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Brain response to food stimulation in obese, normal weight, and successful weight loss maintainers

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Abstract

As many people struggle with maintenance of weight loss, the study of successful weight loss maintainers (SWLM) can yield important insights into factors contributing to weight loss maintenance. However, little research has examined how SWLM differ from people who are obese or normal weight (NW) in brain response to orosensory stimulation. The goal of this study was to determine if SWLM exhibit different brain responses to orosensory stimulation. Brain response to one-minute orosensory stimulation with a lemon lollipop was assessed using functional magnetic resonance imaging (fMRI) among 49 participants, including SWLM (n=17), NW (n=18) and obese (n=14) controls. Significant brain responses were observed in nine brain regions, including the bilateral insula, left inferior frontal gyrus, left putamen, and other sensory regions. All regions also exhibited significant attenuation of this response over one minute. The SWLM exhibited greater response compared to the other groups in all brain regions. Findings suggest that the response to orosensory stimulation peaks within 40 seconds and attenuates significantly between 40-60 seconds in regions associated with sensation, reward, and inhibitory control. Greater reactivity among the SWLM suggests that greater sensory reactivity to orosensory stimulation, increased anticipated reward, and subsequently greater inhibitory processing are associated with weight loss maintenance.

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DISCLOSURE

There are no conflicts of interest.

Keywords

Functional Magnetic Resonance Imaging; Functional Neuroimaging; Weight Loss Maintenance

INTRODUCTION

Long-term weight loss maintenance remains elusive for many overweight and obese individuals (2). As a result, efforts to better understand factors that contribute to successful weight loss maintenance are of particular interest. The National Weight Control Registry (NWCR) was established by members of our research team (Dr. Wing) to study successful long-term weight loss. To be eligible, individuals must maintain at least a 13 kg (30 lb) weight loss for 1 year or longer. On average registry members have lost over 27 kg (60 lb) prior to enrolling and have maintained at least the 13 kg weight loss for an average of 6.5 ± 8.1 years. NWCR research indicates that successful weight loss maintainers (SWLM) report low-calorie, low-fat diets, frequent self-weighing, and high levels of physical activity. SWLM also report higher levels of dietary restraint than obese or always NW controls. However, little work to date has characterized how SWLM respond to the sensory characteristics of food.

Recently, our research team has begun to investigate the neural correlates of presentation of food and food cues in obese and SWLM. Del Parigi and colleagues showed that in response to the sensory experience of a liquid meal, SWLM exhibited increased neural activity in the middle insular cortex, a region associated with sensory experiences, food reward, and craving (4). The increased response in SWLM was similar to an obese group and greater than normal weight (NW) individuals. In other work, Del Parigi and colleagues reported that SWLM (i.e., successful dieters) exhibited greater response to meal consumption in the dorsal prefrontal cortex (DPFC), dorsal striatum and anterior cerebellum compared to non-dieters (5). More recently, McCaffery and colleagues reported that SWLM show increased activity in frontal cortical areas in response to food images compared to NW and obese individuals (6). Thus, relative to obese and NW, SWLM appear to be characterized by increased responsiveness to food stimulation in brain regions, including the insula, dorsal striatum and frontal cortex.

To date, none of these investigations have considered the temporal course of these brain responses. Previous research on salivary response to food cues has shown that slower across-trial habituation rates are related to greater food intake, and that obese individuals habituate slower than NW individuals or SWLM (26-27). Here we assess whether SWLM, obese, and NW individuals differ in regional brain responses to short-term sustained (60 s) orosensory stimulation. FMRI provides the temporal and spatial resolution needed to examine the short-term temporal dynamics of the neural response to sustained orosensory stimulation. Given prior findings on reactivity to food and food cues (4-6), we hypothesized that SWLM would exhibit greater brain responses to orosensory stimulation in regions involved in the sensation and perception of food (e.g., insula), motivational/reward responses (e.g., striatum), and cognitive inhibition (e.g., frontal cortex) compared to the other groups. We also sought to determine whether this heightened responsivity to sustained

orosensory stimulation in SWLM would remain elevated over time or whether response decay would occur more quickly than in obese or NW. Finally, we examined the possibility that the brain response might change across stimulus presentations as suggested by salivary habituation literature (26-27).

METHODS AND PROCEDURES

Participants

Participants included three groups defined by lifetime weight history. The first group, labeled “normal weight (NW)”, reported a current and lifetime maximum BMI of >18.5 and 25 kg/m^2 . The second group included obese subjects with a current BMI ≥ 30.0 . The third group, labeled “successful weight loss maintainers (SWLM)”, reported having lost $\geq 13 \text{ kg}$ (30 lbs) and having maintained $\geq 13 \text{ kg}$ (30 lbs) weight loss from their maximum weight for a minimum of three years, a lifetime maximum BMI ≥ 30.0 and a current BMI >18.5 and ≥ 27 . All reported being weight stable (within 10% for the two previous years). Eighteen NW, 14 obese and 17 SWLM completed the study.

Additional exclusion criteria included weight loss medications, medications that affect salivation (such as antihistamines or antidepressants), binge eating, standard MRI contraindications (e.g., metal implants, claustrophobia, pregnancy), left-handedness, food allergies, and neurological or psychiatric conditions, including but not limited to schizophrenia, bipolar disorder, epilepsy, stroke and traumatic brain injury with loss of consciousness.

NW and obese participants were recruited using advertisements and SWLM were recruited through the National Weight Control Registry (NWCR) and advertisements. The study was conducted from April 2006 – December 2007. The protocol was approved and monitored by University and Hospital institutional review boards according to the Helsinki declaration. All participants provided written informed consent.

Orosensory paradigm

The orosensory paradigm was presented in 1-min trials averaged across 10 trials during ten 1-min imaging runs. Each participant was instructed to place the lollipop on their tongue and hold it on their tongue using their right hand for the duration of 1-min. The 1-min imaging run was then initiated while the participant remained motionless with the lollipop on the tongue. Participants were trained on this procedure outside of the scanner prior to beginning the experiment. There were 30-s intervals between consecutive trials.

Procedures

All participants refrained from food and beverages other than water for 4 hours prior to scanning. Participants also refrained from more than two alcoholic beverages (29 mL (1 oz) hard liquor equivalent) or two equivalents of 236 mL (8 oz) of caffeinated coffee in the prior 24 hours. The Eating Inventory (29), a self-report instrument used to assess levels of dietary restraint and disinhibition, was administered prior to scanning. Items on the restraint subscale reflect behaviors used to control dietary intake (e.g., “consciously control my

intake” and “count calories”). Immediately preceding the scans, participants applied earplugs and MR-compatible vision correction, if applicable, and lay supine on the MR scanner table. Task instructions were presented visually using E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA), back-projected onto a screen positioned at the participant’s head, and viewed through a mirror attached to the head coil.

MRI data acquisition

Neuroimaging was conducted in a single session using a 3T Siemens Tim Trio MRI scanner equipped with an eight channel head coil. Functional imaging was performed using a whole brain blood oxygen level dependent (BOLD) echo-planar imaging (EPI) sequence (TR = 2500 ms, TE = 28 ms, FOV = 192 mm², 64² matrix, 42 axial slices, 3 mm slice thickness). To avoid T₁ saturation artifact, the scanner executed two “dummy” repetitions before each EPI run, which were not saved and therefore, excluded from data acquisition and analyses. High-resolution T₁-weighted magnetization prepared rapid gradient echo (MP-RAGE) scans of the entire brain (256² matrix, FOV = 256 mm², 1 mm slice thickness) were acquired in the sagittal plane for anatomical reference.

FMRI data processing

All images were processed using Analysis of Functional NeuroImages software (AFNI) (7). Time series were concatenated and spatially registered to reduce the effects of head movement. This 3-dimensional registration program also yields information on displacement and rotation for each volume that was later used as a covariate when determining BOLD response to orosensory stimuli. Within trial change in activation during the food stimulus was modeled across all the trials of the session using voxel-wise multiple regression analyses. Specifically, voxel-wise multiple regression analyses contrasted BOLD signal during the second and third 20-s time segments (i.e., 20-40 and 40-60 s) to the first 20 s time segment within each min. Only three time segments were used to maximize reliable sampling per segment, and to provide a within-trial control segment of the same length as the other segments. BOLD signal was modeled using two predictors and covariates. Predictors were two boxcar reference waveforms representing the second (20-40 s) and third (40-60 s) time segments over ten trials. Covariates were observed movement correction parameters and linear drift. This procedure yields parameter estimates and associated t-statistics representing the unique contribution of each time segment to the individual’s BOLD signal time course in each voxel relative to the first time segment. The results from individual multiple regression analyses were transformed to standard stereotaxic space (8), resampled to 1 mm³ voxel size, and a 6 mm Gaussian kernel was applied.

Region of interest analyses

Individual datasets were combined across each group for each time segment. For each group, activation during the 20-to-40 and 40-to-60 s time segments was quantified separately using two Student’s one-sample t-tests that compared activity to a hypothetical mean of zero (i.e., does not differ from BOLD signal during the first time segment). The resulting activation maps of second and third time segments were combined across groups into a set of empirically defined regions of interest (i.e., mask) using equally weighted conjunctive “or” logic, such that a voxel was included in the mask if it exhibited a

significant effect (two-tail $p < 0.10$, corrected for multiple comparisons by false discovery rate) during either time segment in any group (Supplemental Table 1). A cluster threshold of 12 voxels (324 mm^3) was used. A relatively lenient alpha level was used to avoid Type II Error, which is as important as Type I Error in this procedure (i.e., ROI identification). The resulting ROI mask was then applied to individual activation maps associated with each time segment to determine mean task-related activity within each ROI for each individual, which was the dependent variable in subsequent analyses. This “or” masking procedure was employed to spatially define meaningful regions of task-related activity within which hypotheses were tested. It was designed to improve the validity of the measured construct by including only clusters showing significant response to the orosensory experience in at least one of the conditions. This was done to avoid bias from either of the time segments or groups.

Hypothesis testing

The hypothesis that SWLM, obese and NW individuals would differ in their responses to orosensory stimulation over the course of 1-min was tested using a 3×2 repeated measures analysis of covariance with one between subjects factor (group: SWLM, obese and NW), one within subjects factor (time: 20-to-40 s and 40-to-60 s) and one covariate, age. A group \times time interaction term was modeled to determine whether brain response at 20-to-40 s differed significantly from 40-to-60 s by group. A $3 \times 2 \times 3$ follow-up repeated measures ANOVA was also conducted to assess long-term, across trial effects. In this analysis we quantified the within-trial effects in sets of three trials (i.e., imaging runs) for improved reliability. Hypothesis testing was conducted using Statistical Package for the Social Sciences (SPSS version 18, Armonk, New York).

RESULTS

Demographic and weight characteristics are listed in Table 1.

Nine clusters of significant within-trial orosensory stimulation response were observed across the groups during at least one of the two time segments and therefore constituted the empirically defined set of task-associated ROIs (see Figure 1 and Table 2). These regions were bilateral posterior insulae (including the parietal opercula), left inferior frontal gyrus (IFG; *pars opercularis*), left putamen, left postcentral gyrus, left superior temporal gyrus (STG), and bilateral occipital regions.

Group and time effects for the nine ROIs are listed in Table 3, while mean changes within each ROI by group and time are depicted in Figure 2. Significant group main effects were seen in eight ROIs with a trend ($p = 0.08$) in the remaining ROI, the left STG. Significant main effects for time also emerged for all nine ROIs. As can be seen from Figure 2, the significant time effects reflected a decline in activity from the 20-40 s epoch to the 40-60 s epoch. No significant group \times time interactions were detected, indicating that this pattern of brain response was similar across the three groups. No significant across-trial effects were observed ($p > .05$).

As no significant group \times time interactions were detected, the significant group main effects were further probed to specify differences between the SWLM, obese and NW groups (Table 3). Results indicated that SWLM differed significantly from NW in seven regions. Similarly, SWLM significantly differed from obese participants or exhibited near-significant trends in all regions, with the exception of the left middle insula and left temporal gyrus. There were no significant differences between NW and obese groups (Figure 2).

Interestingly, these effects occurred despite significant increases from the control period in the obese group in the insular regions, left STG and left post-central gyrus (Figure 2). SWLM showed significant increases in all regions at 20-40 s, whereas the NW only showed a significant increase at 20-40 s in one region, the left postcentral gyrus.

A follow-up ANOVA using Tukey correction for post-hoc tests was used to examine relationships to the construct of restraint. Significant group differences were observed ($F(2, 44) = 8.27, p < 0.01$), such that the SWLM group scored higher on restraint than either obese ($p = 0.01$) or NW ($p < 0.01$) groups, who did not differ from each other ($p = 0.62$). Zero-order correlations of restraint scores and brain response in the nine regions revealed significant positive correlations in the LIFG ($r = 0.33, p = 0.03$) and left putamen ($r = 0.31, p = 0.04$) during the 2nd time segment and the LIFG ($r = 0.40, p < 0.01$), left putamen ($r = 0.39, p < 0.01$), postcentral gyrus ($r = 0.31, p = 0.03$), and left ($r = 0.32, p = 0.03$) and right ($r = 0.37, p = 0.01$) insula during the 3rd time segment. The remaining correlations were not significant ($p > 0.05$).

DISCUSSION

This is the first study to examine the time course of neural responses to 1-min sustained orosensory presentation. We consistently observed initial increases (20-40 s), followed by significant response decays (40-60 s) across the insulae, left IFG, left putamen, and other primary sensory regions. In addition, we found that SWLM exhibited elevated response during these 1-min sustained food presentations compared to obese and NW control groups in almost all brain regions examined, including bilateral occipital regions, right middle insula, and left middle and posterior insula, IFG, postcentral gyrus, and putamen.

Of particular note is the fact that only SWLM exhibited significant reactivity in the left putamen and IFG. The putamen has been associated with food reward (4,14-19) and the IFG has been associated with inhibitory control (4,19-23). Together, based on known functions of these regions, we hypothesize that SWLM may experience greater reward expectations during sustained orosensory stimulation, but also respond with greater inhibitory restraint. Therefore, this pattern of brain response to a sweet food stimulus may reflect both heightened reward expectation (potentially primed by an exaggerated sensory response) and consequently greater cognitive control (i.e., restraint). It is plausible that this pattern of responses is associated with their success at long-term adherence to a low-calorie diet. In fact, we have previously reported that SWLM score higher on measures of cognitive restraint compared to controls (5,24). In this sample, follow-up analyses revealed significantly greater restraint scores among the SWLM group relative to each of the other groups. Higher restraint scores were also significantly associated with greater brain response

in the LIFG and left putamen during both the 2nd and 3rd time segments among the full sample. An important unanswered question is whether the brain responses of the SWLM are learned as part of the process of losing weight or whether this pattern predates and enables their successful weight loss and maintenance.

It is important to consider these findings in relation to prior studies. Regions demonstrating increased activation in response to sustained orosensory stimulation in this study are similar to those associated with orosensory stimulation (9), taste (12-13,18) and food cues (14-15) in prior studies (i.e., insula, frontoparietal opercula, and striatum)(see reviews 10-11). The insular and opercular reactivity to food observed herein is consistent with existing literature that has localized the response to sweet flavor in these regions in both monkeys (9-10) and humans (11-13). Moreover, our observation of elevated responses for SWLM (i.e., middle insula and striatum) is also consistent with previous studies investigating neural responses in this particular group (4-5). In contrast to prior studies which used stimuli such as 2 ml of a liquid meal to examine the responses of SWLM, our study is unique in utilizing a real-world orosensory stimulus, namely a lemon lollipop. This stimulus also allows us to examine the response to a sustained (60 s) experience of food for the first time.

Prior neuroimaging studies have reported greater response to food taste and consumption among obese compared to NW in regions including the insula and frontoparietal operculum (4,16,19,28). Although we did not observe significant differences in direct comparisons between the obese and NW groups in the present study, there were group differences in patterns of response (Supplementary Table). The obese group exhibited pronounced reactivity to the sustained food stimulation (i.e., significant activation > control period) in six of the nine ROIs, whereas the NW group only demonstrated such increased response in one of the nine ROIs. Our focus on the temporal dynamics of responses to a sustained orosensory stimulus may also contribute to the lack of significant group differences observed between the obese and NW groups. While we specifically examined the within-block factor of time, prior studies collapsed this factor and may have benefited from additional statistical power. Future studies may be able to compensate for this by increasing sample sizes.

Many studies have highlighted the role of reward-related regions in response to food cues, with some suggesting obese individuals may have heightened responsivity to food cues in striatal regions (e.g., nucleus accumbens, putamen) (19, 28), while others have shown an inverse relationship between BMI and activity in these areas (16). Here we show an enhanced response to sustained orosensory stimulation in the putamen for SWLM, but no difference from the control period in either the obese or NW groups. Further research is needed in order to more accurately characterize the striatal response to orosensory stimulation for obese and SWLM.

The effects we observed in brain regions associated with primary visual and auditory processing were not expected. It is possible that this activity was related to heightened sensory attention potentiated by orosensory stimulation, and therefore also declined as the response to the primary stimulation attenuated. Participants were trained to hold the lollipop on their tongue with their right hand, which may have contributed to the effects noted in the

left postcentral gyrus. Other interpretations of the temporal lobe response deserve further study, including emotion factors and episodic memory.

Previous physiological research has examined salivation across trials (habituation) rather than within-trial changes examined here. They have found slower habituation across trials in obese compared to NW groups (26-27) and that slower habituation is related to higher caloric intake (25). One found that SWLM habituation was similar to the NW group and faster than the obese group, despite similar levels of initial reactivity (27). Although not directly comparable because measures and designs differ, our results suggest greater initial reactivity to orosensory stimulation in SWLM, but similar rates of response decay within-trial and no across-trial differences.

Limitations to this study include the small sample size in each group, which may have limited our ability to detect effects, especially interaction effects. Homogenous demographic characteristics also limit generalizability of our findings. The NCWR, from which the SWLM group was recruited, is a self-selected sample predominantly composed of females of European ancestry. Evaluation of randomly selected samples of SWLM including men and women of other racial groups would be needed to determine whether the findings observed in the current study reflect the general SWLM population. Follow-up analyses excluding men attenuated all effects, consistent with decreased statistical power, without affecting directionality or significance levels in all but one comparison (the group effect in the Left Middle Insula changed from $t = 3.45$, $p = 0.04$ to $t = 2.10$, $p = 0.14$). Furthermore, this cross-sectional study cannot resolve whether group differences preceded, or resulted from, weight loss. Future studies would be strengthened by including self-report measures of wanting and liking of the orosensory stimulus (i.e., lemon-flavored lollipop), additional between-trial resting-baseline imaging, and the use of active control conditions (e.g., flavorless lollipop). We did not find evidence of an across-trial effect in this study; however, additional studies aimed at addressing long term effects with increased across-trial statistical power are needed to fully address this question. The need to acquire multiple samples of each condition in functional neuroimaging experiments makes it difficult to balance adequate statistical power and uncontrolled order effects such as boredom and failure to capture the activity associated with the construct within the time frame that it occurs.

In sum, we found that a sustained orosensory stimulus after a 4-hour fast is associated with increased reactivity in brain regions associated with sensory, reward, and inhibitory processes. The response in SWLM was greater in all regions, suggesting heightened sensory reactivity, anticipated reward, and increased inhibitory response. These findings contribute to our understanding of the neural mechanisms underlying successful weight loss maintenance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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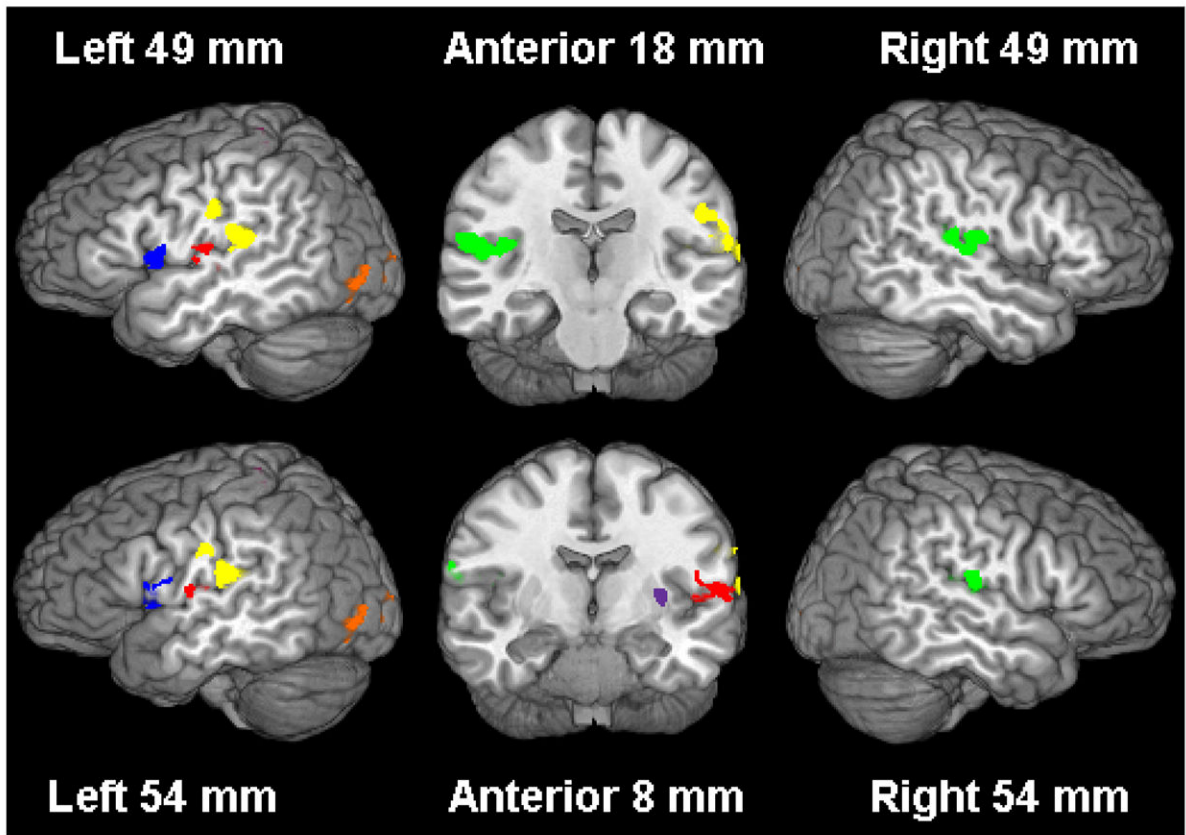


Figure 1. Brain activity associated with sustained food stimulation among all participants (n = 49)

Voxel-wise multiple regression analyses was used to contrast signal during the second and third 20-s time segments to the first 20-s time segment within each min. Individual datasets were combined across each group for each time segment using two Student's one-sample t-tests that compared activity to a hypothetical mean of zero. The resulting activation maps of second and third time segments were combined across groups into a set of empirically defined regions of interest using equally weighted "or" logic, such that a voxel was included if it exhibited a significant effect (two-tail $p < 0.10$, corrected for multiple comparisons) during either time segment in any group. A cluster threshold of 12 voxels (324 mm^3) was used. Red = left middle insula, Blue = left inferior frontal gyrus, Yellow = left posterior insula, Purple = left putamen, Orange = left occipital, Green = right insula.

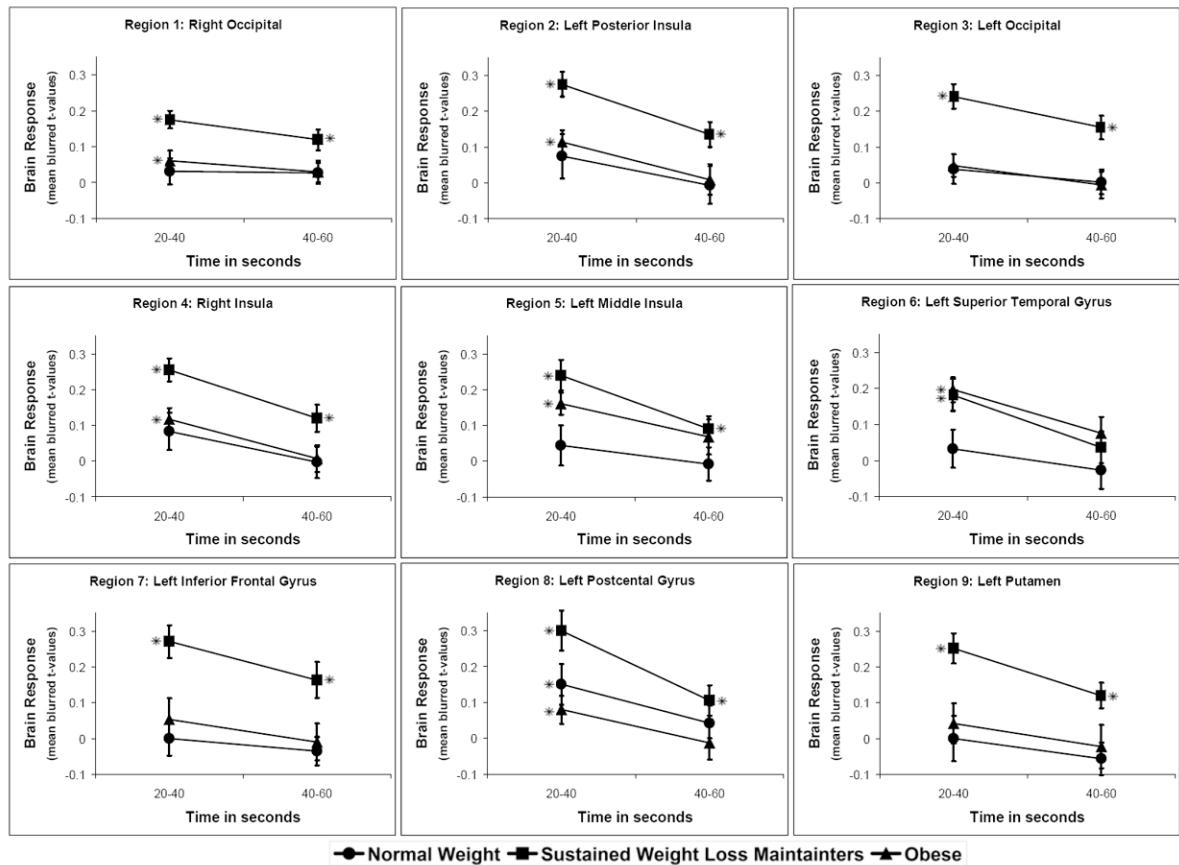


Figure 2. Mean brain response over time in regions of significant activity

The combined activation map (i.e., ROI mask; Figure 1) was applied to individual activation maps associated with each time segment to determine mean task-related activity within each ROI for each individual. These were used in comparisons of group means over time. Groups included 18 NW, 14 obese and 17 SWLM. Error bars indicate standard error of the measure. Asterisks indicate significant (two-tailed $p < 0.05$) differences from the first segment (see Supplemental Table). None of the group by time interactions was significant ($p < 0.05$).

Table 1

Demographic and weight characteristics.

	NW	Obese	SWLM	p-value
Sample Size	18	14	17	
Age [Mean (SD)]	43.6 (8.4)	49.4 (7.4)	48.5 (11.4)	0.16
Percent Male	11.1	0.00	11.8	0.43
Percent Caucasian	100	79	94	0.35
Current BMI [Mean (SD)]	21.6 (2.1)	34.4 (3.7)	23.7 (1.6)	< 0.01
Lifetime Maximum BMI [Mean (SD)]	22.4 (2.2)	35.5 (3.7)	32.8 (3.0)	< 0.01

NW = Normal Weight, SWLM = Successful Weight Loss Maintainers, BMI = Body Mass Index, kg/m².

Significance of mean differences based on one factor ANOVAs. Significance of differences in group distribution of sex and race based on chi-square.

Regions of significant brain response during sustained food stimulation among all participants (n = 49).

Table 2

Region	Center Mass Coordinates			Size in mm ³
	x	y	z	
1 Right Occipital	-14	75	-06	3708
2 Left Posterior Insula	50	24	18	3180
3 Left Occipital	23	82	01	2759
4 Right Insula	-46	21	13	2545
5 Left Middle Insula	52	-09	07	757
6 Left Superior Temporal Gyrus (STG)	59	33	12	653
7 Left Inferior Frontal Gyrus (IFG)	49	-08	07	506
8 Left Postcentral Gyrus	32	38	58	402
9 Left Putamen	30	07	05	390

Note: Regions and methods are shown in Figure 1.

Table 3

Time course of response to sustained food stimulation and group effects.

Region (in order of size)	Main Effect Time		Main Effect Group		Group Contrasts		
	F	p	F	p	SWLM vs NW	SWLM vs Ob	NW vs Ob
1 Right Occipital	4.82	0.03	5.57	<0.01	<0.01	0.04	0.91
2 Left Posterior Insula	34.75	<0.01	5.01	0.01	0.01	0.06	0.88
3 Left Occipital	11.71	<0.01	10.00	<0.01	<0.01	<0.01	1.00
4 Right Insula	27.64	<0.01	4.78	0.01	0.02	0.06	0.91
5 Left Middle Insula	21.47	<0.01	3.45	0.04	0.03	0.68	0.26
6 Left Superior Temporal Gyrus (STG)	34.52	<0.01	2.70	0.08	0.18	0.91	0.09
7 Left Inferior Frontal Gyrus (IFG)	7.67	<0.01	9.53	<0.01	<0.01	<0.01	0.77
8 Left Postcentral Gyrus	24.50	<0.01	4.29	0.02	0.14	0.02	0.56
9 Left Putamen	10.37	<0.01	7.40	<0.01	<0.01	0.03	0.71

NW = 18 normal weight, Ob = 14 obese, SWLM = 17 successful weight loss maintainers

Analyses were conducted using a 3 × 2 repeated measures ANOVA. Interactions were not significant ($p < 0.05$). Group contrasts were combined across time points. Tukey correction for multiple comparisons was used.