Less activation of the left dorsolateral prefrontal cortex in response to a meal: a feature of obesity

Duc Son NT Le, Nicola Pannacciulli, Kewei Chen, Angelo Del Parigi, Arline D Salbe, Eric M Reiman, and Jonathan Krakoff

ABSTRACT

Background: In an exploratory positron emission tomography study of postprandial regional cerebral blood flow, which is a marker of neuronal activity, obese men differed from lean men in several brain regions, including the prefrontal cortex. The subjects received a meal proportional to their body size; therefore, the meal volume was different for each person.

Objective: We investigated whether differences in the brain responses of obese and lean men to a meal represent satiety or feelings of gastric distension.

Design: We studied 9 lean (3 ± SD body fat: 15 ± 5%; age: 33 ± 10 y) and 9 obese (body fat: 31 ± 4%; age: 32 ± 10 y) men given a fixed amount (400 mL) of a liquid meal. We compared their results with those in 11 lean (body fat: 16 ± 5%; age: 35 ± 8 y) and 11 obese (body fat: 33 ± 5%; age: 28 ± 5 y) previously studied men given a meal proportional to their body size. We performed analyses by using a two-level, random-effects approach in the STATISTICAL PARAMETRIC MAPPING software package and a significance level of P ≤ 0.001, uncorrected for multiple comparisons.

Results: Compared with lean men, obese men had consistently less postprandial activation in the left dorsolateral prefrontal cortex, irrespective of meal size.

Conclusion: Because the dorsolateral prefrontal cortex has been implicated in the inhibition of inappropriate behavior, satiety, and meal termination, differential responses of neuronal activity to food intake in this area may contribute to a propensity for obesity or to the difficulty in losing weight experienced by obese men. Am J Clin Nutr 2006;84:725–31.

KEY WORDS  Dorsolateral prefrontal cortex, neuronal activity, feature of obesity, response to food intake, satiety, positron emission tomography, PET

INTRODUCTION

The problem of obesity has grown to epidemic proportions throughout the world (1). In the United States, >60% of the adult population is either overweight or obese (2). However, the exact pathophysiology of obesity is still unclear. Excessive food intake seems to play a role in the development of obesity (1, 3). Neuroimaging studies have shown that the human brain has a central role in the regulation of eating behavior (4–8), and this regulation may differ by sex, obesity status, and eating behavior disorders (4, 8–11). A previous study (from the same laboratory as the current study) of brain responses to the administration of a satiating meal in 11 lean and 11 obese men showed that obese men had greater neuronal activity in the prefrontal cortices and less activity in the limbic and paralimbic areas, insula, and cerebellum than did lean men (12). In that study, subjects received a liquid meal in a satiating amount proportional to their body size.

Investigations of the localization and mechanisms of gastric visceral sensation in the human brain have shown that the application of pure mechanical distension of the stomach (by using air or water) also causes changes in neuronal activity in several brain regions, including the insula, anterior cingulate, caudate nucleus, thalamus, brainstem, cerebellum, superior temporal gyrus, occipital gyrus, and inferior frontal gyrus (13–15). Moreover, the changes in neuronal activity in the insula, temporal gyrus, occipital gyrus, and cerebellum partially overlap those identified in studies of satiation (10, 12). In an early study, the gastric capacity of obese persons was reportedly to be significantly larger than that of lean persons (16). In more recent investigations, however, this finding was confirmed only in obese persons with binge-eating disorder (17), and no relation was found between gastric volume and body size in subjects without binge-eating disorder (18). Because subjects in the previous study from this laboratory received a meal proportional to their body size, we could not discern whether differences between the brain responses of obese and lean persons represented satiety or feelings of gastric distension.

To distinguish the effect of meal size from that of actual satiety, we compared changes in regional cerebral blood flow (rCBF), a marker of neuronal activity, in 9 lean and 9 obese men given a fixed amount of a meal (FIXED group) with those changes in the original subjects (11 lean and 11 obese men) given a meal in an amount proportional to their body size (SAT group). In addition, because of the exploratory nature of the original

1 From the Obesity and Diabetes Clinical Research Section, Phoenix Epidemiology & Clinical Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Health, Phoenix, AZ (DSNTL, NP, ADP, ADS, and JK), and the Banner Alzheimer Institute, Banner Positron Emission Tomography Center, Banner Good Samaritan Medical Center, Phoenix, AZ (KC and EMR).

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3 Reprints not available. Address correspondence to DSNT Le, ODCRS/PECRB/NIDDK/NH/HDHS, 4212 North 16th Street, Room 5-35, Phoenix, AZ 85016. E-mail: leds@mail.nih.gov.

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study, those data were analyzed by using a single-level, fixed-effects analysis and a more lenient statistical threshold (12). In the current study, we used a 2-level, random-effects analysis that allowed more generalized inferences about the population from which the subjects were drawn.

SUBJECTS AND METHODS

Subjects

Forty (20 lean and 20 obese) right-handed, white men were studied under 2 conditions: 11 lean and 11 obese men received a liquid meal in an amount proportional to their body size (SAT group), and 9 lean and 9 obese men received a fixed amount (400 mL) of a liquid meal (FIXED group). Results for the SAT group were reported previously (12). Subjects were recruited from the Phoenix, AZ, metropolitan area by newspaper advertisement.

All subjects were nonsmokers, free of medical disorders, and not taking any medications, as determined by medical history, physical examination, and screening laboratory tests. Subjects with current or past substance or alcohol abuse or addiction, endocrine disorders (including abnormal thyroid function and type 2 diabetes), hypertension, or pulmonary, cardiovascular, gastrointestinal, hepatic, renal, or central nervous system disorders were excluded from the study at screening. The Structured Clinical Interview for DSM-III-R (19) was used to screen for behavioral or psychiatric conditions (ie, claustrophobia, major depression, the presence of psychotic symptoms, anorexia nervosa, and bulimia nervosa) that are incompatible with safe and successful participation in the study.

All subjects were admitted for 1 wk to the metabolic unit of the Obesity and Diabetes Clinical Research Section of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in Phoenix, AZ. Subjects were restricted to the research ward and were limited to sedentary activity for the duration of the study.

Written informed consent was obtained from all subjects. The protocol was approved by the institutional review boards of the NIDDK and the Good Samaritan Regional Medical Center (Phoenix, AZ).

Experimental protocol

The experimental procedures were described previously (5). In brief, on admission, subjects were assigned to a weight-maintenance diet (50% of energy from carbohydrate, 30% from fat, and 20% from protein). Body composition was assessed by dual-energy X-ray absorptiometry (DPX-1; Lunar Corp, Madison, WI); REE was measured for 45 min with the use of a ventilated-hood system (DeltaTrac; SensorMedics, Yorba Linda, CA). Before the imaging session, each subject underwent 2 dress rehearsals of the study to become familiar with the behavioral tasks. Customized foam molds were created and used to immobilize the head during the imaging session. The flavor of the liquid meal (vanilla, chocolate, or strawberry) was selected by each subject. Subjects fasted for 36 h before the imaging session. Water and noncaloric, noncaffeinated beverages were provided ad libitum during the fast.

Imaging procedures

Magnetic resonance imaging (MRI) and positron emission tomography (PET) procedures were done at the Good Samaritan Regional Medical Center as described previously (5). The MRI was performed with the use of a 1.5 T Sigma system (General Electric, Milwaukee, WI) to rule out gross anatomical abnormalities. For the PET procedure, a transmission scan that used a $^{68}$Ge/$^{68}$Ga 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 positioned as if looking straight ahead. PET images of regional brain activity (counts per pixel per minute) were obtained for each subject with the use of 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 were performed after feeding, with intervals of 10 min between scans. Immediately after each scan, subjects were asked to rate their desire to eat, the amount of food they desired, and their feelings of hunger, fullness, and thirst on a 100-mm visual analog scale, ranging from 0 ["not hungry at all (or full, etc)"] to 100 ["extremely hungry (or full, etc)"] (20). Blood samples were drawn immediately after each scan in the fasting and postprandial periods for the measurement of glucose, insulin, and free fatty acids.

Feeding procedures

A fixed amount (400 mL) or a variable amount (providing 50% of the person’s daily REE) of a satiety-inducing liquid formula meal (Ensure Plus, 1.5 kcal/mL; Ross-Abbott Laboratories, Columbus, OH) was administered orally over 25 min with the use of a peristaltic pump (IMED 980; Imed, San Diego, CA). To eliminate possible confounding factors, such as tactile stimulation of the tongue and motor neuron activity, swallowing was consistently induced by administration of 2 mL water before each of the 4 PET scans.

Metabolite analysis

Plasma glucose concentrations were measured by using the glucose oxidase method (Beckman Instruments, Fullerton, CA); plasma insulin concentrations were measured by using an automated radioimmunoassay (Concept 4; ICN Biomedicals Inc, Costa Mesa, CA). Serum concentrations of free fatty acids were measured by using an enzymatic calorimetric method (Wako Chemicals, Richmond, VA).

Image processing and statistical analysis

The analysis was performed with the use of STATISTICAL PARAMETRIC MAPPING software (version 99, SPM99; The Wellcome Institute of Neurology, London, United Kingdom; Internet: http://www.fil.ion.ucl.ac.uk/spm/software/spm99/), compared with SPM96, the earlier version used in the previous study (12). SPM99 has several differences from SPM96, including changes in image realignment, normalization, and analytic methods. The realignment step includes improved motion-correction algorithms; the normalization step includes more robust parameter estimations and a new template based on a larger population. The newer version also includes a more stringent and accurate method of correction for statistical type I errors and the addition of the random-effect modeling approach for balanced design by multilevel analyses. With the use of SPM99, automated algorithms were used to align each subject’s sequential PET images (21), spatially normalize the realigned images to the
stereotactic space as defined by the template provided by the Montreal Neurological Institute (22), and smooth these normalized images with a 15-mm full-width-at-half-maximum Gaussian filter.

All image analyses (including both the SAT and FIXED groups) were done by using a 2-level, random-effects analysis (23). In brief, first, a contrast image of differences in rCBF in response to satiety (satiety minus hunger scans) was created in each subject by using the “single subject, conditions, and covariates” option, which accounts for whole-brain blood flow by proportional scaling. Then, to test for the effects of body size (lean compared with obese), meal size (SAT compared with FIXED), and the body size × meal size interaction on the brain’s responses to a meal across the 4 subgroups, we grouped and input the individual contrast images and used the analysis of variance option without global scaling (with a significant differences were observed in appetite sensation ratings across the subgroups (Table 2).

**Imaging results**

**Effect of body size on brain responses**

In the analysis of the effect of body size on the brain responses to satiety, a significant effect of body size was found on the left dorsolateral prefrontal cortex (DLPFC) (peak voxel: \( x = -34, y = 58, z = 14; P = 0.00009; \) Figure 1). The post hoc comparisons between groups indicated that, when compared with lean men, obese men had significantly less activation in the left DLPFC in response to a meal in all situations (ie, FIXED obese compared with FIXED lean, SAT obese compared with FIXED lean, FIXED obese compared with SAT lean, and SAT obese compared with SAT lean) (Table 3).

**Effect of meal size on brain responses**

In the analysis of the effect of meal size on the brain responses to satiety, a significant effect of meal size was found on the right medial orbitofrontal cortex (OFC) (peak voxel: \( x = 18, y = 58, z = -20; P = 0.00009; \) Figure 2). The post hoc comparisons between groups showed significantly greater activation in the right medial OFC in the SAT obese and SAT lean men given a larger meal than in the FIXED obese and FIXED lean men (Table 4). No differences in the rCBF in response to a meal were found between the SAT lean and FIXED lean men.

**Correlation analysis between changes in regional cerebral blood flow and percentage body fat**

Percentage body fat was negatively correlated with the change in rCBF in the left DLPFC in response to the meal (peak voxel: \( x = -35, y = 59, z = 12; r = -0.53, P < 0.001 \)). Separate analyses of the lean and obese groups showed a similar direction in the associations, but the correlation coefficient was not significant, perhaps because of the smaller sample size in these subgroups.
compared with FIXED), and their interaction. No significant difference was found across the groups, and no significant interactions were found.

Analyses were performed by using general linear model accounting for body size (lean compared with obese), meal size (SAT compared with FIXED group SAT group), and their interaction. No significant difference was found across the groups, and no significant interactions were found.

**TABLE 2** Subjective ratings of appetite sensations using visual analog scales

| Questions | FIXED group | | SAT group | |
|-----------|-------------|--|----------|--|----------|
| Lean subjects | Obese subjects | Lean subjects | Obese subjects |
| (n = 9) | (n = 9) | (n = 11) | (n = 11) |
| Prospective food consumption | | | |
| Before meal | 83 ± 14 | 76 ± 18 | 70 ± 21 | 74 ± 21 |
| After meal | 38 ± 30 | 29 ± 18 | 28 ± 23 | 28 ± 28 |
| ∆ After − before | −45 ± 30 | −47 ± 32 | −43 ± 32 | −46 ± 31 |
| Desire to eat | | | |
| Before meal | 74 ± 20 | 69 ± 20 | 68 ± 29 | 78 ± 18 |
| After meal | 31 ± 21 | 33 ± 22 | 29 ± 24 | 27 ± 17 |
| ∆ After − before | −42 ± 28 | −36 ± 36 | −39 ± 39 | −52 ± 26 |
| Hunger | | | |
| Before meal | 74 ± 20 | 72 ± 19 | 69 ± 28 | 76 ± 21 |
| After meal | 30 ± 21 | 26 ± 14 | 27 ± 22 | 29 ± 28 |
| ∆ After − before | −44 ± 30 | −45 ± 27 | −43 ± 36 | −47 ± 32 |
| Fullness | | | |
| Before meal | 16 ± 18 | 15 ± 15 | 23 ± 23 | 16 ± 12 |
| After meal | 70 ± 15 | 67 ± 23 | 73 ± 21 | 78 ± 21 |
| ∆ After − before | 54 ± 26 | 52 ± 34 | 47 ± 32 | 62 ± 26 |
| Thirst | | | |
| Before meal | 61 ± 22 | 52 ± 20 | 57 ± 21 | 55 ± 27 |
| After meal | 37 ± 27 | 34 ± 24 | 29 ± 17 | 23 ± 19 |
| ∆ After − before | −24 ± 27 | −18 ± 17 | −27 ± 31 | −33 ± 30 |

\( \Delta \), change. In the FIXED group, subjects were given a fixed amount (400 mL) of a liquid meal. In the SAT group, subjects were given a satiating meal proportional to their body size. Analyses were performed using general linear model accounting for body size (lean compared with obese), meal size (SAT compared with FIXED), and their interaction. No significant difference was found across the groups, and no significant interactions were found.

\( \bar{x} \pm SD \) (all such values).

**DISCUSSION**

The current study shows that, across multiple intergroup comparisons, the left DLPPC is the one area that consistently shows significantly less activation in response to the administration of a liquid meal in obese men than in lean men, irrespective of meal size. Furthermore, the coordinates for the response in this region in all comparisons did not differ significantly. The left DLPPC has also been associated with obesity in a voxel-based morphometric analysis of MRI scans, in which obese persons had significantly lower gray matter density in the left DLPPC than did lean persons, although the coordinates of the local maxima were slightly different (\( x = -40, y = 30, z = 38; 24 \).

The prefrontal cortex has a central role in the inhibition of inappropriate behaviors. In particular, it is important in the suppression of a course of action that is no longer appropriate and for the ability to monitor ongoing actions (25). Moreover, Heekeren et al (26) proposed that the left DLPPC of the human brain may contain a general mechanism for integrating perceptual evidence for decision making. In terms of appetite control, previous findings in lean or obese persons indicated that the DLPPC may also play an important role in the central regulation of eating behavior by sending inhibitory inputs to orexigenic areas to suppress hunger and to terminate a feeding episode (5, 10, 12). In one of those exploratory analyses, when changes in rCBF were compared between lean and obese men, significantly greater increases in the prefrontal cortices and significantly greater decreases in the limbic and paralimbic areas (the putative orexigenic areas) after the meal were found in obese men. Those findings led to a hypothetical model that suggested that higher activity in the...
neuronal activity in the left dorsolateral prefrontal cortex (DLPFC) post hoc comparisons between groups showing the effect of body size on neuronal activity in the left dorsolateral prefrontal cortex (DLPFC)

<table>
<thead>
<tr>
<th>Regions</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIXED obese compared with FIXED lean men DLPFC</td>
<td>10</td>
<td>−36</td>
<td>60</td>
<td>14</td>
<td>0.002</td>
</tr>
<tr>
<td>SAT obese compared with FIXED lean men DLPFC</td>
<td>10</td>
<td>−36</td>
<td>60</td>
<td>14</td>
<td>0.001</td>
</tr>
<tr>
<td>FIXED obese compared with SAT lean men DLPFC</td>
<td>10</td>
<td>−32</td>
<td>58</td>
<td>10</td>
<td>0.001</td>
</tr>
<tr>
<td>SAT obese compared with SAT lean men DLPFC</td>
<td>10</td>
<td>−34</td>
<td>58</td>
<td>14</td>
<td>0.001</td>
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¹ BA, Brodmann's area. In the FIXED group (9 obese and 9 lean), subjects were given a fixed amount (400 mL) of a liquid meal. In the SAT group (11 obese and 11 lean), subjects were given a satiating meal proportional to their body size. Coordinates (x, y, z) were from the Montreal Neurological Institute standard brain, 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. Data were analyzed by using 2 × 2 ANOVA and post hoc comparison between the groups in STATISTICAL PARAMETRIC MAPPING, version 99.

When we analyzed the same group comparison in SPM99 by using the same one-level, fixed-effects approach and the same statistical threshold (P < 0.005 uncorrected for multiple comparisons) as in the previous investigation, the results were consistent with the older analysis. Compared with lean men, obese men had significantly greater postmeal increases in rCBF in the DLPFC...
those prefrontal areas (although the increases in rCBF in the left DLPFC were significantly lower than in the previous analysis) and significantly greater decreases in rCBF in the limbic and paralimbic areas.

The differences between the results obtained by using the newer analytic methods and those obtained in the previous exploratory analysis are due to the more stringent and more robust statistical approach used for the present investigation. Inherent in PET studies, that include multiple scan or conditions per subject, are 2 sources of variability—i.e., within-subject (between-scan) and between-subject variability. The one-level, fixed-effects approach used in the previous exploratory analyses takes into account only the within-subject variability (23, 27–29). Hence, a fixed-effect analysis provides areas that are activated “on average” across subjects, and, therefore, it may yield significant results when only a few subjects have high activations, even though the other subjects have no activation at all. Conversely, the multiple-level, random-effects approach used in the current analysis uses a proper mixture of within- and between-subject variance. Hence, this analysis allows for finding areas that are activated in much the same way in all subjects, which makes the results more robust and, therefore, more generalizable (23, 27–32). The random-effect approach uses a 2-stage procedure: first, parameters are estimated from a (fixed-effect) model for each subject, and, second, images of these contrasts become the data for a second design matrix. Moreover, improvements in the preprocessing steps and the statistical methods in SPM99 (see Subjects and Methods) may have made the analysis more sensitive to changes in rCBF in the left DLPFC. Finally, the more restricted statistical threshold used in SPM99 can explain why some differences found in the previous analysis were no longer significant in the current analysis, as reported above.

The only region found to be different between lean and obese men in response to the meal size was the right medial OFC. The finding of significantly greater activation of the right medial OFC in the post hoc comparisons in the SAT lean and SAT obese men than in the FIXED lean and FIXED obese men indicates that activation in this area may be related to meal size. This finding may be either due to a direct effect of gastric distension (i.e., distension was greater in the SAT groups because of the larger meal size) or related to the anticipated reward value of the meal (i.e., the SAT groups received a larger and hence more rewarding meal than did the FIXED group). In fact, the medial OFC, which receives dopaminergic afferents from the ventral tegmental area through the mesocortical pathway (26, 33), has been implicated in the representation of relative reward value in neurophysiologic studies in human and nonhuman primates (26, 34–37).

The general limitations of PET studies were addressed in previous publications (4, 5, 9, 10). They include the following: 1) limitations in the spatial resolution, contrast resolution, and accuracy of the image deformation algorithm used to compute statistical maps; 2) potentially confounding effects of scan order because the satiation condition always follows the baseline condition; and 3) the possibility of statistical type I errors (now minimized in the random-effects approach). In addition, although this study was designed to examine differences in meal size, we found no difference in the subjective hunger or satiety ratings between the groups, which may have limited our ability to distinguish between meal-size and satiety differences. As a result, whether the changes in rCBF were due to satiety or gastric distention is still not clear. Furthermore, because the liquid meal was delivered continuously over a 25-min period, the residual volume of the meal in the stomach at the time of the satiety scan is not precisely known. Finally, because the 2 groups (ie, lean and obese) were defined by the body mass index of the subjects, we cannot further adjust the group comparison for covariates related to the selection criteria, such as percentage body fat, fat-free mass, or meal size, because these variables also defined each group and were nonoverlapping. The fact that this study was only in men may limit the generalization of our findings. However, previous analyses suggested that, although men and women have differences in neuronal activity after receiving a satiating meal, these differences are subtle (9).

In conclusion, previous studies that compare the neuroregulation of food intake in lean and obese persons identified multiple regions with the potential to explain differences in hunger and satiety. Replication of such data, given the multiple factors involved in PET scanning and feeding behavior, has been difficult. The striking feature of the current analysis was the consistent finding of significantly less postprandial activation in the left DLPFC in obese men than in lean men. An impaired response of the left DLPFC to satiety may, therefore, represent a neurofunctional feature of obesity. However, whether the abnormality precedes obesity, and thus is a neural risk factor for weight gain, or occurs as a consequence of obesity, and thus makes weight loss difficult, has yet to be established.

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