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Reanalysis of the Obesity-Related Attenuation in the Left Dorsolateral Prefrontal Cortex Response to a Satiating Meal Using Gyrus Regions-of-Interest

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Abstract

Objective: The left dorsolateral prefrontal cortex (LDLPFC), which includes the inferior (IFG), middle (MFG), and superior (SFG) frontal gyri, has been implicated in satiation. Using a voxel-based approach, we previously identified an LDLPFC region (as reported as peak voxel) in which a reduced neuronal response to a meal was associated with obesity. In this study, we sought to determine which gyri in the LDLPFC best distinguished the neuronal responses to a meal using a different statistical approach.

Methods: We reanalyzed brain responses to a meal using the hypothesis-driven region-of-interest-based (ROI) approach. Regional cerebral blood flow (rCBF), a marker of neuronal activity in the LDLPFC and its 3 gyri, was acquired in 2 conditions (hunger and after the satiating meal)

using ^{15}O -water positron emission tomography scans. rCBF was extracted and estimated using masks of the 3 gyri that were created in MRIcro and Statistical Parametric Mapping 5 software.

Results: Using the ROI approach, a satiation-related reduction in LDLPFC rCBF was observed in the obese ($p = 0.04$) and tended to be significantly greater than that in lean subjects ($p = 0.07$). The rCBF reduction was greater in the obese subjects than in the lean subjects in the left IFG ($p = 0.03$) and MFG ($p = 0.004$) after adjustment was made for age, sex, and number of voxels in these gyri, but not in the SFG ($p = 0.5$).

Conclusions: Our results are consistent with those obtained by the voxel-based approach in showing the association between obesity and a satiation-related reduction in LDLPFC activity. This LDLPFC response preferentially involves the IFG and MFG. We suggest that these brain regions could be targeted by new therapeutic interventions.

INTRODUCTION

Obesity has become a medical epidemic in the United States [1] and is reaching pandemic proportions in industrialized countries. However, the relative contributions of energy intake and energy expenditure in the pathogenesis of obesity are still unclear. Failure to respond to satiation, thus leading to overeating, may play a role in development of the disease [2,3]. Previous studies have examined the role of the human brain in the regulation of food intake using functional neuroimaging techniques (such as functional magnetic resonance imaging [fMRI] and blood oxygenation level-dependent [BOLD] and positron emission tomography [PET]) [4–9].

The left dorsolateral prefrontal cortex, one of the biggest areas in the brain, includes 3 frontal gyri (i.e., inferior, middle, and superior) [10] and has been implicated in inhibition of inappropriate behavior [11], decision making [12], satiation, and meal termination [13].

Two ways to approach neuroimaging analyses are known: voxel-based, which involves whole-brain analysis, and brain region-of-interest (ROI)-based approaches. In the voxel-based approach, analysis of changes in neuronal activity is performed across the whole brain, and the smallest radiologically defined unit of the brain region is used to identify changes in neuronal activity in the peak voxel, with the assumption that each individual voxel represents the same anatomical location between subjects. The results also assume that important neuronal activity changes are occurring in the identified brain region as a whole, which may represent only a small portion of the identified area. The voxel-based approach is therefore more exploratory and does not require a region-specific hypothesis, as it analyzes all voxels across the whole brain. The ROI-based approach involves defining an area of interest in the brain and averaging neuronal activity across this anatomical area; it can serve to test a specific hypothesis about a brain region-of-interest. However, previous ROI-based approaches involved tedious manual tracing of brain regions. The use of fully automated ROI definition eliminates the subjective errors that can occur with manually defined approaches [14,15]. MRIcro, a free software (<http://www.sph.sc.edu/comd/rorden/mricro.html>), provides a fully automated ROI definition using automated anatomical labeling (AAL) procedures and is applicable with several statistical software packages currently used in the neuroimaging field [10,16].

In past analyses, using a whole-brain voxel-based approach, we found that compared with lean individuals, obese subjects had less activation in the left dorsolateral prefrontal cortex (LDLPFC) in response to a meal, indicating that impairment in this area may be a feature of obesity [17,18]. However, the coordinates of the peak voxel were slightly different between men and women, falling in the left middle frontal gyrus in men [18] and the left inferior frontal gyrus in women [17].

Despite these slightly different anatomical findings using the whole-brain voxel-based approach in men and women, we hypothesized that the average neuronal activity across the LDLPFC and its gyri, as anatomically defined, would have different neuronal responses to satiation in lean versus obese individuals using the automatic ROI-based approach.

MATERIALS AND METHODS

Subjects

In this analysis, we included 49 (31 lean [21 male/10 female] and 18 obese [10 male/8 female]) right-handed, Caucasian volunteers recruited from the Phoenix, AZ, metropolitan area by newspaper advertisements. Of these 49 subjects, besides 39 subjects who had been included in previously published studies of neuroanatomical correlates of hunger and satiation or of neuroanatomical structural analysis [13,17–21], we included 10 lean men whose data have not been published elsewhere in this analysis, to increase statistical power. In addition, before including these 10 lean subjects, we compared their data with our previous analysis [13] and noted no significant difference. 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 a history of 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 the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM-III-R) [22] was used to screen for behavioral and psychiatric conditions (claustrophobia, major depression, the presence of psychotic symptoms, anorexia nervosa, or bulimia nervosa) incompatible with safe and successful participation in the study. All subjects were admitted for 1 week 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. The protocol was approved by the Institutional Review Boards of the NIDDK and the Banner Good Samaritan Regional Medical Center. Written informed consent was obtained from all subjects before participation. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

Experimental Protocol

The experimental procedures have been described previously [13]. In brief, upon admission, subjects were placed on a weight-maintaining diet (50% of calories 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, United States); resting energy expenditure was measured for 45 minutes using a ventilated-hood system (DeltaTrac, SensorMedics, Yorba Linda, CA, United States). Before the imaging session was begun, each subject underwent 2 dress rehearsals of the study to become familiar with the behavioral tasks. Customized foam molds were created and were used to immobilize the head during the imaging session. After a 36-hour fast, the volunteer underwent imaging sessions. 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 carried out at the Banner Good Samaritan Regional Medical Center (Phoenix, AZ, United States), as previously described [13]. First, MRI was performed by using a 1.5 Tesla Signa system (General Electric, Milwaukee, WI, United States) to rule out gross anatomical abnormalities and for coregistration in preprocessing of the PET images. For the PET procedure, a transmission scan using a $^{68}\text{Ge}/^{68}\text{Ga}$ 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 were positioned as if looking straight ahead. PET images of regional brain activity (counts per pixel per minute) were obtained for each subject using an ECAT 951/31 scanner (Siemens, Knoxville, TN, United States). 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 minutes between scans. Blood samples were drawn immediately after each scan in the fasting and postprandial periods for measurement of glucose, insulin, and free fatty acids (FFAs).

Feeding Procedures

A satiating amount of a liquid formula meal (Ensure Plus, 1.5 kcal/ml, Ross-Abbott Laboratories, Columbus, OH, United States), providing 50% of the individual's daily resting energy expenditure, was administered orally over 25 minutes using a peristaltic pump (IMED 980 Imed, San Diego, CA, United States). To eliminate possible confounding factors, such as tactile stimulation of the tongue and motor neuron activity, swallowing was consistently induced by 2 ml of water before each PET scan (i.e., 2 scans in hunger and 2 scans after consumption of a liquid meal).

Metabolite Analysis

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

Image Processing and Statistical Analysis

Preprocessing and analysis were performed using Statistical Parametric Mapping 5 (SPM5), which was released on December 1, 2005 (The Wellcome Institute of Neurology, London, UK, <http://www.fil.ion.ucl.ac.uk/spm/software/spm5/>).

Using SPM5, automated algorithms were used to align each subject's sequential PET images [23], to rigidly coregister fPET to anatomical MRI scans [23,24], to spatially normalize the coregistered images to the stereotactic space as defined by the template provided by the Montreal Neurological Institute (MNI) [25], and to smooth these normalized PET images with a 15-mm full-width-at-half-maximum Gaussian filter.

Statistical analyses were performed using a 2-level, random-effects approach [26]. At the first level, an individual contrast image of differences in regional cerebral blood flow (rCBF) in response to satiety (average of the 2 satiety scans minus average of the 2 hunger scans) was first created for each subject using the "single subject, conditions and covariates" option, accounting for whole-brain blood flow by proportional scaling, which basically scales each image to a reference count (i.e., the global brain activity) set at a physiologically realistic value of 50 ml/dl/min [27]. At the second level, the neuronal activity was extracted and analyzed using the Statistical Analysis System (SAS) program (SAS Institute Inc., Cary, NC, United States) instead of SPM5. Masks of the superior, middle, and inferior frontal gyri were created using an ROI panel in the MRIcro. Before the masks were used, they were aligned with each individual's PET scans, and then the masks and individual PET scans were checked to make sure they were well overlapped before the analysis was performed. The average neuronal activity in response to a meal across the whole gyrus was extracted from the individual contrast image using these masks. Neuronal activation in response to a meal in the LDLPFC was estimated based on neuronal activity and on the number of statistically significant voxels in the 3 gyri.

For plasma glucose and insulin concentrations, the average of the 2 fasting and postmeal values for each PET scan session was used in the analysis. Group differences in anthropometric and metabolite variables were analyzed using the Student's t-test. Extracted neuronal activity in response to a meal in the LDLPFC and its gyri was analyzed within the lean and obese groups using a paired t-test. To test for the effects of group (lean and obese) and location (inferior frontal gyri [IFG], middle frontal gyri [MFG], and superior frontal gyri [SFG]) and their interaction (group * location) on neuronal responses, we used a general linear model accounting for age, sex, and number of voxels in the gyri. A *post hoc* comparison was used for comparison of responses to a meal between lean and obese groups while accounting for potential confounders. Values of $p < 0.05$ were considered statistically significant. These analyses were performed using SAS software.

RESULTS

Characteristics of the study population are shown in Table 1. By design, obese individuals had significantly higher waist circumference, percent body fat, and fasting and meal-stimulated plasma glucose and insulin concentrations compared with lean individuals.

In response to a meal within each group, obese individuals had overall decreased rCBF in the LDLPFC, MFG, and IFG, but the differences did not reach statistical significance ($p = 0.3, 0.1, 0.2$, respectively), whereas significant increases in rCBF in the LDLPFC ($p = 0.05$) and the MFG ($p = 0.001$) were found in lean individuals. Across the 3 gyri, differences in neuronal activity were significant in the obese ($p = 0.04$) but not the lean group ($p = 0.1$).

The interaction between group (lean and obese) and location (the 3 gyri) was significant ($p = 0.006$).

Table 2 and Fig. 1 show neuronal activity in response to a meal in the LDLPFC and its gyri in lean and obese individuals using GLM before and after adjustment for potential confounders. IFG and MFG neuronal responses to the meal were significantly different in obese compared with lean subjects, both before ($p = 0.008$ and $p = 0.003$, respectively) and after adjustment for age, sex, and number of voxels ($p = 0.03$ and $p = 0.004$, respectively) (Table 2), whereas the response in the SFG was not significant ($p = 0.5$). Differences in mean neuronal activity in the LDLPFC between lean and obese individuals did not reach formal statistical significance before or after adjustment for age, sex, and number of voxels ($p = 0.06$ and $p = 0.07$, respectively).

No significant correlations of neuronal activity were noted in the LDLPFC and its gyri with changes in insulin and glucose following the meal (data not shown).

DISCUSSION

This study, using the ROI-based approach—an approach that allows investigation of specified brain areas—revealed that, in response to a meal, obese individuals had less neuronal activity in the left inferior and middle frontal gyri, compared with lean individuals, which persisted after adjustment was made for age, sex, and number of voxels in the gyri. These results are consistent with our previous findings using a whole-brain voxel-based approach [17,18], thus indicating that across 2 of the 3 gyri making up the LDLPFC, neuronal activity responds less to satiation in obese than in lean subjects.

Use of the ROI approach to confirm differences in neuronal activity across the left middle and inferior gyri provides important additional evidence that our hypothesis that the left dorsolateral prefrontal cortex, a large brain area, is involved in satiation. As was mentioned previously, the brain region (ROI-based) approach averages activities across the larger brain area of interest. Thus, results are indicative of the involvement of that particular region, and so can specifically test the hypothesis that this region is differentially activated in lean versus obese individuals following a meal. This contrasts with the voxel-based approach, in which analysis of changes in neuronal activity is performed across the whole brain, and the results for differences in neuronal activity are presented for peak voxels, the smallest sub-brain volume unit in a 3-dimensional tomographic dataset. The unbiased nature of the voxel-based approach provides an advantage in identifying brain areas with differential activations, and the ROI-based approach is more useful for hypothesis confirmation. In addition and more important, because the ROI-based approach is free of the multiple comparisons used in the voxel-based approach, this approach is statistically more straightforward to use as an

objective and reasonably powered neuroimaging biomarker to evaluate potential obesity in an appropriately designed clinical trial. It is important to acknowledge that in testing our hypothesis with the ROI-based approach, although we have attempted to enrich our study population by including more subjects and both sexes in the same analysis, a significant limitation to our results is that the study population overlaps those of our previous voxel-based analysis.

The prefrontal cortex, which includes 3 gyri (i.e., inferior [IFG], middle [MFG], and superior frontal [SFG]) [10], has a central role in the inhibition of inappropriate behaviors [11] and decision making [12]. In terms of eating behavior, the LDLPFC has been implicated in the regulation of food intake and meal termination [13]. Recently, a positive association between changes in rCBF in the LDLPFC in response to a meal and changes in plasma concentration of GLP-1, a satiety-inducing hormone, has been demonstrated [28]. It is interesting to note that stimulation of the LDLPFC using repetitive transcranial magnetic stimulation resulted in reduction in food [29,30] and alcohol [31] cravings.

In the present study, the significant interaction between group (lean and obese) and location (the 3 gyri) revealed that neuronal responses in lean versus obese individuals differed by gyri. Fig. 1 and *post hoc* analyses indicate that this interaction is due to significantly different responses in the IFG and the MFG but not the SFG. Taken together, this indicates that the IFG and the MFG may have a critical role in the regulation of food intake, specifically meal termination, and that previously observed differences in neuronal response to a meal in the LDLPFC and obesity were due primarily to a difference in activity in the IFG and the MFG. These findings may explain the results of our previous studies using a voxel-based approach, in which the difference in neuronal activity in response to a meal was found at the peak voxel, located in the middle frontal gyrus in men [18] and the inferior frontal gyrus in women [17]. However, it must be acknowledged that it is still unclear whether segregation of function occurs among frontal gyri within the LDLPFC [32]. Owen et al. [33] reported that specific regions of the lateral prefrontal cortex make identical executive functional contributions to both spatial and nonspatial working memory. By contrast, Courtney et al. [34,35] have found that object working memory activates inferior frontal regions, whereas activation for spatial working memory occurs in the superior frontal gyrus. In terms of the regulation of eating behavior, to our knowledge, no investigations have explored the dissociation in neuronal responses to eating stimulation within the LDLPFC. Given our current and previous results [13,20] showing that obese individuals had less neuronal activity in response to a meal in the left IFG and MFG compared with lean individuals, even though differences in neuronal responses to a meal in the frontal areas in obese individuals did not reach statistical significance, we speculate that the middle and inferior gyri in the LDLPFC are similarly stimulated by food intake, and that obesity is associated with alterations in neuronal activity in this area. It is interesting to note and consistent with impairments in LDLPFC function that obese individuals had greater impairments in decision making as tested by an Iowa gambling task than did lean individuals [36], and these impairments in decision making were positively associated with body size [37]. The authors concluded that this defect in decision making could provide an explanation for overeating behavior in obese individuals caused by difficulties in inhibition of excessive food intake [36,37].

In the present study, the direction of neuronal activity in the left middle and inferior frontal gyri in the obese individuals was different than in the whole-brain voxel-based approach (slightly decreased for the ROI approach versus slightly increased for the whole-brain voxel-based approach). However, these changes in neuronal activity within each group were not significant in either whole-brain voxel-based or ROI-based approaches, but when obese versus lean was compared, the neuronal activity was always significantly less in obese than in lean individuals. Additional statistical explanations should be considered for this slight difference. First, in the whole-brain voxel-based approach, only maximal peak voxels that reached the statistical threshold were reported, whereas neuronal activity was averaged across whole regions in the ROI-based approach. Second, image spatial normalization may also be a cause for the disparity. However, in this study, we used an automated algorithm in SPM5 to normalize the images for whole-brain voxel-based and ROI-based approaches, and the ROI extracted from MRICro was created using the same MNI template [16] as is used in the whole-brain voxel-based approach in SPM.

Limitations of this study also must be acknowledged. The ROI-based approach might clarify the location of the neuronal response, but differences could be related to how the gyral ROI were anatomically defined. Furthermore, the size and location of the neuronal activity may be directly related to the size and location of the ROI. However, to account for this, comparisons of neuronal responses to a satiating meal between lean and obese individuals were adjusted for the number of voxels in the gyri.

In conclusion, by using an ROI-based approach, i.e., an analytic technique used to identify activity within specific brain regions and to investigate the role of larger brain areas, we found that neuronal responses to food stimulation are increased in the left middle frontal gyri in healthy lean individuals, and that average neuronal activity following a meal in the IFG and the MFG was less in obese than in lean individuals. Our findings indicate that the whole LDLPFC area could be a target for future interventions aimed at modulating eating behavior.

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Abbreviations:

AAL	automated anatomical labeling
BOLD	blood oxygen level–dependent

DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised
FFAs	free fatty acids
fMRI	functional magnetic resonance imaging
GLM	general linear model
IFG	inferior gyrus
LDLPFC	left dorsolateral prefrontal cortex
MFG	middle frontal gyrus
MNI	Montreal Neurological Institute
MRI	magnetic resonance imaging
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
PET	positron emission tomography
rCBF	regional cerebral blood flow
ROI	region-of-interest–based approach
SAS	Statistical Analysis System
SFG	superior frontal gyrus
SPM5	Statistical Parametric Mapping 5

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Fig. 1.

Changes in average rCBF in the left dorsolateral prefrontal cortex and its gyri after lean and obese individuals have received a meal. NS = not significant, rCBF = regional cerebral blood flow, a marker of neuronal activity, LDLPFC = left dorsolateral prefrontal cortex, LIFG = left inferior frontal gyrus, LMFG = left middle frontal gyrus, LSFG = left superior frontal gyrus. *Analyzed using analysis of covariates, with adjustments for age, sex, and number of voxels in the areas.

Table 1.

Characteristics of Study Population^{ab}

Variables	Lean (n = 31)	Obese (n = 18)	<i>p</i>
Male/female	21/10	10/8	
Age, y	31 ± 9	29 ± 7	0.3
Waist circumference, in	32 ± 3.2	46 ± 4.4	<0.001
Body fat, %	18 ± 8	36 ± 5	<0.001
Fasting plasma glucose, mg/dL	77 ± 10	83 ± 6	0.01
Postmeal plasma glucose, mg/dL	97 ± 11	97 ± 10	0.9
plasma glucose, mg/dL	20 ± 9	13 ± 10	0.02
Fasting plasma insulin *, µU/mL	18 ± 4	25 ± 6	<0.001
Postmeal plasma insulin *, µU/mL	51 ± 27	99 ± 67	<0.001
plasma insulin *, µU/mL	33 ± 26	74 ± 65	0.01

^aData are means ± SD.

^bAnalyses were performed by using Student's t-test.

*Statistical analyses were performed on natural log-transformed values.

Table 2.

Neuronal Activity in Lean versus Obese Individuals in Response to a Meal and Number of Voxels in the LDLPFC and Its 3 Gyri¹

Variables	Lean (n = 31)	Obese (n = 18)	p^2	p^3
LDLPFC				
rCBF-change, counts/voxel/min	0.3 ± 0.9	-0.2 ± 1.0	0.06	0.07
Voxels, number	9757 ± 931	9442 ± 1598	0.5	—
LIFG				
rCBF-change, counts/voxel/min	0.4 ± 1.4	-0.7 ± 1.5	0.008	0.03
Voxels, number	2414 ± 91	2369 ± 199	0.4	—
LMFG				
rCBF-change, counts/voxel/min	0.6 ± 0.8	-0.3 ± 1.0	0.003	0.004
Voxels, number	4475 ± 375	4309 ± 698	0.4	—
LSFG				
rCBF-change, counts/voxel/min	0.1 ± 1.9	0.3 ± 1.3	0.3	0.5
Voxels, number	2869 ± 547	2765 ± 787	0.6	—

rCBF = regional cerebral blood flow, a marker of neuronal activity, LDLPFC = left dorsolateral prefrontal cortex, LIFG = left inferior frontal gyrus, LMFG = left middle frontal gyrus, LSFG = left superior frontal gyrus.

¹Data are means ± SD.

²Comparison of rCBF changes between lean and obese individuals using Student's t-test.

³Comparison of rCBF changes between lean and obese individuals using analysis of covariates (adjustment for age, sex, and number of voxels).