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Resting-State Brain Connectivity After Surgical and Behavioral Weight Loss

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Objective: Changes in food-cue neural reactivity associated with behavioral and surgical weight loss interventions have been reported. Resting functional connectivity represents tonic neural activity that may contribute to weight loss success. This study explores whether intervention type is associated with differences in functional connectivity after weight loss.

Methods: Fifteen participants with obesity were recruited prior to adjustable gastric banding surgery. Thirteen demographically matched participants with obesity were selected from a separate behavioral diet intervention. Resting-state functional magnetic resonance imaging was collected 3 months after surgery/behavioral intervention. ANOVA was used to examine post-weight loss differences between the two groups in connectivity to seed regions previously identified as showing differential cue-reactivity after weight loss.

Results: Following weight loss, behavioral dieters exhibited increased connectivity between left precuneus/superior parietal lobule (SPL) and bilateral insula pre- to postmeal and bariatric patients exhibited decreased connectivity between these regions pre- to postmeal ($P_{corrected}<0.05$).

Conclusions: Behavioral dieters showed increased connectivity pre- to postmeal between a region associated with processing of self-referent information (precuneus/SPL) and a region associated with interoception (insula) whereas bariatric patients showed decreased connectivity between these regions. This may reflect increased attention to hunger signals following surgical procedures and increased attention to satiety signals following behavioral diet interventions.

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Introduction

Functional neuroimaging has improved our understanding of the hedonic brain systems associated with food motivation and obesity. While reports of resting-state functional connectivity differences based on obesity status are emerging (1-6), differential connectivity associated with weight loss method has not been examined. Intrinsic resting brain connectivity may elucidate tonic neural activity, which may be critical in understanding the underlying neural mechanisms that lead to successful weight loss.

In task-based functional magnetic resonance imaging (fMRI) studies, bariatric surgery has been associated with decreased activation to food cues in both cognitive control and reward regions (7,8).

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Reduction in activation to food cues after surgery is also associated with decreased desire for calorically dense foods (9). We recently showed (10) that behavioral weight loss is associated with increased activation to food images in self-referential processing, valuation [e.g., medial prefrontal cortex (MPFC)], and salience (e.g., precuneus/superior parietal) regions, whereas surgical weight loss is associated with increased cue-reactivity in sensory processing regions (e.g., middle, inferior temporal cortex). This suggests that different methods of weight loss could affect brain responses to food-based stimuli.

The purpose of the present study was to explore whether those brain regions that show differential changes in food-cue reactivity after behavioral and bariatric weight loss interventions (10) also exhibit different resting-state functional connectivity after weight loss. Based on our task results (10), we hypothesized that behavioral dieters would show greater connectivity with valuation and salience regions [i.e., MPFC and precuneus/superior parietal lobule (SPL)], and that bariatric patients would show greater connectivity with sensory processing regions (i.e., middle and inferior temporal cortex). We also hypothesized that functional connectivity would be sensitive to hunger state and would differ between intervention groups following weight loss.

Methods

Participants/recruitment

Participants were not randomized to treatment condition. They were selected from independent sources of candidates who had decided to undergo bariatric weight loss surgery or enroll in a behavioral weight loss intervention research study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Surgical participants. Obese (body mass index (BMI) 30-45 kg/m^2) participants ($n = 15$; three males; age $= 41.40 \pm 9.80$; education $= 13.85 \pm 1.95$ years) planning to undergo adjustable gastric banding weight loss surgery (LapBand®) were recruited from two surgical sites.

Diet participants. Thirteen obese diet participants [four males; age $= 40.23 \pm 8.01$; education $= 15.31 \pm 1.93$ years (some college)] were selected to match demographically with the bariatric group, blind to imaging data, from a larger behavioral weight loss clinical trial ($N = 120$) [NIH DK080090; NCT02031848] recruited via advertisements, and a university-based weight management center. Participants underwent a 3-month weight loss intervention of behavioral strategies, moderate calorie restriction with provided prepackaged meals, and physical activity.

Special diets (e.g., vegetarian and Atkins), appetite or metabolic medications (e.g., thyroid, beta blockers, and Meridia), smoking, and diabetes were exclusions for the diet participants. Because most patient presenting for bariatric surgery have comorbid health conditions, patients who had well-controlled diabetes (most recent hemoglobin A1c<7) and were not taking insulin or other injectable medications (i.e. GLP-1 agonists) were included in the bariatric group. Additional exclusion criteria for both groups included current eating disorder, current major depression, history of neurological disease, pregnancy within the past 6 months, cancer, heart disease, and contraindications for MRI (e.g., metal implants). Participants taking selective serotonin reuptake inhibitors (SSRIs) were included in the bariatric group.

One bariatric participant was unable to complete the resting-state scan and another participant's data were unusable due to excess movement (i.e., greater than 50% censored) during the scan (11). Diet participants with unusable resting-state data were not selected for this study. Therefore, 13 Bariatric participants and 13 Diet participants were included in the final analyses. No significant differences between the final bariatric and diet groups were observed for age [$t(24) = 0.49$; $P = 0.63$], education [$X^2(3) = 3.93$; $P = 0.27$], sex [$X^2(1) = 0.87$; $P = .35$], pre-intervention BMI [$t(24) = 1.68$; $P = 0.11$], or percent weight lost [$t(24) = 0.99$; $P = 0.33$]. Additional demographic and anthropometric data are included in Table 1.

Procedures

Resting-state data were collected 3 months before the intervention. To investigate changes that accompany typical mealtime eating behavior, participants were scanned while hungry (Premeal; following at least a 4-hour fast) and after eating a small, standardized (500 kcal) lunch (Postmeal). As dietary restrictions on certain foods (i.e., bread products) are in place following bariatric surgery, the format of the meal was slightly different between the two groups. Specifically, the bariatric participants' meal included a lean meat (turkey or ham) wrap, while diet participants' meal included an equivalent sandwich. Both groups reported similar levels of satiation postmeal (0-100 visual analog scale, "How full do you feel right now?": Bariatric $= 67.92 \pm 32.29$; Diet $=74.92 \pm 22.63$; $t(24) = -0.64$, $P = 0.53$). Order of scans (Premeal, Postmeal) was counterbalanced across participants (Figure 1). The resting-state scan (6 min 36 s) followed a structural scan and two functional scans while passively viewing food and animal pictures (7,10). Participants were instructed to close their eyes during the resting-state scan. The entire scanning session lasted ~45 min.

fMRI data acquisition

Data were acquired with a 3-Tesla Siemens Allegra, head-only MRI scanner. To minimize susceptibility artifact in ventromedial prefrontal regions, participants were positioned so that the angle of the AC–PC plane was between 17° and 22° in scanner coordinate space (12). T1-weighted anatomic images were acquired with a 3D MPRAGE sequence (repetition time (TR)/echo time (TE) = 23/4 ms, flip angle = 8°, field of view = 192 mm, matrix = 192 mm × 192 mm, 208 slices, slice thickness = 1 mm). Task-based and resting-state gradient echo blood oxygenation level-dependent (BOLD) scans were acquired in 43 contiguous axial slices at an angle of 40° to the AC–PC line (TR/TE 3,000/30 ms, slice thickness = 3 mm (0.5 mm skip), in-plane resolution = 3 mm × 3mm, 130 volumes).

Data preprocessing

Data preprocessing and statistical analysis were conducted using Analysis of Functional NeuroImages (AFNI) (13), and a modified version of the ANATICOR method, developed by Jo et al., implemented in afni_restproc.py (14). The first four volumes of the functional scans were removed and a de-spiking interpolation algorithm (i.e., 3dDespike) was used to remove any transient signal spikes

TABLE 1 Demographic and anthropometric characteristics for participants included in the analyses

Group	Male/female	Age [years] (mean ± SD)	BMI–baseline [kg/m^2] (mean ± SD)	BMI–post-intervention (mean ± SD)	BMI–percent change (mean ± SD)
Bariatric surgery intervention	2/11	42.00 ± 10.35	41.35 ± 1.97	37.43 ± 2.73	−9.50% ± 4.32%
Behavioral diet intervention	4/9	40.23 ± 8.01	40.10 ± 1.80	35.62 ± 2.22	−11.16% ± 4.19%

Body mass index (BMI) is calculated as body weight (in kilograms) divided by height (in meters) squared.

from the data. The volumes were slice time corrected and co-registered to the first volume (which was registered to the anatomical scan). Several nuisance variables were measured [i.e., six motion parameters (three translations, three rotations), average ventricle signal, and average local white matter signal (15 mm spherical neighborhood, 3dLocalstat)]. These nuisance variables' predicted timecourse was constructed and then subtracted from each resting-state voxel time course using multiple regression, yielding a residual timecourse for each voxel. The residual images were smoothed with a 6 mm FWHM Gaussian kernel, resampled to a 2 mm ×2 mm ×2 mm grid, and spatially transformed to stereotaxic space conforming to the Talairach and Tournoux Atlas (15).

Further motion correction procedures (i.e., scrubbing) were utilized to reduce false group differences due to uncontrolled subject motion (16,17). The six motion parameters from the image registration process were used to construct a time series reflecting the Euclidean normalized derivative of the motion. This time series was thresholded so that any time point where the derivative was greater than 0.3 (roughly 0.3 mm motion) was censored. We also censored any time point where more than 5% of brain voxels were considered outliers (3dToutcount). Time points censored by the union of both methods were removed in the subsequent regression analysis. The percentage of data removed in this manner did not differ between the two groups [$t(24) = 1.21$; $P = 0.24$; Bariatric = 11.9 ± 9.2%; Diet = 8.0 ± 7.4%], nor did it differ between imaging sessions [Wilks' $\lambda = 0.96$; $F(3, 24) = 1.12$; $P = 0.30$; $\eta^2 = 0.05$].

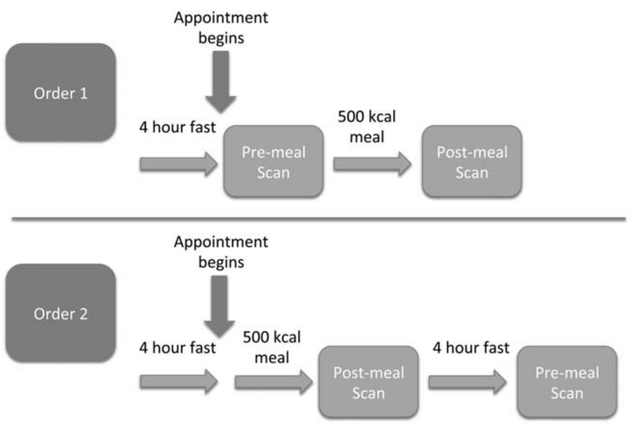

Figure 1 Participants were randomized to receive one of two counterbalanced scanning orders. Half of the participants were scanned premeal, then ate a 500 kcal meal and immediately were scanned postmeal. The other half ate the 500 kcal meal upon arrival for their appointment and were immediately scanned post-meal, then waited for 4 hours and were scanned premeal.

Seed regions were defined as 5 mm radii spheres in regions identified in our previous food-cue reactivity study: MPFC (Talairach (TAL)$X,Y,Z = 6,50,19$), precuneus/SPL (−30, −67,40), right middle (48,−55,7) and left inferior temporal gyrus (−42,−64,−2) (10). At the subject level, the four seed time series (MPFC, precuneus/SPL, right middle, and left inferior temporal gyrus) were constructed by calculating the average time series over the voxels within each of the seed regions. Using multiple regression, we produced for each seed a map of the correlations (r-values) between the seed time series and each voxel in the brain. These r-values were transformed to z-scores. While the motion scrubbing procedure described above removes time points most affected by motion artifact, datasets with more motion may still contain residual effects. These effects may induce spurious correlations in an individual data set and increase noise in the overall sample, reducing power. As an additional conservative approach to minimize effects of motion, z-score maps for each dataset were weighted by multiplying the participant's percentage of TRs remaining after censoring by the z-score at each voxel (e.g., 100% TRs included, weighting factor = 1; 65% included, weighting factor = 0.65). This additional step ensures that participants who moved least contribute more to the final group analyses, while those who moved more contribute less (18).

We implemented two-way mixed effects ANOVA comparing weighted z-scores for fixed-effects of Group (Diet, Bariatric) × Satiety (Premeal, Postmeal) with Participants as random effects. To elucidate differences in functional connectivity to those regions that were previously identified as showing cue-reactivity changes after weight loss, these analyses focus on data collected after the 3-month weight loss intervention (Post-intervention) that each group underwent (either a diet/behavioral intervention, or bariatric surgery), as well as the effect of satiety (Premeal vs. Postmeal). These F-statistic maps were corrected for multiple comparisons at $\alpha<0.05$ using a voxel-wise threshold of $P<.005$, combined with Monte Carlo simulations of minimum cluster size (616 mm^3) determined for the whole brain (19).

Results

For the ANOVA seeded in the left precuneus/SPL (Table 2), there was a significant main effect of intervention type (Bariatric vs. Diet) in the middle temporal gyrus ($P_{corrected}<0.01$). Collapsed across intervention groups, there was no main effect of satiety (Premeal vs. Postmeal) in resting-state correlations with the left precuneus/SPL.

TABLE 2 Resting-state functional connectivity with left precuneus/SPL 3 months post-intervention (behavioral or bariatric surgery)

Region	L/R	BA	X	Y	Z	$P_{corrected}$	mm^3
Intervention main effect							
Middle temporal gyrus	L	39	−39	−69	18	<0.01	944
Satiety main effect							
None							
Intervention × satiety interaction							
Precentral gyrus/Insula	R	4	53	−9	24	<0.01	1,624
Middle occipital gyrus	L	19	−45	−77	8	<0.01	1,384
Superior temporal gyrus	R	22	55	−37	20	<0.01	1,128
Insula	L	13	−41	1	12	<0.02	784

However, there were significant interactions in functional connectivity between satiety (Pre- to Postmeal) and intervention type (Diet vs. Bariatric) between the left precuneus/SPL and the following regions: right precentral gyrus, spreading into insula ($P_{corrected} < 0.01$), left middle occipital gyrus ($P_{corrected} < 0.01$), right superior temporal gyrus ($P_{corrected} < 0.01$), and left insula ($P_{corrected} < 0.02$). Figure 2 illustrates the directionality of these interactions. After the intervention, bariatric participants showed greater functional connectivity between left precuneus/SPL and right precentral gyrus and insula, left middle occipital gyrus, right superior temporal gyrus, and left insula prior to eating compared to the diet participants. Additionally, resting-state functional connectivity changed differentially between the groups after going from a fasted state to a fed state, such that correlations between left precuneus/SPL and each of these regions increased from premeal to postmeal for those in the diet intervention and decreased for those in the bariatric intervention.

No significant main effects or interactions were found for the ANOVA seeded from the MPFC; however, some trends were observed (Table 3). There was a subthreshold main effect of satiety in the posterior cingulate ($P_{corrected} < 0.09$). Subthreshold interactions between satiety and intervention type were observed in the left dorsolateral prefrontal cortex ($P_{corrected} < 0.08$), and the left superior frontal cortex ($P_{corrected} < 0.08$; Figure 3). No significant effects were found for the ANOVAs seeded from either temporal cortex region (all $P\text{'s}_{corrected} > 0.10$).

Discussion

The goal of the current study was to determine whether regions of the brain that showed differential changes in food-cue reactivity after weight loss dependent on weight loss method (i.e., surgical or behavioral) also exhibited group differences after weight loss in functional connectivity with the rest of the brain. Consistent with our hypotheses, we found that the precuneus/SPL and bilateral insula connectivity changed differentially pre- to postmeal depending on whether the participants had completed a behavioral or surgical weight loss intervention. We used the dorsal and lateral part of the precuneus/SPL as a seed for these connectivity analyses, a subregion previously shown to be differentially associated with reactivity to food cues in surgical versus behavioral weight loss (10). This region is also involved in mental imagery involving motor planning and self-awareness (20-23). Differential connectivity was found between the precuneus/SPL and insular regions associated with interoception (24,25). The groups not only show differential connectivity between these two regions of the brain when fasted, but also demonstrate oppositional change in connectivity strength after a meal.

This pattern of connectivity could reflect differences in interoceptive signaling and awareness that may have led to weight loss. Hunger and satiety are components of interoceptive signaling that lead to initiation and cessation of food intake. Though only speculative, greater functional connectivity between the precuneus/SPL and insula could indicate greater interoceptive self-awareness. If true, those individuals who have lost weight through surgery may be more aware of internal bodily signals of hunger, while signals of satiety may be more automatic due to the physical restrictions placed on the stomach through surgery. Alternatively, individuals who have successfully lost weight through dieting may have greater awareness of bodily signals monitoring feelings of fullness to know when to stop eating. These differences in connectivity are not due to differences in weight loss success between groups, as there were no differences in the amount of weight lost between the two groups.

Contrary to expectations, this study found no significant differences in connectivity to either medial prefrontal or temporal cortex. A marginal effect of satiety was found between MPFC and posterior cingulate, and a marginal interaction of satiety and intervention type was found between MPFC and middle and superior frontal cortex. The lack of significance may be due to our modest sample size. Accordingly, our subthreshold results should be interpreted cautiously. One of the strengths of this study is that the analysis was focused on functional connectivity with *a priori* regions that showed differential responsiveness to food cues in these same subjects (10). Due to limited sample size, we have avoided further exploratory analyses. Nevertheless, it is possible that intervention type may differentially impact connectivity patterns with the default mode or salience networks, as has been shown in other recent work in obesity (1-6).

This study is limited by the fact that the groups were not selected via random assignment. Pre-existing factors could lead individuals to consider surgical versus behavioral weight loss. Also, since the bariatric surgery group all underwent laparoscopic gastric banding, results cannot be extended directly to gastric sleeve or gastric bypass patients. Additionally, the groups were not matched for comorbid conditions, such as diabetes, however, in the bariatric surgery group, only those participants with well-controlled diabetes were included.

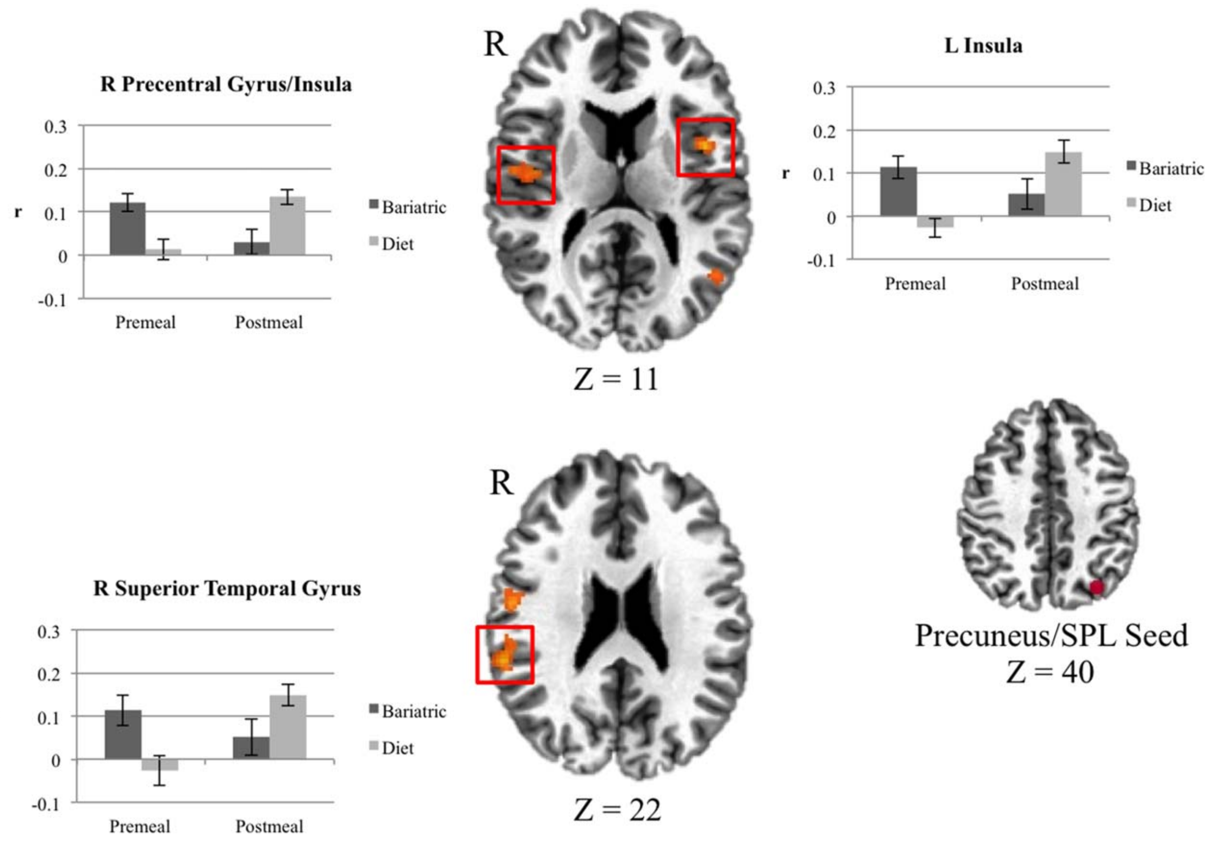

Figure 2 Maps show the interaction between intervention type and satiety on voxel-wise correlations with the precuneus/SPL seed. At 3 months post-intervention, correlations between left precuneus/SPL and right precentral gyrus, right insula, and left insula increased from premeal to postmeal for those in the diet intervention and decreased for those in the bariatric intervention ($P_{corrected}$<0.05). Error bars denote standard error. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

That said, we carefully matched the groups on demographics, pre-intervention BMI, as well as the total weight lost during the intervention. Therefore, results are not simply due to differential treatment effectiveness. Other factors that were not measured in this study, such as menstrual cycle phase for female participants, could also lead to differences in brain connectivity patterns (26-28). In this study, the intervention groups were matched for gender and age, and both men and women were included in the analysis. Therefore, it is unlikely that the results were systematically biased by menstrual cycle phase. It is also unknown whether possible physical activity differences between the groups could influence functional connectivity (4). All surgical participants were under the care of a physician, and physical activity recommendations were monitored on an individual level. Those in the behavioral diet intervention were under standardized physical activity guidelines according to the intervention. As the two groups received different instructions for physical

TABLE 3 Resting-state functional connectivity with right medial prefrontal cortex 3 months post-intervention (behavioral or bariatric surgery)–subthreshold effects

Region	L/R	BA	X	Y	Z	$P_{corrected}$	mm^3
Intervention main effect							
None							
Satiety main effect							
Posterior cingulate	R	7	11	−49	32	<0.09	568
Intervention × satiety interaction							
Middle frontal	L	6	−39	1	50	<0.08	576
Superior frontal	L	6	−13	15	58	<0.08	584

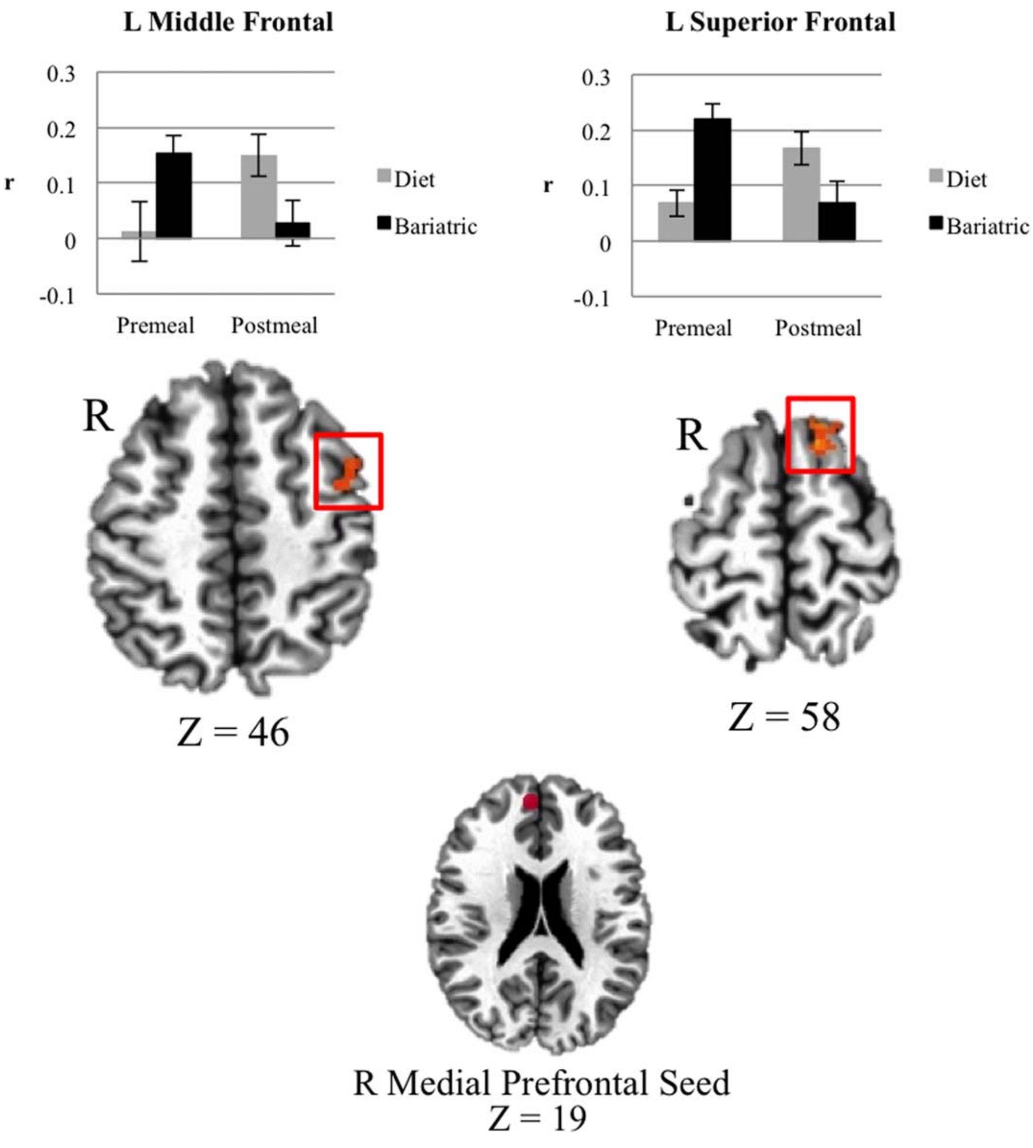

Figure 3 Maps show the interaction between intervention type and satiety on voxel-wise correlations with the MPFC seed. Although subthreshold, at 3 months post-intervention, correlations between right MPFC and left middle and superior prefrontal cortex increased from premeal to postmeal for those in the diet intervention and decreased for those in the bariatric intervention ($P_{corrected} < 0.10$). Error bars denote standard error. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

activity, we cannot confidently conclude that physical activity levels were the same for both groups. Care should be taken in future studies to control for these additional variables.

In conclusion, method of weight loss seems to be related to differential connectivity between regions of the brain involved in self-imagery and interoception, as well as differences in whether that connectivity emerges during states of hunger or satiety. Surgery may lead individuals to increase attention to bodily signals of hunger, whereas successful dieting may require more attention to signals of fullness. While both methods are effective for initial weight loss, patterns of functional connectivity in the brain suggest differences in the underlying mechanisms associated with weight loss approaches. Future research should examine whether these neurofunctional differences are maintained over time in extended longitudinal studies, and how they may be related to successful weight loss maintenance. O

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