Less activation in the left dorsolateral prefrontal cortex in the reanalysis of the response to a meal in obese than in lean women and its association with successful weight loss1–3

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ABSTRACT
Background: We previously found that obese men have less activation in the left dorsolateral prefrontal cortex (LDLPFC) in response to a meal than do lean men, which indicates an association between this altered neuronal response and the pathophysiology of obesity.

Objectives: The objectives of the study were to extend this finding in obese women and to investigate activity in this region in women with a history of severe obesity who have successfully lost weight (ie, formerly obese women, sometimes called postobese women).

Design: We reanalyzed previously collected data to compare postmeal (after receiving a liquid meal) with premeal (after a 36-h fast) regional cerebral blood flow, a marker of neuronal activity, by using 15O-water positron emission tomography in 10 lean [26 ± 6% body fat (BF)], 9 obese (39 ± 3%BF) and 8 formerly obese (28 ± 4%BF) right-handed women. Data were analyzed by using a 2-level, random-effect analysis of variance.

Results: The regional cerebral blood flow in the LDLPFC differed in response to the meal across the 3 groups (P < 0.001, uncorrected for multiple comparisons). Post hoc group comparisons showed that obese women had significantly less activation in this area than did lean and formerly obese women. No significant difference between formerly obese and lean women was found.

Conclusions: These results extend our previous findings, indicating that obese women have less activation in the LDLPFC in response to a meal than do lean or formerly obese women. Neuronal activity in this region did not differ significantly between the latter 2 groups. Longitudinal studies are needed to determine whether these differences in neuronal activity change with or predict weight change. Am J Clin Nutr 2007;86:573–9.

KEY WORDS Dorsolateral prefrontal cortex, neuronal activity, fixation of obesity, weight loss, satiety, formerly obese, positron emission tomography, PET

INTRODUCTION
Obesity has reached 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 central role in the development of the disease (1, 3). Recent studies have examined the role of the human brain in the regulation of food intake by using functional neuroimaging techniques, eg, functional magnetic resonance imaging (MRI) and positron emission tomography (PET) (4–9).

We recently showed that, compared with lean men, obese men had less activation in response to a meal in the left dorsolateral prefrontal cortex (LDLPFC), an area that has been implicated in the inhibition of inappropriate behavior, satiety, and meal termination; this finding indicates that the impairment in this area may be a feature of obesity (10). However, whether this decreased activation in the LDLPFC is also present in obese women is not known. Furthermore, whether this deficit in the DLPFC precedes weight gain or is an acquired feature of obesity, which may make weight loss difficult, could not be determined. Studies in persons who have successfully achieved and maintained a normal body weight despite a history of severe obesity and who are at high risk of relapse may provide insight into this question.

A preliminary comparison of differences in regional cerebral blood flow (rCBF), a marker of neuronal activity, by using a single-level, fixed-effect modeling statistical approach that accounts only for within-subject variability (thus prohibiting inferences beyond the subjects studied) found that obese and formerly obese persons have similar brain responses to a meal and differ from lean persons only in the posterior hippocampus (11). That study included men and women and right- and left-handed subjects; however, reports indicate that human brain responses to stimulations (12, 13) and brain structure (14) differ between left-handed and right-handed persons.

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Given our previous findings obtained in men by using a more generalizable model and a more stringent statistical approach (ie, multilevel, random-effect modeling), we reanalyzed the previously collected data in right-handed women to investigate whether the same alterations in neuronal activity in the LDLPFC were present in both obese and lean women and to investigate rCBF changes in this area in formerly obese women to gain insight into how changes in rCBF in this area (implicated in the center of higher cognitive control) may differ with successful weight loss.

SUBJECTS AND METHODS

Subjects

Thirty right-handed white women (n = 10 lean, 12 obese, and 8 formerly obese) were studied in the follicular phase of the menstrual cycle. Results in these subjects were reported previously (11). Subjects were recruited from the Phoenix, AZ, metropolitan area by newspaper advertisement or, for formerly obese women, by targeted mailing to members of the national Weight Control Registry. The formerly obese women had achieved substantial weight loss, defined as a reduction in body mass index (in kg/m²) from ≥35 to ≤25, and who had successfully maintained their weight loss (by either diet or physical exercise therapy only or by combining the 2 approaches) for ≥3 mo before the admission. All subjects were nonsmokers, were free of medical disorders, and were 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); or hypertension, 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 (15) was used to screen for behavioral and psychiatric conditions (ie, claustrophobia, major depression, the presence of psychotic symptoms, anorexia nervosa, or bulimia nervosa) that were 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 in Phoenix. 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 before participation. The protocol was approved by the institutional review boards of the National Institute of Diabetes and Digestive and Kidney Diseases and Banner Good Samaritan Regional Medical Center (Phoenix).

Experimental protocol

The experimental procedures were described previously (8). In brief, on admission, subjects were placed on a weight-maintaining diet (50%, 30%, and 2% of energy from carbohydrate, fat, and protein, respectively). Body composition was assessed by using dual-energy X-ray absorptiometry (DPX-1; Lunar Corp, Madison, WI), and resting energy expenditure was measured for 45 min by using a ventilated-hood system (Delta-Trac; 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 (ie, vanilla, chocolate, or strawberry) was selected by each subject. After a 36-h fast, the volunteer underwent the imaging sessions. Water and noncaloric, noncaffeinated beverages were provided ad libitum during the fast.

Imaging procedures

MRI and PET procedures were carried out at Banner Good Samaritan Regional Medical Center as described previously (8). First, MRI was performed by using a 1.5-Tesla Sigma system (General Electric, Milwaukee, WI) to rule out gross anatomical abnormalities and for coregistration in the preprocessing of the PET images. For the PET procedure, a transmission scan using a 68Ge/68Ga 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 min) were obtained for each subject by using a scanner (ECAT 951/31; Siemens, Knoxville, TN). For each scan, a 50-mCi intravenous bolus of 15O-water was injected. Two scans were obtained at baseline and 2 after feeding, with intervals of 10 min between the 2 scans in each set. 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 at all hungry (or not at allfull, etc)] to 100 [extremely hungry (or extremely full, etc)] (16). 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 satiating amount of a liquid formula meal [Ensure Plus (1.5 kcal/mL); Ross-Abbott Laboratories, Columbus, OH), providing 50% of the individual’s daily resting energy expenditure was administered orally over 25 min by using 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 2 mL of water before each PET scans (ie, 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); plasma insulin concentrations were measured by using an automated radioimmunoassay (Concept 4; ICN Biomedical 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 by using STATISTICAL PARAMETRIC MAPPING software ([SPM5] version 5; Wellcome Institute of Neurology, London, United Kingdom; Internet: http://www.fil.ion.ucl.ac.uk/spm/software/spm5/], which was released on December 1, 2005. Compared with the version used for the previous study—SPM96 (17)—SPM5 features several
differences including changes in image realignment (improvement of motion correction algorithms), coregistration, and normalization (more robust parameter estimations and a better template). It also includes a more stringent and more accurate method of correction for statistical type I errors and the addition of the random-effects modeling approach for balanced design via multilevel analyses.

With the use of SPM5, automated algorithms were used to align each subject’s sequential PET images (18), to rigidly coregister functional PET to anatomical MRI scans (18, 19), to spatially normalize the coregistered images to the stereotactic space as defined by the template provided by the Montreal Neurological Institute (20), and to smooth these normalized PET images with a 15-mm full-width-at-half-maximum Gaussian filter. Voxel size of original individual PET images are 1.9 mm and 2 mm × 2 mm × 2 mm for normalized images and the template, respectively.

Voxelwise statistical analyses were performed by using a 2-level, random-effects approach (21). An individual contrast image of differences in rCBF in response to satiety (average of the 2 satiety scans minus the average of the 2 hunger scans) was first created for each subject by 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 (ie, the global brain activity) set at a physiologically realistic value of 50 mL·dL⁻¹·min⁻¹ (22). Then, to test for differences in rCBF across the 3 groups, we grouped and inputted the individual contrast images into analysis of variance (ANOVA) without global scaling with a P < 0.001 (uncorrected for multiple comparisons) as the criterion for statistical significance in the second-level analysis. To ascertain the directionality of the significant effects from the ANOVA, a post hoc pairwise comparison was performed between the groups in the context of ANOVA (ie, obese compared with lean, obese compared with formerly obese, and lean compared with formerly obese). On the basis of an a priori hypothesis of the LDLPFC (10), the small volume correction (SVC) for this area was used in the post hoc group comparisons. The small volume was determined by using the anatomically defined LDLPFC obtained from the automated anatomical labeling (AAL) map in the MRicro toolbox (Internet: http://www.sph.sc.edu/comd/rorden/mri-cro.html). The family-wise error (FWE) P < 0.05 (corrected for multiple comparisons within the small volume) was considered statistically significant.

The average of the 2 values of these subjective ratings of appetite sensations and blood tests in each PET scan session was used in the analysis. Group differences in anthropometric and metabolic indexes and subjective ratings of appetite sensations were analyzed by using analysis of covariance in a general linear model. Values of P < 0.05 were considered significant. These analyses were performed by using SAS software (version 8e; SAS Institute Inc, Cary, NC).

RESULTS

Thirty right-handed white women were enrolled in this study. However, 3 obese women who felt uncomfortable with the foam mold and moved their heads excessively during the PET session or who had an inferior-quality MRI scan were excluded from the analysis. Thus, data from 27 (10 lean, 9 obese, and 8 formerly obese) women were available for analysis. The characteristics of the study population are shown in Table 1. By design, obese subjects had significantly higher percentages of body fat (%BF), fasting insulin concentrations and received a larger meal compared with lean and formerly obese women. There were no significant differences in the general, anthropometric and metabolic characteristics between lean and formerly obese women. No significant differences in the subjective ratings across the 3 groups were observed (Table 2).

Results of the ANOVA (with P < 0.001, uncorrected for multiple comparisons as the criterion for statistical significance) indicated that neuronal activity in response to the meal was different across the 3 groups in the left inferior frontal gyrus (belonging to the LDLPFC)—peak voxel: x = −50, y = 14, and z = 20; and F value = 11.7 (Figure 1)—and in the inferior temporal gyrus—peak voxel: x = 56, y = −66, and z = −12; and F value = 14.2.
The left middle frontal gyrus (the local maxima is located in the left inferior prefrontal cortex). The prefrontal cortex is a big area that includes 3 subfrontal gyri (ie, frontal, superior, middle, and inferior frontal gyri), coordinates for both men and women fell within the same brain region. For women, the local maxima is located in the left inferior frontal gyrus (x = −50, y = 14, and z = 20); for men, the local maxima is in the left middle frontal gyrus (x = −34, y = 58, and z = 14). We acknowledge that this separation may indicate functional differences in this large brain area, although there is no clear evidence for this. However, our findings indicate that, within this area, neuronal activity differs in response to a meal between lean and obese persons.

These results also showed that formerly obese women who successfully achieved weight loss by diet and exercise and maintained their weight loss for ≥3 mo before the study have greater activation of the LDLPFC in response to a meal than do obese women; there were no detectable difference between formerly obese and lean (never-obese) women. This indicates either that the functional difference in the LDLPFC is a consequence of obesity and reverses with successful weight loss or that individuals with greater activation in the LDLPFC are more capable of losing weight and maintaining weight loss than are persons with lesser activation in the LDLPFC. These findings reinforce the notion of a role for the prefrontal cortex in the regulation of food intake and its alteration in obesity. In a structural study using voxel-based morphology of MRI scans, obese persons also had significantly lower gray matter density in the LDLPFC than did lean persons (23).

The post hoc comparisons between the groups are shown in Table 3. The only region that was consistently different across the post hoc comparisons between the groups was the left inferior frontal gyrus. Obese women had less activation in the left inferior frontal gyrus in response to a meal than did lean (peak voxel: x = −50, y = 14, and z = 20) and formerly obese (peak voxel: x = −48, y = 14, and z = 14) women (Table 3 and Figure 1). There was no significant difference in rCBF in this area between formerly obese and lean women (Figure 1 and Table 3).

With the use of the SVC, the difference in neuronal activity in the left inferior frontal gyrus between obese and lean women survived the FWE-based correction for multiple comparisons (P = 0.03). The same trend was found in this area after correction for multiple comparisons between formerly obese and obese women (P = 0.1).

### DISCUSSION

The present study showed that obese women have less activation of the LDLPFC in response to a meal than do their lean counterparts. Notably, this difference survived the FWE-based correction for multiple comparisons. Because the dorsolateral prefrontal cortex is a big area that includes 3 subfrontal gyri (ie, superior, middle, and inferior frontal gyri), coordinates for both men and women fell within the same brain region. For women, the local maxima is located in the left inferior frontal cortex (x = −50, y = 14, and z = 20); for men, the local maxima is in the left middle frontal gyrus (x = −34, y = 58, and z = 14). We acknowledge that this separation may indicate functional differences in this large brain area, although there is no clear evidence for this. However, our findings indicate that, within this area, neuronal activity differs in response to a meal between lean and obese persons.

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The prefrontal cortex plays a central role in the inhibition of inappropriate behaviors. In particular, it is important to the suppression of a course of action that is no longer appropriate and to the ability to monitor ongoing actions (24). Moreover, Heekeren et al have proposed that the LDLPFC of the human brain may contain a general mechanism for integrating perceptual evidence for decision making (25) and that the LDLPFC in humans may be a critical component of the decision-making network (26). In terms of appetite control, previous findings in lean or obese persons indicated that the LDLPFC also may play an important role in the central regulation of eating behavior by sending inhibitory inputs to orexigenic areas to suppress hunger and terminate a feeding episode (8, 17, 27). 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 shown (28). It is interesting that the stimulation of the LDLPFC by using repetitive transcranial magnetic stimulation resulted in inhibition of the development of food cravings (29).

Compared with obese women, formerly obese women who have successfully achieved weight loss had greater activation in the LDLPFC in response to a meal, but there was no significant difference in neuronal activation in this area between these women and their lean counterparts. If less activation of this area is an acquired feature of obesity, then our results indicate that this neurofunctional alteration may be reversible. To our knowledge, investigations of the effect of weight loss on brain responses are still scarce. As far as the effects of weight loss on psychology and behavior are concerned, however, studies in formerly obese persons indicate that most of those who have successfully achieved a weight loss and maintained their normal body weight have a better quality of life, greater mobility, and improved general mood and self-confidence than before their weight loss (30). Persons with successful weight loss report more self-monitoring of weight and food intake, both of which may be viewed as one component of successful cognitive control, than do persons who failed to maintain weight loss (30). It is also possible that the subjects who maintain their weight loss have greater activation in the LDLPFC than do subjects who do not. Successful female dieters have a significantly higher level of dietary restraint than do female nondieters, and a positive correlation between dietary restraint level and changes in rCBF in the prefrontal areas in response to a meal has also been observed (31). Moreover, those...
who regain lost weight were characterized by decreases in the level of dietary restraint and cognitive control of food intake and increases in disinhibition—ie, loss of control while eating (30).

We also found that, in response to a meal, obese women had greater neuronal activity in the right orbitofrontal cortex (OFC) than did formerly obese women (Table 3). The OFC has been implicated in the representation of relative reward value (32, 33), which may explain the greater activation of the OFC in the obese women who received a larger meal (based on body size) than in the formerly obese women.

Subjects in the current study participated in previous studies (11, 17) that provided somewhat different results. Several factors can account for these differences. First, in the current study, only right-handed female subjects without motion-related artifacts during the PET session were included. Therefore, confounders such as sex (34, 35), handedness (12–14), and motion-related artifacts were avoided, whereas both men and women and both left- and right-handed persons had been included in the previous analyses (11). Second, the newer analytic methods—ie, the 2-level, random-effects approach, characterized by a more stringent and robust statistical inference—was used in the present investigation. A detailed explanation of the benefit of using a 2-level, random-effects approach rather than a single-level, fixed-effect analysis, as used in the previous analyses (11, 17), has been reported elsewhere (10). In brief, inherent in PET scan studies are 2 sources of variability: within subject (ie, between scans) and between subjects. The single-level, fixed-effects approach takes into account only the within-subject variability, and thus the inferences relate only to those subjects in the study (21, 36–38). The random-effects analysis, in contrast, accounts for both sources of variability, thus making the results more robust and, therefore, more generalizable to the population of which the

FIGURE 1. Top: Statistical parametric maps of the difference in regional cerebral blood flow (rCBF) in response to the consumption of a meal at the level of the left dorsolateral prefrontal cortex (LDLPC) (peak voxel: $x = -50, y = 14$, and $z = 20$) across the 3 groups (lean, obese, and formerly obese women) at $P < 0.001$, (uncorrected for multiple comparisons) by ANOVA [left: horizontal (bottom), coronal (upper right), and sagittal (upper left) sections] and within-group analysis (right) in the SPM5 software package. Coordinates ($x, y, z$) referred to 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. Bottom: Changes in rCBF in the LDLPC after a meal in lean, obese, and formerly obese women.
study group is a sample (21, 36–41). Moreover, improvements in the preprocessing steps and the statistical methods in SPM5 (as detailed in the Methods section) may have made the analysis more sensitive to changes in rCBF in the LDLPFC. Finally, we used a coregistration step in the image processing that improves localization of neuronal activation loci (18). In this study, we examined only women (because members of the formerly obese group were primarily female) to confirm the results previously obtained in men, but the results of the pooled analysis of men and women (including some left-handed subjects) were consistent with our main findings in the LDLPFC (data not shown).

Limitations in the study design also must be acknowledged. Because of the exploratory nature of the study, subjects underwent a 36-h fast. This may not be considered a physiologic, fast but this prolonged fast was designed to maximize the chances of observing significant differences between the states of hunger and satiety. The general limitations of PET studies have been addressed in previous publications (8, 17, 35). They include the following: 1) limitations in spatial resolution, contrast resolution, and the accuracy of the image deformation algorithm used to compute statistical maps (now partly minimized with the coregistration step); 2) potentially confounding effects of scan order that result from the fact that the satiation condition always follows the baseline condition; and, 3) the possibility of statistical type I errors (now minimized in the random-effects approach and with SVC in the area of our primary hypothesis).

In conclusion, our findings confirm that less activation in the LDLPFC in response to a meal is a neurofunctional feature of obesity. In addition, normalized neuronal activity in this area in women who have successfully lost weight indicates that such a functional abnormality may be either an acquired feature of obesity that reverses with successful weight loss or an inherent feature in those persons who are able to successfully maintain weight loss. These hypotheses require further testing in longitudinal studies.

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The authors’ responsibilities were as follows—DSNTL, NP, ADS, and JK: planned the study, collected and analyzed data, and wrote the manuscript;

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**TABLE 3**

Between-group post hoc comparisons of neuronal activity in response to a meal

<table>
<thead>
<tr>
<th>Region</th>
<th>BA</th>
<th>Cluster size</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less neuronal activity in response to a meal in obese than in lean women</td>
<td>Left dorsolateral prefrontal cortex (inferior frontal gyrus)</td>
<td>45</td>
<td>251</td>
<td>-50</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>Less neuronal activity in response to a meal in formerly obese women</td>
<td>Right dorsolateral prefrontal cortex (middle frontal gyrus)</td>
<td>46</td>
<td>69</td>
<td>44</td>
<td>48</td>
<td>6</td>
</tr>
<tr>
<td>Comparisons between formerly obese and obese women</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Less neuronal activity in response to a meal in obese than in formerly obese women</td>
<td>Left dorsolateral prefrontal cortex (inferior frontal gyrus)</td>
<td>45</td>
<td>37</td>
<td>-48</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Less neuronal activity in response to a meal in formerly obese women</td>
<td>Right orbitofrontal cortex</td>
<td>47</td>
<td>46</td>
<td>58</td>
<td>34</td>
<td>-6</td>
</tr>
<tr>
<td>Right occipital gyrus</td>
<td>18</td>
<td>47</td>
<td>40</td>
<td>-86</td>
<td>20</td>
<td>3.5</td>
</tr>
<tr>
<td>Comparisons between lean and formerly obese women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less neuronal activity in response to a meal in formerly obese women than in lean women</td>
<td>Left superior temporal gyrus</td>
<td>22</td>
<td>45</td>
<td>-60</td>
<td>-2</td>
<td>-4</td>
</tr>
<tr>
<td>Left middle temporal gyrus</td>
<td>39</td>
<td>64</td>
<td>-56</td>
<td>-66</td>
<td>-12</td>
<td>3.7</td>
</tr>
<tr>
<td>Less neuronal activity in response to a meal in lean than in formerly obese women</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

1 BA, Broadmann's area. Coordinates (x, y, and z) and z score were from the peak voxel in every cluster and referred to the Montreal Neurological Institute standard brain. Data were analyzed by ANOVA and post hoc comparison between the groups by a 2-level, random-effect approach in the SPM5 software package. All brain regions in this table had significant comparisons, P ≤ 0.001 (uncorrected for multiple comparisons), except the left dorsolateral prefrontal cortex, P = 0.003.

2 x is the distance in millimeters to the right (+) or left (−) of the 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. 3 n = 10 lean and 9 obese women. 4 n = 8 formerly obese and 9 obese women. 5 n = 10 lean and 8 formerly obese women.
REFERENCES