Food-Related Odor Probes of Brain Reward Circuits During Hunger: A Pilot fMRI Study

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Food aromas can be powerful appetitive cues in the natural environment. Although several studies have examined the cerebral responses to food images, none have used naturalistic food aromas to study obesity. Ten individuals (five normal-weight and five obese) were recruited to undergo 24 h of food deprivation. Subjects were then imaged on a 3T Siemens Trio-Tim scanner (Siemens, Erlangen, Germany) while smelling four food-related odors (FRO; two sweet odors and two fat-related) and four "nonappetitive odors" (NApO; e.g., Douglas fir). Before the imaging session, subjects rated their desire to eat each type of food to determine their most preferred (P-FRO). Across all 10 subjects, P-FRO elicited a greater blood oxygenation level dependent (BOLD) response than the NApO in limbic and reward-related areas, including the bilateral insula and opercular (gustatory) cortex, the anterior and posterior cingulate, and ventral striatum. Obese subjects showed greater activation in the bilateral hippocampus/parahippocampal gyrus, but lean controls showed more activation in the posterior insula. Brain areas activated by food odors are similar to those elicited by cues of addictive substances, such as alcohol. Food odors are highly naturalistic stimuli, and may be effective probes of reward-related networks in the context of hunger and obesity.

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INTRODUCTION

Obesity is a significant risk factor for cardiovascular disease, diabetes, and cancer (1). Although obesity can stem from behavioral factors such as diet and physical inactivity (2–4), central nervous system changes are also likely to mediate appetitive behavior and restraint. As our understanding of hypothalamic and hindbrain regulation of food intake has rapidly expanded (5–8), less is understood about how gut and adipose tissue hormonal signaling integrates with environmental cues, memory, motivation, and appetitive behavior. Food aromas are powerful appetitive cues that are intrinsic to foods' flavor and hedonic qualities. Others have shown that such cues are key determinants of actual intake (9) that can facilitate overeating (10–12). For example, Jansen *et al.* (13) showed that the smell of a snack provoked overconsumption in overweight vs. normal-weight children. BMI also positively correlates with the magnitude of food odors' appetitive effects (14).

Studies of differential brain responses to food cues between normal-weight and obese subjects are nevertheless largely limited to visual images of food (15–24). While visual images have proven useful, a food's aroma could be considered as a more visceral conditioned stimulus that is more suggestive of a food's immediate presence.

The principal aim of this pilot investigation was therefore to assess the feasibility of measuring the brain's response to appetizing food-related aromas (compared to nonappetitive odors (NApO) of objects that cannot be ingested) during a fasted state in a mixed sample of 10 lean and obese women. As a secondary aim, we also studied preliminary differences in activation between the normal-weight and obese subjects. We paid particular attention to the dopaminergic limbic reward circuit, comprising the ventral tegmental area, the ventral striatum, and medial prefrontal cortex, to which the ventral striatum projects (23). We also hypothesized that we would find food odor-related activation in the insula, which has been identified as important to drug craving (24).

METHODS AND PROCEDURES

Subjects

Five lean ((mean ± s.d.) BMI 22.0 ± 2.9 kg/m^2, age 23.4 ± 1.1 years) and five obese (BMI 41.6 ± 5.0 kg/m^2, age 31.6 ± 8.8 years) women were recruited from the community. There was no difference in years of education between the groups (16.2 ± 1.3 vs. 14.4 ± 2.6). No subject had evidence of Axis-I psychiatric disorders or neurological disorders

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of the brain. All performed normally on a 20-item version of the Smell Identification Test ((25); range 16–19), with no between-group differences. Nine of the ten subjects were nonsmokers, with the 10th indicating only occasional smoking (average 0.10 cigarettes/day). Individuals were excluded if they were pregnant within the past 6 months, breast feeding, or if their food preferences were inconsistent with the food aromas used. All voluntarily signed informed consent statements approved by the institutional review board at the Indiana University School of Medicine.

Subjects were admitted to the General Clinical Research Center the day before imaging. At their arrival on day 1 (12 PM), weight and height were recorded and the subjects were provided a standard lunch meal (sandwich or pasta) providing one-third of the daily kilocalories required for weight maintenance (range ~60% carbohydrate, ~30% fat). After eating lunch, subjects were not allowed to eat (water *ad libitum* was allowed) before the imaging session on day 2 (2 PM), resulting in an ~24-h fast before imaging.

Procedure

Olfactory stimuli. Odorants were delivered using an eight-channel air-dilution olfactometer as previously described (26,27), with air delivered to the subject's nose via a small polytetrafluoroethylene tube at 2.0 l/min. Three classes of odorants (International Flavors & Fragrances, Union Beach, NJ) were used: (i) fat food-related odors (F-FRO), with each subject choosing two of three F-FRO from potato chips, roast beef, and pasta, (ii) sweet food-related odors (S-FRO), with each subject choosing two of three from strawberry shortcake, chocolate cake, and caramel ice cream, and (iii) NApO, with subjects choosing from four of the seven odors of grass, leather, lilac, Douglas fir, lily of the valley, balsam, and patchouli. By allowing subjects to choose odors, unpleasant or aversive odors could be excluded. Small, porous polyethylene disks were used to absorb the NApO, F-FRO and S-FRO, and then placed at the bottom of a glass vial, over which the olfactometer airstream passed before being delivered to the subject.

Stimulus training. Before entering the scanner room, subjects were familiarized with the odorants by smelling each (grouped by the stimulus classes of FRO and NApO) through the olfactometer while simultaneously viewing representative images on a computer monitor (e.g., roast beef odor presented with an appealing photograph of a plate of roast beef).

Craving/mood questionnaire and preferred food-related odors (P-FRO). Just before the combined odor/picture cue-exposure, subjects answered questions probing craving/desire to eat and mood. Subjects rated food craving by responding to three questions ("I want to eat right now," "Right now I crave something sweet," "Right now I crave something salty") on visual analogue scale (1 = strongly disagree, 7 = strongly agree). Subjects also rated their desire to eat each of the four specific foods corresponding to the four FRO they had chosen (e.g., "If given the opportunity to eat (roast beef) right now, I would," 1 = be uninterested, 7 = definitely eat it). Subjects similarly rated mood ("Right now, I feel angry, grouchy, annoyed, bad-tempered," "Right now, I feel happy, energetic, full of pep, cheerful, vigorous"). Craving/desire to eat scores were then used to define each subject's preferred type of food at the time of imaging. These preferred odors were used in the analysis as P-FRO, as preliminary analyses showed these to provide the most robust results.

Activation paradigm. Six functional imaging scans of olfactory stimulation per subject were performed, for a total of 36 odor events per class (**Figure 1**). However, due to two subjects' inability to complete the full functional imaging protocol and excessive motion in one subject, only four scans could be analyzed for three obese subjects. Compliance was established by prompting (via a tone) the report of an odorant's presence (button 1) or absence (button 2) on a two button response-box. Unlike the odor familiarization period, no pictures were presented during imaging, and subjects were instructed to close their eyes during image acquisition.

Odor ratings. In a post-imaging evaluation session outside the scanner room, subjects rated on a linear 9-point visual analog scale the odors' intensity, pleasantness, and representativeness (how well the odor represented its intended source).

Image acquisition

Subjects were imaged on a Siemens 3T Magnetom Trio-Tim scanner (Siemens). A whole-brain high-resolution anatomical image volume (1.0 × 1.0 × 1.2 mm voxels) was first collected using a 3D magnetization prepared rapid gradient echo sequence to enable anatomic registration of the functional volumes. Six functional scans were then performed with a blood oxygenation level dependent (BOLD) contrast sensitive gradient echo, echo-planar imaging sequence (repetition time 2,250 ms, echo time 30 ms, flip angle 78°, 37 3-mm thick interleaved axial slices without a gap, in-plane voxel dimension 2.5 × 2.5 mm, field of view 220 × 220 mm) using a 12-channel head coil array and incorporating a 3D prospective acquisition correction that minimizes motion effects by adjusting the acquisition of functional volumes in real time.

Imaging processing and data analysis

Data were analyzed using SPM5 (Welcome Department of Imaging Neuroscience, University College, London, UK). Functional volumes were corrected for slice acquisition timing differences and rigid-body realigned to the initial volume of the first functional imaging scan (used as a reference volume), correcting for residual movement after prospective correction. Each subject's high-resolution anatomic image was coregistered to subject's reference volume and segmented into gray, white, and cerebrospinal fluid tissue components producing nonlinear spatial transformation parameters for converting functional volumes to the Montreal Neurological Institute coordinate space (isotropic 2 mm voxels). Normalized functional volumes were smoothed by a 6 mm full-width at half-maximum isotropic Gaussian kernel.

Within-subject effects were first estimated. Discrete 2 s periods of odorant (or sham) valve openings (**Figure 1**) were modeled in the general linear model using as basis functions SPM's canonical hemodynamic response function and its time and dispersion derivatives to account for variations in response onsets and durations. Individual odorant pulses were modeled as initial investigation showed that convolving the hemodynamic response function with the individual 2-s odor pulses provided better olfactory sensory system (piriform and orbitofrontal cortex) responses than convolution with the entire 40 s blocks (**Figure 1**). Movement parameters from realignment were included as regressors to control for residual movement-induced effects. A high-pass filter with a cut-off of 1/128 Hz was applied to each voxel's time series to remove low-frequency noise but autoregression was not used given the long interstimulus interval. This first level, within-subject model, yielded contrast images representing activation within an odorant condition ((P-FRO derived from either F-FRO or S-FRO and NApO), as well as the differences between conditions (P-FRO > NApO)). These contrast images were then used in second level (group) random effects analyses. Statistical significance was inferred using corrected cluster statistics with a height threshold of $P < 0.05$, false discovery rate (FDR) corrected.

RESULTS

Odor perception and craving

Odor ratings. Six of ten subjects (three normal-weight and three obese subjects) rated S-FRO as their P-FRO and four rated F-FRO as their P-FRO. Subjects perceived P-FRO as somewhat more intense (8.20 ± s.d. = 1.14) than NApO (7.53 ± 1.06; paired t, $P <$ 0.05). P-FRO were also perceived as somewhat more pleasant (8.30 ± 0.92) than NApO (7.13 ± 1.73, paired t, $P < 0.05$). Both P-FRO and NApO were, however, perceived as equally representative (P-FRO = 8.25 ± 1.01; NApO = 7.73 ± 1.06) of their intended sources. There were no group differences in perceived intensity, pleasantness, and representativeness ($P > 0.19$).

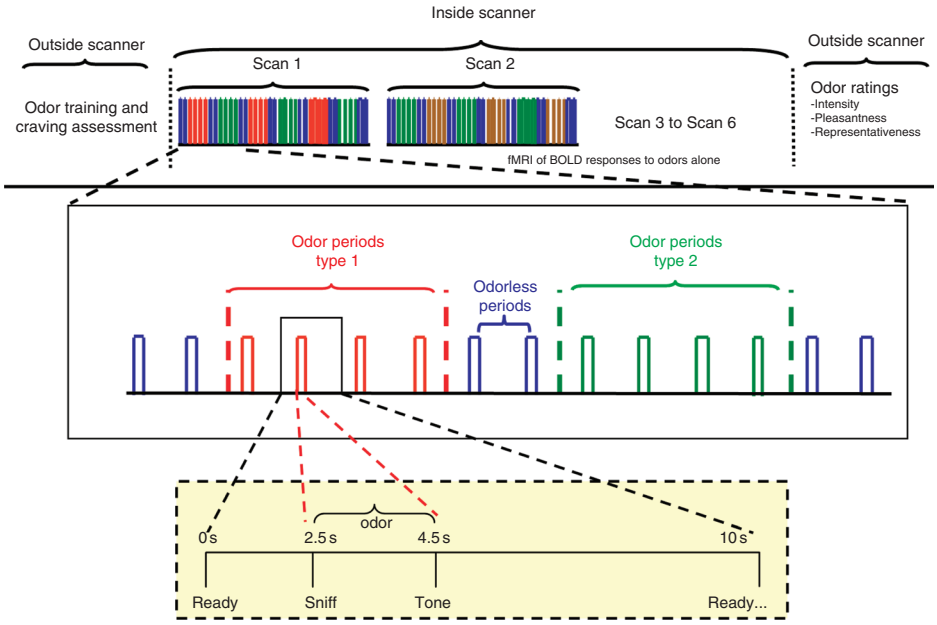

Figure 1 Odor stimulation paradigm. During 40 s epochs, subjects sniffed either fat food-related odors (F-FRO; e.g., roast beef, potato chips), sweet food-related odors (S-FRO; e.g., strawberry shortcake, chocolate cake), or nonappetitive odors (NApO; e.g., grass, Douglas fir), as well as odorless air (sham stimuli) over 20 s epochs. Each epoch consisted of 2 s odor valve openings, with auditory commands (yellow inset) instructing subjects to sniff. Each odorant in a given class was delivered twice in alternate order (e.g., roast beef, potato chips, roast beef, potato chips) over the course of three 40 s periods, with a 10-s stimulus onset asynchrony (SOA) between single-odorant pulses. Different stimulation sequences were randomized across subjects such that no stimulus class was repeated without another intervening class, and any one odor class was always followed by an odorless baseline period. Within each scan, food-related odors were always presented in alternate order with NApO. Periods 1 and 2 correspond to either F-FRO and NApO, or S-FRO and NApO, depending on odor presentation randomization.

Craving/mood. There was no difference between the obese and normal-weight subjects on the subjective ratings of craving/desire to eat following the 24-h fast (5.6 ± 1.1, 5.0 ± 0.8, respectively, U = 7, $P = 0.25$, Mann–Whitney *U*-test). Across all 10 subjects, mood was clearly positive (4.6 ± 0.9), with no difference between the two groups ($P = 0.92$). Negative mood was limited (1.8 ± 1.1), and also not different between groups ($P = 0.20$).

BOLD activation of P-FRO compared to NApO. Given significant perceived differences in intensity and pleasantness between P-FRO and NApO stimulus classes, we first examined activation using these interclass pair-wise differences as covariates. The intensity covariate (i.e., the difference in perceived intensity between the odorant classes of P-FRO and NApO) had no significant effect on the (P-FRO > NApO) activation map, which contained no significant clusters at a conservative threshold of $P < 0.05$, FDR corrected (as was the case in the activation map obtained without using the intensity covariate). However, including pleasantness as a covariate (i.e., the difference in perceived pleasantness between P-FRO and NApO) led to many significant clusters with peaks surpassing $P < 0.05$, FDR corrected. Thus, the activation results were assessed only using stimulus class (P-FRO–NApO) differences in perceived pleasantness as a covariate. In this manner, the effects of any differences in perceived pleasantness between the food and nonfood-related odors are regressed out of the (P-FRO > NApO) BOLD activation results.

Across all 10 subjects, P-FRO elicited greater activation than NApO in several reward-related areas (**Table 1**, **Figure 2a**), including the medial frontal/anterior cingulate cortex, precuneus, and insular/opercular cortices. Although we did not see ventral striatal and ventral tegmental area activation using our cluster thresholds for these smaller anatomic regions, there were significant voxel-level activations in both areas at $P < 0.05$, FDR (ventral tegmental area at (8, −18, −12), 45 voxels at $P = 0.04$ FDR corrected; ventral striatum at (−16, 14, −8), 32 voxels at $P = 0.04$ FDR corrected).

Between-group comparison. Although no differences between groups met our strict criteria for significance, we noted some trends (**Table 2**). In particular, obese subjects had greater activation than normal-weight subjects in the bilateral hippocampus/parahippocampal area (**Figure 2b**, left panel). In reward-related areas, normal-weight subjects had greater activation in the posterior insula.

DISCUSSION

Results from this study of naturalistic food aromas showed greater activation from highly desired food odors (relative to NApO) in brain regions implicated in reward processing. Specifically, P-FRO induced a larger BOLD response in the ventral tegmental area and ventral striatum (nucleus accumbens, ventral caudate), and the medial frontal cortex to which they project (23). Activation in the insula was present, as well.

Table 1 Odorant effects across all subjects

		Peak voxel[a]	Peak MNI coordinates (mm)		
	Cluster size[a]	*Z*	*x*	*y*	*z*
Preferred food-related odors > nonappetitive odors (P-FRO > NApO)					
Left calcarine cortex	1,242	4.55	–4	–88	2
Right dorsolateral prefrontal cortex (middle frontal gyrus; MFG)	345	4.63	22	28	46
Left dorsolateral prefrontal cortex (MFG)	63	4.61	–32	0	62
Right frontal/temporal opercular cortex	155	4.60	60	–6	6
Left dorsolateral prefrontal cortex (MFG)	347	4.56	–34	14	38
Right dorsolateral prefrontal cortex (inferior frontal gyrus)	132	4.56	50	10	42
Right and left thalamus, extending into left ventral caudate with subpeak at (–10, 8, 8)	643	4.55	22	–16	20
Left frontal/temporal opercular cortex	301	4.52	–56	–8	6
Right/left ventromedial frontal cortex, extending to medial frontal cortex with subpeak at (0, 46, 0)	785	4.50	2	40	–8
Left posterior temporal (middle temporal gyrus)	128	4.31	–60	–56	16
Left post-central gyrus	267	4.29	–56	–16	20
Supplementary motor area	117	4.29	–6	–6	60
Right insula/temporal operculum	256	4.26	44	–12	–2
Right parieto-occipital cortex	94	4.25	46	–68	34
Left inferior frontal gyrus (pars orbitalis)	53	4.21	–42	26	–4
Left precuneus, extending into posterior/retrosplenial cingulate, with subpeak at (0, –46, 26)	427	4.12	–8	–64	42
Right hippocampus	187	4.11	16	–28	–8
Right dorsal cingulate cortex	423	4.05	4	22	30
Left precuneus	53	3.95	–10	–78	50
Right precentral gyrus	65	3.89	40	–12	40
Left inferior occipital gyrus	187	3.89	–48	–64	–12
Left dorsolateral prefrontal cortex (MFG)	310	3.89	–36	44	6
Right posterior middle temporal gyrus	114	3.84	66	–40	2
Right lateral precentral gyrus	82	3.83	54	–4	26
Right superior temporal sulcus	105	3.77	62	–10	–10
Right intraparietal sulcus/middle occipital gyrus	53	3.67	32	–82	28
Right posterior parahippocampal gyrus	56	3.62	–12	–34	–2
Right dorsolateral prefrontal cortex (MFG)	92	3.45	36	32	36
Nonappetitive odors > preferred food-related odors (NApO > P-FRO)					
(No significant results at $P < 0.001$, uncorrected)					

MNI, Montreal Neurological Institute; NApO, nonappetitive odors; P-FRO, preferred food-related odors.
[a]All cluster sizes are significantly large (corrected for volume) assessed at a height threshold of $P < 0.05$, corrected for the false discovery rate.

The medial frontal/anterior cingulate cortex activation from food odors during hunger is consistent with findings related to perceived reward value. Kable and Glimcher (28) showed that anterior cingulate/medial frontal area activation was correlated with subjective monetary reward value in a delayed discounting task, whereas Hare *et al.* (29,30) found that the "goal value" of food correlated with activation in the same region. Anatomically, medial frontal cortex receives extensive projections from the dopaminergic ventral striatum (23,31,32), which is thought to code the "incentive salience" of rewards' conditioned cues (33), and was likewise activated by the food aromas in this study. Our own group has noted both medial frontal and ventral striatal responses in heavy drinkers exposed to the odors of preferred alcoholic beverages (26,27,34). The frontal activation foci in this study are quite similar to those we obtained using alcoholic drink aromas (26), where such activation varied as a function of a family history of alcoholism (34). Other groups also find remarkably similar medial frontal locations responding to reward cues (28,30,35,36). The significance of this medial frontal reward signal is underscored in

Table 2 Group differences in activation

	Cluster size	Peak voxel[a]	Peak MNI coordinates (mm)		
		Z	*x*	*y*	*z*
Obese subjects > lean subjects (P-FRO > NApO)					
Left hippocampus/ parahippocampal gyrus	7	3.94	–14	–16	–20
Left fusiform cortex	15	3.85	–26	–62	–4
Right hippocampus	6	3.73	26	–14	–12
Left superior parietal	10	3.62	–24	–48	52
Right posterior hippocampal gyrus	10	3.58	22	–48	–4
Right lateral midbrain area	5	3.41	20	–16	–8
Lean subjects > obese subjects (P-FRO >NApO)					
Right opercular frontal cortex	9	4.01	58	32	8
Left prefrontal cortex	15	3.86	–30	34	28
Left posterior insula	9	3.85	–32	–12	12
Left posterior middle temporal gyrus	8	3.82	–56	–58	6
Right cingulate sulcus	8	3.80	6	8	40
Left dorsolateral prefrontal cortex	9	3.59	–22	28	38
Left superior medial frontal cortex	7	3.54	–8	30	52
Right prefrontal	5	3.46	34	42	22
Right inferior prefrontal	5	3.35	42	42	4

MNI, Montreal Neurological Institute; NApO, nonappetitive odors; P-FRO, preferred food-related odors.
[a]Results surpassing $P < 0.001$, uncorrected, shown.

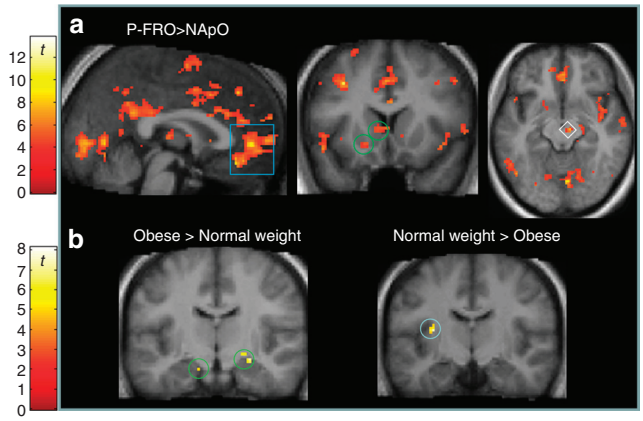

Figure 2 (**a**) Blood oxygenation level dependent (BOLD) activation induced by sniffing the odors of preferred foods (P-FRO), contrasted against sniffing nonappetitive control odors (NApO) in a mixed sample of 10 obese and normal-weight women who were food-deprived for 24 h before imaging. Left panel: blue box, medial frontal activation, center panel: green circles, ventral striatum (left circle, nucleus accumbens; right circle, ventral caudate), and right panel: white diamond, VTA/ dopaminergic midbrain. Display threshold, $P < 0.05$, false discovery rate corrected, see text for extent threshold. (**b**) Bilateral hippocampus/ parahippocampal gyrus (green circles) activates more in obese than in normal-weight subjects in the (P-FRO > NApO) comparison. (**c**) Increased posterior insula activation in normal-weight as compared to obese subjects in the (P-FRO > NApO) comparison. Display threshold, $P < 0.001$, uncorrected, extent threshold, $k = 5$.

animal models, where medial frontal lesions abolish cue-driven feeding (37). In addition, medial frontal cortex can modulate visceral responses to affective stimuli in a highly motivational context (38), as would be the case after an extended fast. The data from this experiment therefore suggest that naturalistic odors can be effective appetitive probes of the brain's reward circuits in studies of obesity.

Despite the sample size, we did note some preliminary differences in the brain's response to food odors between these normal-weight and obese women. In particular, obese subjects had a greater (P-FRO >NApO) BOLD response in the hippocampus/parahippocampal gyrus. Traditionally regarded as an important substrate for learning and memory, the hippocampus also participates in sensing the metabolic and hormonal status of the body (39), and in the regulation of food intake (40,41). When the hippocampus is lesioned in rodents, animals have difficulty distinguishing between interoceptive signals of hunger and satiety (42) and alter their feeding patterns by feeding more frequently and in smaller bouts (43). In humans, hippocampal stimulation generates autonomic and endocrine effects such as gastric secretion (44) and increased food consumption (41). Hippocampal activation also occurs in a number of studies involving food-related stimuli, hunger, and food craving (e.g., refs. 20,45–47). The hippocampal coordinates at which we found group differences are within 10 mm of those found by Rothemund *et al.* (16) in their study of normal-weight and obese women described as neither hungry nor satiated, and of those reported by Stoeckel *et al.* (17) where subjects fasted for 8 h. Martin *et al.*(21) also reported greater hippocampal activation from food images in obese subjects compared to lean subjects, although in this case it was following a meal (with premeal imaging showing no hippocampal effects). In comparison to lean men, Gautier *et al.*, (48) also observed that obese subjects had larger hippocampal decreases in regional cerebral blood flow during satiety (compared to a baseline of hunger). However, normal-weight subjects showed greater activation in the left posterior insula, a region implicated in somatosensory processing (see ref. 49). Larger samples will be needed to fully understand such differences.

In summary, this study shows the feasibility of using naturalistic food odors in brain imaging studies of obesity, with robust activation effects compared to nonfood odors in a well-documented medial frontal/mesolimbic reward network. Although replication with larger numbers of subjects using this paradigm is needed, differences between lean and obese individuals may be most visible in the hippocampus, whose role in feeding and satiety is becoming increasingly evident.

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DISCLOSURE

The authors declared no conflict of interest.

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