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PAPER

Persistence of abnormal neural responses to a meal in postobese individuals

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OBJECTIVE: To determine whether abnormal obese-like neural responses to a meal persist in postobese individuals, who achieved and maintained a normal body weight despite a past history of severe obesity.
DESIGN AND SUBJECTS: Cross-sectional study of the brain's response to tasting and consuming a satiating meal in 11 postobese (age: 40 ± 6 y, body mass index (BMI): 23.6 ± 1.9 kg/m^2), 23 obese (age: 29 ± 6 y, BMI: 39.6 ± 3.8 kg/m^2) and 21 lean (age: 33 ± 9 y, BMI: 22.8 ± 2.1 kg/m^2) subjects.
MEASUREMENTS: Regional cerebral blood flow (rCBF, a marker of neural activity) at baseline (after a 36-h fast), after tasting and after consuming a satiating liquid meal was assessed using positron emission tomography and state-dependent changes (taste-baseline; satiation-baseline), and compared across groups. Subjective ratings of hunger and fullness were measured by a visual analogue scale and body fatness by dual-energy X-ray absorptiometry.
RESULTS: In response to tasting the liquid meal, changes in rCBF were different in the obese as compared to the lean individuals ($P<0.05$, corrected for multiple comparisons) in the middle insula (peak voxel, $x=-41$, $y=1$, $z=8$; Montreal Neurological Institute coordinates) and posterior cingulate cortex (peak voxel, $x=17$, $y=-47$, $z=40$). The middle insular cortex exhibited a similar increase of neural activity in the obese and postobese subjects, whereas in the lean subjects the regional activity did not change. In the posterior cingulate cortex, the changes in rCBF in the postobese subjects were not different from those in the other groups. In response to a satiating amount of the same liquid meal, changes in rCBF were different in the obese as compared to the lean individuals ($P<0.05$, corrected for multiple comparisons) in the posterior hippocampus (peak voxel, $x=21$, $y=-45$, $x=4$), posterior cingulate cortex (peak voxel, $x=17$, $y=-47$, $z=40$), and amygdala (peak voxel, $x=27$, $y=1$, $z=-24$). The posterior hippocampus exhibited a similar decrease of neural activity in the obese and postobese subjects, whereas in the lean subjects the regional activity increased. In the posterior cingulate cortex and amygdala, the changes in rCBF were not different between the postobese and lean individuals. None of the changes in neural activity were correlated with the age of the individuals, the subjective ratings of hunger and fullness, or the meal induced-changes in plasma glucose, insulin, or serum free fatty acids.
CONCLUSION: Persistence of abnormal neural responses to a meal in the postobese individuals, a group at high risk for relapse, indicates that a predisposition to obesity may involve areas of the brain that control complex aspects of eating behavior including anticipation and reward, chemosensory perception, and autonomic control of digestion (insular cortex), as well as enteroception and learning/memory (hippocampus).
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Keywords: positron emission tomography; brain; postobese

Introduction

Obesity is a progressive, chronic, and relapsing disease that represents the largest nutrition-related health problem in many affluent and developing countries. Whereas the etiology of obesity is not completely resolved, studies in animals[1] and humans[2] indicate that excessive energy intake plays a major role in its development.

The role of the brain, particularly the hypothalamus, in energy homeostasis is well established in animals[3] and in humans.[4] However, knowledge of the neural network involved in the regulation of ingestive behavior is limited. Food ingestion elicits multisensory responses, which include olfaction, taste, texture, and temperature, as well as changes

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in the peripheral and central concentrations of hormones and metabolites. At the same time, higher-order processing of sensory and autonomic inputs elicited by the ingestion of food produces cognitive and emotional responses that modulate ingestive behavior. By combining sensory, metabolic/autonomic, and cognitive information, the brain determines when it is time to start or stop eating and coordinates the autonomic and somatic motor systems accordingly.

We[5–8] and others[9,10] have previously described the differences in the neuroanatomical correlates of a meal between obese and lean individuals in some limbic/paralimbic areas and prefrontal cortex. However, it is not known if these differences underlie the hyperphagia that leads to obesity or are a consequence of it. Studies in the postobese, who are at high risk for relapse, indicate that this population is informative for the identification of phenotypic characteristics that antecede and possibly cause the development of obesity.[11] Thus, the neurophysiology of postobese individuals may reveal central responses to nutritional stimuli that permit identification of regions of the brain involved in the development of the hyperphagia that leads to obesity.

To test if abnormal neural responses to a meal persist in individuals who achieved and maintained a normal body weight despite a past history of severe obesity, we compared positron emission tomography (PET) measurements of regional cerebral blood flow (rCBF, a marker of local neural activity) in response to tasting and to ingesting a satiating meal in obese, postobese, and lean subjects. We hypothesized that limbic and paralimbic areas of the brain involved in the anticipation of and reward due to food ingestion (the insula, cingulate, orbitofrontal cortex, hippocampus and parahippocampal gyrus, temporal pole, and amygdala) and in the termination of a meal (prefrontal cortex) may respond similarly in the obese and postobese individuals.

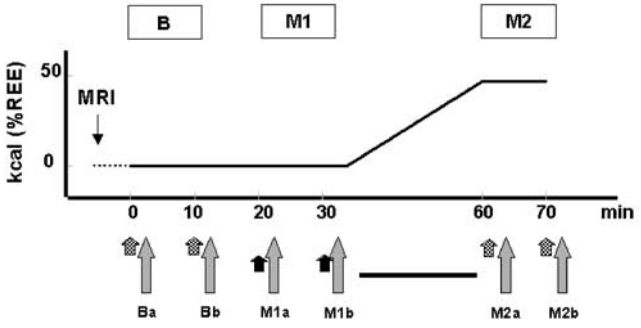

Figure 1 Schematic representation of the experimental design. Following a magnetic resonance imaging (MRI) scan, individuals underwent six consecutive positron emission tomography (PET) scans (gray arrows) to measure the regional cerebral blood flow (rCBF): two (Ba and Bb) at baseline (B, after a 36 h fast), two (M1a and M1b) after ingestion of 2 ml of a liquid formula meal (M1, black arrows), and two (M2a and M2b) after ingestion of a satiating amount of the same meal (M2, black bar). The checkered arrows preceding each PET scan in B and M2 indicate the administration of 2 ml of tap water.

Methods

Subjects

In all, 23 obese (body mass index (BMI) = $39.6 \pm 3.8\,kg/m^2$, mean ± s.d.), 11 postobese (BMI = $23.6 \pm 1.9\,kg/m^2$), and 21 lean (BMI = $22.8 \pm 2.1\,kg/m^2$) subjects were recruited from the Phoenix (AZ, USA) metropolitan area by newspaper advertisement or by targeted mailing to members of the National Weight Control Registry (postobese). The postobese subjects were selected from people who, based on a telephone screening interview, had achieved (by diet and physical exercise) the weight loss necessary to change their BMI from at least 35 to a BMI of $25\,kg/m^2$, and who had successfully kept their weight stable for at least 3 months prior to the admission. All subjects were nonsmokers, in good health, and not taking any medication. Women were studied while in the follicular phase of the menstrual cycle. Subjects were admitted for 1 week to the Clinical Diabetes and Nutrition Section of the National Institutes of Health in Phoenix and were restricted to the metabolic ward and 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, the Indian Health Service, and the Good Samaritan Regional Medical Center. A written informed consent was obtained from all subjects prior to participation.

Experimental protocol

Experimental procedures have been described previously.[12] In brief, on admission all subjects were placed on a weight-maintaining diet (50% carbohydrate, 30% fat, 20% protein). Resting energy expenditure was measured by indirect calorimetry (DeltaTrac, SensorMedics, Yorba Linda, CA, USA), and body composition by dual-energy X-ray absorptiometry (DPX-l, Lunar, Madison, WI, USA). Prior to the brain imaging session, subjects fasted for 36 h. Water and noncaloric, noncaffeinated beverages were provided *ad lib* during the fast.

Imaging procedures

PET and magnetic resonance imaging (MRI) procedures were conducted at Good Samaritan Regional Medical Center (Phoenix, AZ, USA). MRI of the brain was performed using a 1.5 T Sigma system (General Electric, Milwaukee, WI, USA) to rule out gross anatomical abnormalities and to allow for the identification of regional activation. PET maps of regional brain activity (counts per voxel per minute) were obtained for each subject using an ECAT-951/31 scanner (Siemens, Knoxville, TN, USA). During each 1-min scan, subjects rested in the supine position without movement and were asked to keep their eyes closed and pointing forward. For each scan, a 50-mCi intravenous bolus of ^{15}O-water was injected. Two scans (Ba and Bb) were obtained in resting conditions after a 36 h fast (baseline, B), two (M1a and M1b) after the oral administration of 2 ml of a liquid

meal (Ensure Plus, 1.5 kcal/ml, 56% carbohydrate, 29% fat, 15% protein; Ross-Abbott Laboratories, Columbus, OH, USA) (M1), and two (M2a and M2b) after the administration (over 25 min) of a satiating amount of the same meal (M2), which provided 50% of the individual daily resting energy expenditure (Figure 1). There was an interval of 10 min between Ba and Bb, M1a and M1b, and M2a and M2b. At B and M2, 30 s before each scan, to control for swallowing, subjects were asked to retain and swallow 2 ml of tap water administered from a syringe through a plastic tube into the mouth of the subject. Immediately after each scan, subjects were asked to rate feelings of hunger and fullness on a 100-mm visual analogue scale, ranging from 0 ('not at all hungry', 'not at all full') to 100 ('very hungry', 'very full'). At M1, 30 s before each scan, subjects were asked to retain and swallow 2 ml of the liquid formula meal administered in the same manner as for the tap water at B. The experimental session continued with the administration of the same liquid meal to induce satiation (M2). The subjects were anticipating being fed to satiety. They had been fully familiarized with the experimental protocol in order to minimize the risk of learning-related artifacts (prior to the imaging session, the procedure was performed twice in the research ward).

Statistical analysis

Group differences in gender composition, age, body composition, and subjective ratings of hunger and fullness were tested by χ^2 for the gender composition, and general linear models (SAS Institute, Cary, NC, USA). Automated algorithms were used to align each subject's sequential PET images, normalize to the stereotactic space as defined by the template provided by the Montreal Neurological Institute (MNI), and smooth the images by a Gaussian filter with a 15 mm full-width at half-maximum and a mapping localization of <2 mm.[13] The results from the two scans per each condition were averaged (B, M1, and M2). Statistical parametric mapping (SPM99, Wellcome Department of Cognitive Neurology, University College, London, UK) was used for the analysis. To test our hypothesis, we first assessed the interaction between condition (B, M1, and M2) and group (obese, postobese, and lean subjects) with an F-test, after adjusting for the whole brain blood flow by ANCOVA. Random-field theorem and a small volume correction (SVC) procedure were applied to correct for multiple comparisons over the volume of 4 mm radius spheres centered on the foci of the maximal F-values in the regions related to our original hypothesis. A $P<0.05$ (corrected) was considered significant. Then, *t*-tests ($P<0.05$, two-tailed, SVC corrected for multiple comparisons) were used to assess the pairwise group differences in changes in rCBF after meal ingestion (M1-B and M2-B) between the obese and lean subjects, and between the postobese and the other two groups in the foci of significant differences between the obese and lean subjects.

Results

Body weight, percent body fat, and the amount of a liquid meal administered to induce satiation were larger in the obese than in the other two groups (Table 1). Subjective ratings of hunger and fullness were not different among the three groups. After eating the meal, the postobese subjects exhibited an increase in plasma glucose that was intermediate between the obese and lean subjects. The increase in plasma insulin after the meal was larger in the obese than in the lean and postobese subjects. The decrease in serum free fatty acids (FFAs) was smaller in the obese than in the other two groups.

In response to the oral administration of 2 ml of a liquid meal (M1, Figure 1), changes in rCBF (M1-B) were different in the obese as compared to the lean individuals ($P<0.05$, corrected for multiple comparisons) in the middle insula (peak voxel, $x=-41$, $y=1$, $z=8$; MNI coordinates) (Figure 2a) and posterior cingulate cortex (peak voxel, $x=17$, $y=-47$, $z=40$) (Table 2). The middle insular cortex exhibited a similar increase of neural activity in the obese and postobese subjects, whereas in the lean subjects the regional activity did not change (Figure 3, upper panel;

Table 1 Anthropometric characteristics, ratings of hunger and fullness, and changes in plasma glucose, insulin, and serum free fatty acids

	Obese	*Postobese*	*Lean*
n	23	11	21
Gender (M/F)	11/12[a]	3/8[a]	11/10[a]
Age (y)	29±6[a]	40±6[b]	33±9[c]
Weight (kg)	112±13[a]	65±6[b]	67±10[b]
Body fat (%)	39±5[a]	26±4[b]	22±7[b]
Intake (kJ)	3793±650[a]	2637±320[b]	2858±405[b]
Subjective ratings of hunger (0–100 mm)	78±19[a]	83±22[a]	70±28[a]
Subjective ratings of fullness (0–100 mm)	80±19[a]	81±23[a]	72±27[a]
Change in glucose (M2-B) (mmol/l)	1.76±1.09[a]	2.25±0.94[a,b]	2.80±0.96[b]
Change in insulin (M2-B) (mU/ml)	81.96±98.73[a]	17.13±11.04[b]	42.36±29.58[b]
Change in FFA (M2-B) (mmol/l)	−0.17±0.22[a]	−0.42±0.36[b]	−0.42±0.22[b]

Different superscripts identify significant group differences ($P<0.05$, general linear models or χ^2 for the gender composition). B = baseline; M2 = ingestion of a satiating amount of a liquid meal.

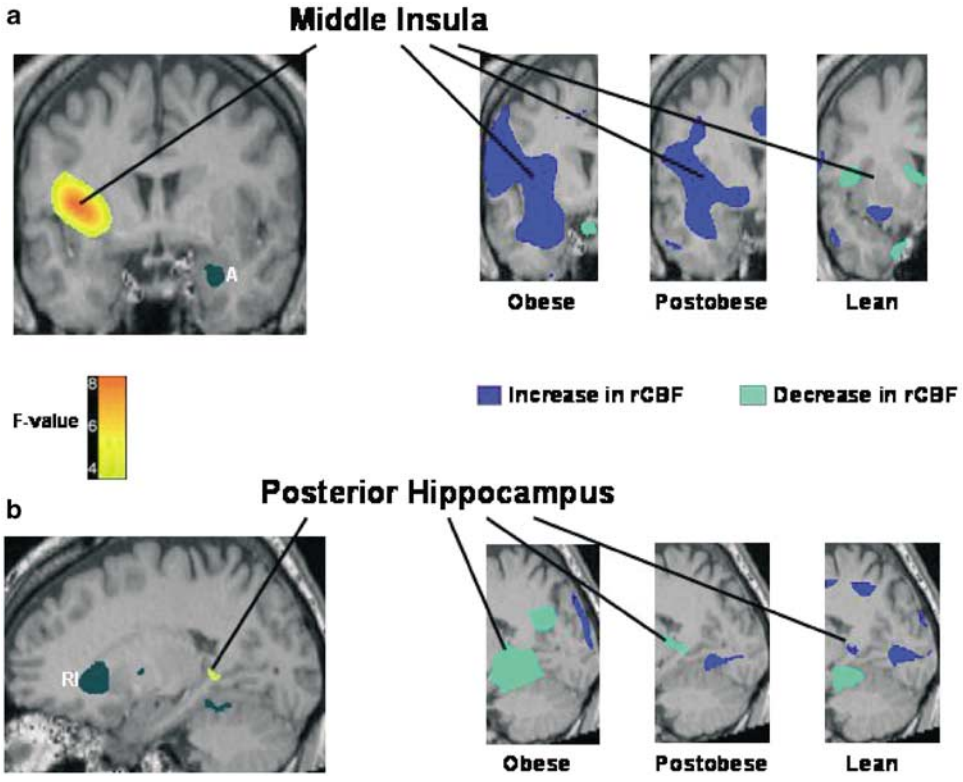

Figure 2 Statistical parametric maps. Left side: statistical parametric maps of condition × group interaction ($P<0.05$, F-test, corrected for multiple comparisons over 4 mm radius spheres centered on the foci of maximal F-value). The color-coded areas were regions of the brain in which there were similarly abnormal responses to the ingestion of a meal in the obese and postobese individuals as compared to the lean controls ($P<0.05$, corrected for multiple comparisons), that is, an increase in neural activity in the middle insula and a decrease in neural activity in the posterior hippocampus. This was not the case of the responses in the amygdala A and rostral insula RI. Right side: statistical parametric maps of significant changes ($P<0.05$, *t*-test) in each group. The color-coded areas were regions of the brain in which significant changes in blood flow were detected in response to the meal stimulation. (a) Coronal section passing through the middle insular cortex (1 mm anterior to the anterior commissure). (b) Sagittal section passing through the posterior hippocampus (21 mm left of the midline).

Table 2 Change in regional neural activity after tasting and consuming a liquid meal

	rCBF change after tasting meal (M1-B)			*rCBF change after consuming meal (M2-B)*		
Regions	*Obese*	*Postobese*	*Lean*	*Obese*	*Postobese*	*Lean*
n	23	11	21	23	11	21
Posterior hippocampus				-1.4 ± 0.5^{a} [−6.5−1.8]	-1.3 ± 0.6^{a} [−4.4−1.9]	1.1 ± 0.6^{b} [−4.1−5.9]
Posterior cingulate	-1.2 ± 0.4^{a} [−5.0−2.2]	-0.2 ± 0.4^{ab} [−3.3−1.9]	0.7 ± 0.4^{b} [−3.6−3.5]	-2.1 ± 0.4^{a} [−4.6−2.6]	0.3 ± 0.7^{b} [−4.3−4.5]	0.02 ± 0.6^{b} [−5.6−8.3]
Middle insula	1.0 ± 0.4^{a} [−2.1−4.2]	1.5 ± 0.3^{a} [0.3−3.9]	-0.4 ± 0.4^{b} [−4.6−3.3]			
Amygdala				-2.2 ± 0.6^{a} [−8.7−3.1]	0.1 ± 0.7^{b} [−4.6−3.1]	-0.3 ± 0.5^{b} [−6.7−6.2]

The change in regional cerebral blood flow (rCBF) is expressed in counts per voxel per minute (mean±s.e.m. and [range]). The data were adjusted for the whole brain blood flow by ANCOVA.Different superscripts identify significant group differences ($P<0.05$, two-tailed *t*-test, after small volume correction for multiple comparisons). B = baseline; M1 = ingestion of 2 ml of a liquid meal; M2 = ingestion of a satiating amount of a liquid meal.

Table 2). In the posterior cingulate cortex, the changes in rCBF in the postobese subjects were not different from those in the other groups (Table 2).

In response to a satiating amount of the same liquid meal (M2, Figure 1), changes in rCBF (M2-B) were different in the obese as compared to the lean individuals ($P<0.05$, corrected for multiple comparisons) in the posterior hippocampus (peak voxel, $x=21$, $y=-45$, $x=4$) (Figure 2b), posterior cingulate cortex (peak voxel, $x=17$, $y=-47$, $z=40$), and amygdala (peak voxel, $x=27$, $y=1$, $z=-24$) (Table 2). The

posterior hippocampus exhibited a similar decrease of neural activity in the obese and postobese subjects, whereas in the lean subjects the regional activity increased (Figure 3, lower panel; Table 2). In the posterior cingulate cortex and amygdala, the changes in rCBF were not different between the postobese and lean individuals (Table 2).

Owing to the unbalanced gender composition of the postobese group, data analyses were also conducted in women only (12 obese, 8 postobese, and 10 lean). The changes in rCBF were consistent with the results in the larger groups (Table 3)

None of the observed changes in regional activity and group differences were correlated with the age of the individuals, the subjective ratings of hunger and fullness, or the meal-induced changes in plasma glucose, insulin, or serum FFAs (data not shown).

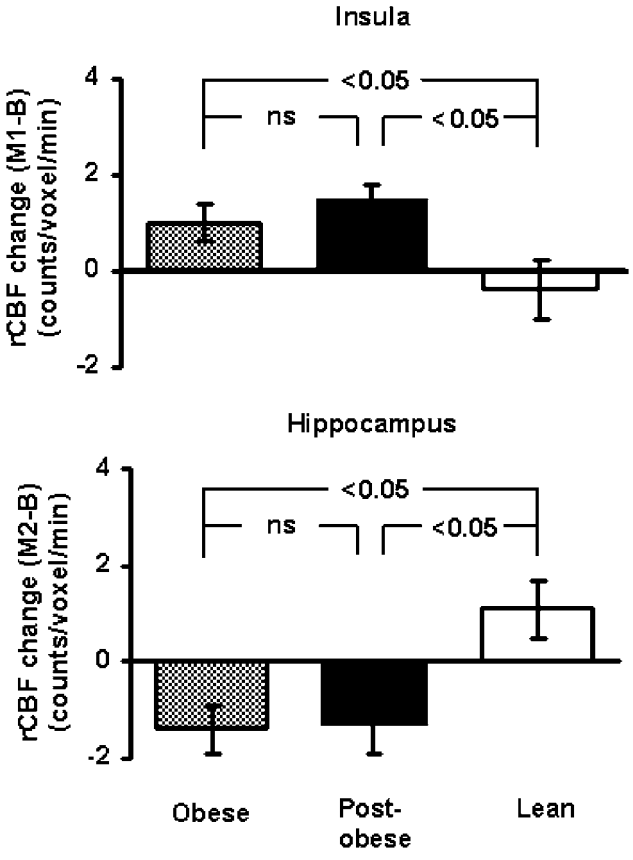

Figure 3 Changes in regional cerebral blood flow (rCBF) after meal ingestion in obese (O), postobese (PO) and lean (L) individuals. Upper panel: changes in rCBF in the middle insular cortex in response to the oral administration of 2 ml of a liquid meal (M1). Lower panel: changes in rCBF in the posterior hippocampus in response to the oral administration of a satiating amount of the same liquid meal (M2). Changes in rCBF in the obese and postobese subjects were not different. Both were different from changes in rCBF in the lean subjects ($P<0.05$, two-tailed *t*-test, corrected for multiple comparisons).

Discussion

In two (posterior cingulate and amygdala) of the four regions of the brain showing significant differences in response to the meal between the obese and the lean individuals, data in the postobese individuals suggest that these differences are likely to be reversible with weight loss or to be unrelated to the pathophysiology of obesity. On the other hand, the persistence in the postobese subjects of abnormal responses in the middle insular cortex and hippocampus indicated that these responses may be involved in the pathophysiology of obesity. Whether these are primary etiologic defects or neuroanatomical correlates of nonreversible neuronal structural/functional changes caused by the initial weight gain cannot be resolved by this study.

The insular cortex has been implicated in a variety of functions related to the integration of autonomic, behavioral, and emotional responses.[14] Specifically, classical electrophysiological,[15] as well as modern neuroimaging studies documented the response in the insula to swallowing,[16] distension of the esophagus,[17] smell (ortho- and retronasal),[18–21] taste,[22] tongue somatosensation,[23] and flavor,[19] suggesting that the insular cortex can be broadly considered the primary ingestive cortex.[24] We[5,6] and others[25,26] have observed activation of the insula in response to hunger and the sight of food in hungry people. Thus, analogous to the activation of this region in response to a variety of other cravings,[27–29] the increase in neural activity in the middle

Table 3 Change in regional neural activity after tasting and consuming a liquid meal in women only

	rCBF change after tasting meal (M1-B)			*rCBF change after consuming meal (M2-B)*		
Regions	*Obese*	*Postobese*	*Lean*	*Obese*	*Postobese*	*Lean*
n	12	8	10	12	8	10
Posterior hippocampus				-1.2 ± 0.5^{a} [−3.5–1.2]	-1.7 ± 0.6^{a} [−4.4–0.5]	2.5 ± 0.6^{b} [−0.7–6.3]
Middle insula	1.4 ± 0.4^{a} [−0.9–4.9]	1.0 ± 0.8^{a} [−0.7–6.4]	-1.2 ± 0.6^{b} [−3.8–1.6]			

The change in regional cerebral blood flow (rCBF) is expressed in counts per voxel per minute (mean ± s.e.m. and [range]). The data were adjusted for the whole brain–blood flow by ANCOVA. Different superscripts identify significant group differences ($P<0.05$, two-tailed *t*-test, after small volume correction for multiple comparisons). B = baseline; M1 = ingestion of 2 ml of a liquid meal; M2 = ingestion of a satiating amount of a liquid meal.

insula in the obese and postobese but not in the lean individuals may reflect an increased craving for the forthcoming meal. Alternatively, because the insular cortex is known to be activated in response to anticipation of reward[30] and animal models of obesity show abnormally high food-anticipatory activity,[31–33] it is possible that exposure to the orosensory stimulation of a liquid meal elicited a more intense feeling of reward-anticipation in the obese and postobese than in the lean subjects. Both the increased craving and anticipation of reward may ultimately result in excessive energy intake.

The dorsal motor nucleus of the vagus has been shown to receive afferents from the insula[34] and it is known that the cephalic phase response (CPR), the cascade of neuroendocrine phenomena activated by anticipation of meal ingestion, is mediated by vagal stimulation of exocrine (salivary glands and gastric secretion) and visceral motor activity.[35,36] Increased parasympathetic nervous system (PNS) activity has been reported in many animal models of obesity,[37,38] but the data in humans are controversial.[39,40] If the increased neural activity in the middle insula after tasting the meal reflects the contribution of the insular cortex to the activation of the PNS, it is possible that the obese and postobese subjects share this autonomic response in preparation for the consumption and digestion of food. However, we cannot experimentally test this hypothesis as no measures of autonomic nervous system activity were collected, nor can we infer from the literature a direct link between the activity of the PNS and food intake. Finally, the dorsal motor nucleus of the vagus is too small to be resolved by ^{15}O-water PET.

After the administration of a satiating meal, the posterior hippocampus was the only area of the brain showing functional similarities between the obese and postobese subjects. The hippocampus is mainly involved in spatial learning and memory processing,[41] but has also been implicated in sensing the metabolic and hormonal status of the body (the so-called 'enteroception')[42] and in the regulation of food intake.[43]

The hippocampus is, in fact, very rich in signaling molecules and relative receptors (glucocorticoids, neuropeptide Y, orexins, leptin, and insulin), which have been shown to play an important role in other regions of the brain in the control of energy metabolism. Specifically, the insulin receptor is also prominently expressed in this region,[44] and insulin has been shown to suppress the activity of the hippocampal neurons *in vitro*.[45] However, it is unlikely that our findings are related to the central effect of insulin, since postmeal increases in plasma insulin concentrations were observed in all three groups, while neural activity decreased only in the posterior hippocampus of the obese and postobese subjects.

There is evidence in rats that selective lesions of the hippocampus are associated with behavioral changes in both eating and drinking, described as 'little and often'.[46] In humans, it has been reported that electrical and chemical stimulation of the hippocampus elicits autonomic and endocrine effects, such as gastric secretion[47] and increased food consumption.[43] The case of a patient (HM) with hippocampal damage is also well known, who consistently rated his hunger at half scale, regardless of when the rating was taken in relation to a meal.[43]

Surprisingly, we found no correlations between changes in the hippocampal blood flow and subjective ratings of hunger or fullness. This indicates that cognitive processes other than the appetitive motivation to eat[48] (such as learning and memory of eating experiences[43]) may underlie the similar response to meal ingestion in the posterior hippocampus of obese and postobese individuals.

PET results should be interpreted in light of the limitations of this imaging technique. Spatial resolution, contrast resolution of individual subtraction images, and accuracy of the image deformation algorithm make it difficult to specify in greater detail the structures that are responsible for the observed changes in regional brain activity. Limitations in the study design must also be acknowledged. The baseline condition was characterized by a rather accentuated state of hunger after a 36-h fast. This was done to produce behavioral states of sufficient intensity to maximize our chances to detect brain regions selectively affected during these conditions. Subjects were studied in a resting condition, rather than during systematically manipulated mental activity. Although we cannot exclude the possibility that the subjects engaged in more spontaneous visual imagery in one condition *vs* the other, it is our experience that the subject's behavioral state is not significantly different during sequential 1-min scans. Finally, while acknowledging the potentially confounding effects of scan order, we note that we could not counterbalance the conditions in a within-session study. To study hunger and satiation during the same PET session, it was not possible to control for scan order (ie, perform the satiation scan first). However, since all three groups were studied with the same scan-order paradigm, our group comparisons between state-dependent changes in rCBF at least partially addresses this potential confounder. Furthermore, we point out that between-session studies have lower statistical power. We also examined the effects of scan order by comparing PET rCBF data acquired in the same resting state (with an interscan duration of 40–60 min) in eight previously studied normal volunteers (Eric M Reiman, personal communication). Although the second scan was associated with increased rCBF in a region of the left dorsolateral prefrontal cortex ($x=-54$, $y=40$, $z=12$), it was not associated with rCBF increases or decreases in any of the regions reported in the present study. While the observed changes in rCBF do not appear to be entirely attributable to the effects of scan order, we cannot exclude the possibility that they were at least partly attributable to the interaction between scan order and the fasting state.

In conclusion, we show that in the obese and postobese individuals, the middle insular cortex and posterior hippocampus respond similarly to the taste and ingestion of a satiating meal, respectively. These observations suggest that

increases in neural activity in the middle insula and decreases in the posterior hippocampus in response to a meal represent neural markers of an increased risk of obesity, a hypothesis that needs to be confirmed in longitudinal studies. Assuming our approach identified neural abnormalities that underlie the development of the disease, these findings indicate that the predisposition to obesity involves areas of the brain that control complex aspects of eating behavior including anticipation and reward, chemosensory perception, autonomic control of digestion (insular cortex), as well as enteroception and learning/memory (hippocampus).

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