Differential Brain Responses to Satiation in Obese and Lean Men

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Knowledge of how the brain contributes to the regulation of food intake in humans is limited. We used positron emission tomography and measures of regional cerebral blood flow (rCBF) (a marker of neuronal activity) to describe the functional anatomy of satiation (i.e., the response to a liquid meal) in the context of extreme hunger (36-h fast) in 11 obese (BMI ≥35 kg/m^2, age 27 ± 5 years, weight 115 ± 11 kg, 38 ± 7% body fat; mean ± SD) and 11 lean (BMI ≤25 kg/m^2, age 35 ± 8 years, weight 73 ± 9 kg, 19 ± 6% body fat) men. As in lean men, satiation in obese men produced significant increases in rCBF in the vicinity of the ventromedial and dorsolateral prefrontal cortex and significant decreases in rCBF in the vicinity of the limbic/paralimbic areas (i.e., hippocampal formation, temporal pole), striatum (i.e., caudate, putamen), precuneus, and cerebellum. However, rCBF increases in the prefrontal cortex were significantly greater in obese men than in lean men (P < 0.005). rCBF decreases in limbic/paralimbic areas, temporal and occipital cortex, and cerebellum were also significantly greater in obese men than in lean men (P < 0.005), whereas rCBF decreases in the hypothalamus and thalamus were attenuated in obese men compared with lean men (P < 0.05). This study raises the possibility that the brain responses to a meal in the prefrontal areas (which may be involved in the inhibition of inappropriate response tendencies) and limbic/paralimbic areas (commonly associated with the regulation of emotion) may be different in obese and lean men. Additional studies are required to investigate how these differential responses are related to the pathophysiology of obesity. *Diabetes* 49:838–846, 2000

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FFA, free fatty acid; GLP-1, glucagon-like peptide 1; MRI, magnetic resonance imaging; PET, positron emission tomography; PP, pancreatic polypeptide; rCBF, regional cerebral blood flow; ROI, region of interest.

Obesity is a chronic relapsing disease with a prevalence reaching epidemic proportions in most industrialized countries (1,2). Whereas the exact pathophysiology of this disease remains unclear, studies in animals (3,4) and numerous reports in humans (5–10) indicate that eating behavior disorders (i.e., hyperphagia) and the resulting excessive energy intake play a major role in the development of obesity.

The role of the brain (especially the hypothalamus) in the regulation of body weight is well established in animals (11). In humans, substantial molecular (12) and neuropharmacologic evidence (13) attest to the importance of the central nervous system in maintaining energy balance. However, the neuroanatomical correlates of human feeding behavior are largely unknown. Some information comes from pathological conditions associated with hyperphagia and obesity such as hypothalamic tumors (14) and Prader-Willi syndrome, the most common type of inherited human hypothalamic disorder (15). In addition, patients with frontal lobe dementia with computerized tomography documented prefrontal atrophy frequently present with hyperphagia (16). Furthermore, seizures of the opercula (including the insular cortex) induce mastication, salivation, swallowing, and gustatory hallucinations (17). Finally, in 1 study, 50% of patients with eating epilepsy showed electro-encephalographic abnormalities in the fronto-temporal cortex (18). A few functional imaging studies seem to confirm the existence of a complex neuronal network controlling human feeding behavior. In healthy men, neuronal activity increases in the prefrontal cortex and decreases in the hypothalamus, insular cortex, orbitofrontal cortex, thalamus, and hippocampal formation in response to a single meal (19). Bulimic patients have been reported to have hypometabolism of the right prefrontal cortex (20). An increased neuronal activity in the right parieto-temporal cortex has been observed in obese women after food presentation (21). Taken together, these findings suggest that the prefrontal cortex, the limbic and paralimbic areas, and the parieto-temporal cortex may be part of the neuronal network controlling human feeding behavior and that obesity may be associated with differential activation of some of these areas of the brain.

In the present study, we assessed the brain response to satiation (i.e., administration of a liquid meal in the context of extreme hunger) in obese men. We report that compared with lean men, satiation in obese men produces greater neuronal activation of the prefrontal cortex and greater neuronal deactivation of the limbic and paralimbic areas and temporal cortex. Our results also suggest that the neuronal

deactivation of the hypothalamus in response to satiation may be attenuated in obese men.

RESEARCH DESIGN AND METHODS

Subjects. Eleven obese (BMI ≥35 kg/m^2, age 27 ± 5 years, weight 115 ± 11 kg, 38 ± 7% body fat; mean ± SD) and 11 lean (BMI ≤25 kg/m^2, age 35 ± 8 years, weight 73 ± 9 kg, 19 ± 6% body fat) right-handed male volunteers were recruited from the greater Phoenix area by newspaper advertisement (some of the results in the lean men were previously reported [19]). Subjects were in good health and free of drugs as determined by medical history, physical examination, and laboratory screening tests. Alcohol and drug abuse (and/or history of substance abuse or addiction), endocrine disorders (including abnormal thyroid function and type 2 diabetes), hypertension, and pulmonary, cardiovascular, gastrointestinal, hepatic, renal, and central nervous system disorders were excluded at screening. Behavioral or psychiatric conditions (claustrophobia, major depression, presence of psychotic symptoms, bulimia nervosa) were screened for using the Structured Clinical Interview for DSM-III-R (22). All subjects were admitted for ~1 week to the Clinical Research Unit of the National Institutes of Health in Phoenix. Subjects were restricted to the research ward and were limited to sedentary activity for the duration of the study. The protocol was approved by the Institutional Review Boards of the National Institute of Diabetes and Digestive and Kidney Diseases and Good Samaritan Regional Medical Center, and informed written consent was obtained from all subjects before participation.

Experimental protocol. Experimental procedures have been previously described (19). In brief, on admission, all subjects were placed on a weight-maintaining diet (50% carbohydrate, 30% fat, 20% protein). Body composition was assessed by dual-energy X-ray absorptiometry (DPX-l; Lunar, Madison, WI), and measurement of daily resting energy expenditure was performed for 45 min using a ventilated hood system (DeltaTrac; Sensormedics, Yorba Linda, CA). Before brain imaging procedures, subjects fasted for 36 h. Water and noncaloric noncaffeinated beverages were provided ad libitum during the fast.

Imaging procedures. Positron emission tomography (PET) and magnetic resonance imaging (MRI) procedures were conducted at Good Samaritan Regional Medical Center. An MRI of the brain was performed using a 1.5 Tesla Sigma system (General Electric, Milwaukee, WI) to rule out gross anatomical abnormalities and facilitate comparisons between brain structure and function as described below. For the PET procedure, a transmission scan using a ^{68}germanium/^{68}gallium ring source was performed to correct subsequent emission images for radiation attenuation. During each scan, subjects rested quietly in the supine position without movement and were asked to keep their eyes closed and pointing forward. PET images of regional brain activity (counts/pixel/min) were obtained in each subject using an ECAT 951/31 scanner (Siemens, Knoxville, TN). For each scan, a 50-mCi intravenous bolus of ^{15}O-water was injected. Two scans were obtained at baseline and 2 after feeding with intervals of ~10 min between scans. Blood samples were collected immediately after each scan for the measurement of glucose, free fatty acids (FFAs), insulin, leptin, glucagon-like peptide 1 (GLP-1), pancreatic polypeptide (PP), and gastrin concentrations.

Feeding procedure. A liquid formula meal (53% carbohydrate, 32% fat, 15% protein; Ensure-Plus 1.5 kcal/ml; Ross-Abbott Laboratories, Columbus, OH) was administered orally to induce satiation. To eliminate possible confounding factors, such as tactile stimulation of the tongue and motor neuron activity, swallowing was consistently induced by administering 2 ml of water before each of the 4 PET scans. Between the PET scans in the baseline and satiated states, a peristaltic pump (IMED 980; Imed, San Diego, CA) was set to deliver a liquid meal providing 50% of the previously measured daily energy expenditure over 25 min (meal intake: 954 ± 54 kcal for the obese men and 725 ± 105 for the lean men). Subjective ratings of hunger and satiation were recorded after each PET scan (23). To familiarize each subject with the experimental setting and minimize the risk of learning-related artifacts, the feeding procedure was repeated twice on the research ward before PET scanning.

TABLE 1
Hormones and metabolites before and after a liquid meal in 11 right-handed obese men compared with 11 right-handed lean men

	Obese	Lean	*P* (meal effect)	*P* (group effect)
Metabolites				
Glucose (mmol/l)				
Before meal	4.6 ± 0.3	4.2 ± 0.6		
After meal	5.6 ± 0.4	5.8 ± 0.5	0.0001	0.11
FFAs (mmol/l)				
Before meal	0.92 ± 0.34	0.64 ± 0.36		
After meal	0.72 ± 0.30	0.48 ± 0.06	0.0001	0.02
Hormones				
Insulin (μU/ml)				
Before meal	7 ± 4	6 ± 2		
After meal	106 ± 121	53 ± 31	0.0001	0.13
Leptin (ng/ml)				
Before meal	8.8 ± 3.1	0.5 ± 0.2		
After meal	9.0 ± 3.3	0.5 ± 0.3	0.6	0.7
Gastrin (ng/l)				
Before meal	46 ± 13	40 ± 9		
After meal	59 ± 24	46 ± 10	0.013	0.43
PP (pmol/l)				
Before meal	16 ± 7	18 ± 8		
After meal	70 ± 37	71 ± 31	0.0001	0.9
GLP-1 (ng/l)				
Before meal	7.1 ± 0.6	7.4 ± 1.1		
After meal	7.1 ± 0.6	7.6 ± 1.2	0.4	0.3
Subjective ratings				
Hunger (mm)				
Before meal	76 ± 21	74 ± 25		
After meal	29 ± 28	31 ± 21	0.0001	0.9
Satiation (mm)				
Before meal	16 ± 12	23 ± 24		
After meal	78 ± 21	70 ± 20	0.0001	0.4

Data are means ± SD. Subjects reported ratings of hunger and satiation on a 0- to 100-mm visual scale. Meal-induced changes and relative group differences were tested by analysis of variance for repeated measures.

Analytical measurements. Plasma glucose concentrations were determined by the glucose oxidase method (Beckman Instruments, Fullerton, CA) and plasma insulin concentrations by an automated radioimmunoassay (Concept 4; ICN, Costa Mesa, CA). Serum FFAs were determined by an enzymatic colorimetric method (Wako Chemicals, Richmond, VA). Leptin, GLP-1, gastrin, and PP were determined by commercially available radioimmunoassay.

Image processing and statistical analysis. Automated algorithms were used to align each subject's sequential PET images (24), transform PET images into spatial coordinates of a standard brain atlas (25), investigate increases/decreases in regional cerebral blood flow (rCBF) independent of variations in whole-brain measurements using analysis of covariance (statistical parametric mapping) (26), and generate normalized *t* value (i.e., *Z*-score) maps of increases and decreases in rCBF. To reduce type I errors, a critical *Z*-score ≥2.58 ($P < 0.005$, uncorrected for multiple comparisons) was used to characterize significant increases/decreases in rCBF. Automated algorithms were used to transform each subject's brain MRI into standard atlas coordinates (27) and superimpose each *Z*-score map onto the averaged MRI to allow visual inspection of the composite images. To directly test the hypothesis that obese subjects have a different pattern of brain activation, we tested the interaction between condition (before meal vs. after meal) and group (obese vs. lean) using statistical parametric mapping. Pearson's product moment correlations were used to test the relationship between state-dependent changes in rCBF in regions of interest (ROIs) and state-dependent changes in plasma levels of hormones and metabolites and subjective ratings of satiation. Two approaches were used to define ROIs: *1*) tridimensional coordinates for each ROI were defined using anatomical coordinates from the brain atlas of Talairach and Tournoux (25); *2*) after obtaining the coordinates of maximal increases/decreases in regional brain activity in response to satiation in all 22 subjects, we defined a ROI as a sphere of 1.2-cm diameter around these coordinates. In each ROI, a mean rCBF (normalized for whole brain rCBF) was calculated in each individual. An interaction term (group*variable) was used to assess possible differences between obese and lean men in the slope of the correlation between changes in rCBF and variable of interest in each ROI. Plasma insulin concentrations were $\log_{10}$ transformed to approximate a normal distribution before parametric analyses.

RESULTS

The characteristics of the subjects are shown in Table 1. Except for plasma insulin and FFA concentrations, postmeal changes in glucose, PP, and gastrin concentrations were similar in the 2 groups. No postmeal changes in GLP-1 and leptin concentrations were observed in either group. Ratings of hunger (after a 36-h fast) and satiation (after the liquid meal) were also similar in obese and lean men.

Regions of the brain affected in response to satiation in obese subjects. The administration of the liquid meal (satiation) was associated with increased rCBF bilaterally in the vicinity of the ventromedial, lateral, and dorsomedial prefrontal cortex (Table 2, Fig. 1). Satiation was also associated with decreased rCBF bilaterally in the vicinity of limbic and paralimbic areas (insular cortex, hippocampus/parahippocampal gyrus, and a region that includes the anterior temporal and posterior orbitofrontal cortex), caudate, precuneus, and cerebellum, and unilaterally in the vicinity of the right putamen and the left occipital cortex (Table 3, Fig. 1). These results are consistent with those previously reported in lean men (19).

In addition, we observed significant decreases in rCBF in a region of the parietotemporal cortex (including Brodmann's areas 40, 21, and 22) and in the midbrain that were not previously observed in lean men (19). The decreased rCBF in the vicinity of the hypothalamus and thalamus previously described in lean men (19) did not reach statistical significance in obese men.

Comparison between obese and lean subjects (analysis of covariance). In response to satiation, obese subjects had greater increases in rCBF in the vicinity of the right dorsolateral and ventromedial prefrontal cortex and bilaterally in the dorsomedial prefrontal cortex (Table 4).

In response to satiation, obese men had a greater decrease in rCBF in the right insular/anterior temporal region (*Z*-score marginally significant in the left hemisphere at 2.165), right hippocampal formation, bilaterally in a large region including the orbitofrontal cortex and temporal pole, and the cerebellum. A greater decrease in rCBF was also observed in regions not previously described in lean subjects, such as Brodmann's areas 18 and 19 in the occipital cortex and areas 21 and 22 in the posterior temporal cortex (Table 5). Decreases in rCBF in the hypothalamus, thalamus, and anterior cingulate tended to be smaller in obese subjects than in lean subjects (*Z*-scores = 2.142, 1.884, and 2.417, respectively; $P < 0.05$).

Correlation between postprandial changes in brain activity, metabolites/hormones, and subjective ratings of satiation. Correlation analyses were performed using 2 approaches for the definition of ROIs (see RESEARCH DESIGN AND METHODS), and results varied depending on the approach used (Tables 6 and 7). The only consistent finding (regardless of ROI definition) was the opposite correlation between changes in plasma insulin concentration and changes in

TABLE 2
Significantly greater increases in regional brain activity in response to satiation (liquid meal ingested after an ~36-h fast) in 11 obese men

Region	Brodmann's area	Atlas coordinates*			*Z*-score†
		x	*y*	*z*	
Dorsolateral prefrontal cortex‡	10, 46	46	52	16	3.2
Dorsomedial prefrontal cortex	9, 10	–12	68	20	3.197
		8	68	24	2.84
Anterolateral prefrontal cortex‡	10	–38	46	–20	2.959
		44	44	–20	4.303
Ventromedial prefrontal cortex‡	11	–6	54	–24	2.485
		14	54	–24	3.896
Inferior parietal lobule‡	—	—	—	—	—
Occipital cortex	19	–18	–100	16	3.007
Cuneus	19	8	–96	32	2.713

*Coordinates are from the brain atlas of Talairach and Tournoux (25), such that *x* is the distance in millimeters to the right (+) or left (–) of midline, *y* is the distance in millimeters anterior (+) or posterior (–) to the anterior commissure, and *z* is the distance in millimeters superior (+) or inferior (–) to a horizontal plane through the anterior and posterior commissures. †$P < 0.005$, without correction for multiple comparisons. ‡Regions previously reported to participate in aspects of satiation in lean subjects (19).

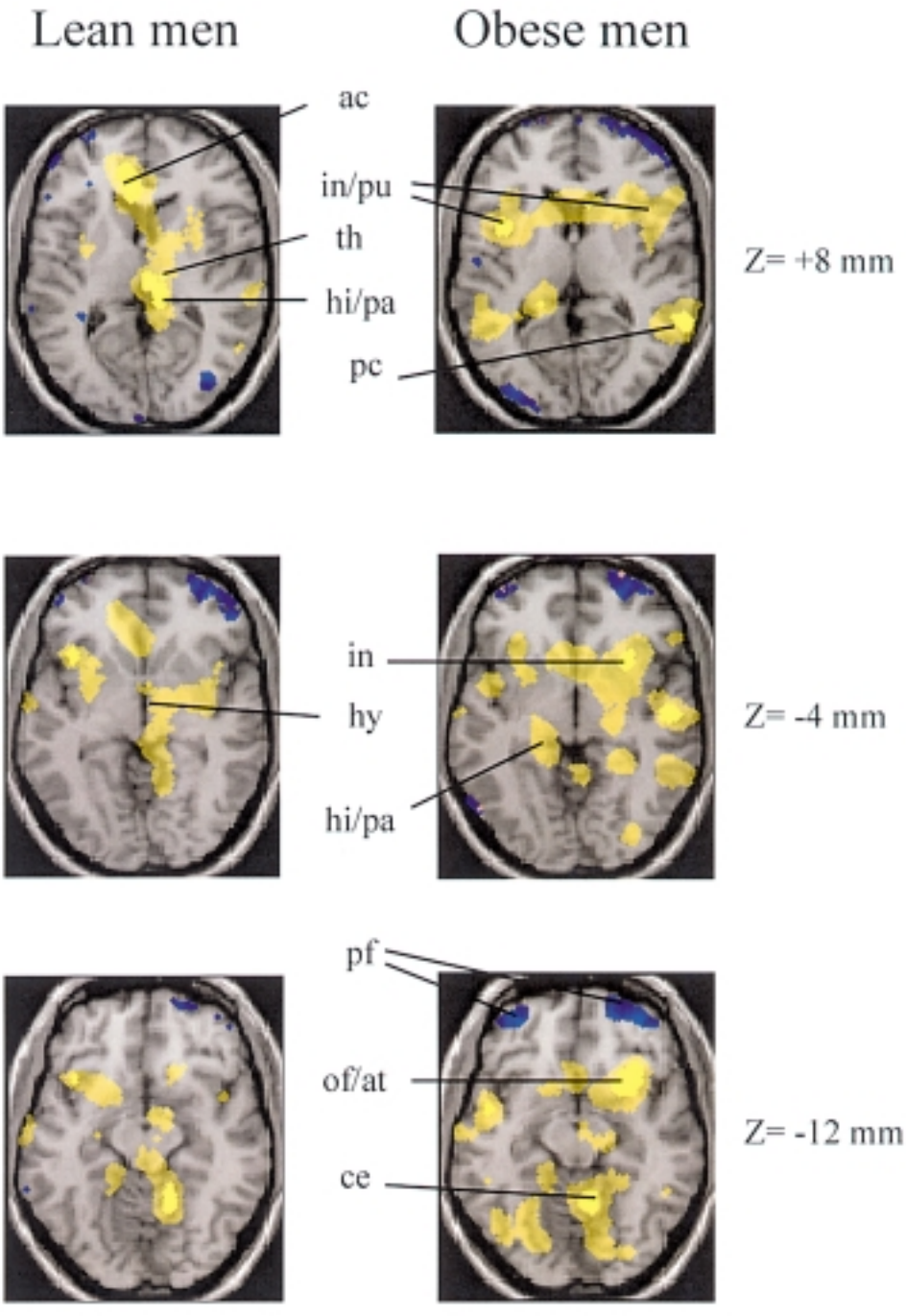

FIG. 1. Images of brain responses to satiation in 11 obese individuals (right images) and 11 lean individuals (left images) at +8 mm (upper images), –4 mm (middle images), and –12 mm (lower images) from a horizontal plane between the anterior and posterior commissures (coordinates from the Talairach and Tournoux brain atlas [25]). The right hemisphere in each section is on the reader's right. Brain regions with significant increase in rCBF in response to satiation are shown in blue; brain regions with significant decrease in rCBF in response to satiation are shown in yellow. Solid colors represent the statistical level of $P < 0.001$ uncorrected for multiple comparisons, and transparent colors represent the level of $P < 0.05$. Images were generated using PET and MRI data. Color-coded images are superimposed onto an average of the subjects' brain MRIs (gray scale image). The figure is intended for visual inspection only of several areas of the brain, including the anterior cingulate (ac), insula/putamen (in/pu), thalamus (th), hippocampus/parahippocampal gyrus (hi/pa), parietal cortex (pc), insular cortex (in), hypothalamus (hy), prefrontal cortex (pf), orbitofrontal and temporal cortex (of/at), and cerebellum (ce). Group differences in brain response to satiation and relative level of statistical significance were calculated by analysis of covariance and are presented in Tables 4 and 5.

rCBF in the vicinity of the precuneus between obese and lean subjects (Tables 6 and 7). Otherwise, changes in plasma insulin concentrations were generally negatively correlated with changes in rCBF in several regions inhibited in response to satiation (Tables 6 and 7). Changes in FFA concentrations were correlated with changes in rCBF in the prefrontal cortex but the slope of the correlation was negative in obese men and positive in lean men ($P < 0.05$ for group interaction). Changes in gastrin concentrations were negatively correlated with changes in rCBF in the vicinity of the putamen and

TABLE 3
Significantly greater decreases in regional brain activity in response to satiation (liquid meal ingested after an ~36-h fast) in 11 obese men

Region	Brodmann's area	Atlas coordinates*			Z-score†
		x	*y*	*z*	
Hypothalamus‡	—	—	—	—	—
Thalamus‡	—	—	—	—	—
Anterior cingulate cortex‡	—	—	—	—	—
Insular cortex/claustrum/		–42	6	8	3.5
anterior temporal cortex‡		48	12	8	2.83
Posterior orbitofrontal cortex/	21, 25, 38, 47	–52	–2	–12	3.3
anterior temporal cortex‡		30	16	–16	4.098
Hippocampus/parahippocampal gyrus‡		–18	–38	4	3.543
		30	–42	1	2.52
Precuneus‡		–8	–46	45	3.387
		14	–48	45	4.047
Caudate ventricle‡		–6	22	4	2.65
		6	18	4	3.49
Putamen‡		16	2	–4	2.82
Parietotemporal cortex	40, 21, 22	–56	–44	28	3.342
		64	–50	1	3.306
Occipital cortex	18, 37	–42	–72	–12	2.747
Midbrain		2	–20	–24	3.655
Cerebellum‡		–20	–52	–20	3.093
		6	–54	–16	3.406

*Coordinates are from the brain atlas of Talairach and Tournoux (25), such that *x* is the distance in millimeters to the right (+) or left (–) of midline, *y* is the distance in millimeters anterior (+) or posterior (–) to the anterior commissure, and *z* is the distance in millimeters superior (+) or inferior (–) to a horizontal plane through the anterior and posterior commissures. †$P < 0.005$, without correction for multiple comparisons. ‡Regions previously reported to participate in aspects of hunger in lean subjects (19).

anterior cingulate in obese subjects but not in lean subjects (Tables 6 and 7), and the slope of correlation was significantly different between the 2 groups in the anterior cingulate (Table 7). Changes in PP concentrations were negatively correlated with changes in rCBF in the precuneus (Table 6) and several areas of the prefrontal cortex, where the slope of the correlations was different between the 2 groups (Table 7). The slope of the correlation between changes in ratings of satiation and changes in rCBF in the right dorsomedial prefrontal cortex was also significantly different between the 2 groups.

DISCUSSION

The present study continues to investigate regions of the human brain that are involved in the regulation of feeding. In obese men, satiation produced significant increases in rCBF in the vicinity of ventromedial and dorsolateral prefrontal cortex and significant decreases in rCBF in the vicinity of the limbic/paralimbic areas, caudate, precuneus, putamen, and cerebellum, corroborating our findings in lean men. Neuronal activation of the prefrontal cortex was, however, significantly greater in obese men than in lean men. Neuronal deactivation of limbic/paralimbic areas, temporal and occipital cortex, and cerebellum was also greater in obese men than in lean men. In contrast, neuronal deactivation of the hypothalamus, thalamus, and anterior cingulate was attenuated in obese men compared with lean men.

The prefrontal cortex is known to exert an inhibitory control on brain activation in response to external and internal stimuli (28,29). While generally performing well on standard tests of memory and cognitive function, subjects with alterations of the prefrontal cortex suffer from inappropriate social behavior (28), altered cardiovascular homeostasis (30), and hyperphagia (16). We postulate that the activation

TABLE 4
Significantly greater increases in regional brain activity in obese men in response to satiation as compared with lean men

Region	Brodmann's area	Atlas coordinates*			Z-score†
		x	*y*	*z*	
Dorsolateral prefrontal cortex	9	36	22	40	2.768
Dorsomedial prefrontal cortex	10	–12	68	20	3.094
		10	66	24	2.738
Ventromedial prefrontal cortex	11	20	28	–24	2.761

*Coordinates are from the brain atlas of Talairach and Tournoux (25), such that *x* is the distance in millimeters to the right (+) or left (–) of midline, *y* is the distance in millimeters anterior (+) or posterior (–) to the anterior commissure, and *z* is the distance in millimeters superior (+) or inferior (–) to a horizontal plane through the anterior and posterior commissures. †$P < 0.005$, without correction for multiple comparisons.

TABLE 5
Significantly greater decreases in regional brain activity in response to satiation after a liquid meal in obese men as compared with lean men

Region	Brodmann's area	Atlas coordinates*			*Z*-score†
		x	*y*	*z*	
Insular cortex/anterior		–56	2	1	2.165
temporal cortex	21, 22	56	–16	1	3.128
Posterior orbitofrontal cortex/	47, 38, 21	–54	4	–12	3.378
temporal pole		30	6	–16	2.58
Hippocampus/parahippocampal gyrus		–20	–36	1	1.933
		32	–38	1	2.674
Posterior temporal cortex	21, 22	–36	–44	8	3.998
		58	–48	1	2.795
Occipital cortex	18, 19	–20	–82	–4	3.061
		34	–84	1	4.002
Cerebellum		–22	–56	–16	2.731
		4	–54	–12	2.57

*Coordinates are from the brain atlas of Talairach and Tournoux (25), such that *x* is the distance in millimeters to the right (+) or left (–) of midline, *y* is the distance in millimeters anterior (+) or posterior (–) to the anterior commissure, and *z* is the distance in millimeters superior (+) or inferior (–) to a horizontal plane through the anterior and posterior commissures. †$P < 0.005$, without correction for multiple comparisons.

TABLE 6
Pearson's correlation coefficients between changes (postmeal values – premeal values) in hormone/metabolite concentrations or satiation ratings and changes in rCBF in predefined ROIs according to the brain atlas of Talairach and Tournoux (25) in obese men ($n = 11$), lean men ($n = 11$), and all subjects

ROI and independent variable	Obese subjects	Lean subjects	All subjects	Group effect
Left posterior orbitofrontal cortex				
Insulin	–0.25 (0.5)	–0.65 (0.03)	–0.46 (0.03)	
Left hippocampus/parahippocampal gyrus				
Insulin	–0.21 (0.5)	–0.57 (0.04)	–0.26 (0.2)	
Right hippocampus/parahippocampal gyrus				
Insulin	–0.41 (0.2)	–0.66 (0.03)	–0.48 (0.02)	
Left precuneus				
Insulin	–0.55 (0.08)	0.70 (0.02)	–0.15 (0.5)	(0.009)
PP	–0.73 (0.03)	–0.14 (0.7)	–0.48 (0.04)	
Satiation	0.53 (0.09)	0.67 (0.03)	0.52 (0.01)	
Right precuneus				
Insulin	–0.42 (0.2)	0.65 (0.03)	–0.001 (1)	(0.02)
PP	–0.81 (0.008)	–0.02 (1)	–0.41 (0.08)	
Satiation	0.51 (0.1)	0.29 (0.4)	0.4 (0.07)	
Left putamen				
Insulin	–0.58 (0.06)	–0.66 (0.03)	–0.61 (0.003)	
Gastrin	–0.71 (0.03)	–0.06 (0.9)	–0.48 (0.04)	
Right putamen				
Insulin	–0.69 (0.02)	–0.43 (0.19)	–0.55 (0.008)	
Gastrin	–0.73 (0.02)	0.27 (0.4)	–0.56 (0.03)	
Anterior cingulate				
FFAs	–0.05 (0.9)	–0.76 (0.007)	–0.15 (0.09)	
Left thalamus				
Insulin	–0.65 (0.03)	–0.46 (0.2)	–0.58 (0.004)	
Right thalamus				
Insulin	–0.58 (0.06)	–0.34 (0.3)	–0.46 (0.03)	
Left dorsolateral prefrontal cortex				
FFAs	–0.53 (0.18)	0.62 (0.04)	–0.23 (0.7)	(0.03)
Right dorsolateral prefrontal cortex				
Gastrin	–0.09 (0.8)	–0.77 (0.005)	–0.29 (0.08)	

P values, uncorrected for multiple comparison, are given in parentheses.

TABLE 7
Pearson's correlation coefficients between changes (postmeal values – premeal values) in hormone/metabolite concentrations or satiation ratings and changes in rCBF in ROIs predefined as a sphere (1.2 cm in diameter) around the greater increases in regional brain activity during hunger and satiation obtained from the 22 subjects (11 obese men and 11 lean men)

ROI and independent variable	Obese subjects	Lean subjects	All subjects	Group effect
Right posterior orbitofrontal cortex				
Insulin	0.08 (0.8)	–0.66 (0.03)	–0.19 (0.09)	(0.05)
Left parietotemporal cortex				
PP	–0.49 (0.18)	–0.55 (0.08)	–0.50 (0.03)	
Satiation	0.84 (0.001)	0.36 (0.3)	0.47* (0.004)	
Left precuneus				
Insulin	–0.61 (0.05)	0.27 (0.4)	–0.24 (0.3)	(0.04)
Satiation	0.54 (0.09)	0.39 (0.3)	0.44* (0.04)	
Right precuneus				
Satiation	0.64 (0.03)	0.18 (0.6)	0.33 (0.15)	
Left putamen				
PP	–0.07 (0.8)	–0.64 (0.04)	–0.31 (0.1)	
Right putamen				
Insulin	–0.64 (0.03)	–0.46 (0.2)	–0.59 (0.01)	
Anterior cingulate				
Gastrin	–0.66 (0.05)	0.70 (0.02)	–0.38 (0.9)	(0.009)
Left dorsolateral prefrontal cortex				
PP	–0.66 (0.05)	0.43 (0.2)	–0.13 (0.6)	(0.02)
Right dorsolateral prefrontal cortex				
PP	–0.09 (0.8)	0.54 (0.08)	0.26 (0.3)	(0.04)
Right dorsomedial prefrontal cortex				
Satiation	0.65 (0.03)	–0.46 (0.2)	0.19 (0.5)	(0.01)*
Left anterolateral prefrontal cortex				
FFAs	–0.90 (0.0002)	0.71 (0.01)	–0.06 (0.06)	(0.004)
Glucose	–0.15 (0.7)	–0.73 (0.01)	–0.39 (0.09)	
PP	–0.19 (0.6)	0.63 (0.04)	0.14 (0.6)	
Right anterolateral prefrontal cortex				
Glucose	–0.07 (0.8)	–0.62 (0.04)	–0.33 (0.03)	
Gastrin	–0.17 (0.7)	–0.58 (0.06)	–0.31 (0.05)	

P values, uncorrected for multiple comparisons, are given in parentheses. *Statistically different correlation between hemispheres.

of the prefrontal cortex in response to a meal is an important component of the central response aimed at promoting termination of the feeding episode. Decreased neuronal activity in response to satiation was observed in the limbic and paralimbic areas, including the insular cortex, orbitofrontal cortex, and hippocampal/parahippocampal areas. We previously postulated that in humans, as in animals (31–34), these regions may represent a central orexigenic network (19). Because the prefrontal cortex has efferent inhibitory connections to the limbic/paralimbic areas, hypothalamus, caudate, and putamen (28,35), we postulate that the prefrontal cortex exerts its inhibiting effect on feeding behavior by suppressing the neuronal activity of these structures. Interestingly, in rodents and primates, discrete areas of the prefrontal cortex have been found to have direct efferent projections to the lateral region of the hypothalamus (35,36).

Our study indicates that compared with lean individuals, obese individuals have a greater activation of the prefrontal cortex and a greater deactivation of the limbic/paralimbic areas in response to satiation. Obese subjects also have an attenuated deactivation of the hypothalamus, thalamus, and anterior cingulate in response to satiation. A deficient hypothalamic response to an oral glucose load has been recently reported in a study using functional MRI (37). Differences in macronutrient and hormonal postprandial excursion between obese and lean individuals are well established and were observed in the present study. It is therefore possible that the differential brain response to satiation in obese and lean men reflects in part such differences. We previously reported that insulin and FFAs might act as metabolic modulators of postprandial brain neuronal events (19). Findings from the present study are generally consistent with our previous report (19), although the strength of the correlation between insulin/FFAs and changes in rCBF in several areas of the brain differed depending on the type of analysis used (Tables 6 and 7). Whether or not insulin and FFAs exert a different effect on neuronal events in obese individuals compared with lean individuals, as suggested by some of our correlation analyses, remains to be elucidated. We found very little evidence for an effect of glucose on early postprandial neuronal events. We did not explore the possibility that differences in postprandial amino acid metabolism between lean and obese men may underlie, at least in part, the observed differences in neuronal activity.

Not reported in our previous work are the correlations between changes in gastrin and PP and changes in neuronal events. Gastrin and PP are not known to have direct anorectic effects in humans. However, they are both released after food intake as part of the gastrointestinal response to a meal. PP belongs to the neuropeptide Y family and is a weak agonist for neuropeptide Y receptors (38). Infusion of gastrin-releasing peptide has been reported to increase satiety in

humans (39). Our findings suggest that gastrin and PP may play a role in satiation and that the effect of gastrin may be different in obese individuals.

The limitations of our experimental approach have largely been addressed in previous publications (19,40). They include the following: *1*) limitations in spatial resolution, contrast resolution, and the accuracy of the image deformation algorithm used to compute statistical maps, which may prevent detection of significant state-dependent changes in regional brain activity in small regions, such as specific hypothalamic, thalamic, or brainstem nuclei; *2*) potentially confounding effects of scan order because the satiation condition always followed the baseline condition; and *3*) the possibility of statistical type I errors. Because brain activity changes in the vicinity of the insular cortex, orbitofrontal cortex, hippocampal formation, caudate, precuneus, cerebellum, and prefrontal cortex were bilateral or previously reported in these conditions, we believe these changes are unlikely to reflect statistical type I errors. Other factors could explain differences in pattern of brain activity between lean and obese subjects. Meal size was a function of body size, and differences in gastric distension between the 2 groups cannot be completely excluded. However, we believe that the confounding effects of gastric distension should have been minimal because *1*) gastric capacity is higher in obese subjects than in lean subjects (41,42), and *2*) obese men had similar satiation ratings compared with lean men. Finally, we cannot exclude the possibility that obese subjects laid less comfortably while in the PET scanner, although none of them expressed any complaint. The limitations of this experimental approach emphasize the need for replication studies to confirm our exploratory findings, including those involving correlation analyses.

In conclusion, our findings confirm that several regions of the brain are preferentially affected by satiation in humans. This study raises the possibility that the brain responses to feeding stimuli in the prefrontal areas (often associated with the inhibition of inappropriate response tendencies) and limbic/paralimbic areas (commonly associated with the regulation of emotion) may be different in obese and lean men. Additional studies are required to investigate how these differential responses are related to the pathophysiology of obesity.

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