HHS Public Access

Author manuscript

Obesity (Silver Spring). Author manuscript; available in PMC 2017 April 01.

Published in final edited form as:

Obesity (Silver Spring). 2016 April ; 24(4): 829–836. doi:10.1002/oby.21424.

Brain Imaging Demonstrates a Reduced Neural Impact of Eating in Obesity

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Abstract

Objective—We investigated functional brain response differences to food in women with either BMI <25kg/m^2 (lean) or >35kg/m^2 (severe obesity).

Methods—Thirty women 18-65 years old from academic medical centers participated. Baseline brain perfusion was measured with arterial spin labeling. Brain activity was measured via blood-oxygen-level-dependent functional magnetic resonance imaging (fMRI) in response to food cues, and appeal to cues rated. Subjective hunger/fullness was reported pre- and post-imaging. After a standard meal, measures were repeated.

Results—When fasting, brain perfusion did not differ significantly between groups; and both groups significantly increased activity in the neo- and limbic cortices and midbrain compared to baseline ($p<0.05$, family-wise-error whole-brain corrected). Once fed, the lean group showed significantly decreased activation in these areas, especially the limbic cortex, while the group with severe obesity showed no such decreases ($p<0.05$, family-wise-error whole-brain corrected). After eating, appeal ratings of food decreased only in lean women. Within groups, hunger decreased ($p<0.001$) and fullness increased ($p<0.001$) fasted to fed.

Conclusion—While fasting, brain response to food cues in women did not differ significantly despite BMI. After eating, brain activity quickly diminished in lean women but remained elevated in women with severe obesity. These brain activation findings confirm previous studies.

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All authors claim no potential conflicts of interest.

Keywords

women; brain; food; imaging; hunger

Introduction

Even if not hungry, seeing food or thinking about food can stimulate eating (see Smeets, Erkner and de Graaf(1), and Berthoud(2) for recent and broader discussion). The anticipatory or conditioned responses to food cues, rather than hunger, affects us each differently depending on gender, energy state, menstrual status, and previous associations to those foods or food cues, to name a few(3-5). Those with the insight and/or inhibitory control of visual cue urges succeed in maintaining a healthy weight(6). In contrast, individuals with obesity are highly vulnerable to external food-related cues(7, 8) and eat differently than lean individuals in identical environments (9, 10).

Much current research on eating involves characterizing the role of the brain. Central nervous system mechanisms of homeostatic (energy-based) circuits integrate with hedonic (reward/motivation-based) circuits to influence eating(11). Given that homeostatic needs are easily met, differences in eating for pleasure are likely central to overeating. Physiological feedback to our brain upon eating — in the form of changed levels of satiety-related gut hormones, adipokines and/or vagal stimuli — mediate and regulate our intake and activation of key eating-related brain centers (12-14). In turn, these changes to brain region activation further influence behaviors and processes involving eating. If food eaten is pleasurable, its intake is reinforced. Interestingly, while taste-based food choices compel women of all body mass indices (BMI) to eat, when full, lean women will either stop eating or just sample a food they crave rather than eating a large volume as do women with obesity(15).

Functional magnetic resonance imaging (fMRI) has been used in numerous studies to assess differences in regional brain response to visual food cues between individuals with and without obesity. A common outcome has been differential activation of brain regions mediating reward behaviors. Although space limitations prevent mention of all these works, some key findings from this literature follow: In woman with obesity as compared to those who are lean, the dorsal striatum, which mediates decision-making related to producing reward attainment actions, shows greater activation in the fed state. (16), reward-system-associated regions—the ventral tegmental area, nucleus accumbens, amygdala, orbital frontal cortex (7) and left anterior cingulate(5) — exhibit greater brain activation in the fasted state, and when anticipating ingesting (rather than viewing) a basic sweet taste, brain response is down-regulated in a fed state(4). In both fasted and fed states, women and men with obesity, exhibit significantly greater activity in the medial prefrontal cortex when viewing food cues compared to lean individuals (8), which is important because the prefrontal cortex mediates motivated behaviors aimed at obtaining a reward. Also, individuals with proneness to obesity do not attenuate their neural response after a meal as do women and men with obesity resistance(17). Identifying brain circuit activation pattern differences between individuals with or without obesity may generate functional biomarkers that facilitate the development of obesity treatments. Similarly, identifying brain circuit

activation differences predicted to occur with bariatric surgery-induced weight loss may bring opportunities for developing efficacious non-surgical treatments.

We examined brain responses to visual food cues in women with severe obesity or leanness before and after a standard meal. We contrasted alterations in functional brain activation within regions that regulate eating behaviors—both homeostatic and hedonic. We hypothesized that regions important in mediating reward behaviors (ventral tegmental area, nucleus accumbens, hippocampus and prefrontal cortex) would be differentially activated by viewing food cues in the fasted or fed states, contrasting groups with severe obesity or leanness.

Methods

Participants

Fifteen women with severe obesity and 15 age-matched lean women (18-65 years old) were recruited through two academic medical centers. The University of Texas Southwestern Medical Center and the Veterans Administration North Texas Health Care System Institutional Review Boards approved the protocol and all participants gave informed consent. Participants with severe obesity were BMI 35-50 kg/m^2 and pre-bariatric surgery. Lean controls were BMI 18.5-24.9 kg/m^2. Exclusion criteria included untreated Axis I psychiatric diagnoses, previous serious head injury, left-handedness, contraindications to MRI, prior bariatric surgery, or untreated severe medical illness.

Study Design

Demographic characteristics were collected (Table 1). Psychiatric diagnoses were determined using the Structured Clinical Interview for the Diagnostic and Statistical Manual-4 (18). Current depressive symptoms were determined using the 16-item Quick Inventory of Depressive Symptomatology ($QIDS\text{-}SR_{16}$) (19).

Participants arrived at 9 AM in a fasted state (no food after midnight). Subjective hunger or fullness (visual analog scale) was rated prior to imaging using a scale from -50 (least hunger/fullness ever experienced) to +50 (greatest hunger/fullness ever experienced). Participants were then positioned in the MRI scanner with their heads comfortably immobilized. Baseline brain perfusion, measured by Arterial Spin Labeling (ASL), was acquired prior to fMRI scanning. Participants' brain activities were measured with fMRI blood-oxygen-level-dependent (BOLD) response to seeing food cues interleaved with directional arrows. An appeal rating (scale of 1-3, not appealing to very appealing) for each food shown was recorded. After this imaging session, subjective hunger or fullness was rated again. During the next hour, a standard meal of 337 kcals (52% carbohydrate, 30% fat and 18% protein) was served. Calories consumed were quantified. The meal consisted of: lean beef or chicken, with potato or rice, and green beans; water-packed canned peaches; and iced tea +/-splenda or water. After eating, participants again rated hunger or fullness. Then participants were re-scanned using an fMRI paradigm identical to the first session except with different food cues, avoiding familiarity. Afterward, subjective hunger or fullness was rated again.

fMRI Food Task

Visual food cues (pictures) were similarly sized and presented (Supporting Figure S1). Five fMRI BOLD runs per scan session were acquired in an event-related design. In each run, 40 food pictures were presented for 3 seconds each in a pseudo-randomized sequence over 3.5 minutes. Null "arrow" events (each 1.5 seconds) were randomly interleaved between the food pictures. Ten additional "arrow" events were placed at the run beginning and end to establish a baseline BOLD signal. The pictures included 10 high-calorie savory foods, 10 high-calorie sweet foods, and 20 low-calorie foods. While viewing food pictures, participants were asked to rank foods by appeal ("not appealing", "appealing" or "very appealing") using button press. Details on MRI procedures, and parameters are reported in the Supporting Methods.

MRI Data Analysis

Brain images were processed using Statistical Parametric Mapping 5 (20) and fMRI Brain Software Library (FSL; Oxford University, UK) (21). fMRI images were realigned to correct for motion artifacts; runs with motion exceeding one voxel size were excluded. The MPRAGE image was then co-registered to the realigned fMRI images. The Brain Extraction Tool (in FSL) was used to extract the brain from the skull and subcutaneous fat in MPRAGE images, because excess subcutaneous fat was found to generate distortions in the normalized images. Image normalization was done to transform the skull-stripped MPRAGE image into Montreal Neurological Institute template space, and the transformation parameters were used to normalize the fMRI images. Normalized fMRI images were re-sampled into 2 mm cubic voxels and smoothed using an 8mm full-width half-maximum Gaussian kernel to minimize inter- participant anatomic variability. Time and dispersion derivatives of the hemodynamic response function were included to obtain a better model of the data. A 128 seconds high-pass filter removed low-frequency noise and slow signal drifts.

Cerebral blood flow (CBF) data were acquired in the "before-meal" session only. CBF procedures, parameters and analysis are reported in the Supporting Methods.

fMRI Statistical Analysis

fMRI data were analyzed using a general linear model in which stimulus onsets were modeled as events and specified as regressors. These onsets were convolved with the hemodynamic response function to account for lag between event onset and the expected BOLD signal response. To account for variance from head movement, realignment parameters were included as regressors. Flexible factorial design was used for two-group (BMI >35kg/m^2, BMI <25kg/m^2) and two-condition (fasted, fed) analysis. Predicted activations were considered significant at $p<0.05$ after correcting for family-wise-error (FWE) across voxels.

Descriptive Statistical Analysis

Continuous demographic and clinical characteristics data were described by means and standard deviations and compared by t-test. Categorical variables were described by number and proportion of participants, and analyzed by Chi-square or Fisher's exact test. A repeated-measures analysis of variance was used to assess subjective hunger and fullness with effects

for within-group (fasted versus fed), between-group (lean versus obese) and a within-group by between-group interaction. Appeal ratings of food cues were collapsed to a binary outcome ("very appealing/appealing" versus "not appealing") before analysis. The outcome was the proportion of very appealing/appealing responses given for the 200 rated pictures. The arc sine transformation was applied to the square root of the proportions to improve the normality of the data, and then the repeated measures analysis of variance was applied. SAS version 9.3 (SAS Institute Inc., Cary, North Carolina) was used for all descriptive statistical analyses.

Results

Group Characteristics

Thirty women entered and completed the protocol. Of the demographic/clinical characteristics and current/lifetime Axis I diagnoses, only weight and BMI differed significantly between groups (p=0.001, Table 1). No participants met criteria for current depression (QIDS-SR_{16}, all <11).

Eating Behavior

There were no significant differences between groups in standard meal calories consumed (BMI <25kg/m^2: 301 kcals, (SD 51); BMI >35kg/m^2: 302 kcals, (SD 66); p=0.95; table 2). Subjective hunger was significantly greater in the fasted versus fed states for both groups (p<0.001; see absolute hunger values table 2). The subjective hunger group effect was significant (p=0.02), indicating that participants with severe obesity, whether fasted or fed, showed quantitatively less hunger than lean controls.

Subjective fullness was significantly lower in the fasted versus fed states for both groups (p<0.001; see absolute fullness values table 2). Subjective fullness did not differ significantly between groups, at any time point, either before or after eating their standard meal (p=0.40, group effect). The groups did not differ significantly in their fullness ratings in response to the meal (p=0.45, group × fasted-fed effect), suggesting that each group was satiated.

Participants with severe obesity and lean participants differed in how they rated the appeal of food cues between the fasted and fed states. The lean group showed a drop of 15% (95% Confidence Interval: 5.0 to 24.1) in their rating of *appeal* as they moved from fasted to fed (65% versus 50% rated very appealing/appealing). In contrast, the group with severe obesity reported a drop of 4% (95% Confidence Interval: -3.1 to 11.5) (68% versus 64%), which indicates sustained appeal of food cues after eating. The fasted/fed-by-group interaction was not significant (p=0.070).

Lean Group fMRI outcomes (whole brain, Supporting Figure S2)

In fasted lean participants (Figure 1a), diverse brain regions were activated by food cues. Activation of visual/striate cortices was consistent with visual stimuli and the visual cortical activations extended to the cerebellum and parietal cortex. Areas within the prefrontal cortex (including the anterior cingulate, medial prefrontal cortex and dorsolateral prefrontal cortex)

were activated, as were regions of the basal ganglia (particularly the caudate nucleus). The medial temporal cortex, including the hippocampus and midbrain, in the region associated with the ventral tegmental area, was also activated. After eating, activation diminished in the anterior cingulate, medial prefrontal cortex, dorsolateral prefrontal cortex, caudate nucleus, and midbrain (Figure 1b). The lean [fasted minus fed] analysis (Figure 1c; Table 3) showed significant activation reductions after eating ($p<0.05$, FWE corrected) in the prefrontal cortex (anterior cingulate, medial prefrontal cortex and dorsolateral prefrontal cortex), basal ganglia/caudate nucleus, medial temporal cortex and midbrain regions. Activation in the visual cortex and cerebellum were also significantly diminished ($p<0.05$, FWE corrected), while activations in the ventral cortex were sustained.

Group with severe obesity fMRI outcomes (whole brain, Supporting Figure S3)

Fasted participants with severe obesity showed widespread activations by food cues ($p<0.05$, FWE corrected) as did fasted lean participants (Figure 2a). The severe obesity-fasted group showed brisk activations in the ventral cortex, with extension into the parietal cortex and cerebellum. Prefrontal cortex activations were prominent, including the anterior cingulate, medial prefrontal cortex and dorsolateral prefrontal cortex, extending to the inferior prefrontal cortex and insula. Also prominent were medial temporal cortex activations, including the hippocampus, and brainstem regions, including the ventral tegmental area. In the fed state, many areas remained significantly activated ($p<0.05$, FWE corrected), unlike the lean group (Figure 2b). The prefrontal, medial temporal, parietal and ventral cortical regions all remained active, making the 'fed' activations in the obese brain resemble the 'fasted' state. The group with severe obesity [fasted minus fed] analysis showed significantly reduced activations [$p<0.05$, FWE corrected] only in the insula, inferior prefrontal cortex, and inferior midbrain; with no significant activation diminution within the prefrontal, medial temporal, parietal or ventral cortices (Figure 2c; Table 3).

The lean group deactivated brain regions when fed compared to fasted, in contrast to the group with severe obesity (Figure 3; Table 4). Regions in the prefrontal cortex, particularly the anterior cingulate, dorsolateral prefrontal cortex and posterior cingulate cortex, significantly changed going from fasted to fed state in the lean, but not in the group with severe obesity. Additionally, in the severe obesity-fasted group, the hypothalamus activation did not differ statistically ($p=0.07$) to the lean-fasted group. Both groups showed no meaningful within-group differentiated hypothalamus activation from the fasted to fed states.

Baseline Perfusion

To confirm that brain activation findings were not the result of differences between the groups in their fasted (baseline) state, we analyzed baseline CBF data. A mask was obtained from the regions that showed differences between the groups for the [fasted minus fed] state (color voxels, Figure 3) and baseline CBF was obtained for each participant from this mask. Baseline CBFs during the fasted state were: lean group = 70.5±9.8 ml/100g/min, group with severe obesity = 69.7±9.8 ml/100g/min, demonstrating that the groups were not different in the fasted state ($p=0.83$).

Discussion

Significant activation of brain regions known to mediate hedonic behaviors occurred in fasted participants, both lean and with severe obesity, in response to visual food cues: the prefrontal cortex (especially the anterior cingulate), basal ganglia (especially the caudate nucleus) and medial temporal cortex, as well as sensory perceptual areas and the parietal cortex. The hypothalamus, viewed as a center for body weight homeostasis, showed no significant change between groups or across feeding states. After eating, the group with severe obesity showed sustained "hungry" activation despite no statistical difference in subjective reports of satiation to the lean group who had diminished "non-hungry" activation.

These brain activation findings confirm previously shown characteristics for lean or groups with obesity studied: without comparators (22, 23), in a different demographic (adolescents, males, BMI 25 - 35kg/m^2) (24, 25) or in a single state (fasted or fed, but not both) (7, 26, 27). Few study designs show the clear fed-versus-fasted state differences simultaneously between and within groups. Similar to findings by Cornier et al. in obesity-resistant versus obesity-prone participants(17), this *a priori*-designed study demonstrates an ongoing brain response to visual food cues in severe obesity—especially in the neo- and limbic cortices, and midbrain—after eating a satisfying meal, distinct from lean controls. These findings suggest participants with severe obesity fail to engage a brain-wide eating-related process associated with satiation. It remains to be clarified whether this brain response to food cues is a trait or state response induced by obesity. We are following the participants with severe obesity after bariatric surgery to test this outcome.

In this study, key aspects of brain response to eating are reflected by objective behavioral response (appeal) and subjective motivation (hunger, fullness)—a translation of brain findings to eating behavior. The brain response when fasted is congruent with behavioral and motivation experience in both groups; brain activation is high, food pictures are appealing and participants are at their hungriest. The brain response when fed remains congruent with behavior and motivation experience in lean participants but is divergent in participants with severe obesity. Unlike leans, despite diminished hunger/peak fullness, the group with severe obesity-fed maintain high brain activation to and appeal ratings of food. Participants with severe obesity reported significantly less absolute hunger than lean participants whether fasted or fed, but group differences between pre- and post-meal hunger/fullness were identical. Taken together, the severe obesity-fed state depicts an 'uncoupling' of effective brain response to eating and degree of hunger/fullness. These findings may explain why participants with severe obesity report an underlying drive to eat continually despite not feeling hungry (28), or eat differently, consuming more than lean controls (29, 30).

The lean group decreased regional brain activation to visual food cues after eating, which suggests that the brain withdraws attention from food-related stimuli when satiated. The lack of diminished brain activation in participants with severe obesity once fed, lends support to an appetitive-conditioning psychopathology model (31). Despite satiation, a high brain activation pattern identical to fasting in participants with severe obesity reflects a neuronal pressure around eating which is absent in lean participants. These brain differences may

assist clinical weight loss treatment by utilizing brain-based therapies or validating patients' feelings of ‘something being wrong’ with regard to eating. Similar to the variability of genetically driven weight gain and loss (32, 33), clinicians can acknowledge a disparity in response to eating and do so without undermining treatment success.

This study has limitations. The sample size, while sufficient for fMRI data stability, is not large per usual clinical study size. Our study meal (337 kcals) was set at the recommended lunch caloric level for a 1200 kcal diet(34) and is less than the average 626 kcals meal consumed by U.S. women (35); brain activation differences between groups may change after a larger meal. While our focus on women is essential as the experience of obesity in women differs in many respects from that in men—including heightened perceived physical impairments (36), weight-related social stigma and discrimination (37), risk of depression (38) and distinct risk factors (39)—our results may not be generalizable to men. Though age-matched, with equal numbers of postmenopausal women per group, we could not control for menstrual cycles, oral contraceptives or hormone replacement therapy. Sex hormones are known to modulate appetite(40) and may affect these results. Finally, neither molecular markers nor gut hormones known to affect brain function were analyzed; such correlations are forthcoming. This study's strengths include its use of a longitudinal within- and between-group design of absolute and change in brain activation, coupled with behavior measures, and post-bariatric surgery follow-up in the obese group. This study contributes to the high priority of developing effective obesity targets and treatment strategies.

Conclusion

This study's comparison between lean and participants with severe obesity's brain responses to food cues demonstrates how brain activation patterns vary in a fasted versus a fed state. In response to food cues, the brains of both lean and participants with severe obesity when fasted show fMRI BOLD activation patterns widely distributed in the neo- and limbic cortices. Once lean participants are fed, their brain BOLD activations to food pictures are broadly reduced. In contrast, after participants with severe obesity are fed, they fail to show remarkably altered patterns of brain activation to food cues. In particular, after eating, participants with severe obesity maintain activation in the midbrain, one of the most potent reward centers. Thus, once satiated after eating, participants with severe obesity continue to perceive food as appealing and their brains continue to be activated by visual food cues as though they were hungry. Future experiments will determine whether the observed participants with severe obesity's brain activation patterns will change following bariatric surgery, correlate with changes in body weight-related gut hormones, or differ between high- versus low-caloric density visual food cues.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to acknowledge the editorial support of Jon Kilner, MS, MA (Pittsburgh, PA), the dietary-recall assessments by Rosemary Son, PA-C, RD (Dallas, TX), and the preliminary fMRI BOLD analyses by Yan Fang, PhD (Dallas, TX).

Sources of financial funding: 1. Department of Surgery, University of Texas Southwestern Medical Center, Dallas, TX 75390 provided funding for all aspects of the research.

2. NIH/NCATS Grant Number UL1TR000451 provided pilot research funding.

3. Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, TX 75390 provided pilot research funding.

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Study Importance Questions

What is already known about this subject?

- Differences in brain activity response to food and eating exist between people with versus without obesity.
- Studies showing differences in brain activity response to food, generally focus on one state (fasted or fed), and rarely include a group with BMI >35m/kg^2 (severe obesity).

What does our study add?

- Our study uncovers a critical difference in the brain response to eating between women with or without severe obesity. We uniquely establish no significant difference in baseline brain perfusion, a surrogate of neural activity, between groups at study onset.
- The difference, a failure in obesity of brain reward center activity to diminish after a meal, uniquely augments previous findings by studying brain activity across states (fasted and fed), providing within- and between-group comparisons, and focusing on women with severe obesity.

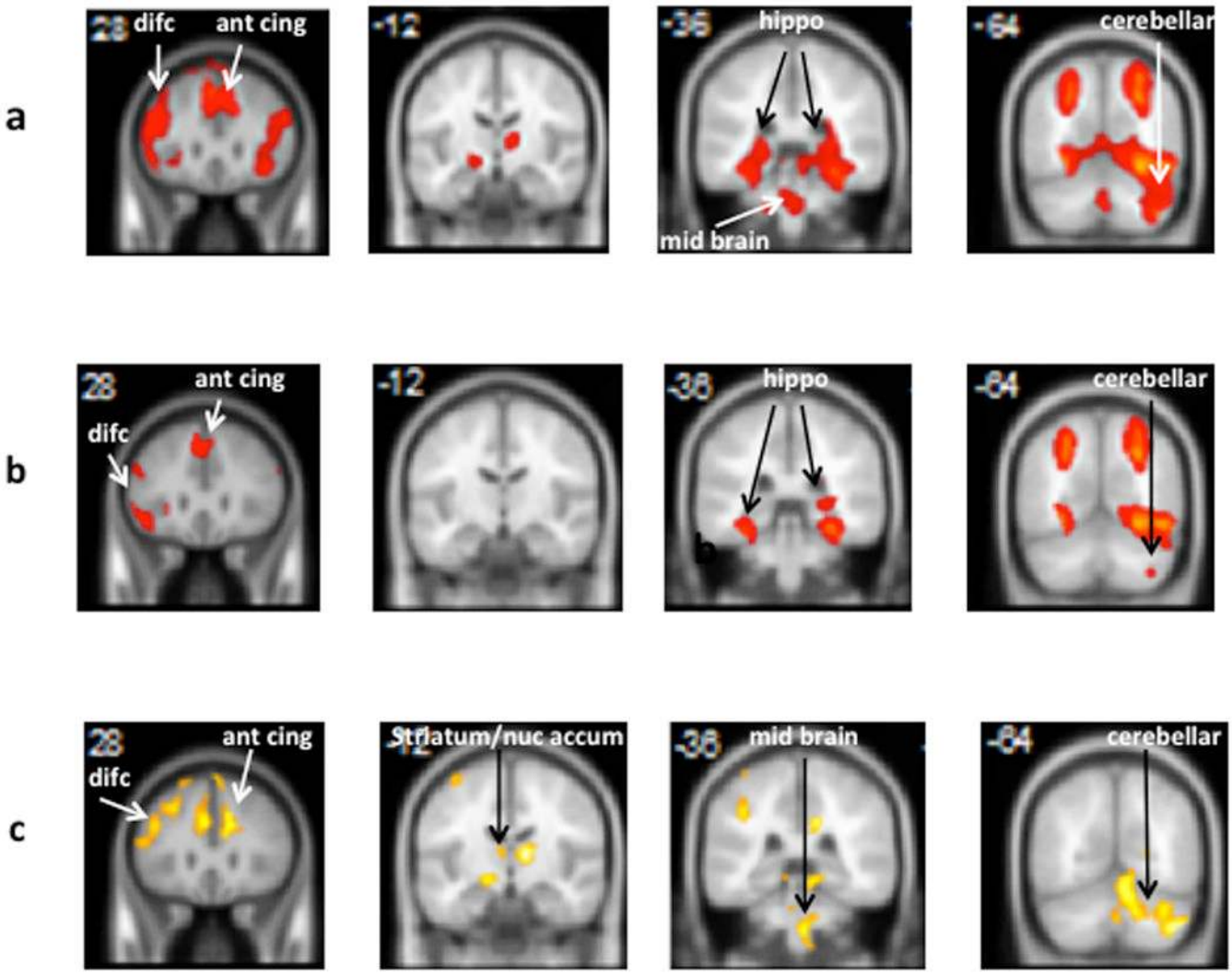

Figure 1. Lean Controls

1a. The group average image from lean controls in a fasted state shows areas of significant activation during the imaging task (viewing food cues/pictures), contrasting activation during food cues with directional arrows. These regions are significant at $p<0.05$, family-wise-error corrected. Illustrative coronal slices show the anterior cingulate (ant cing), dorsolateral frontal cortex (dlfc), basal ganglia (caudate and nucleus accumbens) and hippocampal regions (hippo) as well as the ventral tegmental area in the midbrain, visual cortex and cerebellar regions with extensive activations.

1b. After a meal and when rating themselves as satiated, the lean controls show highly attenuated regions of brain activation to food cues compared to directional arrows. The same illustrative coronal slices show limited regions of activation in the anterior cingulate, dorsolateral frontal, and hippocampal cortex along with the visual cortex, relative to directional arrows.

1c. Subtraction of the fed from the fasted group average images in lean controls (Lean, fasted-fed) show regions in the lean controls where activations to food cues are greater in the fasted state than in the fed state. Illustrative coronal slices show regions in the anterior

cingulate, dorsolateral frontal, and medial temporal cortex, striatum and nucleus accumbens (nuc accum) as well as the ventral tegmental area/midbrain and cerebellum, with significantly lower activation in the lean group while viewing food cues after eating than in a fasted state. Cluster size and coordinates for all significant clusters are detailed in Table 2 and dense coronal slices from anterior to posterior brain are shown in Supporting Figure S2.

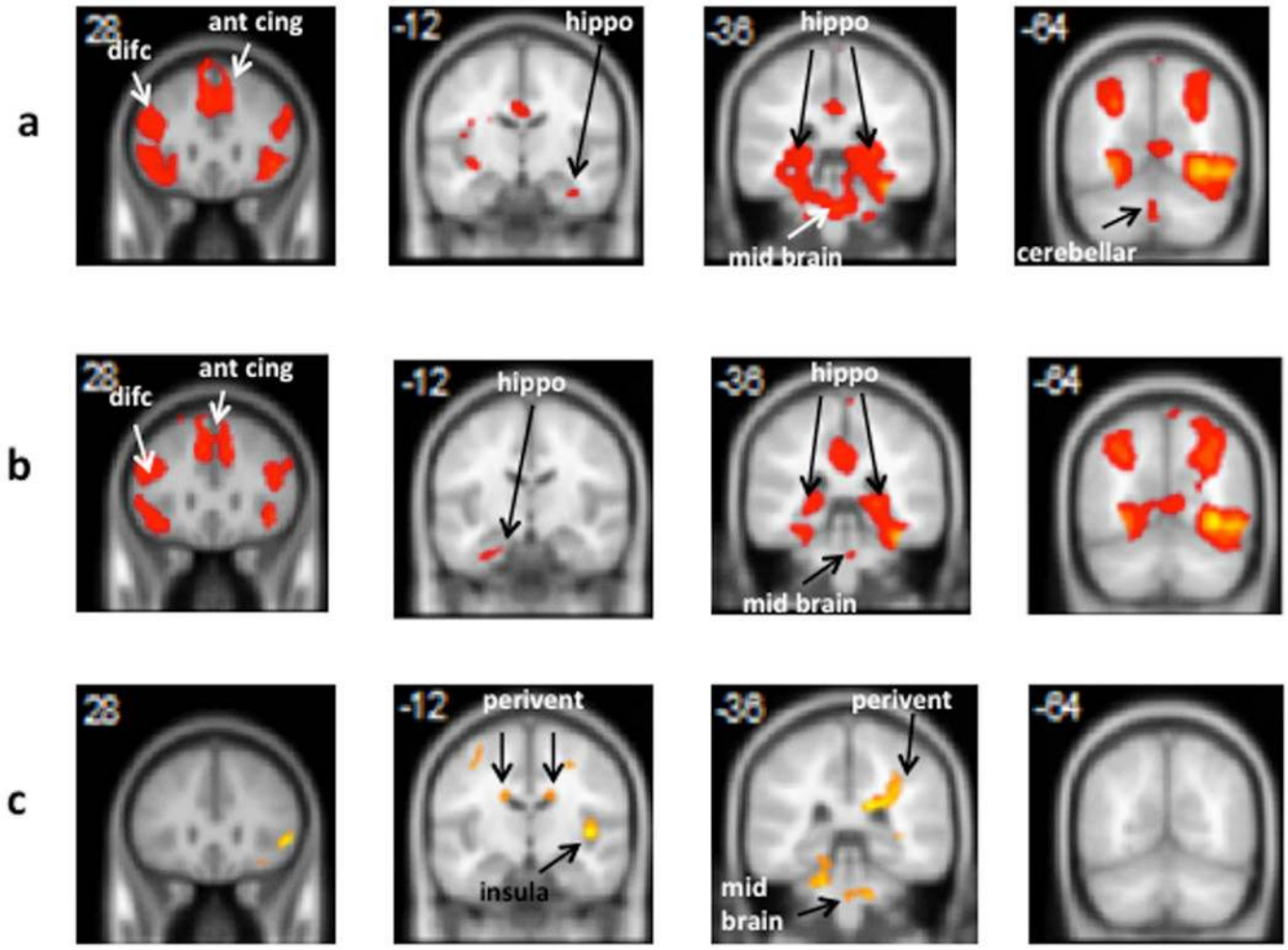

Figure 2. Severe Obesity

2a. The group average image from the women with severe obesity in a fasted state shows extensive areas of activation during the imaging task (viewing food cues/pictures) when contrasting activation during food cues with directional arrows. The regions are significant at $p<0.05$, family-wise-error corrected. The illustrative coronal sections show prominent activation in the anterior cingulate, dorsolateral frontal, basal ganglia, and hippocampal regions as well as the ventral tegmental area/midbrain, visual cortex and cerebellar regions. The fasting activations in the group with severe obesity have the appearance of those in the lean fasting scans.

2b. After a meal and when rating themselves as satiated, the women with severe obesity show little attenuation of brain activation to food cues in the 'hedonic' regions of the brain, including the nucleus accumbens, hippocampus, and ventral tegmental area/midbrain regions where lean controls show significant activation attenuation.

2c. Subtraction of the fed from the fasting group with severe obesity average images (severe obesity, fasted-fed) show regions in the group with severe obesity where activations to food cues are greater in the fasted state than in the fed state. It is merely the insula, periventricular regions (perivent) and midbrain regions, which show significantly lower activation in the group with severe obesity after eating, and in a satiated state while viewing the food cues.

Cluster size and coordinates for all significant regions are detailed in Table 2; dense coronal slices from anterior to posterior are available in Supporting Figure S3.

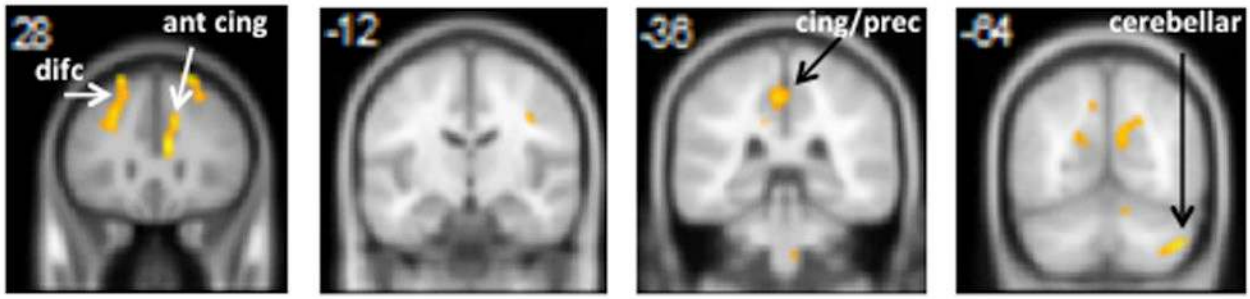

Figure 3. Lean-Severe obesity (fasted-fed)

In the [fasted-fed] state × [lean-with severe obesity] group interaction (double subtraction), we see the most conservative activation of regions where Lean controls deactivate after eating but women with severe obesity maintain activation to the food cues even when no longer hungry. Here it is the anterior cingulate and the dorsolateral frontal cortex as well as the posterior cingulate cortex, precuneus (prec) and regions in the cerebellum that show significant differences. Cluster size and coordinates for all significant regions distinguishing fasted/fed states between the Lean/Severe obesity women are detailed in Table 4.

Table 1

Group Characteristics

Characteristic	Lean (n=15)	Severe Obesity (n=15)	p-value[a]
Age in Years			
Mean (SD)	45.1 (9.9)	40.6 (12.0)	0.27
Range	30-58	24-61	
Height in Inches			
Mean (SD)	65.5 (2.9)	64.5 (2.7)	0.34
Range	61-71	61-69.5	
Weight in Pounds			
Mean (SD)	136.3 (16.6)	254.2 (36.2)	0.001
Range	111-176.5	202-316	
BMI in kg/m^2			
Mean (SD)	22.3 (2.0)	42.7 (4.8)	0.001
Range	18.7-24.6	35.7-50.2	
Ethnicity, n (%)			0.39
Non-Hispanic	10 (67)	13 (87)	
Hispanic	5 (33)	2 (13)	
Race, n (%)			1.00
African-American	3 (20)	4 (27)	
Caucasian	11 (73)	11 (73)	
Asian	1 (7)	0 (0)	
Axis I Diagnosis[b] n (%)			
Active	0 (0)	2 (14)	0.48
Lifetime	2 (14)	6 (43)	0.21
$QIDS\text{-}SR_{16}$			
Mean (SD)	3.9 (2.2)	5.8 (3.8)	0.13

Note: The means presented in this table are the arithmetic means.

Abbreviations: BMI, Body Mass Index; $QIDS\text{-}SR_{16}$, 16-item Quick Inventory for Depressive Symptomatology – Self-Report; SD, Standard Deviation.

[a] Continuous variable means were compared by t-test. Categorical variable frequencies were analyzed by Chi-square or Fisher's exact test.

[b] As determined by Structural Clinical Interview for DSM-IV Axis I Disorders; n=14 per group.

Table 2

Eating Measures

Measure	Lean(n=15)	With Obesity(n=15)	p-value[a]
intake standard meal kcals			
Mean (SD)	301 (51))	302 (66)	0.95
Range	176-337	135-337	
Hunger[b] (fasted)			
Mean (SD)	16 (30)	-3 (23)	
Hunger (fed)			
Mean (SD)	-24 (25)	-37 (17)	
Hunger (fasted v. fed; within group)		lean, with obesity	< 0.001, < 0.001
Hunger (lean v. with obesity; between group)			0.02
Fullness (fasted)			
Mean (SD)	-41 (9)	-39 (14)	
Fullness (fed)			
Mean (SD)	10 (24)	13 (26)	
Fullness (fasted v. fed; within group)		lean, with obesity	< 0.001, < 0.001
Fullness (lean v. with obesity; between group)			0.40
Within-group × between group interaction			0.45

Note: The means presented in this table are the arithmetic means.

Abbreviations: SD, Standard deviation, VAS, Visual analog scale

[a]Continuous variable means were compared by t-test. Repeated-measures analysis of variance used to assess within group (fasted v. fed), between group (lean v. with obesity), and within-group by between-group interaction.

[b]Hunger/Fullness VAS scale -50 (least hunger/fullness ever experienced) to +50 (greatest hunger/fullness ever experienced).

Table 3

Cluster size, t-values, peak coordinates and brain region labels for the lean group, and group with severe obesity, (fasted-fed) contrast, significant at p = 0.05 (family-wise-error corrected).

Cluster size (voxels)	T-value	Coordinates: x,y,z	Region
Lean Group			
6361	4.97	8 -50 -18	Culmen, cerebellum anterior lobe
	4.85	16 -88 -14	Lingual gyrus
	4.85	10 -12 10	Thalamus
375	4.58	14 -36 32	Cingulate gyrus
	3.02	14 -50 16	Precuneus
	3.02	-6 -56 16	Posterior cingulate
6076	4.56	8 40 46	Medial frontal gyrus
	4.27	-26 24 44	Middle frontal gyrus
	4.23	-2 66 24	Superior medial frontal lobe
146	4.29	-64 -22 36	Postcentral gyrus
114	3.85	-10 -20 36	Cingulate gyrus
182	3.74	4 -34 -46	Medulla
	3.44	2 -30 -38	Pons
Group with Severe Obesity			
585	5.68	42 -20 4	Insula
	4.02	46 -2 12	Insula
	3.40	34 -32 2	Sub-lobar
735	5.23	-38 -2 -24	Sub-gyral Temporal lobe
	4.35	-38 18 -26	Superior Temporal gyrus
	4.34	-36 16 -34	Superior Temporal gyrus
2148	4.79	18 8 42	Sub-gyral Frontal lobe
	4.64	12 14 56	Superior Frontal gyrus
	4.58	26 -6 48	Middle Frontal gyrus
163	4.28	-4 -30 -36	Pons
	3.42	14 -36 -38	Pons
	2.57	0 -38 -42	Pons
233	3.71	48 28 -2	Inferior Frontal gyrus
	3.09	52 16 -4	Inferior Frontal gyrus
156	3.48	-18 -36 -28	Culmen, Cerebellum anterior lobe
	2.99	-16 -38 -16	Culmen, Cerebellum anterior lobe
	2.44	-14 -44 -26	Culmen, Cerebellum anterior lobe
116	3.36	32 14 -24	Superior Temporal gyrus
	3.12	34 26 -16	Inferior Frontal gyrus
127	3.11	-32 -4 64	Middle Frontal gyrus
	3.03	-40 -14 48	Precentral gyrus

Cluster size (voxels)	T-value	Coordinates: x,y,z	Region
	2.84	-36 -10 54	Precentral gyrus

Table 4

Cluster size, t-values, peak coordinates and brain region labels for the lean group versus group with severe obesity ([fasted-fed] × [lean-with obesity]) interaction, significant at p = 0.05 (family-wise-error corrected).

Cluster size (voxels)	T-value	Coordinates: x,y,z	Region
526	5.03	8 -76 -34	Cerebellum posterior lobe
	3.61	14 -76 -44	Cerebellum posterior lobe
	3.05	8 -82 -22	Cerebellum posterior lobe
699	4.92	-32 46 8	Sub-gyral Frontal lobe
	3.73	-20 50 14	Medial Frontal gyrus
	3.15	-16 62 14	Superior Frontal gyrus
101	4.50	36 -6 38	Precentral gyrus
726	4.44	-28 10 68	Middle Frontal gyrus
	4.14	-22 18 30	Sub-gyral Frontal lobe
	3.54	-32 34 44	Middle Frontal gyrus
246	4.36	8 -48 -16	Cerebellum anterior lobe
	3.17	-2 -50 -22	Cerebellum anterior lobe
405	4.20	10 32 14	Anterior Cingulate
	3.38	6 44 12	Anterior Cingulate
	3.36	12 28 36	Medial Frontal gyrus
201	3.74	40 -60 -46	Cerebellum posterior lobe
	3.50	30 -52 -48	Cerebellum posterior lobe
776	3.62	14 -50 14	Sub-lobar
	3.59	8 -54 18	Posterior Cingulate
	3.34	-12 -58 18	Sub-lobar
432	3.60	26 32 48	Superior Frontal gyrus
	3.55	26 18 42	Middle Frontal gyrus
114	3.55	6 40 50	Superior Frontal gyrus
	2.69	-8 34 52	Superior Frontal gyrus
	2.43	10 40 42	Medial Frontal gyrus
118	3.48	-8 -68 42	Precuneus
142	3.37	-2 -26 -4	Midbrain
	3.32	6 -24 -2	Midbrain
175	3.04	-6 -36 48	Precuneus
	2.92	-12 -50 38	Precuneus
	2.74	-10 -48 30	Precuneus