

# A Comparison of Functional Brain Changes Associated with Surgical Versus Behavioral Weight Loss

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**Objective:** Few studies have examined brain changes in response to effective weight loss; none have compared different methods of weight-loss intervention. Functional brain changes associated with a behavioral weight loss intervention to those associated with bariatric surgery were compared.

**Methods:** Fifteen obese participants were recruited prior to adjustable gastric banding surgery and 16 obese participants were recruited prior to a behavioral diet intervention. Groups were matched for demographics and amount of weight lost. Functional magnetic resonance imaging scans (visual food motivation paradigm while hungry and following a meal) were conducted before and 12 weeks after surgery/behavioral intervention.

**Results:** When compared to bariatric patients in the premeal analyses, behavioral dieters showed increased activation to food images in right medial prefrontal cortex (PFC) and left precuneus following weight loss. When compared to behavioral dieters, bariatric patients showed increased activation in bilateral temporal cortex following weight loss.

**Conclusions:** Behavioral dieters showed increased responses to food cues in medial PFC—a region associated with valuation and processing of self-referent information—when compared to bariatric patients. Bariatric patients showed increased responses to food cues in brain regions associated with higher level perception—when compared to behavioral dieters. The method of weight loss determines unique changes in brain function.

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## Introduction

Benefits of weight-loss and body fat reduction in obese people include decreased blood pressure and triglycerides, and improved cholesterol ratio and glucose tolerance (1,2). Although behavioral interventions that modify diet and or physical activity are common, the short-term effects (weight loss) and longer term effects (weight maintenance) of these approaches are variable (3). Bariatric surgery is also an effective method for weight loss yielding long-term outcomes superior to behavioral methods (4), though the enduring effectiveness has not been established. Laparoscopic adjustable gastric banding (LAGB) is one form of bariatric surgery that has become a favored procedure with mild to moderately obese individuals (5). With faster recovery and lower risk of complications

compared to gastric bypass surgery, it is very successful. People who undergo LAGB achieve 30% excess weight loss 6 months post-surgery, 40% 1 year postsurgery, and 50% 2 years postsurgery (6,7). The majority of successful LAGB patients experience reduced hypertension, hyperlipidemia, sleep apnea, diabetes, and depression (8,9).

There has been recent interest in characterizing the brain's role in appetite, food motivation, and obesity. Functional magnetic resonance imaging (fMRI) studies provide evidence that the brains of obese and healthy weight individuals differ in their responses to visual food cues in regions associated with reward (striatum, orbitofrontal cortex, insula), homeostatic regulation (hypothalamus), and

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**Abbreviations** fMRI, functional magnetic resonance imaging; BMI, body mass index; OFC, orbitofrontal cortex; PFC, prefrontal cortex; MPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; ROI, region of interest

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**TABLE 1** Participant demographics

Diet group	Total N	Sex	Age (years) $\bar{X}$ , $\sigma$	Attended college	% Weight lost
Behavioral	16	5 males	40.6, 7.1	14	10.8%
Bariatric	15	3 males	41.4, 9.8	11	9.3%

cognitive control (prefrontal cortex (PFC), cingulate cortex) (10). One study examined brain responses to visual food stimuli in individuals who had successfully maintained long-term weight loss. They found that successful weight-loss maintainers showed greater functional activation in left superior frontal and right middle temporal cortex (11). Cross-sectional studies have determined that post-obese individuals demonstrate greater activation in dorsolateral PFC when exposed to food cues, a pattern of activation that is most consistently found among lean individuals (12,13). Taken together, these findings suggest that higher neural activation in regions associated with cognitive control or “rational” decision-making is associated with successful weight loss. This may serve as one mechanism by which healthy choices are made, and weight loss is achieved and maintained.

Few studies have employed a longitudinal approach to examine the effects of behavioral weight loss on the brain. Rosenbaum and colleagues induced a 10% weight loss in an inpatient setting with a liquid diet, and used fMRI to demonstrate increased activations in PFC (inferior frontal gyrus), parahippocampus, middle temporal gyrus, lingual gyrus, and brainstem (14). Conversely, the same study demonstrated decreases in activation in hypothalamus, cingulate, and middle frontal gyrus. A study examining brain changes associated with an outpatient behavioral weight loss intervention reported decreased activation to food versus control pictures in medial prefrontal cortex, inferior parietal lobule, precuneus, posterior cingulate, premotor cortex, and angular gyrus (15). This study only examined a fasted state, did not include a control group comparison, did not collect data on a postmeal state, and the authors encouraged future studies to examine both fasted and fed appetite states. The changes observed in these studies may be because of the weight loss itself or due more specifically to the nature of the intervention (i.e. inpatient liquid diet or outpatient behavioral intervention). To our knowledge, no study has examined that how behavioral weight loss interventions change brain function when controlling for the type of weight loss intervention.

A few published studies have examined the effects of bariatric surgical interventions on brain function. Specifically, our group examined LAGB and found increased activation in anterior PFC, and decreased activity in insula, parahippocampal gyrus, and medial PFC (16). Ochner and colleagues reported similar findings associated with Roux-en-Y gastric bypass surgery (17,18). Specifically, they noted reduced activations in both reward (striatum) and inhibitory regions (ventromedial and dorsolateral PFC) in a fasted state, but no significant changes in a fed state.

The goal of the current study was to examine brain activation changes associated with successful weight loss in dieters and bariatric patients in both hungry and fed states. It was hypothesized that diet and bariatric participants would exhibit different functional

brain changes from pre to post weight loss. Specifically, it was predicted that in both hungry and fed states, dieters would exhibit greater *increases* in brain activation in regions associated with cognitive control when compared to bariatric patients. In contrast, bariatric patients were expected to show greater *decreases* in food motivation and reward brain regions in both hungry and fed states when compared to diet participants.

## Methods and Procedures

### Participants

**Diet participants.** Sixteen diet participants (five males) were selected from a larger behavioral weight-loss intervention study (120 participants) [NIH DK080090] that recruited using advertisements placed in local news outlets, broadcast emails, and a university-based weight management center (Table 1). Obese participants with a BMI between 30 and 45 kg/m<sup>2</sup> were recruited to participate in a three-month weight loss and six-month maintenance intervention that involved behavioral strategies, moderate calorie restriction, and titrated physical activity. Exclusion criteria included participation in a research project involving weight loss or physical activity in the previous six months, smoking, special diets (i.e. vegetarian, Atkins), use of appetite or metabolic medications (i.e. thyroid, beta blockers, Meridia), or the inability to exercise (i.e. walk). Participants' age range was 23-52 years,  $M = 40.6$ ,  $SD = 7.1$ ). Fourteen of the dieting participants had attended college. Participants were selected for this study, blind to imaging data, based solely on demographic criteria.

**Surgical participants.** Fifteen presurgical participants (three males) were identified at two surgical sites in the Kansas City area. Obese participants who had decided to undergo adjustable gastric banding weight loss surgery (LapBand®) were recruited for the study (Table 1). As the majority of participants seeking bariatric surgery in the recruited BMI range had a history of diabetes, patients who had well-controlled diabetes and were not taking insulin (most recent hemoglobin A1c < 7) were included. Participants' age range was 21-56 years,  $M = 41.4$ ,  $SD = 9.8$ ). Eleven of the bariatric patients had attended college.

Exclusion criteria for both groups included current eating disorder, current major depression, history of neurological disease, pregnancy within the past 6 months, planning a pregnancy within 12 months, cancer, recent cardiac event (heart attack), and internal metal objects that pose risks in a strong magnetic field. Individuals with a BMI  $\geq 46$  kg/m<sup>2</sup> were also excluded, as these individuals were unable to comfortably lie in the MRI scanner. Individuals were ineligible if they reported use of insulin, appetite suppressants, and stimulants. In contrast, given the prevalence of subclinical depression among patients seeking bariatric surgery, participants taking psychotropic medications not directly targeting the mesolimbic dopamine system (selective serotonin reuptake inhibitors) were included in the bariatric study.

No statistically significant differences between the diet and bariatric groups were observed for age [ $t(29) = 0.27$ ;  $P = 0.79$ ], education [ $\chi^2 = -1.89$ ;  $P = 0.60$ ], sex [ $\chi^2 = 0.51$ ;  $P = 0.47$ ], pre-intervention BMI [ $t(29) = 1.59$ ;  $P = 0.12$ ], postintervention BMI

[ $t(29) = 1.71$ ;  $P = 0.10$ ], or percent of weight lost [9.3% bariatric vs. 10.8% diet;  $t(29) = 1.02$ ;  $P = 0.32$ ].

## Design and procedure

We scanned 31 obese participants at two time points: once before commencing weight loss intervention and once 12 weeks after completing the intervention (16 following the behavioral intervention; 15 following LAGB surgery). At each time point, participants were scanned while hungry (following at least a 4-hour fast) and after eating a small standardized meal. Prior to scanning, participants were weighed and their height was recorded. Immediately prior to each of the scans (premeal and postmeal), participants were asked to rate their hunger on a visual analog scale (VAS) ranging from 1 to 100. The study was approved by the Human Subjects Committee of the University of Kansas Medical Center and the Institutional Review Board at the University of Missouri-Kansas City. All participants provided written informed consent.

## fMRI Food motivation paradigm

The block experimental paradigm is detailed in previous reports (19,20) and in Figure 1. Participants viewed pictures of food, animals, and blurred baseline images during two scanning sessions: (1) after fasting for at least 4 hours (pre-meal condition) and (2) immediately after eating a small uniform meal (postmeal) that was standardized for energy [kcal = 500] and micronutrient content (e.g., a weighed lean meat [turkey or ham] sandwich, carrot sticks, a piece of fruit, and skim milk). The order of sessions (premeal, postmeal) was counterbalanced across subjects. The caloric and macronutrient contents of the meals were matched across diet and surgical groups pre-intervention. The format of the foods (i.e., wraps vs. sandwiches) was different for the bariatric participants so they could adhere to postsurgical dietary guidelines.

Food and animal images were obtained from professional stock photography and matched to baseline images on brightness, resolution, and size. Animal (nonfood) images were used to control for general interest and visual richness. In a pilot image validation study, food and animal images were rated based on the extent to which they were appetizing, exciting (arousal), and pleasant (valence), using established methods (21). Selected food images were significantly more appetizing than selected animal images ( $P < 0.001$ ). No significant difference existed between the food and animal image groups with regard to valence ( $P = 0.55$ ) or arousal ( $P = 0.96$ ). These food and animal images were blurred so as to be unrecognizable with a phase randomized Fast Fourier Transform in MATLAB (The MathWorks, Natick, MA) program. Blurred images were used as baseline visual comparison stimuli to control for visual cortex activation during the paradigm. All images were presented once to each subject. Each functional scan involved three repetitions of each block of each stimulus condition type (i.e., food or animal), alternated between blocks of blurred images). This well-validated food motivation paradigm has been described in several published studies (19,22,23). Visual stimuli were projected from the stimuli-generating software (Presentation, Neurobehavioral Systems, Albany, CA) onto a screen. Stimulus presentation time was 2.5 seconds, with an interstimulus interval (ISI) of 0.5 seconds. Within each of the two functional scans there was a total of 13 blocks of stimuli presentation; within each block, 10 images were presented. The order of category presentation was counterbalanced across subjects.

## Image acquisition

Scanning was performed at the Hoglund Brain Imaging Center on a 3 Tesla head-only Siemens Allegra scanner (Siemens, Erlangen, Germany) fitted with a quadrature head coil. Participants' heads were immobilized with head cushions. Following automated scout image acquisition and shimming to optimize field homogeneity, a structural scan was completed. T1-weighted anatomic images were acquired with a 3D magnetization prepared rapid acquisition gradient echo sequence (TR/TE = 23/3.06 ms, flip angle = 8°, field of view [FOV] = 192 × 100 mm, matrix = 192 × 192, slice thickness = 1 mm) used for slice localization for the functional scans, Talairach transformation, and coregistration with fMRI data. After structural scans, two gradient echo BOLD scans were 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 skip, in-plane resolution = 3 × 3 mm, 130 data pts).

## Data analysis

Preprocessing steps included trilinear 3D motion correction, sinc-interpolated slice scan time correction, 3D spatial smoothing with 4-mm Gaussian filter, and high pass filter temporal smoothing. Functional images were realigned to the anatomic images obtained within each session and normalized to Talairach and Tournoux's stereotaxic atlas (24). Runs containing motion of more than 4 mm along any axis ( $x$ ,  $y$ , or  $z$ ) were discarded.

## Whole brain statistical analyses

Activation maps were generated using statistical parametric methods (25) and random effects in Brain Voyager QX (Brain Innovation, Maastricht, Netherlands, 2004). Statistical contrasts were conducted using multiple regression analysis with the general linear model, allowing multiple predictors to be built into the model. Regressors representing experimental conditions of interest were modeled with a hemodynamic response filter and entered into the multiple regression analysis. Contrasts between conditions of interest were assessed with  $t$ -statistics. Voxel values were considered significant if the activation survived a statistical cluster-based threshold ( $\alpha < 0.05$  [ $P < 0.01$ ,  $k = 7$  voxels]), determined by Monte Carlo simulation (26,27) to correct for multiple comparisons across whole brain. The results from one bariatric participant in the fed condition were removed because of motion on two runs in excess of 4 mm. Separate 3-way ANOVAs (Group × Condition × Stimulus) were performed for the hungry and fed conditions. First, analyses were conducted *premeal* while participants (diet vs. bariatric) were hungry using a Condition (Preweight loss, Postweight loss) × Stimulus (Food, Nonfood) repeated measures ANOVA model. Next, analyses were conducted *postmeal* (diet vs. bariatric) after participants had been fed also using a Condition (Preweight loss, Postweight loss) × Stimulus (Food, Nonfood) repeated measures ANOVA model. Statistical parametric maps were overlaid on three-dimensional renderings of an averaged-group brain.

## Results

### Self-reported hunger ratings

We conducted independent samples  $t$ -tests for the VAS hunger ratings taken prior to the pre-meal scans. Behavioral diet and bariatric groups did not differ significantly on VAS hunger ratings taken

**TABLE 2** Regions reaching significance for the contrasts between food and nonfood stimuli categories between groups

Contrast and Region	Coordinates				Extent of activation (mm <sup>3</sup> )
	x	y	z	t	
Premeal (Hungry)					
Diet patients > Bariatric patients					
Right Medial prefrontal cortex BA 9	6	50	19	3.72	216
Left Precuneus BA 19	-30	-67	40	4.04	567
Bariatric patients > Diet patients					
None					
Postmeal (Fed)					
Diet patients > Bariatric patients					
None					
Bariatric patients > Diet patients					
Right Middle Temporal gyrus	48	-55	7	3.98	216
Left Inferior temporal gyrus/occipital	-42	-64	-2	4.82	783

$\alpha < 0.05$ , corrected, random effects.

prior to the premeal scans ( $P > 0.1$ ,  $t$ -test). We conducted independent samples  $t$ -tests for the VAS hunger ratings prior to the postmeal (fed) scans as well. Again, behavioral and bariatric groups were not significantly different ( $P > 0.1$ ). In contrast, both groups reported substantially decreased hunger following the meal ( $P$ 's  $< 0.001$ ).

When participants were collapsed across treatment groups (diet, bariatric), independent samples'  $t$ -tests revealed that before the weight loss intervention there were group differences in hunger ratings before the pre-meal scan between those who had the pre-meal scan first ( $M = 60.4$ ) vs. those who had the postmeal scan first ( $M = 30.6$ ); [ $t(28) = 3.5$ ;  $P = 0.002$ ]. However, the percentage of participants in each of the groups (premeal scan first, postmeal scan first) did not differ by treatment group [ $\chi^2 = 0.29$ ,  $P = 0.59$ ]. There were no significant group differences before the weight loss intervention between hunger ratings before the postmeal scan. Further, there were no significant differences after the weight loss intervention in hunger ratings premeal or postmeal.

### Hungry: diet vs. bariatric $\times$ pre to post weight loss interaction

In the premeal Condition (Pre-, Post-weight loss)  $\times$  Stimulus type (Food, Nonfood) interaction, diet participants showed significantly greater changes in right medial prefrontal cortex (Figure 2) and left precuneus. Bariatric participants showed no significantly greater changes in brain activation from pre- to post-weight loss than diet participants (Table 2).

### Fed: diet vs. bariatric changes $\times$ pre to post weight loss interaction

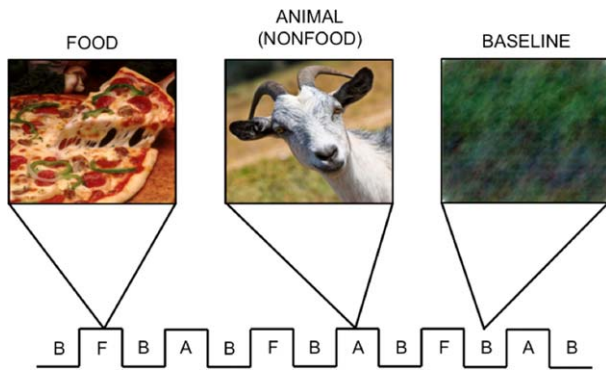
In the Postmeal Condition (Pre-, Post-weight loss)  $\times$  Stimulus type (Food, Nonfood) interaction, bariatric participants showed signifi-

cantly greater changes in bilateral temporal cortex (Figure 3). Diet participants showed no significantly greater changes pre to post weight loss than bariatric participants (Table 2).

## Discussion

We compared brain activation changes associated with weight loss in individuals who underwent behavioral diet intervention vs. laparoscopic banding surgery. This study provides the first evidence of the neural mechanisms supporting weight loss in two distinct methods of successful, intentional weight loss. Both diet and surgical participants have altered brain activations in response to visual food cues following weight loss. However, changes in activation patterns were different in the two treatment groups.

Consistent with our hypotheses, we observed significant activation changes for behavioral diet weight loss participants compared to surgical participants in brain regions associated with self-referential processing and valuation when participants were hungry. Interestingly, not only did diet weight loss participants demonstrate increases in medial prefrontal cortex activation, the bariatric weight loss participants demonstrated decreases in medial prefrontal cortex activation. This could be because of the behavioral dieters experiencing greater salience and importance when viewing food cues. Behavioral and recent neuroimaging data demonstrate that if one voluntarily restricts one's intake of food, the reward value, attentional bias, and salience of food cues increase (28). The bariatric participants, on the other hand, showed decreased activation in medial prefrontal cortex, which supports the notion that surgical weight loss patients undergo a "forced" dietary restriction in avoiding discomfort that renders food cues to be less rewarding and less salient. This may be evident in our observed decreases in medial prefrontal cortex activation in surgical participants. Bariatric

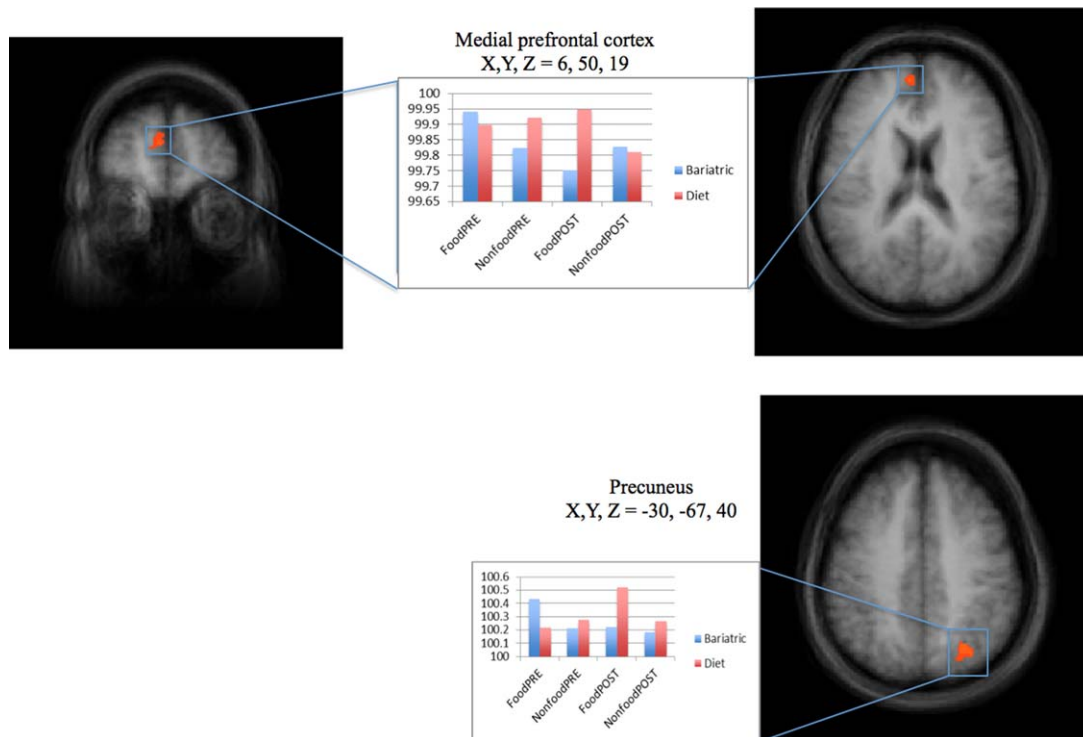


**FIGURE 1** fMRI cognitive activation paradigm (block design) of visual stimuli: food, animals, and blurred baseline images.

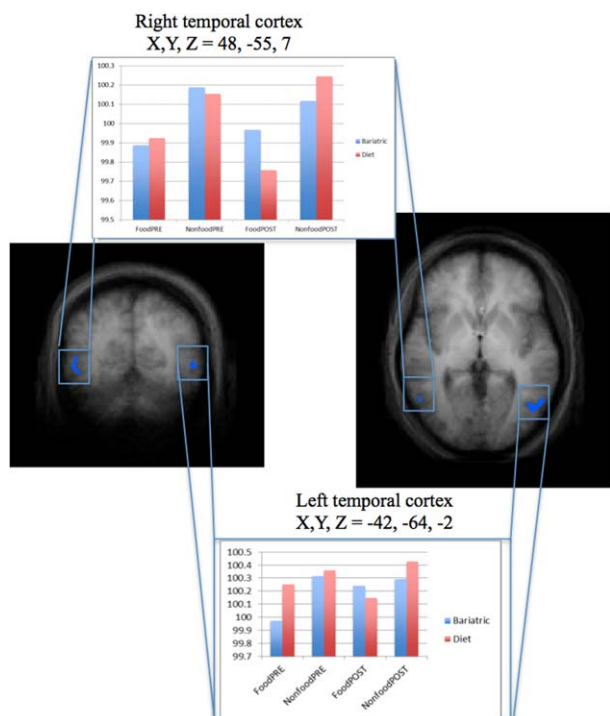
participants may be also more disconnected from the self-referent experience of hunger. In Hare and colleagues' study (29), healthy weight individuals who were classified as "self-controllers" had greater activation in medial prefrontal cortex, consistent with our findings. It may be that the bariatric participants have the salience of food and self-referential thought decreased through the surgically placed laparoscopic band. Converging evidence from Ochner and colleagues (17) demonstrated decreased activations in ventromedial and dorsolateral prefrontal cortex in a fasted state after Roux-en-Y surgical participants had lost weight.

Also in the hungry condition, we observed significant changes in the precuneus, parallel to the medial prefrontal cortex changes. The diet weight loss participants showed increases in precuneus activity after losing weight, whereas the bariatric participants showed decreases. The decreased activity in precuneus demonstrated by bariatric participants is consistent with a study by Murdaugh and colleagues (15), showing decreased activation to food pictures in precuneus post-weight loss. The precuneus is associated with the fronto-parietal network of theory of mind and mental representations of the self (30,31), therefore making the changes similar to medial PFC. Precuneus and posterior cingulate have been shown in other studies to be associated with the salience and relevance of stimuli, independent of valence (32,33). The medial PFC and precuneus may be working together to facilitate both increased valuation and salience of food-related cues in the behavioral diet group of participants.

Results did not support our hypothesis that participants would exhibit differential significant changes in reward-processing regions of the brain for diet participants or for surgical weight loss participants in hungry or fed states. This is consistent with Murdaugh and colleagues (15) who did not find changes in traditional reward brain regions in dieting participants. However, this is contrary to other findings in Roux-en-Y surgical patients, who demonstrated reduced activation in striatum (18). However, their patients may have experienced greater levels of hunger and higher food motivation, as they were in a fasted state of 12 hours, whereas we only requested patients to fast for 4 hours to reflect a more typical, ecologically valid eating schedule. If we had scanned participants after a longer fasted state or during delivery of a rewarding food stimulus, we may



**FIGURE 2** Regions showing significantly greater change in the behavioral diet group vs. the bariatric group in right medial prefrontal cortex, and left precuneus to food vs. nonfood pictures in the premeal condition.



**FIGURE 3** Postmeal, the bariatric group showed significantly greater change to food vs. nonfood images in bilateral temporal cortex compared to the diet group.

have observed reduced brain activation in reward regions. We did not observe brain activation changes in any reward or self-control regions, which is similar to Ochner et al. (17), who reported no brain activation changes in reward or self-control regions after weight loss when patients were in a fed state.

Findings postmeal indicated increases in bilateral temporal cortex in bariatric participants compared to behavioral diet participants. Activations in middle temporal cortex are commonly reported in studies of food motivation and are associated with higher level perception including visual and semantic processing, and semantic memory (34,35). Rosenbaum and colleagues (14) reported increases in middle temporal cortex in patients who underwent an inpatient liquid diet weight loss program. Increases in temporal cortex have also been reported in studies using positron emission tomography (PET) following food deprivation (36). It is possible that food cues evoke more semantic processing for those who have undergone a more drastic weight loss procedure (such as a surgery or an inpatient liquid diet) but further research is needed.

This is the first study of brain changes associated with two different methods of weight loss. Using two successful weight loss strategies, a behavioral weight loss intervention and a laparoscopic banding surgical intervention, we demonstrated that the functional brain changes observed may not be because of decreased body mass alone, but appear to be associated with the process by which weight loss is achieved. One of the major strengths of the study is that the participants in two different weight loss interventions were matched on demographics and on the percent of weight lost during the 12-


week period. Though we found evidence of neural change in areas associated with food motivation and reward after weight loss, our sample size was relatively small, and we are unable to fully dissect the mechanism of this change. One limitation is that participants were not randomized to treatment group. Another limitation is the lack of a control group, which should be included in future work. Although the standardized meals differed in that bariatric participants received a wrap instead of the bread eaten by diet participants, because the groups were matched on BMI, the percentage of daily caloric needs was consistent across groups. In addition, we found that hunger ratings in both the hungry and fed states were not significantly different. Diet and bariatric groups did not report different hunger levels before or after eating the provided meal. We did observe differences in the hunger ratings in the premeal scan based on the order of scans, such that participants who were assigned to the premeal scan first reported greater hunger than those who had the premeal scan second. This effect, however, was minimized because of the equal division of scan order across the diet and bariatric groups.

There were also some differences in baseline characteristics between the groups. Some bariatric patients had well-controlled diabetes whereas none of the dieters had a diabetes diagnosis. Although dieters included in the study reported that they had not lost weight in the six months prior to intervention, bariatric patients frequently dieted prior to surgery. Finally, some of the bariatric group used antidepressant medication. It should be noted that the aforementioned differences between the groups are those of which we are aware. Individuals who seek out and submit to an obesity intervention like laparoscopic banding surgery may have a longer history with weight problems and may possess more diverse psychological characteristics than those enrolling in a dieting weight loss intervention. However, the matching on demographic characteristics and percent of weight lost during the 12-week intervention helped control for some of the potential differences. Longitudinal research that includes matched obese controls and measures of behavior and hormonal change may better elucidate the mechanisms associated with brain changes following gastric banding and behavioral weight loss.

This fMRI study is the first to examine the longitudinal effects of diet versus surgical weight loss on brain function. It provides evidence not only that brain responses are altered in response to weight loss, but that the brain responses might be specific to the method of weight loss. Results suggest that weight loss differentially changes brain functioning, specifically in areas known to be related to food motivation, the experience of hunger, and other aspects of self-referent processing. Findings have potential clinical implications, including using obesity interventions to target specific brain activation changes. Some experts have called for the development of “knifeless” pharmacological and/or behavioral treatments for the prevention and treatment of obesity (37). Ultimately, this knowledge may be used to improve the effectiveness of interventions for health behavior change.

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