Ventral frontal satiation-mediated responses to food aromas in obese and normal-weight women

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ABSTRACT

Background: Sensory properties of foods promote and guide consumption in hunger states, whereas satiation should dampen the sensory activation of ingestive behaviors. Such activation may be disordered in obese individuals.

Objective: Using functional magnetic resonance imaging (fMRI), we studied regional brain responses to food odor stimulation in the sated state in obese and normal-weight individuals targeting ventral frontal regions known to be involved in coding for stimulus reward value.

Design: Forty-eight women (25 normal weight; 23 obese) participated in a 2-day (fed compared with fasting) fMRI study while smelling odors of 2 foods and an inedible, nonfood object. Analyses were conducted to permit an examination of both general and sensory-specific satiation (satiation effects specific to a given food).

Results: Normal-weight subjects showed significant blood oxygen level-dependent responses in the ventromedial prefrontal cortex (vmPFC) to food aromas compared with responses induced by the odor of an inedible object. Normal-weight subjects also showed general (but not sensory-specific) satiation effects in both the vmPFC and orbitofrontal cortex. Obese subjects showed no differential response to the aromas of food and the inedible object when fasting. Within- and between-group differences in satiation were driven largely by changes in the response to the odor of the inedible stimulus. Responses to food aromas in the obese correlated with trait negative urgency, the tendency toward negative affect-provoked impulsivity.

Conclusions: Ventral frontal signaling of reward value may be disordered in obesity, with negative urgency heightening responses to food aromas. The observed nature of responses to food and nonfood stimuli suggests that future research should independently quantify each to fully understand brain reward signaling in obesity. This trial was registered at clinicaltrials.gov as NCT02041039. Am J Clin Nutr 2014;99:1309–18.

INTRODUCTION

The identification of mechanisms that promote energy intake in excess of need is important to combat obesity. Meal satiation (and termination) stem partly from food’s reduced reward (1). One instance of this devaluation is sensory-specific satiation (2) or the targeted devaluation of a specific food after prolonged exposure to its sensory qualities during eating. Thus, although a desire for a recently consumed food is quelled, the appetite for an alternative food with different sensory properties is preserved. Therefore, sensory-specific satiation has been posited to play a role in meal cessation and food choice (1–6). Conversely, disordered sensory-specific satiation could be important in overeating. Similar dynamics may also be at play with satiety, which determines intermeal intervals.

Trait impulsivity is implicated in developing and maintaining obesity (7–9) and may also work against internal satiety and satiation signals. The specific form of impulsivity known as negative urgency (NU) (10) reflects a tendency to act rashly as a consequence of strong negative affect. NU is higher in obese and overweight individuals (11), associated with BMI (12), and related to binge and dysregulated eating (13–15). A similar eating-specific behavioral trait, emotional eating (eating provoked by negative emotions), has also been associated with obesity (16). With such traits, emotionally driven reward urges may override executive control (17, 18). Consistent with these concepts, work in addiction has shown that ventral frontal responses to alcoholic drink odors correlated positively with trait urgency (19).

Four studies have examined adiposity group differences in premeal and postmeal responses to food images (20–23), one study of which focused on adolescents (20). Only one study involved eating to satiation (21) and showed that right lateral orbital responses of normal-weight subjects to high-energy food images...
(compared with low-energy food control images) were lower than those of obese subjects, albeit only after eating to satiation. In this study, we used fMRI to determine how responses to food-related stimuli would differ with adiposity, normal meal interval fasting, and both general and sensory-specific satiation. In lieu of images, we used food aromas matched to the subjects’ meals. Palatable food aromas (arguably more naturalistic Pavlovian-conditioned stimuli than food images) play an important role in flavor perception via retrolingual olfaction and help drive consumption (24–28). We focused our analyses on the ventral frontal regions that encode stimulus reward value (29, 30) and hypothesized that lateral orbital and ventromedial frontal responses would follow a pattern of sensory-specific satiation (reduced activation to an eaten food's aroma or devaluation; preserved activation from an uneaten food’s aroma or nondevaluation) in normal-weight but not obese women. We also examined associations between ventral frontal responses to food aromas and trait NU and emotional eating.

**SUBJECTS AND METHODS**

**Subjects**

Twenty-five normal-weight [BMI (in kg/m²) from 18 to 27] and 25 obese (BMI from 30 to 45), nonsmoking women, all of whom performed normally on the 20-item Smell Identification Test (31), were recruited (Table 1). Women were excluded if pregnant or breastfeeding within the past 6 mo, had diagnosed diabetes or a fasting blood glucose concentration ≥126 mg/dL, self-reported symptoms consistent with (or a history of) Axis-I psychiatric or known neurologic disorders, or food preferences inconsistent with odorants or meals used in the study. Two of 25 obese subjects were excluded for excessive motion during imaging. Data from 11 normal-weight and 7 obese subjects were included in an earlier preliminary report (32). All subjects gave informed consent as approved by the Indiana University Institutional Review Board.

**Procedures**

This study was conducted over 2 randomized, noncontiguous fed and fasting days. Subjects reported to the Indiana Clinical Research Center (ICRC) at 0630. A standardized breakfast was provided at 0740 (this included turkey sausage, French toast with margarine and syrup, a fruit cup, and coffee, tea, diet soda, or water) with portions adjusted to account for 20% of the participant’s daily energy requirement for weight maintenance (33). Normal-weight and obese subjects consumed 86.1% ± 10.5% (SE) and 85.6% ± 11.3%, respectively, of the total energy offered at breakfast.

**Fed day**

After breakfast, subjects remained in the ICRC until lunch at 1215. A luncheon casserole (1500 kcal) of either pasta combined with ground beef and Italian tomato sauce or with shredded beef and beef gravy was served in a deep, black, slanted bowl to minimize the appearance of excess food. To preserve aroma, the bowl was covered with plastic wrap before final heating (~170°F) and removed by the subject just before consumption (~2 min after heating). Subjects, who had been screened for liking both foods, were instructed to eat over a 30-min period until full. Between breakfast and lunch, subjects were allowed ad libitum water (volume documented) and sedentary activity (eg, reading, television, and computer use) but not sleep. Subjects were imaged at 1300, returned to the ICRC after imaging, and were discharged between 1500 and 1600.

**Fasting day**

After breakfast, subjects remained in the ICRC until imaging took place at 1300 and returned to the ICRC after imaging to break their fast for a late lunch (at ~1500–1600).

**Personality trait measures**

Subjects completed 2 scales to measure emotionally provoked (impulsive) action, both in general [NU as extracted from the UPPS-P Impulsive Behavior Scale (34)] and specifically as applied to eating [Emotional Eating (EmE) subscale extracted from Three-Factor Eating Questionnaire, revised 21 (16)]. The second question from the NU subscale [“I have trouble resisting my cravings (for food, cigarettes, etc.)”] was removed to avoid criterion contamination when correlating this scale with EmE.

**Olfactory stimuli**

All odorants were delivered by using an 8-channel air-dilution olfactometer as previously described (35–37), with air delivered to the participant’s nose via a polytetrafluoroethylene tube at a constant rate of 2.0 L/min. The following 2 classes of odorants (International Flavors & Fragrances) were presented: 1) food-related odors of Italian meat sauce (5% solution in 1,2 propanediol diluent; Sigma-Aldrich) and roast beef (20% solution in diluent) and 2) the odor of an inedible object, Douglas fir (undiluted). Diluent alone was used as an odorless sham control odor (CO).

**Hunger- and odorant-perception assessment**

Before imaging, odorant intensity was reassessed on a horizontally oriented 100-mm labeled magnitude scale (38) until each odorant’s intensity was ≤5 mm of the others (~1 adjustment/participant). Subjects rated hunger after exiting the MRI by using a vertically oriented 100-mm labeled magnitude scale (38, 39). Odorant pleasantness and representativeness were rated on horizontally oriented Likert-type scales that spanned from 1 (“very unpleasant, not at all representative”) to 9 (“very pleasant, very representative”) with 0.5-point increments (32).

**Olfactory paradigm**

Brain responses were assessed by using 4 consecutive 6:27-min BOLD fMRI scans. OptSeq2 software (http://surfer.nmr.mgh.harvard.edu/optseq/) was used to generate 4 pseudorandom,
mixed-event odor-stimulation sequences, with 8–22-s interstimulus intervals (average: 11.5 s). Each sequence was presented once per session in a pseudorandomized fashion. Each odorant (Italian meat sauce, roast beef, Douglas fir, and the CO) was presented 6 times/scan (24 total events/scan; 24 presentations of each odorant/session). Subjects inhaled at a verbal prompt and exhaled after a tone when they reported detecting (left-button press) or failing to detect (right-button press) odors on a trackball (HHSC-TRK-1 or HHSC-TRK-2; Current Designs).

Image acquisition

Imaging was performed on a 3T Magnetom Trio-Tim scanner (Siemens) using a 12-channel head coil array. Functional imaging volumes were positioned on a high-resolution (1.0 × 1.0 × 1.2-mm³ voxels) anatomic volume acquired with a 3-dimensional magnetization-prepared rapid-gradient echo (MPRAGE) sequence. Functional, BOLD contrast-sensitive data were acquired with an echo-planar imaging pulse sequence [gradient echo, repetition/echo time: 2250/29 ms, flip angle: 78°; field of view: 220 × 220 mm; 39 interleaved, 3-mm-thick slices; 2.5 × 2.5 × 3.0-mm³ voxels; generalized autocalibrating parallel acquisition (GRAPPA) factor 2]. Subjects were instructed to keep their eyes closed during functional imaging. Head movement and motion-related artifacts were minimized by using deformable foam pads on both sides of the participant’s head and a real-time 3-dimensional artifacts were minimized by using deformable foam pads on both sides of the participant’s head and a real-time 3-dimensional prospective acquisition correction algorithm (40). The surface displacement variable (41) in all participants’ sessions showed a mean residual head motion of 0.13 ± 0.04 mm and peak residual head motion of 0.43 ± 0.20 mm. Data from 2 obese subjects whose mean and peak surface displacements exceeded 2 SDs were discarded.

Imaging processing and analysis

Imaging data were preprocessed with SPM8 software (Welcome Department of Imaging Neuroscience, University College London) including slice-time acquisition correction, rigid-body realignment, and coregistration. Each participant’s MPRAGE image was segmented into tissue type; parameters from this nonlinear transformation were used to convert the participant’s structural MRI and realigned, coregistered BOLD volumes into Montreal Neurological Institute stereotactic space. The resulting normalized BOLD volumes were interpolated to 2 mm/side isotropic voxels and smoothed by a 6-mm full-width at half-maximum isotropic Gaussian kernel.

Responses to discrete, 2-s odorant (or CO) presentations in the postprocessed image time series were convolved with a standard hemodynamic response function as well as its time and dispersion derivatives. The 6 movement parameters from realignment were included as regressors while a high-pass filter with a cutoff of 1/128 Hz was applied to remove low-frequency noise. This first-level analysis estimated within-participant odorant effects. To allow the examination of any sensory-specific satiation, activation to eaten food odors (FEs) and noneaten food odors (FNEs) were assessed separately, as was the activation to the inedible (IEd) Douglas fir odor. All odorant effects were assessed by using contrasts of interest that compared a given odor to the CO baseline. This approach avoided relative food- and nonfood-odor comparisons and permitted an independent assessment of the baseline IEd odor response.

Three BOLD contrasts (C) tested sensory-specific satiation by separating: 1) effects of odors from eaten foods (C_{FE} = (FE > CO)), 2) the effects of odors from noneaten foods (C_{FNE} = (FNE > CO)), and 3) the odor of the inedible stimulus (C_{IEd} = (inedible > CO)). These contrasts were entered in an SPM8 factorial model of group (normal-weight and obese), odor contrast (C_{FE}, C_{FNE} and C_{IEd}), and session (fasting and fed) with the latter 2 factors as repeated measures.

Importantly, C_{FE} in the fed state indicated responses to odors from foods that had already been eaten. However, in the context of the sensory-specific satiation experiment, C_{FE} in the fasting session included responses to foods that had not yet been eaten at the time of imaging (and, thus, would, in theory, still be valued). C_{FNE} represented responses to odors of foods that were not consumed at any time on either fed or fasting days. The sensory-specific satiation hypothesis was tested by comparing postmeal responses to food odors (C_{FE-Fed}) to average responses of odors of foods that had not been consumed (ie, nonvalued) by the time of imaging (C_{FNE-Fed} C_{FNE-Fasting} and C_{FE-Fasting}).

The test of generalized (nonsensory-specific) satiation compared the average of food odors to the odor of the inedible stimulus (ie, C_{IEd+FNE} = (FNE-IEd) across fasting and fed states.

Given our hypotheses of effects related to food devaluation from satiation, we focused on the following specific ventral frontal regions of interest (ROIs): 1) the ventromedial prefrontal cortex (vmPFC), where activity reflects perceived reward value (see, eg, references 29 and 42–44) and 2) the lateral orbitofrontal cortex (OFC), which has been implicated in the coding of both primary rewards and sensory-specific satiation (30).

These regions were localized by using independent data derived from Bragulat et al (35), in which healthy normal-weight and obese women, after a 24-h fast, underwent olfactory stimulation during fMRI with food and inedible odors (see Supplemental Figure 1 under “Supplemental data” in the online issue). Peak effects from this former study of all odors against an odorless baseline (P-uncorrected < 0.001, k > 20 voxels; see Supplementary Figure caption under “Supplemental data” in the online issue for coordinates) were then used to place 8-mm radius spherical search volumes in the current study. Peak effects shown in the current data within these spheres were interpreted as significant after correcting for family-wise error (FWE) (P-FWE < 0.05) across all voxels in the sphere’s volume. Significant voxel-wise effects in these regions were extracted by using the MarsBar utility (version 0.43) (45) (cluster formed at P-uncorrected < 0.005) and plotted to examine individual stimulus effects.

RESULTS

Odor ratings

A group (obese and normal-weight) × session (fed and fasting) × rating type (intensity, pleasantness, and representativeness) linear mixed model was conducted with SPSS 20 software (IBM Corp) and showed neither a group × session × rating type interaction (P = 0.43) nor main effects of adiposity (group P = 0.84) or session (P = 0.35).

Hunger ratings

A group (obese and normal weight) × session (fed and fasting) × hunger type (general, food eaten, and food not eaten) linear mixed
model showed a main effect of session ($P < 0.001$), but no main effects of group ($P = 0.23$) or hunger type ($P = 0.10$), and no group $\times$ session $\times$ hunger type interaction ($P = 0.71$). The main effect of session reflected greater hunger when fasting ($74.8 \pm 1.35$) than when fed ($41.1 \pm 2.3$).

Food consumption

No subject finished the lunch provided ($\sim 1100$ g; 1500 kcal). On the fasting day, and after returning from imaging, normal-weight subjects consumed $508.3 \pm 153.5$ g, and obese subjects ate $602.0 \pm 188.9$ g. On the fed day, normal-weight subjects consumed $532.5 \pm 152.6$ g, and obese subjects ate $575.9 \pm 178.2$ g. A group (obese and normal weight) $\times$ session (fed and fasting) linear mixed model showed no main effects of group ($P = 0.13$) or session ($P = 0.96$) and no group $\times$ session interaction ($P = 0.20$).

BOLD activation

Olfactory sensory stimulation

Odorant activation compared with the CO resulted in a robust ventral frontal (and piriform/medial temporal olfactory) cortex response (Figure 1).

Sensory-specific satiation

The sensory-specific satiation hypothesis was tested by comparing the postmeal food odor response ($C_{FE,Fed}$) to average responses induced by odors of foods that had not been consumed by the time of imaging ($C_{FNE,Fed}$, $C_{FNE,Fasting}$, and $C_{FE,Fasting}$). The hypothesis would be supported if the response to a consumed food’s odor in the fed session ($C_{FE,Fed}$) was reduced relative to responses to odors of the 3 unconsumed (nondevalued) food contrasts. We found no ventral frontal (or other) regions that conformed to this directional hypothesis. Because of the lack of observable sensory-specific satiation, subsequent analyses compared the activation from both food odors to the activation from $C_{IEd}$ (ie, $[C_{FE} + C_{FNE}] > C_{IEd}$).

Fasting

Within the normal-weight group, the only a priori region in which $[C_{FE} + C_{FNE}]$ activation was significantly greater than the activation from $C_{IEd}$ was in the left vmPFC ($[-8, 40, -8]$; $P$-FWE = 0.025; Figure 2, Table 2). There was no $[C_{FE} + C_{FNE}] > C_{IEd}$ effect in any a priori ROI within obese subjects (also see Figure 1, top row).

Effects of satiation

After the consumption of lunch to satiation (fed session), normal-weight subjects showed no significant effects in any ROI for the $[C_{FE} + C_{FNE}]$ comparison, which reflected diminished differential responses across odorant classes after consumption. When effects of the fed session were directly compared against activation after fasting (fasting > fed) in normal-weight subjects, significant peak differences emerged in the left OFC ($[-34, 36, -12]$; $P$-FWE = 0.038) and the right vmPFC ($[8, 44, -12]$; $P$-FWE = 0.029; Figure 3, Table 2). Notably, however, effects in these regions stemmed largely from increases in $C_{IEd}$ after eating to satiation rather than changes in response to food odors (see plots in Figure 3 for regional and left panels of Figure 1 for voxel-wise illustrations).

As in the fasting session, obese subjects displayed no $[C_{FE} + C_{FNE}] > C_{IEd}$ effects after consuming lunch to satiation and no differential response between fed and fasting states in the a priori regions examined.

Group-by-session interactions

When we compared the $[C_{FE} + C_{FNE}] > C_{IEd}$ effect across groups and sessions, peak frontal effects occurred in the right...
OFC [(32, 34, 210); P-FWE = 0.023] and right vmPFC [(10, 40, 210); P-FWE = 0.029; Figure 4, Table 3]. As with effects within normal-weight subjects, group- and session-activation differences were largely driven by changes in CIEd (also see Figure 1).

### Trait measures

NU and EmE ratings were positively correlated across all subjects ($r = 0.54$, $P < 0.001$). The normal-weight group had NU scores (19.7 ± 1.2) that were significantly lower than those of the obese group (23.4 ± 1.3; $t$ test, $P = 0.040$). The normal-weight EmE score (10.7 ± 0.8) was also lower than that for the obese group (14.4 ± 1.0; $t$ test, $P = 0.004$).

In the context of group differences in NU and EmE as well as the interaction between group and session, we examined NU and EmE correlations with the $\frac{C_{PE} + C_{FNE}}{C_{138}C_{IEd}}$, the average of the contrasts of eaten and noneaten foods as compared with the inedible control odor.

### TABLE 2

BOLD activation coordinates of the $\frac{C_{PE} + C_{FNE}}{C_{138}C_{IEd}}$ contrast

<table>
<thead>
<tr>
<th>Region</th>
<th>Cluster size</th>
<th>Peak $z$</th>
<th>$P$-uncorrected</th>
<th>MNI coordinates (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal weight (fasting)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L vmPFC</td>
<td>48</td>
<td>3.8</td>
<td>&lt;0.001</td>
<td>$-6$ 60 2</td>
</tr>
<tr>
<td>R vmPFC</td>
<td>18</td>
<td>3.47</td>
<td>&lt;0.001</td>
<td>$8$ 50 $-4$</td>
</tr>
<tr>
<td>L vmPFC</td>
<td>10</td>
<td>3.41*</td>
<td>&lt;0.001</td>
<td>$-8$ 40 $-8$</td>
</tr>
<tr>
<td>Obese (fasting)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No significant voxels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese (fed)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight (fed)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No significant voxels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L middle/superior frontal gyrus</td>
<td>31</td>
<td>4.16</td>
<td>&lt;0.001</td>
<td>$-26$ 30 38</td>
</tr>
<tr>
<td>R amygdala/globus pallidus</td>
<td>25</td>
<td>3.87</td>
<td>&lt;0.001</td>
<td>$22$ $-8$ $-8$</td>
</tr>
<tr>
<td><strong>Normal weight (fasting &gt; fed)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L hippocampus</td>
<td>10</td>
<td>3.87</td>
<td>&lt;0.001</td>
<td>$-16$ $-10$ $-16$</td>
</tr>
<tr>
<td>L fusiform gyrus</td>
<td>10</td>
<td>3.74</td>
<td>&lt;0.001</td>
<td>$-34$ $-44$ $-10$</td>
</tr>
<tr>
<td>R vmPFC</td>
<td>20</td>
<td>3.43*</td>
<td>&lt;0.001</td>
<td>$10$ 42 $-12$</td>
</tr>
<tr>
<td>L inferior frontal gyrus</td>
<td>7</td>
<td>3.39</td>
<td>&lt;0.001</td>
<td>$-44$ 32 $14$</td>
</tr>
<tr>
<td>R superior temporal gyrus</td>
<td>12</td>
<td>3.32</td>
<td>&lt;0.001</td>
<td>$46$ $-56$ $14$</td>
</tr>
<tr>
<td>L OFC (lateral orbital gyrus)</td>
<td>6</td>
<td>3.3</td>
<td>&lt;0.001</td>
<td>$50$ $-64$ $18$</td>
</tr>
<tr>
<td>Obese (fasting &gt; fed)</td>
<td>10</td>
<td>3.26*</td>
<td>0.001</td>
<td>$-34$ 36 $-12$</td>
</tr>
</tbody>
</table>

| Note | Height threshold $P < 0.001$. *$P$-family-wise error < 0.05 adjusted for a priori search regions (see Subjects and Methods for details of search regions). $\frac{C_{PE} + C_{FNE}}{C_{138}C_{IEd}}$ the average of the contrasts of eaten and noneaten foods as compared with the inedible control odor; L, left; MNI, Montreal Neurological Institute; OFC, orbitofrontal cortex; R, right; vmPFC, ventromedial prefrontal cortex. |
differentiated groups across sessions. Neither NU nor EmE correlated with any ventral frontal ROI BOLD responses during the fasting session. Similarly, fed-session BOLD responses and EmE did not correlate. However, obese subjects showed a significant, positive relation between NU and the right OFC BOLD response to food odors ($r = 0.51$, $P = 0.01$; Figure 5) and a non-significant trend in nonfood odors ($r = 0.37$, $P = 0.08$). The correlation between NU and the right OFC response to food odors was significantly different (Fisher's $z = 2.55$, $P < 0.01$) between normal-weight ($r = 0.22$, $P = 0.29$) and obese subjects.

**DISCUSSION**

The following 4 principal findings emerged in this study of ventral frontal regions that code primary rewards and their subjective value: 1) we did not find brain responses suggestive of sensory-specific satiation in normal-weight or obese subjects; 2) vmPFC responses reflected generalized satiation in normal-weight but not obese subjects; 3) in both groups, ventral frontal satiety-induced changes were not reflected by food-odor responses but, instead, by nonfood odor responses; 4) in obese subjects, trait NU (but not emotional eating) correlated significantly with food-odor responses.

Three smaller studies (5–13 subjects) showed orbitofrontal responses to food cues that were silenced selectively after eating (46–48). Each study reported decreased BOLD activation to cues of foods eaten to satiation but preserved activation to cues of unconsumed foods—a phenomenon that would be important for varied nutrient intake (1–6). However, we showed no sensory-specific satiation in orbitofrontal BOLD responses from food aromas. Some differences in designs are relevant. First, our subjects experienced a naturalistic fast of 5 h between breakfast and lunch, whereas fasting was marginally longer in Kringelbach et al (47); fasting periods in O’Doherty et al (48) and Gottfried et al (46) were unspecified. Second, foods in our study more closely approximated a typical meal, which contrasted with the more homogeneous foods of bananas (compared with a vanilla aroma) (48), chocolate milk and tomato juice (47), or vanilla ice cream and peanut butter (46). Thus, sensory-specific satiation might not be as evident in our more typical and complex meals in which flavor and aromatic qualities were largely savory. Our subjects also ate ad libitum to perceived satiation without specific instructions to eat to unpleasantness [49, 50; also see reference 51 for a similar negative study of sensory-specific satiation with common design considerations]. This contrasts with the study of Kringelbach et al (47), in which subjects drank nearly 1 L tomato juice or chocolate milk to the point of aversiveness. Thus, it could be concluded that satiation from more typical meals does not induce sensory-specific effects in limbic frontal regions. Whether adiposity group differences might be present in less-naturalistic circumstances remains uncertain.
Normal-weight subjects did show a generalized satiation effect. The vmPFC of fasted, normal-weight subjects was more responsive to food odors than to similarly intense and pleasant odors of inedible stimuli; after eating to satiation, the vmPFC no longer discriminated between food and nonfood odors. In nonhuman primates, vmPFC’s responses to reward cues are most sensitive to internal satiety states (52), whereas human vmPFC BOLD responses scale according to a stimulus’ subjectively perceived value (29, 42–44, 53, 54). Accordingly, we reported a similar food odor–induced vmPFC activation in a mixed sample of normal-weight and obese participants after a 24-h fast (35) as well as vmPFC responses to alcoholic drink aromas (compared with grape and chocolate aromas) in heavy and social drinkers (19, 55, 56). Elsewhere, normal-weight individuals viewing food images activated the vmPFC (57–59) as did a mixed sample of normal-weight and obese subjects (60). However, many studies have not observed vmPFC responses to visual food cues (61–70). Food aromas may be more effective in provoking this region, but our subjects were also screened for disliking the foods used (and their aromas), which ensured a positive valuation. When food images are used, only a subset might be of high subjective value, thereby reducing the vmPFC activation. Such speculation requires additional research.

The lateral OFC also mediates the response to primary reinforcers (30), the assessment of subjective goal value (29), and the monitoring of environmental cues that signal both rewarding and punishing outcomes (52, 71). Lateral OFC responses to food images are more commonly reported in normal-weight individuals and after fasting (57, 58, 61, 63, 67, 70, 72–74), although many do not report OFC effects (23, 59, 65, 68, 69, 75). An OFC effect was also absent in our normal-weight individuals who, during premeal fasting, did not differentially activate the lateral OFC to food aromas (although the OFC did respond robustly to any odor compared with an odorless baseline). Like normal-weight subjects, ventral frontal regions in the obese also responded to odors when contrasted against the odorless sham stimulation. After fasting, the ventral frontal cortex of obese subjects did not differentiate between food and nonfood odors, as it did in normal-weight subjects. This absence of a differential response is in conflict with reports of appetizing food images that did activate the lateral OFC in fasted, obese adults and children (21, 68, 69) [however, a number of studies did not report within-group findings for obese subjects alone (70, 72)]. In our study, the absence of ventral frontal discrimination between food and nonfood cues persisted in the obese after satiation, which is an effect at odds with the response in normal-weight subjects.

How OFC and vmPFC signaled postsatiation changes was complex: responses to food aromas remained unchanged after eating, whereas responses to the nonfood aroma changed most. The most-pronounced example was in the right vmPFC of normal-weight

![Figure 4](attachment://labelling.png)

**FIGURE 4.** Plots of mean regional BOLD values extracted from clusters defined by the group × session interaction (n = 48) of the \( [C_{FE} + C_{FNE}] > C_{IEd} \) effect within the right orbitofrontal cortex (a) and right ventromedial cortex (b). Voxel-wise map (P < 0.005, k > 40) illustrates cluster locations. \( [C_{FE} + C_{FNE}] > C_{IEd} \) is the average of the contrasts of eaten and noneaten foods as compared with the inedible control odor.
subjects, where the fasting nonfood-odor response was, as hypothesized, lower than that of the food odor. However, food-odor responses remained essentially unchanged after eating, with changes in the nonfood stimulus driving the satiation effect. This finding has important implications as most studies of normal-weight and obese subjects (for review, see reference 76) relied only on a relative food versus nonfood contrast, whereby the nonfood activation could have driven the response. The interpretive problem is compounded by group comparisons of these complex subtractions. Only a small number of studies compared food and nonfood stimuli to a baseline (see, eg, reference 74) or plotted the effects to allow the direction of group differences to be assessed (see, eg, reference 21).

Our results suggest that the ventral frontal coding of food value in normal-weight individuals may reflect these relative stimulus valuations, with satiation enhancing the nonfood stimulus rather than devaluing the food odor. Alternatively, and with satiation as the more desirable homeostatic state, hunger might be thought of as devaluing the nonedible stimulus. From either perspective, it may not be evolutionarily adaptive to devalue food’s presence. Rather, our findings may reflect relative shifts of motivated attention within a complex stimulus environment. This aspect might have been heightened by our mixed-event stimulation paradigm rather than the more common block-design of food-image studies. In the obese, the relative response relations between stimuli was reversed (heightened responses to nonfood during fasting; depressed to nonfood during satiation), which suggests impaired orbital signaling in obesity. Ventral frontal involvement has long been suspected in impaired reward learning in behavioral disorders (77), and our findings suggest that obesity is accompanied by a disordered value-attribute system, wherein ventral frontal systems do not accurately assign rewarding (or nonrewarding) outcomes to stimuli (71). Thus, future research should be alert for effects attributable to the nonfood baseline.

Finally, trait NU was significantly higher in the obese. Although food odors in the obese did not differentially activate the orbital cortex when compared with the effect of nonfood odors, food odors compared with the odorless baseline induced orbital activation, which correlated with NU (albeit, only after satiation). Thus, the more prone obese subjects were to impulsive behavior in negative emotional states, the more pronounced were their responses to food aromas, which is a finding that comports with the role of NU in overeating, binge eating, and obesity (11, 13–15). That the correlation emerged only under the fed condition suggests a possible priming effect, wherein eating may sensitize the reward centers of obese individuals in a manner that scales with NU. The finding was similar to that in our recent report (19) of vmPFC responses to alcoholic drink odors that correlated with NU in social drinkers.

There are several factors to consider. Some effects occurred unilaterally, although other studies of food-related stimuli also report unilateral responses (for review, see reference 76).

**FIGURE 5.** Illustrative plot of significant positive correlation between negative urgency and the average BOLD response to food odors in the obese (n = 25) during the fed session as extracted from the right orbitofrontal cortex region that interacted with the group and session.
Satiation was not assessed directly but inferred by changes in rated hunger and the voluntary cessation of eating. Hunger is highly related to fullness, although neither fullness nor hunger is tightly correlated with energy intake (78). We also studied only women, and effects in men remain to be investigated.

In conclusion, the largest sample to date, to our knowledge, of normal-weight and obese subjects did not show sensory-specific satiation effects within ventral frontal regions. During fasting, differential activation between food and nonfood odors was present in these regions in normal-weight women but not in the obese. These effects were driven primarily by nonfood odors, emphasizing the importance of a baseline. Last, we showed a positive association between NU and OFC responses to food odors in satiated obese women, providing further evidence that trait NU is important in obesity.

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