Human Cortical Specialization for Food: a Functional Magnetic Resonance Imaging Investigation[1]

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ABSTRACT Although specialized cortical pathways that process specific sensory stimuli and/or execute cognitive functions have been identified, the neuro-specificity for food-related stimuli has not been clearly demonstrated. We employed functional magnetic resonance imaging (fMRI) to compare neural systems associated with the appreciation of foods and nonfoods. Healthy, normal weight, right-handed men and women (n = 12; age 29.8 ± 1.8 y, BMI 21.8 ± 0.8 kg/m^2) were imaged by fMRI while fasting. Real food and nonfood items were presented to subjects both visually and tactilely, during scanning. Subjects were instructed to pay attention to the items. A randomized 2 × 2 block design consisted of 4 conditions: visual food, visual nonfood, tactile food, and tactile nonfood. Brain regions that were significantly activated to a greater extent during the presentation of foods compared with nonfood items included the anterior cingulate, superior temporal gyrus, parahippocampal gyrus, hippocampus, and the insula. These findings support the claim that the presence of food (either seen or felt) elicits a unique cortical response that is differentiated from nonfood items. This neural substrate specialized for processing of foods informs models of food-related behavior. J. Nutr. 135: 1014–1018, 2005.

KEY WORDS: • *functional magnetic resonance imaging* • *food* • *eating* • *appetite* • *obesity* • *neurocircuitry* • *cross-modal conjunction*

The regulation of food intake and energy expenditure, which leads to body weight control, involves complex and precisely regulated cortical systems (1,2) despite the various disturbances affecting energy balance. Evidence from brain lesion and animal studies suggests that discrete neuronal pathways generate integrated responses to afferent inputs related to changes in body energy stores (3). The hypothalamus has been identified as an area that is richly innervated by input from gastrointestinal as well as adiposity signals (4). These signals act in regulating meal termination and meal size in response to changes in body fuel stores or adiposity (4). However, feeding behavior also encompasses other phases such as initiation and procurement (5). The initial steps in ingestive behaviors, in contrast to meal termination, are highly dependent on several societal and environmental cues. For example, meal initiation depends on one's inclination to turn to food, and procurement requires cognitive processing such as planning, learning, and memory (5). These 2 initial phases of ingestive behavior are further affected by emotional factors, time of day, availability and palatability of foods, and societal and environmental cues (3,4) and are therefore highly driven by learned behaviors.

Although some genes have been implicated in the development of human obesity, the recent rise in human obesity is likely not the result of single-gene defects; rather, it is due to an interaction between an obesigenic environment and perhaps genes that render some individuals more susceptible to developing obesity under these conditions (5). Therefore, if meal termination is highly regulated and meal initiation more dependent upon environmental and emotional factors, then perhaps these more cognitive parameters play an important role in the development of obesity in the general population. If so, then the study of global cortical systems involved in food-related behavior may enhance and extend current obesity models based on molecular and cellular systems such as hormones and peptides.

Current brain imaging techniques such as positron emission tomography (PET)[3] and functional magnetic resonance imaging (fMRI) enable examination of in vivo human brain activity in response to specific stimuli and tasks. For example, PET has been used to study brain activity in response to viewing images of food and in both fasted and fed states (6) and in fasted and fed lean and obese individuals (7,8). Unfortunately, factors such as toxicity due to the arterial injection of radionuclides and low spatial and temporal resolution exclude PET as a technique of choice for studies of cognitive and perceptual

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[3] Abbreviations used: EPI, echo planar imaging; fMRI, functional magnetic resonance imaging; MNI, Montreal Neurological Institute; OFC, orbitofrontal cortex; PET, positron emission tomography.

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systems in healthy volunteers. Alternatively, fMRI is noninvasive, has high resolution, is of minimal risk, and is without contraindication for the study of subjects on multiple occasions. As in PET studies, however, fMRI identifies cardiovascular changes in brain blood oxygen level coupled with neural activity (9).

Previous imaging studies of the neurocircuitry associated with food-elicited responses employed pictorial representations of food. Thus, the observed cortical responses may represent various visual encoding strategies in addition to the food-elicited responses. We employed fMRI to isolate neuronal circuits involved in the appreciation of real foods and real nonfood items in healthy, normal weight, fasting individuals.

SUBJECTS AND METHODS

Subjects. Adult subjects were recruited from the St. Luke's/Roosevelt Hospital Center and Columbia University Medical Center in Manhattan, New York according to institutional guidelines. Subjects were healthy, normal weight and right-handed according to the Edinburgh Handedness Inventory (10), and were not eligible if they could not fast for >12 h, had gastrointestinal or eating disorders, or had contraindications for MRI scanning, including the presence of a cardiac pacemaker or pacemaker wires, surgical clips, staples, wire sutures, or other metallic fragments in the body. Women were excluded if they were pregnant or lactating. The study protocol was approved by the Columbia University Medical Center Institutional Review Board and all subjects provided informed consent before starting the study.

A total of 12 subjects, 6 men and 6 women (age 29.8 ± 1.8 y, BMI 21.8 ± 0.8 kg/m^2), participated in this study (**Table 1**). All of the subjects reported being healthy and all but one subject (female) had fasted for at least 12 h before scanning. This person had eaten a small piece of brownie >2 h before scanning but reported feeling hungry before scanning and therefore was included in the analyses. Half of the women were tested in the follicular phase of their menstrual cycle; the other half were in the luteal phase.

Study protocol. Subjects were asked to come to the fMRI Research Center of Columbia University (New York, NY) the morning after a 12-h fast. They were instructed not to eat or drink anything but water 12 h before their scheduled scan. Subjects were given instructions about the study, the scanning procedures, and safety issues and were given the opportunity to ask questions regarding the study purpose and protocol before scanning. They were then weighed and measured, with their shoes off, to the nearest 0.2 kg and 0.1 cm, respectively. The imaging studies lasted ~45 min during which time both structural and functional images of each subject's brain were acquired.

TABLE 1

Subject characteristics

Subject	Gender	Age	BMI	Handedness score[1]
		y	*kg/m^2*	*%*
01	Female	38	18.0	95.8
02	Female	25	20.7	87.5
03	Female	28	20.9	79.2
04	Female	22	24.8	54.2
05	Female	30	19.9	91.7
06	Female	28	17.9	66.7
07	Male	33	23.2	72.2
08	Male	30	22.1	100.0
09	Male	24	18.31	58.3
10	Male	45	24.7	100.0
11	Male	27	25.5	91.7
12	Male	28	25.7	58.3

[1] Edinburgh handedness score for the right hand (10).

Experimental design and methods. A 2 × 2 block design with 2 categories of stimuli, foods and nonfoods, and 2 modalities of stimulation, visual and tactile, resulted in 4 conditions. The order of each run was randomly assigned a priori, but was the same for each subject. In each run, the first baseline period consisted of 56 s, the activation period was 48 s, and was followed by the second baseline period (50 s). All conditions, visual food, tactile food, visual nonfood, and tactile nonfood, were run twice, as a block, and each activation period consisted of 12 different food or nonfood items presented at 4-s intervals. During the visual runs, items were placed one at a time in view of the subject via a mirror on the head coil. Food and nonfood items were presented in a clear container and baseline images were acquired during fixation on an empty container. During the tactile runs, subjects were blindfolded and given food or nonfood items to hold in their right hand held to the side of their body. A neutral object was placed in the subject's hand during the baseline image acquisition period. During all scanning procedures, subjects were instructed to passively "pay attention to" the food and nonfood items being presented to them and to remain attentive to the stimuli.

Food and nonfood items (**Table 2**) were selected on the basis of ease of recognition both visually and tactilely and their potential desirability for consumption (in the case of food). Food items included fruits and vegetables, bread products, cheese, and candy. Nonfood items included office supplies, plastic toys and dolls, and personal care products. No food-related objects, such as plastic utensils and paper plates and cups, were presented as nonfood items.

Imaging parameters. Imaging was performed at the fMRI Research Center of Columbia University (New York, NY) on a 1.5-T GE Twinspeed MRI scanner (General Electric) using a standard GE head coil. Three-plane localization was used to verify head position. Head motion was minimized by placing restraint pads around the head and a tape strap across the subject's forehead. Sagittal T1-weighted images were employed to localize anterior and posterior commissures for axial acquisitions of the functional data sets. A single-shot gradient echo planar imaging (EPI) sequence was used with 25 contiguous T2*-weighted axial images (time to echo of 60 ms, time to repetition of 4000 ms, and flip angle of 60°) with a field of view of 190 × 190 mm and matrix size of 128 × 128. In-plane resolution was 1.5 × 1.5 mm, with a slice thickness of 4.5 mm. Seventy-two images were acquired in each condition which lasted 4 min 48 s. T1-weighted images were also collected for every subject along the sagittal plane and along the same plane at which the T2* images were acquired. These high-resolution structural images served as reference images for anatomical labeling.

Image analysis. Image analysis included both group and individual subject analyses. In the case of the individual analyses, preprocessing involved alignment to a single acquisition of the first run using the Woods algorithm (11), and a 2-dimensional Gaussian filter was applied for spatial smoothing. Significant signal changes were identified with a voxel-by-voxel analysis based upon comparison of the mean signal amplitude during the periods of stimulation and the periods of resting baselines as determined by *t* test comparisons using *P*-values of 0.005 corrected for multiple comparisons (12). Voxels are volume elements, the smallest units imaged. Results were displayed on the actual acquisition grid with resolution of 1.5 × 1.5 mm without coregistration to the structural scans. These image analysis techniques were evaluated using conventional direct cortical stimulation and somatosensory evoke potentials and are applied routinely for brain-mapping of critical functions for planning neurosurgical procedures for individual patients (12).

In the case of group analyses, all volumes were corrected for slice timing and spatially realigned to the first volume. A mean image was created from the realigned volumes and coregistered to the structural T1*-weighted volumes. Individual images were spatially normalized to the standardized coordinate space of the Montreal Neurological Institute (MNI) brain template for group comparisons, and resliced to a common unit size of 2 × 2 × 2 mm within stereotaxic space using sinc interpolation (SPM 99, Wellcome Department of Cognitive Neurology). A spatial transformation was then applied to the realigned T2*-weighted volumes and spatially smoothed with a 6-mm full-width half-maximum Gaussian kernel. Signals were convolved with a modeled hemodynamic response function, and the general

TABLE 2

Food and nonfood items used as stimuli

Foods		Nonfoods	
Bagel	Crackers	Bags	Pens
Baguette	Grapes	Candles	Plastic cell phone
Bananas	Gummi bears	Car toy	Ring
Bread	Hershey kisses	Comb	Rubber bands
Broccoli	Lemons	Compact discs	Scarves
Cake	Lollipops	Dice	Scotch tape
Carrots	Muffin	Jump rope	Soap
Celery	Pear	Key	Sponges
Cheese	Potato chips	Marbles	Stuffed animal
Chocolate bar	Pretzels	Matches	Sunglasses
Cookies	Twizzlers	Notepad	Tennis balls
Corn	Wrapped candies	Paper tissue	Toothbrush

linear model was applied to fit the blood oxygen level–dependent response properties.

Advantages for both the single subject and group analysis approaches included confirmation of all reported effects for individual subjects (a fixed-effects model) with the advantages of generalization to a population (a random-effects model). For both single subject and group analyses conjunction across modalities (visual and tactile) was followed by a contrast between foods and nonfoods. This approach yielded brain regions that were more robustly activated by food stimulation than by nonfood stimulation (and vice versa) excluding effects of visual and tactile presentations (**Table 3**). The statistical criterion for a single voxel was set at a conventional level of $P < 0.005$ with a cluster size of at least 10 activated voxels with an uncorrected P-value of < 0.05 using SPM99. MNI coordinates obtained with SPM were translated to Talairach coordinates (13) and the corresponding anatomical regions and Brodmann's Areas were determined using the Talairach Daemon (Research Imaging Center, University of Texas Health Science Center at San Antonio, San Antonio, TX). Error on estimate for Brodmann areas is reflected by including neighboring areas within a cluster.

RESULTS

Group analyses of the conjoined visual and tactile images revealed that the cingulate gyrus, superior temporal gyrus, hippocampus, parahippocampal gyrus, and insula were significantly activated to a greater extent during the presentation of foods compared with nonfoods (**Fig. 1***A*, **Table 4**). This activation was demonstrated in 2 illustrative subjects (**Fig. 2**). Of the brain regions that met group statistical criteria, the cingulate gyrus and insula also met individual statistical criteria ($P \leq 0.005$) in 10 of 12 subjects. Similarly, the superior temporal gyrus, the hippocampus, and parahippocampal gyrus met the same individual statistical criteria in 8 of 12 subjects.

TABLE 3

Analytical protocol

	Visual	Tactile	Computation[1]
Food	A	B	A + B
Nonfood	C	D	C + D
		Final analysis	(A + B) − (C + D)

[1] Activated brain regions common to both visual and tactile foods and common to both visual and tactile nonfoods were isolated. Brain regions that were common to both foods and nonfoods were dismissed. The final analysis represents all brain regions activated by both visual and tactile foods but not by visual and tactile nonfoods. The reverse computation was done to examine brain regions activated by nonfoods but not by foods.

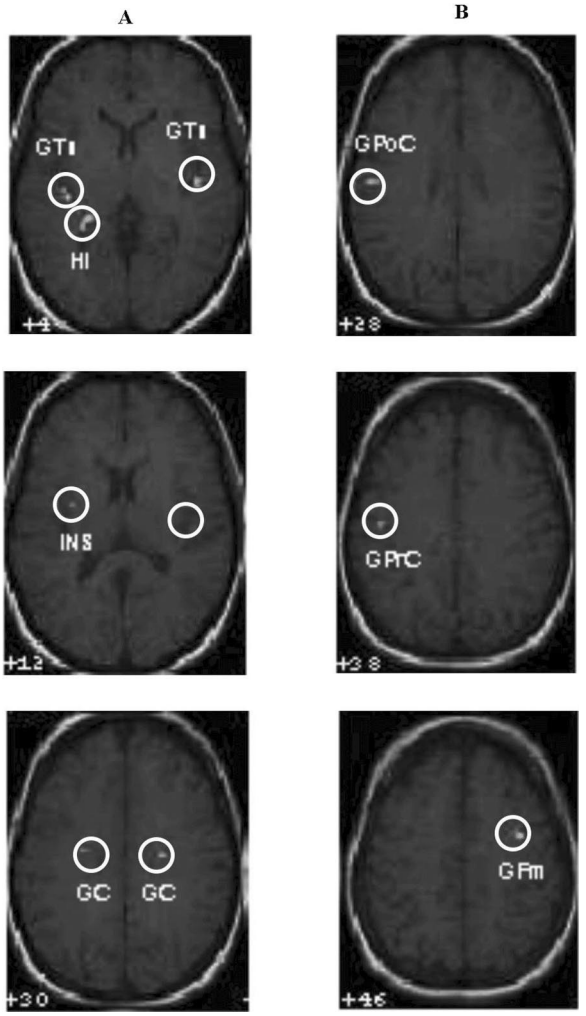

FIGURE 1 Activated brain regions in normal weight men and women (n = 12) when exposed to visual and tactile presentations of food and nonfood items. *Panel A* illustrates activity that was greater when foods were presented than when nonfoods were presented. *Panel B* illustrates the reverse (nonfoods > foods). Brain left is image left. Abbreviations: GC, cingulate gyrus; GFm, middle frontal gyrus; GPrC, precentral gyrus; GPoC, postcentral gyrus; GTs, superior temporal gyrus; Hi, hippocampus/parahippocampal gyrus; INS, insula.

The signal amplitudes of a single voxel located in the insula of a single subject during stimulation with visual foods, visual nonfood objects, tactile foods, and tactile nonfood objects are shown (**Fig. 3**). The amplitude elevations during both visual and tactile food conditions were higher than amplitudes for nonfood conditions. Thus, this signal illustrates the basis for the main findings presented here.

Group-level analyses also revealed brain regions active during exposure to nonfood items, including the middle frontal gyrus and the pre- and postcentral gyri (Fig. 1*B*, **Table 5**). These brain regions were not significantly modulated by food stimuli in most individuals.

DISCUSSION

The results of this study demonstrate that neuronal activity during exposure to food differs from that during exposure to

TABLE 4

Group-level analysis of responses to food stimuli greater than nonfood stimuli, using voxel-level P < 0.005 with cluster size >10 and uncorrected P < 0.05, in normal weight men and women

Anatomical area[1]	Brodmann area[2]	Cluster size	*P*-value uncorrected	Talairach coordinates		
				x[3]	*y*[4]	*z*[5]
GC	32/23	34	0.02	+28	−12	32
Hippocampus/GH		40	0.013	−30	−43	2
GH				−26	−37	6
GTs	22	39	0.014	46	−17	6
Insula		39	0.014	40	−23	3
				44	−16	1
Insula/Caudate		74	0.001	26	−20	19
				20	−26	22
Insula		63	0.003	32	−9	15

[1] Abbreviations: GC, cingulate gyrus; GH, parahippocampal gyrus; GTs, superior temporal gyrus.
[2] Error on estimate for Brodmann areas is reflected by including neighboring areas within a cluster. Brodmann areas were determined using the Talairach Daemon.
[3] Left brain is indicated by − sign. For regions that were bilaterally activated when an individual brain was analyzed, + and − signs were not specified.
[4] (−) indicates posterior to the posterior commissure landmark (13).
[5] All values are above the anterior-posterior commissure line (13).

nonfood items. The use of this cross-modality paradigm (14) allows us to examine brain regions activated by food stimuli irrespective of the sensory systems because only voxels activated in both modalities were included. Thus, these areas can be associated with the cognitive aspects of food-related behaviors such as association, memory, cognitive control, and decision making rather than visual or tactile processing. Subjects were scanned while fasting; thus, they were hungry during the protocol, which may have enhanced the appeal of food-related items. Each of the 5 areas identified in this study relate to these functions: memory (hippocampus and parahippocampus), cognitive control and decision making (cingulate gyrus), association and interpretation (superior temporal gyrus), and food-related interest (insula). The 2 sensory systems employed for the cross-modality protocol, sight and touch, were chosen to present real items (rather than pictures as in the more conventional approach). Both foods and objects could be seen and touched easily while in the scanner without excessive head movement. This technique offers a realistic exposure to the stimulus items, as well as a technique to isolate brain areas involved in higher cognitive processes.

Although fMRI offers many advantages for neuroimaging including high resolution and sensitivity using an endogenous signal without invasive injections of radioactivity, there are some notable disadvantages due to a lack of homogeneous image quality in specific brain regions. In particular, the amygdala and orbital frontal gyrus are frequently located in regions compromised by image susceptibility artifacts (15). A previous study involving PET showed that the amygdala and the medial OFC play a role in the appraisal and selection of highly valued food items (14). Similar results were also found by de Araujo et al. (16) who reported that taste and olfactory inputs converge in the far anterior insular cortex, the caudal OFC, the amygdala, the ventral forebrain, and the anterior cingulate cortex. In this study, we did not consistently observe activity

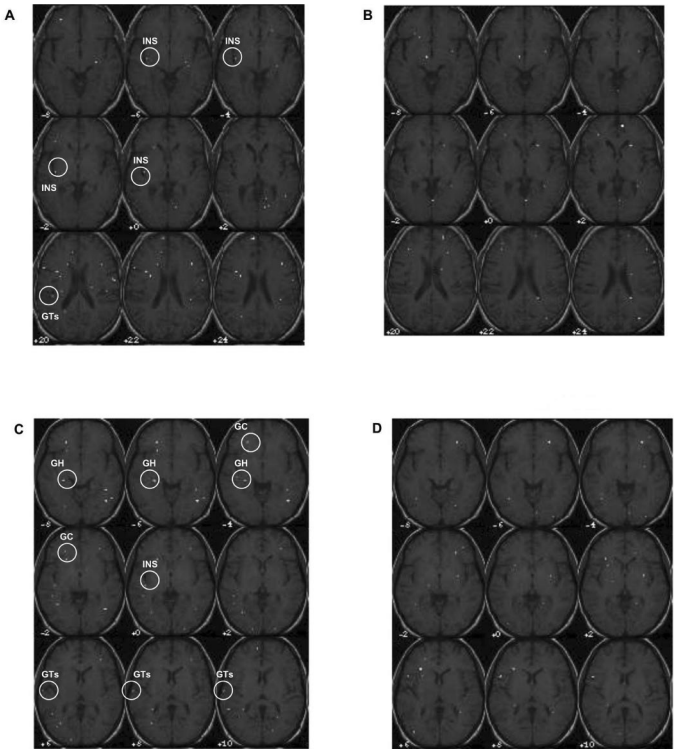

FIGURE 2 Activated brain regions in 2 subjects (#10 and #6) exposed to visual and tactile presentations of food and nonfood items. *Panels A* and *C* illustrate activity that was greater when foods were presented than when nonfoods were presented. *Panels B* and *D* illustrate the reverse (nonfoods > foods). Brain left is image left. Abbreviations: GC, cingulate gyrus; GTs, superior temporal gyrus; GH, hippocampus/parahippocampal gyrus; INS, insula.

in either the amygdala or the OFC in the individual subject or group analyses, possibly due to the locations adjacent to sinuses where the air-water interface creates in-plane distortions

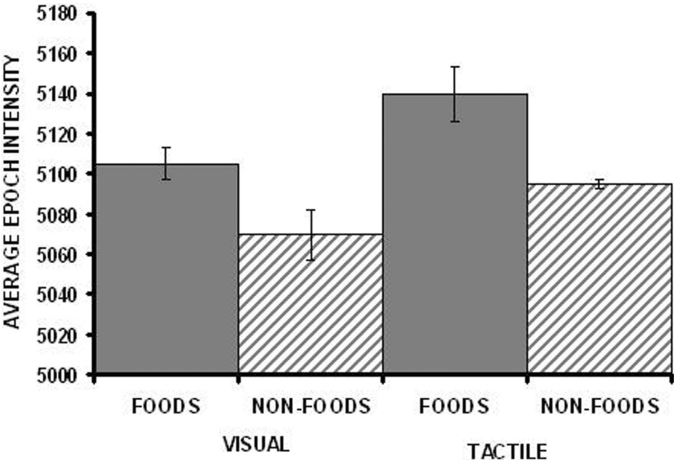

FIGURE 3 Average signal amplitudes of a single voxel (*x*, *y*, *z*: 83, 57, 13) located in the anterior insula of a subject (#12) for each stimulation epoch: visual foods, visual nonfood objects, tactile foods, and tactile nonfood objects. Averages are based on 20 acquisitions (10 per epoch and 2 epochs per condition), and bars indicate the SEM. The intensity scale (*y*-axis) is in the arbitrary units of the scanner. Elevated amplitudes during exposure to the food-related stimuli (visual and tactile) illustrate the basis for the main findings of this study.

TABLE 5

Group-level activated brain region responses to nonfood but not food stimuli, using voxel-level $P < 0.005$ with cluster size >10 and uncorrected $P < 0.05$, in normal weight men and women

Anatomical area[1]	Brodmann area[2]	Cluster size	*P*-value uncorrected	Talairach coordinates		
				x[3]	*y*[4]	*z*[5]
GFm	6	24	0.046	40	2	44
GPoC/GPrC	3	38	0.015	57	−14	28
				48	−14	36
				50	−14	27

[1] Abbreviations: GFm, middle-frontal gyrus; GPoC, postcentral gyrus; GPrC, precentral gyrus.
[2] Error on estimate for Brodmann areas is reflected by including neighboring areas within a cluster. Brodmann areas were determined using Talairach Daemon.
[3] Left brain is indicated by − sign. For regions that were bilaterally activated when an individual brain was analyzed, + and − signs were not specified.
[4] (−) indicates posterior to the posterior commissure landmark (13).
[5] All values are above the anterior-posterior commissure line (13).

of EPI images (15). However, our observations that the cingulate gyrus, superior temporal gyrus, the hippocampus, parahippocampal gyrus, and insula were activated by food to a greater extent than by nonfood stimuli are consistent with previous findings (14), and the cross modal technique not only adds precision to interpretation of the findings by confirming that the responses are food-related rather than general-object or sensory related, but also contributes a no-risk approach for future studies of food-related systems in normal subjects.

All subjects in this study were within normal weight ranges. One study comparing brain activity in response to a liquid meal using PET in normal weight and obese women found differences between the groups in activated brain regions (7). Women were scanned after a 36-h fast and again after consuming a liquid meal providing 50% of their daily energy requirements over a 25-min period. The insular cortex, parahippocampal gyrus, and temporal superior gyrus were among those differentially activated between lean and obese women, further suggesting that these regions are associated with interest in food.

In this study, subjects did not perform a specific task during the scanning procedure. The passive tasks were employed to minimize engagement of other cognitive systems that would be elicited during other tasks such as object naming or discrimination. Subjects were instructed to "pay attention to" the stimuli that they were seeing and touching. However, we did not directly measure their level of attention. Nonetheless, foods and nonfood items were placed into the subjects' hands every 4 s during the tactile period and we assume a constant level of attentiveness during these times. Because the findings observed during the tactile periods were also present during the visual presentations, we can assume that the levels of attentiveness were constant.

Images were analyzed both for individual subjects and as grouped data. These 2 presentations are complementary. Differences between individual and group analyses in areas more strongly activated with food than with nonfood stimuli arise from the differences in methodology. Group brain analyses require registration of images onto one brain template; as a result, individualities in brain structure tend to be lost. However, using group data has the advantage of a larger sample size. Thus, in a group analysis, all findings are not necessarily observed in all subjects. In this study, findings at both the group and individual level are included. This combined approach serves to enhance and clarify conclusions by including individual variability in the findings.

Finally, although our study did not allow us to determine the exact role of each activated brain region in appetite regulation, it did document the unique neuronal substrate associated with the appreciation of foods in fasting subjects. The cross-model paradigms rule out interpretations related to sensory systems and leave open the possibility that these brain areas are involved in emotion, motivation, response selection, and behavioral regulation of food items. Aspects of this circuitry may therefore be involved in the early phases of feeding behavior.

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