized controlled trial (RCT) to assess the effects of a commercially available weight loss program (WW; formerly Weight Watchers) on neural response to food cues and memory tasks, as well as on structural brain morphology. Participants with obesity will be randomized to either 16 weeks of a group-based WW program (n=30) or a wait-list control (WLC; n=30). Both groups will have structural and blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) scans at baseline and after the end of the intervention. Participants will complete the following fMRI tasks: 1) structural scans; 2) food cue task to measure reactivity to high and low-calorie food images;[10] and 3) N-back task to measure working memory (i.e., the ability to temporarily hold information available for processing).[54] In addition, participants will complete self-report and behavioral measures of eating behaviors, appetite, physical activity, mood, quality of life, attention and memory at baseline, and weeks 8 and 16 (and at the end of the intervention).

2.1 Primary Objectives

Aim 1: To compare differences between the WW and WLC groups at the end of the intervention in changes in BOLD fMRI response to food cues.
Hypothesis 1: We hypothesize that compared to the WLC, the WW group will have significantly greater declines in BOLD response to high-calorie foods in the reward regions of the brain (insula, orbitofrontal cortex, anterior cingulate cortex, nucleus accumbens) and significantly greater increases in BOLD response to low-calorie foods in these reward regions.

Aim 2a: To compare differences between the WW and WLC groups at the end of the intervention in changes in self-reported and behavioral measures of appetite, and **Aim 2b**: to test whether changes in self-reported and behavioral measures of appetite are associated with changes in neural responsivity to high and low-calorie foods in each study arm.
Hypothesis 2a: We hypothesize that at the end of the intervention the WW group, compared to the WLC group, will have significantly greater declines in self-reported reward-based eating, food cravings, hunger, and preference for high-calorie foods, and significantly greater increases in fullness after meals and preference for low-calorie food. *Hypothesis 2b:* We hypothesize that in the WW group, greater declines in BOLD responses to high-calorie foods will be associated with decreased (self-reported) wanting, liking, preference and craving of these foods, and that greater increases in BOLD response to low-calorie foods will be associated with increased wanting, liking, preference, and craving of low-calorie foods.

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Aim 3: To evaluate whether WW, compared to WLC, increases hippocampal volume from baseline to the end of the intervention.
Hypothesis 3: We hypothesize that compared to the WLC, WW will be associated with a significantly greater increase in the size of the hippocampus.

Aim 4: To compare differences between the WW and WLC groups at the end of the intervention in changes in BOLD fMRI response to the N-back task.[54]
Hypothesis 4: We hypothesize that during the working memory task, the WW group, relative to the WLC group, will have significantly greater increases in BOLD activation in the hippocampus, dorsolateral and midventrolateral prefrontal cortex, posterior parietal cortex, and premotor cortex.

2.2 Secondary Objectives

Aim 5a: To compare differences between the WW and WLC groups at the end of the intervention in changes in N-back behavioral performance, and **Aim 5b:** to assess the associations between pre- to post-treatment behavioral changes in memory, and pre- to post-treatment neural changes on the N-back task within each study arm.
Hypothesis 5a: We hypothesize that at the end of the intervention, the WW group, relative to the WLC group will have significantly shorter reaction times and improved accuracy on the N-back task (indicating significantly greater improvements in working memory). *Hypothesis 5b:* We hypothesize that in the WW group, greater improvements in BOLD response in the hippocampus, dorsolateral and midventrolateral prefrontal cortex, posterior parietal cortex, and premotor cortex during the N-back task will be associated with greater improvements in N-back reaction time and accuracy.

3 Study Endpoints

3.1.1 Primary Study Endpoints

The primary endpoints are baseline to end of intervention changes in BOLD fMRI response to food images and to the N-back task as well as baseline to end of intervention changes in hippocampal volume and appetite (i.e., reward-based eating, food cravings, hunger, preference for high- and low-calorie food, and fullness).

3.1.2 Secondary Study Endpoints

Secondary endpoints include baseline to end of intervention changes in N-back task behavioral performance; association between changes in changes in memory and baseline to week 16 changes in N-back task performance; and baseline to end of intervention changes in weight, blood pressure, waist circumference, eating behavior, perceived nutrition environment, quality of life, self-regulation, physical activity, stress, inhibitory control, and resilience.

4 Study Design

4.1 General Design

The proposed investigation is an open-label, RCT to assess changes in neural responses to food images and memory tasks in 60 participants with obesity who are randomized to a 16-week behavioral weight loss program (WW; n=30) versus a WLC group (n=30). Participants will be assessed at baseline and 16 weeks and at the end of the intervention, with the baseline and end of intervention assessments including structural and functional neuroimaging with BOLD fMRI. An additional assessment will occur at week 8 and include self-report measures only. Neither subjects nor investigators will be masked to treatment assignment.

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COVID-19 Changes. Due to the mandatory restrictions in research related to COVID-19, we have transitioned our in-person groups to group-based, remotely delivered sessions via Blue Jeans. We are also not able to conduct fMRI scans on participants and have extended weekly treatment for those people who are currently in the intervention arm (currently our first cohort of 10 participants). Extending treatment will help participants in the intervention arm continue to lose weight, which is an important mechanism we believe will be related to the fMRI results. The treatment will continue as it has, with remotely-delivered, group-based, behavioral weight loss sessions. Those on the wait-list have also had an extended time on the wait-list until we are able to conduct in-person, group treatment in accordance with University Guidance. We will administer the questionnaires at week 16 as in the original protocol. However, we will re-administer these questionnaires at the end of the intervention, once we are able to conduct fMRI scans on participants.

5 Study Population and Duration of Participation

5.1 Total Number of Subjects and Sites

This is a single-site study. We will randomly assign 60 females with obesity to either WW or a WLC.

5.2 Inclusion Criteria

- Ages 18-60 years
- Female
- BMI$\geq$30 kg/m^2
- Eligible female patients will be:
    - non-pregnant
    - non-lactating
    - surgically sterile or postmenopausal, or they will agree to continue to use an accepted method of birth control during the study
      Acceptable methods of birth control are: hormonal contraceptives; double barrier method (condom with spermicide or diaphragm with spermicide); intrauterine device; surgical sterility; abstinence; and/or postmenopausal status (defined as at least 2 years without menses).
- Participants must:
    - understand and be willing to comply with all study-related procedures and agree to participate in the study by giving written informed consent

5.3 Exclusion Criteria

- Weight>158.8 kg (350 lbs, due to scanner weight restrictions)
- Serious medical risk such as type 1 or 2 diabetes, cancer, or recent cardiac event (e.g., heart attack, angioplasty)
- Untreated thyroid disease or any changes (type or dose) in thyroid medication in the last 6 months
- Current psychiatric disorder that significantly interferes with daily living
- Active suicidal ideation
- Current substance use disorder (current or in remission < 1 year)
- Presence or history of orthopedic circumstances, metallic inserts, pacemaker, claustrophobia, or other conditions that may interfere with magnetic resonance imaging
- Participation in a structured weight loss program in the prior 6 months
- Active WW member within the past 12 months

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- Use of medications known to induce significant weight loss/gain, including chronic use of oral steroids in the past 3 months
- Psychiatric hospitalization within the past 6 months
- Loss of ≥10 lbs of body weight within the past 3 months
- History or plans for bariatric surgery
- Visual, auditory, or other impairment affecting task performance
- Epilepsy
- Neurological trauma (e.g., concussion)
- Inability to attend treatment and/or assessment visits
- Participant from same household
- Adherence to specialized diet regimes, such as vegetarian, macrobiotic
- Lack of capacity to provide informed consent
- Inability to walk 5 blocks comfortably or engage in some other form of aerobic activity (e.g., swimming)
- Any serious or unstable medical or psychological condition that, in the opinion of the investigator, would compromise the patient's safety or successful participation in the study

5.4 Duration of Study Participation

The maximum amount of time subjects in the WW group will participate in the study is 45 weeks (screening which may be up to 4 weeks before baseline fMRI; baseline fMRI which may occur up to 4 weeks before start of intervention; 16 to 36-week intervention; final fMRI up to 1-week post intervention period). The maximum amount of time the WLC subjects will participate in the study is 61 weeks (screening which may be up to 4 weeks before baseline fMRI; baseline fMRI which may occur up to 4 weeks before start of wait-list; 16 to 36 weeks on wait-list; final fMRI up to 1 week post wait-list period; 16 week intervention).

5.5 Vulnerable Populations:

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

6 Study Procedures

6.1 Subject Recruitment

Subjects will be recruited using print, radio and online advertisements. We will recruit participants through local media advertisements and news shows/outlets, as well as Internet-based advertising outlets and flyers and brochures around our community. We also will advertise using clinician referrals from clinics affiliated with the University of Pennsylvania Health System. We will be recruiting from the university-based website, iConnect, which allows access to their volunteer registry data of potential participants. We will use study condition terms such as obesity. Recruitment may also use Penn media services (e.g., communications) and social media (e.g., Facebook, Twitter; please see attached for information about Facebook recruitment). Social media recruitment will be limited to one-way advertisements.

6.2 Screening Procedures

6.2.1 Phone screening

Interested subjects will call in and be consented verbally, over the phone, by study staff to participate in the initial telephone screening. Study staff from the Center for Weight and Eating

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Disorders will describe the study, explain that the research is completely voluntary, and conduct a brief screening of candidates who express an interest in proceeding (e.g., BMI and MRI eligibility). We request a waiver of written documentation of consent for the telephone and questionnaire screen.

Those who appear to meet eligibility criteria and remain interested in the trial will be scheduled for an in-person interview. The Weight and Lifestyle Inventory (WALI),[25] an inventory that assesses general eating and lifestyle behaviors, and the Beck Depression Inventory-II (BDI-II),[26] will be forwarded to eligible subjects via REDCap following the phone screen and completed by them prior to their screening/informed consent visit. (All patients and subjects at our Center complete the WALI and BDI to facilitate their initial interview.)

6.2.2 Screening visit

Following the initial telephone screening assessment, eligible participants will attend a 2-hour intake visit at the Center for Weight and Eating Disorders at the University of Pennsylvania. The in-person interview will be conducted by study staff, who will obtain informed consent and evaluate subjects' behavioral eligibility (i.e., willingness and appropriateness to participate). This will include our assessment of the applicant's mood (as measured by interview and the BDI[26]) and suicidality (including history of suicidal ideation and behavior, as assessed at screening by interview and the Columbia-Suicide Severity Rating Scale[55]). Subjects who remain interested and pass this portion of the assessment will be asked about their medical history to determine medical eligibility. The following procedures will be completed at the screening visit:

- Informed consent
- Behavioral evaluations
- Review of Weight and Lifestyle Inventory[25]
- Height and weight to assess BMI
- MRI-eligibility checklist
- Routine medical history
- Review of medications
- Psychiatric exam using the Columbia Suicide Severity Rating Scale[55] and Beck Depression Inventory-II[26]
- Waist circumference
- Blood pressure and heart rate
- Urine pregnancy test (if unsure about pregnancy status)
- Practice session of the N-back task to minimize the learning effects of the experiment
- Questionnaires (emailed via REDCap or printed)
    - Edinburgh Handedness Inventory (Short Form)[56]
    - Reward-Based Eating Drive Scale (RED-13)[57]
    - Eating Inventory (EI) [58]
    - Questionnaire on Weight and Eating Pattern-5 (QEWP-5)[59]
    - Food Cravings Questionnaire- Trait (FCQ-T) [60]
    - Paffenbarger Physical Activity Questionnaire (PPAQ)[61]
    - Yale Food Addiction Scale 2.0 (YFAS)[62]
    - Power of Food Scale (PFS)[63]
    - Palatable Eating Motives-Revised (PEMS-R)[64]
    - Eating Disorder Examination Questionnaire (EDE-Q)[65]
    - Perceived Stress Scale (PSS)[66]
    - Perceived Nutrition Environment (NEMS-P)[67]
    - Brief Resilience Scale (BRS)[68]

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- Short Form-36 (SF-36)[69]
- Impact of Weight on Quality of Life-Lite (IWQOL-Lite)[70]
- Index of Self-Regulation (ISR)[71]
- Behavioral Avoidance/Inhibition Scales (BAS/BIS)[72]

After participants complete the screening procedures, provide their informed consent to participate, and are enrolled into the study, they will complete two study assessment visits that include fMRIs (one at baseline and one after 16-weeks) as well as a mid-point assessment at week 8 (that does not include an fMRI).

6.3 FMRI Assessments.

Prior to randomization, participants will complete a baseline fMRI assessment that will occur up to 4 weeks before the intervention begins. They will complete another fMRI assessment between 2 weeks before the end of the intervention (or up to 1 week after the study intervention is completed). The timeframe for the follow-up assessment was selected so participants in the WW group will be actively engaged in weight loss efforts at the time of the second scanning. Participants will be compensated $100 for each fMRI assessment visit.

Planning for the Assessment Visit. Study assessment visits will be scheduled for the morning and last approximately 3 hours (60 minutes in the fMRI scanner and 120 minutes to complete questionnaires, behavioral tasks, and physical measurements). The visits will be held at the Hospital of the University of Pennsylvania. Participants will be asked to fast (including no caffeine or alcohol) for at least 8 hours prior to the appointment to increase the stimulus salience[41] and create a more homogeneous hunger state across participants. Participants will be asked to remove all jewelry and metal objects at the visit. Participants who require vision correction will be instructed to wear contact lenses or will be provided with MRsafe glasses in their prescription strength.

Imaging Procedures

Pre-scan preparation. Visits on imaging days will begin in the morning at the Hospital of the University of Pennsylvania. Upon arriving, participants will be greeted by research staff who will review the MRI-eligibility checklist to ensure no changes have occurred that would render MRI unsafe or uncomfortable. The MRI technician will review this checklist. All participants will be asked about pregnancy status. For those who are unsure, a urine pregnancy will be completed prior to the scan. Those who attest to being pregnant or test positive will be withdrawn. Participants will be asked to wear clothing without metal or to change into a hospital gown and be weighed, without shoes, on a calibrated electronic scale. They will then complete a self-report measure of current mood (i.e., the Profile of Mood States[73]), Food Cravings Questionnaire- State (FCQ-S), and Eating Behaviors Questionnaire, and visual analog scales for stress, hunger, food cravings, and fatigue level. They also will be required to demonstrate understanding of the task and use of the response device prior to entering the scanner.

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

The research scanner is equipped with stimulus delivery and monitoring systems for fMRI research. This includes Sanyo SXGA 4200 lumens projectors with Sanyo Long Throw zoom lens

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for rear-view/rear projection onto Mylar screens. Video signals are carried into the magnet room using a Lightwave FiberLynx optical-fiber VGA connection. Both the projector and the FiberLynx units are housed in custom RF shield boxes with filtered power receptacles. Images are viewed through mirrors mounted on the head coils. Responses will be monitored using a color-coded keypad made of non-ferromagnetic components (FORP Current Design Inc., Philadelphia, PA) installed at the 3T system. The MRI scan has been designed to last 55 minutes. To ensure completion of all scans, each procedure will be timed and every effort will be made to keep as close to the designated schedule as possible. In respect of time and data quality, if necessary, scans will be skipped or re-run at the discretion of the research team.

Protocol for structural MRI (5 minutes). A magnetization-prepared, rapid acquisition gradient echo (MPRAGE) image will be acquired for anatomic overlays of functional data and spatial normalization using the following parameters: TI/TR/TE=900/2200/4.67ms, flip=8°, matrix=256x192, FOV=240x180mm, slices=160, slice thickness=1mm.

Protocol for BOLD fMRI (~10 minutes). Resting and Task fMRI data will be acquired using a whole-brain, single-shot, multi-slice, gradient-echo EPI sequence.

FMRI Tasks. We will use two tasks to assess the impact of WW on neural activity to food-cues and to memory. Our tasks have been selected to target relevant cognitive and neural models of weight loss. The timing of the stimulus presentation will be synchronized with trigger pulses from the magnet in order to ensure precise temporal integration of stimulus presentation and fMRI data acquisition. These tasks will be presented in a fixed order with the N-back occurring first and food cue task occurring second.

BOLD fMRI Task (N-back; ~15 minutes). The N-back task is one of the most extensively used measures of working memory and requires the storage and updating of information. During the task, participants will be presented with a sequence of images one-by-one.[54] For each stimulus, they will need to indicate if the current stimulus is the same as the one presented in a previous set. We will use four different difficulty levels for this study, one in which participants are asked to recall a stimulus that occurred 0, 1, 2, and 3 back (i.e.,0-, 1-, 2- and 3-back). For example, during the 2-back task, the response would be “yes” if the stimulus currently presented matches the stimulus presented two earlier. A 0-back task will be used as a control condition, in which participants are asked to simply respond yes to the stimuli they are being shown. Increasing memory load is determined by the increase in the number of items the participant has to keep in mind. A slower reaction time and less accuracy are indicative of worse working memory. The stimuli and blocks are presented in a pseudorandom order.

BOLD fMRI task (Food images; 15 minutes). The food images task will be composed of five blocks of high-calorie foods (e.g., bacon, ice cream, cake, burger, French fries, pizza), five blocks of low-calorie foods (e.g., apples, broccoli, banana, salmon, lentils), and five blocks of neutral images (e.g., office supplies). Participants will passively view the images and be asked to imagine how much they want the object right now. Pictures have been matched for complexity, brightness, and color composition. Stimuli are digital photographs of food items depicted in the ready-to-eat state (e.g., all packaging is removed) on identical backgrounds that are validated and are available in publicly available databases.[74,75] Each block will be 30 seconds in duration and presented in pseudorandom order. Each block will contain five photographs of food (5 seconds) separated by 1-second inter-stimulus interval (fixation point). Food blocks will be followed by a 30-second rest period. Following the fMRI, participants will be asked to rate the liking and desirability of the food images (e.g., “How much do you like this food?”), using visual analog scales.

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Task Assessments and Questionnaires. After the fMRI is completed, participants will complete questionnaires to assess response to the fMRI tasks and manipulations and treatment outcomes. To assess the response to the tasks using the food images, participants will be asked about their liking and wanting and palatability of the presented foods on visual analog scales. Participants will complete physical measurements and additional questions, if they have not been completed before their screening visit.

6.4 Cognitive Assessments

After participants complete the questionnaires, they will be asked to complete two cognitive assessments. We will also use the **Leeds Food Preference Questionnaire**, a computerized procedure to assess liking, wanting, and relative preferences for high versus low-fat foods and sweet versus savory foods.[76] The Leeds Food Preference Questionnaire assesses different components of food preference and food reward. Participants are presented with an array of pictures of individual food items common in the diet that are high or low in fat but similar in familiarity, protein content, sweet or non-sweet taste and palatability. The task takes approximately 10 minutes to complete. **Cognitive function** will be assessed with the NIH Toolbox Cognitive Function Battery which includes 7 tests covering different cognitive abilities including attention and executive functioning, episodic memory, working memory, language, and processing speed.[77] The cognitive assessments will be administered in a private room at both fMRI scans as well as a week 8 visit.

Week 8 Assessment.

We will also conduct a mid-point assessment. During this visit we will obtain participants' weight, cognitive assessments, and questionnaires as listed on Table 1 and Table 2. Given the restrictions with COVID, we will only use self-report weight and self-report questionnaires at the week 8 visit.

6.5 Wait-List Post-Treatment Visit (Wait-list Group Only)

After individuals in the WLC group complete their second fMRI assessment, they will be offered the WW treatment. The WLC group will be asked to complete questionnaires as well as their height, weight, and behavioral measures at their end of intervention visit.

6.6 Randomization Visit

Participants who meet all eligibility criteria assessed at the screening visit will be scheduled for a baseline fMRI assessment. The visit will occur within approximately 4 weeks of beginning treatment. They will be instructed to complete the self-reported outcomes either online (using a link e-mailed to them) or using paper-and-pencil questionnaires (for those who prefer this method) approximately 10 days before their fMRI scan. Their questionnaires will be reviewed for completeness at the fMRI visit, with any omissions or errors corrected. The randomization visit will include a weight, waist circumference, blood pressure, and heart rate, and completion of additional baseline assessments (as described in Table 2). Participants will then be randomly assigned to the two groups in equal numbers (i.e., 1:1 ratio). This will be accomplished using a computer-generated algorithm operated by faculty at the Center for Weight and Eating Disorders at the University of Pennsylvania (e.g., Dr. Jena Tronieri). Assignment will be made from randomly varied block sizes (2 or 4). This is an open-labelled randomized trial. Due to COVID-19, we have combined the randomization visit with the baseline fMRI visit. After they complete their fMRI visit, they will be randomized to a treatment group.

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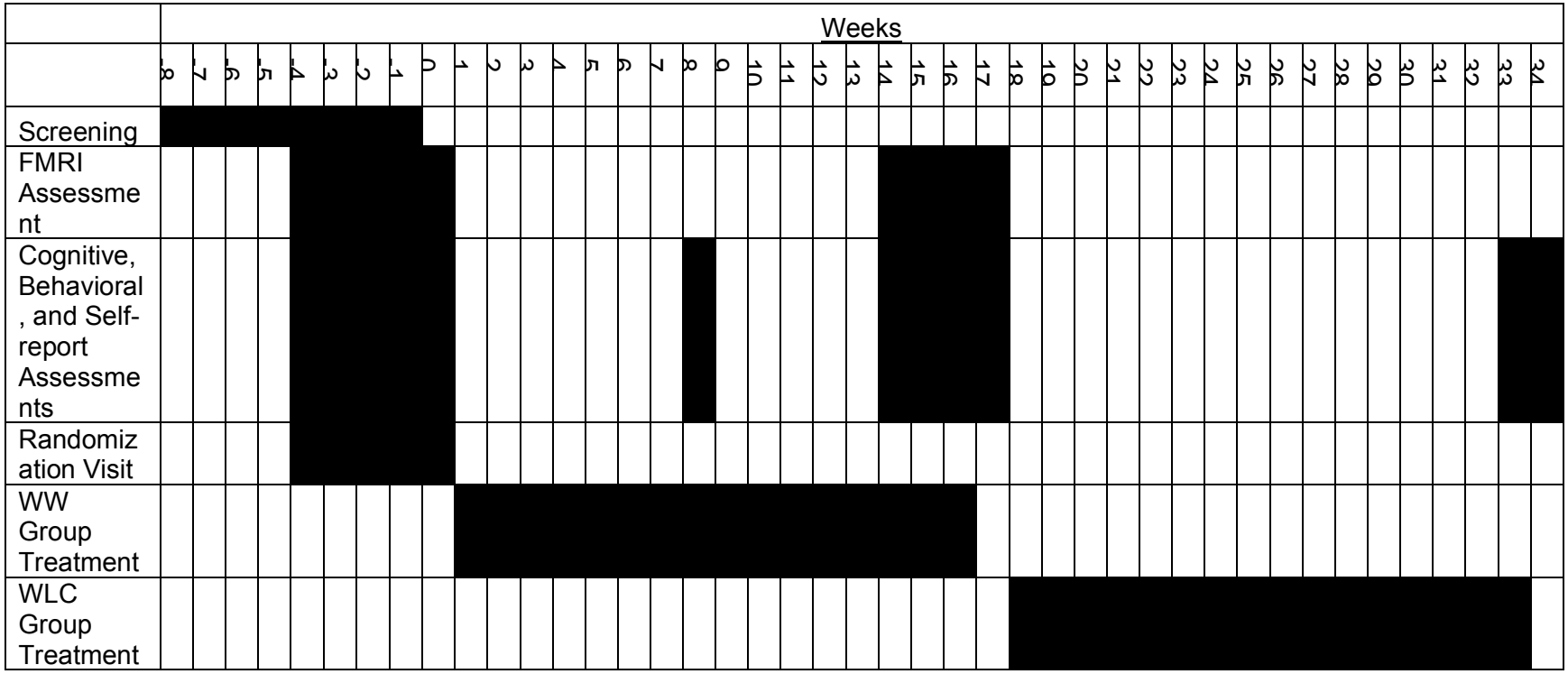
Table 1. Schedule of Study Assessments and Treatment Visits



*WLC group only. For participants affected by COVID-19 and subsequent mandates necessary to help mitigate the transmission of the virus (e.g., stay-at-home orders), their fMRI assessments will occur at the end of the intervention. They will have questionnaire assessments administered at week 16 and then again at the end of the intervention when they can have their fMRI scan. The randomization visit will now be combined with the fMRI visit.

Table 2. Schedule of Procedures

Study Phase	**Screening**	**Baseline FMRI Assessment[a,b]**	**Randomization Visit[c]**	**Intervention**	**Cognitive, Behavioural, and Self-report Assessments**	**Follow-up FMRI Assessment[b]**
Informed consent	X					
Review inclusion/exclusion criteria	X					
Demographics	X					
Medical history	X					
Blood pressure, heart rate	X		X		X	
Height	X					
Waist circumference	X	X	X		X	X
Prior/concomitant medications	X					
Weight	X	X	X	X	X	X
Randomization			X			
FMRI Tasks						
Structural scans		X				X
Food cue task		X				X
N-back task		X				X
Behavioral Measures						
Leeds Food Preference Questionnaire (LFPQ)		X			X	X
National Institutes of Health Toolbox- Cognitive Function Battery		X			X	X
Questionnaires						
Weight and Lifestyle Inventory (WALI)	X					

Edinburgh Handedness Inventory (Short Form)	X					
Beck Depression Inventory-II (BDI-II)	X	X			X	X
Profile of Mood States (POMS)[#]		X			X	X
Food Cravings Questionnaire-State (FCQ-S)[#]		X			X	X
Eating Behaviors Questionnaire (Ratings of appetite, satiety, food preoccupation)[#]		X			X	X
Reward-Based Eating Drive Scale (RED-13)		X			X	X
Eating Inventory (EI)		X			X	X
Questionnaire on Weight and Eating Pattern-5 (QEWP-5)		X			X	X
Food Cravings Questionnaire-Trait (FCQ-T)		X			X	X
Paffenbarger Physical Activity Questionnaire (PPAQ)		X			X	X
Yale Food Addiction Scale 2.0 (YFAS 2.0)		X			X	X
Power of Food Scale (PFS)		X			X	X
Palatable Eating Motives-Revised (PEMS-R)		X			X	X
Modified Eating Patterns Questionnaire (MEPQ)			X		X	X
Eating Disorder Examination Questionnaire (EDE-Q)			X		X	X
Perceived Stress Scale (PSS)			X		X	X
Perceived Nutrition Environment (NEMS-P)			X		X	X
Brief Resilience Scale (BRS)			X		X	X

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Short Form-36 (SF-36)			X		X	X
Impact of Weight on Quality of Life-Lite (IWQOL-Lite)			X		X	X
Index of Self-Regulation (ISR)			X		X	X
Behavioral Avoidance/Inhibition Scales (BAS/BIS)			X		X	X
Adherence Measures						
Sessions attended*				X		X
Self-monitoring food records*				X		X
Additional treatment sought for weight or eating				X	X	X

*Weekly measure. [a]Questionnaries will be sent after the screening visit and before the fMRI. [b]Questionnaires will be distributed 10 days before scheduled fMRI and participants will be asked to be complete them before the fMRI visit (except those marked with #, which will be completed at the day of the fMRI scan). [c]Participants will be asked to complete these questionnaires at the randomization visit or via email if preferred. For participants affected by COVID-19 and subsequent mandates necessary to help mitigate the transmission of the virus (e.g., stay-at-home orders), their fMRI assessments will occur at the end of the intervention. They will have questionnaire assessments administered at week 16 and then again at the end of the intervention when they can have their fMRI scan. The randomization measures will be combined with the baseline fMRI visit.

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7 Study Intervention

WW Group Lifestyle Modification Program. The WW intervention will consist of weekly, group weight loss workshops (formerly meetings) for 16 or more weeks. Each workshop will be approximately 1 hour and include 8 to 12 participants. Participants will have access to both in-person or web-based, group meetings as well as digital tools (e.g., self-monitoring of intake, activity, and weight). The meetings will be led by a trained coach and a guide. All group sessions will be conducted at the University of Pennsylvania's Center for Weight and Eating Disorders, following the WW program. Due to the coronavirus pandemic, all non-essential visits at the University of Pennsylvania will be canceled starting March 16, 2020. As a result, each group workshop after Week 8 will be moved to a virtual video chat platform, BlueJeans. Participants have the option of calling in through video or audio. All participants will be sent standardized scales and will self-report their weight. Blood pressure will not be measured until the participants' next in-person visit. The program uses a SmartPoints® System that encourages consumption of fruits, vegetables, lean proteins, and less sugar and unhealthy fats. Participants will have their weight, blood pressure, and heart rate measured at each session. Changes in medications and adverse events will be reported privately to research staff at clinic meetings.

Wait-list control (WLC) group. Participants in the WLC group will be asked to stay weight stable and not to make changes in their eating and physical activity behaviors and not to seek treatment for weight or eating during the waiting period. They will be contacted between week 6-8 via phone by a research assistant to keep participants engaged, enhance retention and schedule their week 8 assessment visit. We will use a structured script and ask participants about any additional treatments they may have sought during the study. All WLC participants will be offered the WW intervention (as described above) after they complete the second fMRI assessment at the end of treatment.

7.1 Unscheduled Visits

Participants who miss a session will be contacted by their coach, guide, or study staff following the absence. An in-person or phone make up visit will be offered.

7.2 Subject Withdrawal

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

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

7.3 Safety Evaluations

Safety evaluations include adverse events (AEs) and assessments of blood pressure and heart rate. At weeks 8 and 16, we will check for possible complications of weight loss, and will also encourage participants to inform the study team sooner if applicable. At weeks 8 and 16, study subjects will be asked whether there has been any change in their health or medications. In the event of adverse mental health events, participants will be referred to the study's psychologist or psychiatrist for further evaluation, if required. For all non-study-related medical events, participants will be referred to their own primary care provider.

8 Safety and Adverse Events

8.1 Definitions

8.1.1 Adverse Event

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

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

8.1.2 Serious Adverse Event

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

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

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

8.2 Recording of Adverse Events

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

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All events meeting the definition of an adverse event will be collected and reported from the first trial related activity after the subject has signed the informed consent and until the end of the post-treatment follow-up period. Serious adverse events that are still ongoing at the end of the study period will be followed up until either resolved or stable. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

8.3 Relationship of AE to Study

- Probable: Good reasons and sufficient documentation to assume a causal relationship
- Possible: A causal relationship is conceivable and cannot be dismissed
- Unlikely: The event etiology is most likely not related to the study procedures

The PI will evaluate all unexpected events and adverse reactions.

8.4 Outcome Categories and Definitions:

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

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

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

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

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

9.1.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to

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the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

9.1.2 Investigator reporting: notifying the study sponsor

Study-related unanticipated problem posing risk to subjects or others, and any type of serious adverse event, will be reported to the study sponsor within 24 hours of the event. To report such events, a Serious Adverse Event (SAE) form will be completed by the investigator and sent to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Within the following 48 hours, the investigator will provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor.

10 Study Administration, Data Handling and Record Keeping

10.1 Confidentiality

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

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

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

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

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

11 Privacy

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

12 Study Monitoring, Auditing, and Inspecting

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

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

13 Ethical Considerations

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

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

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

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

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

13.1 Risks

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

Risks of Assessments, Behavioral Weight Loss Treatment, and Wait-list
Some of the questions in the interview that assess history of psychological conditions may be of a personal nature. All such questions will be asked by trained study staff. Appropriate referrals will be given as necessary.

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Participants in the WLC group will be contacted at week 8 via phone by a research assistant to keep participants engaged and enhance study retention. All wait-list participants will be provided with the 16-week intervention after they complete the end-of-study testing at week 16. Though we considered other designs, a wait-list control comparison was selected as it was deemed ethical, while also permitting a non-intervention comparison and maximizing power to detect differences between groups.

Weight loss

Risk of Gallstones: Rapid weight loss may increase the risk of gallstones. Symptoms of gallstones include abdominal pain, nausea, vomiting, fever, and chills. The risk of gallbladder disease will be reduced by limiting weight loss to no more than 3 pounds per week for 4 consecutive weeks.

Risks of MRI

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

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

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

Incidental findings: This MRI is not a clinical scan. It is possible that during the course of the research study, the research staff may notice an unexpected finding(s). In the event of abnormal findings are identified by study MRI personnel (e.g., technologists, physicists, image processing scientists), the PI (Dr. Chao), will inform Dr. John Detre. Dr. Detre has agreed to be included in this study to address safety issues and incidental findings for this study. The participant will be contacted and Center Staff will arrange for the images to be sent to participants and/or their physician. These possible finding(s) may or may not be significant and may lead to anxiety about

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a person's condition and to further work-up by a physician.

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

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

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

Loss of Confidentiality Risk

Because information about participant's identity will be collected and stored for research purposes, there is a chance that the information could be viewed by others not associated with the research team and therefore, there is a potential for loss of confidentiality. The study team will work to uphold the privacy of the participants in several ways. Communications made among study staff regarding participants will use ID numbers only and never include names or other personal information. All participant data and recordings will be kept in locked files. In all data sets, we will use ID numbers only. A separate dataset linking names with ID numbers will be accessible only by the primary study investigators.

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

13.2 Benefits

All participants who enroll in this study will receive the WW program including access to the in-person workshops and digital tools. Based on results of previous studies, we expect participants to lose an average of approximately 5% of their initial weight during the 16-week treatment program and have improvements in their eating behaviors and physical activity. Weight losses of this size may be associated with improvements in medical conditions made worse by excess weight including pre-diabetes (high blood sugar), high blood pressure, and high triglyceride levels. Participants will undergo assessment and monitoring of several health factors including weight and blood pressure. These results will be made available to participants. Despite all of these potential benefits, there is no guarantee that participants will lose weight or get any medical benefits from this study. This study may also benefit society at large by providing information about the effectiveness of a behavioral weight loss program on brain changes related to food cue responsiveness and memory.

13.3 Risk Benefit Assessment

The benefits of this research to the subjects studied, and to society at large, far surpass the risks. We believe that this study poses minimal risk to participants, while providing potential benefit to women with obesity. The treatments and procedures used in this study have been shown to be relatively safe. Numerous clinical trials have demonstrated the safety of MRI scans and efficacy of WW for obesity. Research staff will monitor subjects closely during their participation. We

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anticipate that after the WW treatment participants will have improvements in their eating, physical activity, and weight. Results of this study hold promise of significantly improving the management of obesity and its associated complications.

13.4 Informed Consent Process / HIPAA Authorization

Following the screening telephone call, trained clinical assessors will meet in person with all potential participants to describe the study, its requirements, and its likely risks and benefits. Participants will be provided a written copy of the Consent Form/HIPAA Authorization at this meeting and will be given an opportunity to read it and have all of their questions answered. Persons who wish to participate in the study will be asked to give their written consent at the time of consent discussion and will then continue with the screening visit. Participants will also be permitted to discuss the consent form and procedures and return the signed form and continue with the screening at a later date (within 2 weeks), if they prefer. Participants will be told that they can contact the Principal Investigator at any time if they have questions about the study. The study team member who reviews the consent document will emphasize that participation in the study is voluntary and that medical care will not be influenced by the participants decision to participate or not. The consent process will take place in a private office or exam room to help protect subject privacy. Subject comprehension of the nature of the study will be assessed using interactive conservation methods (e.g., asking the potential subject to paraphrase different points of discussion, asking open-ended questions, encouraging questions).

13.4.1 Waiver of Written Documentation of Consent

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

14 Study Finances

14.1 Conflict of Interest

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

14.2 Subject Stipends or Payments

Participants will be compensated $100 for each fMRI scan, $10 to help with travel costs to each of the 16 study intervention visits, and $25 for the week 8 study visit. The total compensation if all study visits are completed is $385. No extra compensation will be provided for changes due to COVID-19.

15 References

1. Schwartz MW, Seeley RJ, Zeltser LM, et al. Obesity pathogenesis: an Endocrine Society scientific statement. Endocrine reviews 2017;38:267-96.
2. Ravussin E, Ryan DH. Three New Perspectives on the Perfect Storm: What's Behind the Obesity Epidemic? Obesity 2018;26:9-10.

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3. Profenno LA, Porsteinsson AP, Faraone SV. Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders. Biol Psychiatry 2010;67:505-12.
4. Bocarsly ME, Fasolino M, Kane GA, et al. Obesity diminishes synaptic markers, alters microglial morphology, and impairs cognitive function. Proceedings of the National Academy of Sciences 2015;112:15731-6.
5. Alford S, Patel D, Perakakis N, Mantzoros C. Obesity as a risk factor for Alzheimer's disease: weighing the evidence. Obes Rev 2018;19:269-80.
6. Sindi S, Hagman G, Håkansson K, et al. Midlife work-related stress increases dementia risk in later life: The CAIDE 30-year study. Journals of Gerontology Series B: Psychological Sciences and Social Sciences 2016;72:1044-53.
7. Alkadhi KA. Chronic psychosocial stress exposes Alzheimer's disease phenotype in a novel at-risk model. Front Biosci (Elite Ed) 2012;4:214-29.
8. Albanese E, Launer LJ, Egger M, et al. Body mass index in midlife and dementia: Systematic review and meta-regression analysis of 589,649 men and women followed in longitudinal studies. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 2017;8:165-78.
9. Prickett C, Brennan L, Stolwyk R. Examining the relationship between obesity and cognitive function: a systematic literature review. Obesity research & clinical practice 2015;9:93-113.
10. Pursey KM, Stanwell P, Callister RJ, Brain K, Collins CE, Burrows TL. Neural responses to visual food cues according to weight status: a systematic review of functional magnetic resonance imaging studies. Frontiers in nutrition 2014;1:7.
11. Stoeckel LE, Weller RE, Cook III EW, Twieg DB, Knowlton RC, Cox JE. Widespread reward-system activation in obese women in response to pictures of high-calorie foods. Neuroimage 2008;41:636-47.
12. Demos KE, Heatherton TF, Kelley WM. Individual differences in nucleus accumbens activity to food and sexual images predict weight gain and sexual behavior. Journal of Neuroscience 2012;32:5549-52.
13. Yokum S, Ng J, Stice E. Attentional bias to food images associated with elevated weight and future weight gain: an fMRI study. Obesity 2011;19:1775-83.
14. Moreno-Padilla M, Verdejo-Román J, Fernández-Serrano MJ, del Paso GAR, Verdejo-García A. Increased food choice-evoked brain activation in adolescents with excess weight: Relationship with subjective craving and behavior. Appetite 2018;131:7-13.
15. Lawrence NS, Hinton EC, Parkinson JA, Lawrence AD. Nucleus accumbens response to food cues predicts subsequent snack consumption in women and increased body mass index in those with reduced self-control. Neuroimage 2012;63:415-22.
16. Pelchat ML, Johnson A, Chan R, Valdez J, Ragland JD. Images of desire: food-craving activation during fMRI. Neuroimage 2004;23:1486-93.
17. Neseliler S, Hu W, Larcher K, et al. Neurocognitive and hormonal correlates of voluntary weight loss in humans. Cell metabolism 2019;29:39-49. e4.
18. Farr OM, Chiang-shan RL, Mantzoros CS. Central nervous system regulation of eating: Insights from human brain imaging. Metabolism 2016;65:699-713.
19. Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. New England Journal of Medicine 2011;365:1597-604.
20. Yang Y, Shields GS, Guo C, Liu Y. Executive function performance in obesity and overweight individuals: A meta-analysis and review. Neuroscience & Biobehavioral Reviews 2018;84:225-44.
21. Cherbuin N, Sargent-Cox K, Fraser M, Sachdev P, Anstey K. Being overweight is associated with hippocampal atrophy: the PATH Through Life Study. International Journal of Obesity 2015;39:1509.

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22. Willette AA, Kapogiannis D. Does the brain shrink as the waist expands? Ageing research reviews 2015;20:86-97.
23. Bauer C, Moreno B, González-Santos L, Concha L, Barquera S, Barrios F. Child overweight and obesity are associated with reduced executive cognitive performance and brain alterations: a magnetic resonance imaging study in M exican children. Pediatric obesity 2015;10:196-204.
24. Gonzales MM, Tarumi T, Miles SC, Tanaka H, Shah F, Haley AP. Insulin sensitivity as a mediator of the relationship between BMI and working memory-related brain activation. Obesity 2010;18:2131-7.
25. Simons JS, Spiers HJ. Prefrontal and medial temporal lobe interactions in long-term memory. Nature reviews neuroscience 2003;4:637.
26. Hofmann W, Gschwendner T, Friese M, Wiers RW, Schmitt M. Working memory capacity and self-regulatory behavior: toward an individual differences perspective on behavior determination by automatic versus controlled processes. Journal of personality and social psychology 2008;95:962.
27. Wing RR, Lang W, Wadden TA, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care 2011;34:1481-6.
28. Nicklas BJ, Ambrosius W, Messier SP, et al. Diet-induced weight loss, exercise, and chronic inflammation in older, obese adults: a randomized controlled clinical trial. The American journal of clinical nutrition 2004;79:544-51.
29. Group LAR. Impact of intensive lifestyle intervention on depression and health-related quality of life in type 2 diabetes: the Look AHEAD Trial. Diabetes care 2014;37:1544-53.
30. Foster GD, Wadden TA, Peterson FJ, Letizia KA, Bartlett SJ, Conill AM. A controlled comparison of three very-low-calorie diets: effects on weight, body composition, and symptoms. The American journal of clinical nutrition 1992;55:811-7.
31. Foster G, Wadden T, Swain R, Stunkard A, Platte P, Vogt R. The Eating Inventory in obese women: clinical correlates and relationship to weight loss. International journal of obesity 1998;22:778.
32. Chao AM, Wadden TA, Tronieri JS, et al. Effects of addictive-like eating behaviors on weight loss with behavioral obesity treatment. Journal of behavioral medicine 2019;42:246-55.
33. Kahathuduwa CN, Binks M, Martin CK, Dawson JA. Extended calorie restriction suppresses overall and specific food cravings: a systematic review and a meta-analysis. Obesity reviews 2017;18:1122-35.
34. Andriessen C, Christensen P, Nielsen LV, et al. Weight loss decreases self-reported appetite and alters food preferences in overweight and obese adults: Observational data from the DiOGenes study. Appetite 2018;125:314-22.
35. Martin CK, Rosenbaum D, Han H, et al. Change in food cravings, food preferences, and appetite during a low-carbohydrate and low-fat diet. Obesity 2011;19:1963-70.
36. Cameron JD, Goldfield GS, Finlayson G, Blundell JE, Doucet É. Fasting for 24 hours heightens reward from food and food-related cues. PloS one 2014;9:e85970.
37. Führer D, Zysset S, Stumvoll M. Brain activity in hunger and satiety: an exploratory visually stimulated FMRI study. Obesity 2008;16:945-50.
38. LaBar KS, Gitelman DR, Parrish TB, Kim Y-H, Nobre AC, Mesulam M. Hunger selectively modulates corticolimbic activation to food stimuli in humans. Behavioral neuroscience 2001;115:493.
39. Goldstone AP, Prechtl de Hernandez CG, Beaver JD, et al. Fasting biases brain reward systems towards high-calorie foods. European Journal of Neuroscience 2009;30:1625-35.
40. Siep N, Roefs A, Roebroeck A, Havermans R, Bonte ML, Jansen A. Hunger is the best spice: an fMRI study of the effects of attention, hunger and calorie content on food reward

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processing in the amygdala and orbitofrontal cortex. Behavioural brain research 2009;198:149-58.
41. Stice E, Burger K, Yokum S. Caloric deprivation increases responsivity of attention and reward brain regions to intake, anticipated intake, and images of palatable foods. Neuroimage 2013;67:322-30.
42. Rosenbaum M, Sy M, Pavlovich K, Leibel RL, Hirsch J. Leptin reverses weight loss–induced changes in regional neural activity responses to visual food stimuli. The Journal of clinical investigation 2008;118:2583-91.
43. Bruce AS, Bruce JM, Ness AR, et al. A comparison of functional brain changes associated with surgical versus behavioral weight loss. Obesity 2014;22:337-43.
44. Chen EY, Olino TM, Conklin CJ, et al. Genetic and neural predictors of behavioral weight loss treatment: a preliminary study. Obesity 2017;25:66-75.
45. McDermott KD, Williams SE, Espeland MA, et al. Impact of Intensive Lifestyle Intervention on Neural Food Cue Reactivity: Action for Health in Diabetes Brain Ancillary Study. Obesity 2019.
46. Kahathuduwa CN, Boyd LA, Davis T, O'Boyle M, Binks M. Brain regions involved in ingestive behavior and related psychological constructs in people undergoing calorie restriction. Appetite 2016;107:348-61.
47. Deckersbach T, Das S, Urban L, et al. Pilot randomized trial demonstrating reversal of obesity-related abnormalities in reward system responsivity to food cues with a behavioral intervention. Nutrition & diabetes 2014;4:e129.
48. Veronese N, Facchini S, Stubbs B, et al. Weight loss is associated with improvements in cognitive function among overweight and obese people: A systematic review and meta-analysis. Neuroscience & Biobehavioral Reviews 2017;72:87-94.
49. Firth J, Stubbs B, Vancampfort D, et al. Effect of aerobic exercise on hippocampal volume in humans: a systematic review and meta-analysis. Neuroimage 2018;166:230-8.
50. Hao S, Dey A, Yu X, Stranahan AM. Dietary obesity reversibly induces synaptic stripping by microglia and impairs hippocampal plasticity. Brain, behavior, and immunity 2016;51:230-9.
51. Stomby A, Otten J, Ryberg M, Nyberg L, Olsson T, Boraxbekk C-J. A Paleolithic Diet with and without Combined Aerobic and Resistance Exercise Increases Functional Brain Responses and Hippocampal Volume in Subjects with Type 2 Diabetes. Frontiers in aging neuroscience 2017;9:391.
52. Prehn K, Jumpertz von Schwartzenberg R, Mai K, et al. Caloric restriction in older adults—differential effects of weight loss and reduced weight on brain structure and function. Cerebral Cortex 2016;27:1765-78.
53. Boraxbekk C-J, Stomby A, Ryberg M, et al. Diet-induced weight loss alters functional brain responses during an episodic memory task. Obesity facts 2015;8:261-72.
54. Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. Human brain mapping 2005;25:46-59.
55. Posner K, Brown GK, Stanley B, et al. The Columbia–Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. American journal of psychiatry 2011;168:1266-77.
56. Veale JF. Edinburgh handedness inventory–short form: a revised version based on confirmatory factor analysis. Laterality: Asymmetries of Body, Brain and Cognition 2014;19:164-77.
57. Mason AE, Vainik U, Acree M, et al. Improving assessment of the spectrum of reward-related eating: the RED-13. Frontiers in psychology 2017;8:795.
58. Stunkard AJ, Messick S. The Three-Factor Eating Questionnaire to measure dietary restraint, disinhibition and hunger. Journal of Psychosomatic Research 1985;29:71-83.

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59. Yanovski SZ, Marcus MD, Wadden TA, Walsh BT. The questionnaire on eating and weight patterns-5 (QEWP-5): An updated screening instrument for binge eating disorder. The International journal of eating disorders 2015;48:259.
60. Cepeda-Benito A, Gleaves DH, Williams TL, Erath SA. The development and validation of the state and trait food-cravings questionnaires. Behavior therapy 2000;31:151-73.
61. Paffenbarger Jr RS, Hyde R, Wing AL, Hsieh C-c. Physical activity, all-cause mortality, and longevity of college alumni. New England journal of medicine 1986;314:605-13.
62. Gearhardt AN, Corbin WR, Brownell KD. Development of the Yale Food Addiction Scale Version 2.0. Psychology of Addictive Behaviors 2016;30:113.
63. Lowe MR, Butryn ML, Didie ER, et al. The Power of Food Scale. A new measure of the psychological influence of the food environment. Appetite 2009;53:114-8.
64. Boggiano MM. Palatable Eating Motives Scale in a college population: Distribution of scores and scores associated with greater BMI and binge-eating. Eating behaviors 2016;21:95-8.
65. Fairburn CG, Beglin SJ. Assessment of eating disorders: Interview or self-report questionnaire? International journal of eating disorders 1994;16:363-70.
66. Cohen S, Kamarck T, Mermelstein R. Perceived stress scale. Measuring stress: A guide for health and social scientists 1994;10.
67. Green SH, Glanz K. Development of the perceived nutrition environment measures survey. American journal of preventive medicine 2015;49:50-61.
68. Smith BW, Dalen J, Wiggins K, Tooley E, Christopher P, Bernard J. The brief resilience scale: assessing the ability to bounce back. International journal of behavioral medicine 2008;15:194-200.
69. Maruish ME. User's manual for the SF-36v2 Health Survey: Quality Metric Incorporated; 2011.
70. Kolotkin RL, Crosby RD. Psychometric evaluation of the impact of weight on quality of life-lite questionnaire (IWQOL-lite) in a community sample. Quality of Life Research 2002;11:157-71.
71. Fleury J. The index of self-regulation: development and psychometric analysis. Journal of Nursing Measurement 1998.
72. Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS scales. Journal of personality and social psychology 1994;67:319.
73. Shacham S. A shortened version of the Profile of Mood States. J Pers Assess 1983;47:305-6.
74. Blechert J, Meule A, Busch NA, Ohla K. Food-pics: an image database for experimental research on eating and appetite. Food cravings 2015:40.
75. Foroni F, Pergola G, Argiris G, Rumiati RI. The FoodCast research image database (FRIDa). 2013.
76. Finlayson G, Arlotti A, Dalton M, King N, Blundell JE. Implicit wanting and explicit liking are markers for trait binge eating. A susceptible phenotype for overeating. Appetite 2011;57:722-8.
77. Weintraub S, Dikmen SS, Heaton RK, et al. Cognition assessment using the NIH Toolbox. Neurology 2013;80:S54-S64.
78. Simmons JP, Nelson LD, Simonsohn U. False-positive psychology: Undisclosed flexibility in data collection and analysis allows presenting anything as significant. Psychological science 2011;22:1359-66.
79. Thirion B, Pinel P, Mériaux S, Roche A, Dehaene S, Poline J-B. Analysis of a large fMRI cohort: Statistical and methodological issues for group analyses. Neuroimage 2007;35:105-20.
80. Desmond JE, Glover GH. Estimating sample size in functional MRI (fMRI) neuroimaging studies: statistical power analyses. J Neurosci Methods 2002;118:115-28.

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81. Geuter S, Qi G, Welsh RC, Wager TD, Lindquist MA. Effect size and power in fMRI group analysis. Biorxiv 2018:295048.
82. Monti MM. Statistical analysis of fMRI time-series: a critical review of the GLM approach. Front Hum Neurosci 2011;5.

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