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Cortical and limbic activation during viewing of high- versus low-calorie foods

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Abstract

Despite the high prevalence of obesity, eating disorders, and weight-related health problems in modernized cultures, the neural systems regulating human feeding remain poorly understood. Therefore, we applied functional magnetic resonance imaging (fMRI) to study the cerebral responses of 13 healthy normal-weight adult women as they viewed color photographs of food. The motivational salience of the stimuli was manipulated by presenting images from three categories: high-calorie foods, low-calorie foods, and nonedible dining-related utensils. Both food categories were associated with bilateral activation of the amygdala and ventromedial prefrontal cortex. High-calorie foods yielded significant activation within the medial and dorsolateral prefrontal cortex, thalamus, hypothalamus, corpus callosum, and cerebellum. Low-calorie foods yielded smaller regions of focal activation within medial orbitofrontal cortex; primary gustatory/somatosensory cortex; and superior, middle, and medial temporal regions. Findings suggest that the amygdala may be responsive to a general category of biologically relevant stimuli such as food, whereas separate ventromedial prefrontal systems may be activated depending on the perceived reward value or motivational salience of food stimuli.

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Food consumption is one of the most essential human behaviors, yet the factors that regulate eating and dietary choices are complex and poorly understood (Karhunen et al., 2000). Many factors influence a person's motivation to consume or abstain from eating certain foods. Enterceptive cues, which include stomach contractions and other physiological changes, contribute significantly to the experience of hunger or satiation and are associated with specific patterns of regional cerebral blood flow (rCBF), particularly within brain regions commonly implicated in motivation, emotion, memory, and behavioral control (Gautier et al., 2001; Tataranni et al., 1999). The physical characteristics of a food, such as its taste, smell,

texture, and appearance, and the contextual cues within the immediate environment can also significantly influence the motivation to eat. The sensation of taste serves as a primary reinforcer and provides immediate reward or punishment for food consumption (Rolls, 1999). Furthermore, through learning, the visual characteristics of food and associated contextual cues can become rapidly conditioned as secondary reinforcers, which are then capable of influencing future eating-related behavior (Lappalainen and Sjoden, 1992; Rolls, 1999; Wardle, 1990).

Regions within the primate brain, including the orbitofrontal cortex, hypothalamus, and amygdala, have populations of neurons that respond specifically to visual presentations of food (Rolls, 1994). The amygdala appears to be engaged at a relatively early stage of processing, showing consistent responsiveness to visually presented food stimuli (Rolls, 1990, 1999), and specific subregions of the amygdala may play different roles in the control of feeding behavior. For instance, some evidence suggests that the

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central nucleus may be responsible for engaging approach and withdrawal behaviors to potential food sources, whereas the basolateral complex serves to evaluate the current reinforcement value of available food items given the immediate physiological status of the organism and guides response selection among potential food sources (Baxter and Murray, 2002). Anticipation or expectancy of reward is an important component of food-seeking and consummatory behavior (Bateson and Kacelnik, 1995) and helps an organism to alter behavioral strategies to obtain such rewards. The anticipatory physiological changes that occur during exposure to food-related cues are known as cephalic phase responses and serve to prepare the organism to ingest food (Powley, 1977; Powley and Berthoud, 1985). Research with primates suggests that neurons within the dorsolateral prefrontal cortex are selectively activated when a reward is expected following a behavioral response (Watanabe, 1996). The orbitofrontal cortex is also important in food seeking because it is responsive to changes in reward value, thereby permitting flexible behavioral responses in the face of changing reinforcement contingencies (Rolls, 1990; Thorpe, Rolls, and Maddison, 1983). Thus, in primates, the evaluation of a food stimulus for its motivational significance occurs in multiple brain regions, particularly the limbic and prefrontal motivational systems.

In contrast to a large body of research on primates (Rolls, 1994, 1999, 2000), little is known about the regions involved in the appetitive processing of visual presentations of food stimuli in healthy humans. Studies using single-photon emission computed tomography (SPECT) and positron emission tomography (PET) have shown only minor changes in regional cerebral blood flow (rCBF) in normal-weight women in response to visually presented food stimuli, although significant changes in frontal, prefrontal, temporal, and parietal regions have been observed in obese and binge-eating women (Gordon et al., 2000; Karhunen, Lappalainen, Vanninen, Kuikka, and Uusitupa, 1997, 1999; Karhunen et al., 2000). The only published study to use functional magnetic resonance imaging (fMRI) to explore human appetitive function found increased amygdala responsiveness to food stimuli when subjects were hungry but not when satiated (LaBar et al., 2001). As discussed earlier, the motivation to eat is also influenced by qualities intrinsic to the food itself. For food to have survival value (i.e., motivational significance) it must provide the organism with needed energy. No fMRI study of healthy normal-weight individuals has examined the question of how the brain responds to visual presentations of foods that differ in their energy value (i.e., calorie content). In the present study, we presented healthy subjects with color photographs of food stimuli classified as either high or low in calorie content, as well as a control condition of nonedible food-related utensils. We hypothesized that, relative to nonfood stimuli, the perception of food images, regardless of caloric content, would be associated with greater activation within regions of the brain important for reward-guided behavior and the

formation of stimulus–reward associations (Price, 1999), particularly the amygdala, hippocampus, and the orbital and medial prefrontal cortex. It was further hypothesized that high-calorie foods, relative to nonfood or low-calorie food items, would have greater motivational salience and therefore be associated with significantly greater activation of the medial and dorsolateral prefrontal cortices, given the importance of these regions in evaluating the potential outcomes of emotionally relevant behaviors (Reiman, 1997; Reiman et al., 1997) and the expectation and evaluation of reward (Rolls, 1990; Watanabe, 1996, 1998).

Methods

Subjects

Functional neuroimaging data were collected from 13 healthy right-handed female participants with no history of eating disorder, psychiatric diagnoses, or neurologic illness, recruited from the staff of McLean Hospital. Participants ranged in age from 21 to 28 years ($M = 23.5$, $SD = 2.1$) and were within normal limits for body mass ($M = 22.1$, $SD = 2.4$ kg/m²) according to the guidelines suggested by the Department of Health and Human Services Consensus Conference on Obesity (April, 1992). All subjects had normal or corrected-to-normal vision and were unaware of the food-related or dietary nature of the experiment prior to viewing of the stimuli in the scanner. Following the imaging protocol, all subjects were requested to complete a questionnaire regarding their hourly dietary intake over the preceding day. For each subject, two raters independently calculated calorie intake for the 6 h prior to the scan using an internet based resource for determining the caloric content of foods (www.freeweightlosscenter.com), supplemented with other resources as needed. Interrater reliability was high for the calculation of calorie intake (Pearson's $r = .90$) and the mean calorie counts provided by the two raters did not differ significantly [Mean difference = 12.2, $SD = 154.8$ calories; $t(12) = 0.29$, $P = .78$]. The mean of the calorie counts provided by the raters was used to estimate total calorie consumption for each subject. On average, participants consumed 500.6 ($SD = 336.9$) calories during the 6 h prior to the fMRI scan, and no subject consumed any food within the 90 min preceding the scan. Last ingestion of food ranged from 1.6 to 6.8 h prior to the scan ($M = 3.9$, $SD = 1.5$). All subjects were scanned between the times of 1500 and 1900 h to limit possible circadian rhythm effects on hunger.

Imaging methods

Functional imaging data were acquired on a 1.5-T GE LX MRI scanner equipped with a quadrature RF head coil (TR = 3 s, TE = 40 ms, flip angle = 90°). Head motion was minimized by comfortable placement of foam padding around the head and a tape strap across the forehead. Func-

tional images were collected over 20 coronal slices with a 20-cm field of view and a 64×64 acquisition matrix, with an in-plane resolution of $3.125 \times 3.125 \times 7$ mm. Blood oxygen level-dependent (BOLD) activation data were acquired during three 50-scan (i.e., 150 s) runs, each consisting of five alternating 30-s control/task periods. Three dummy images were taken at the outset of each functional scan to reduce non-steady-state effects. Matched T1-weighted high-resolution images were also collected for every subject at the beginning of the scanning session.

Stimulation paradigms

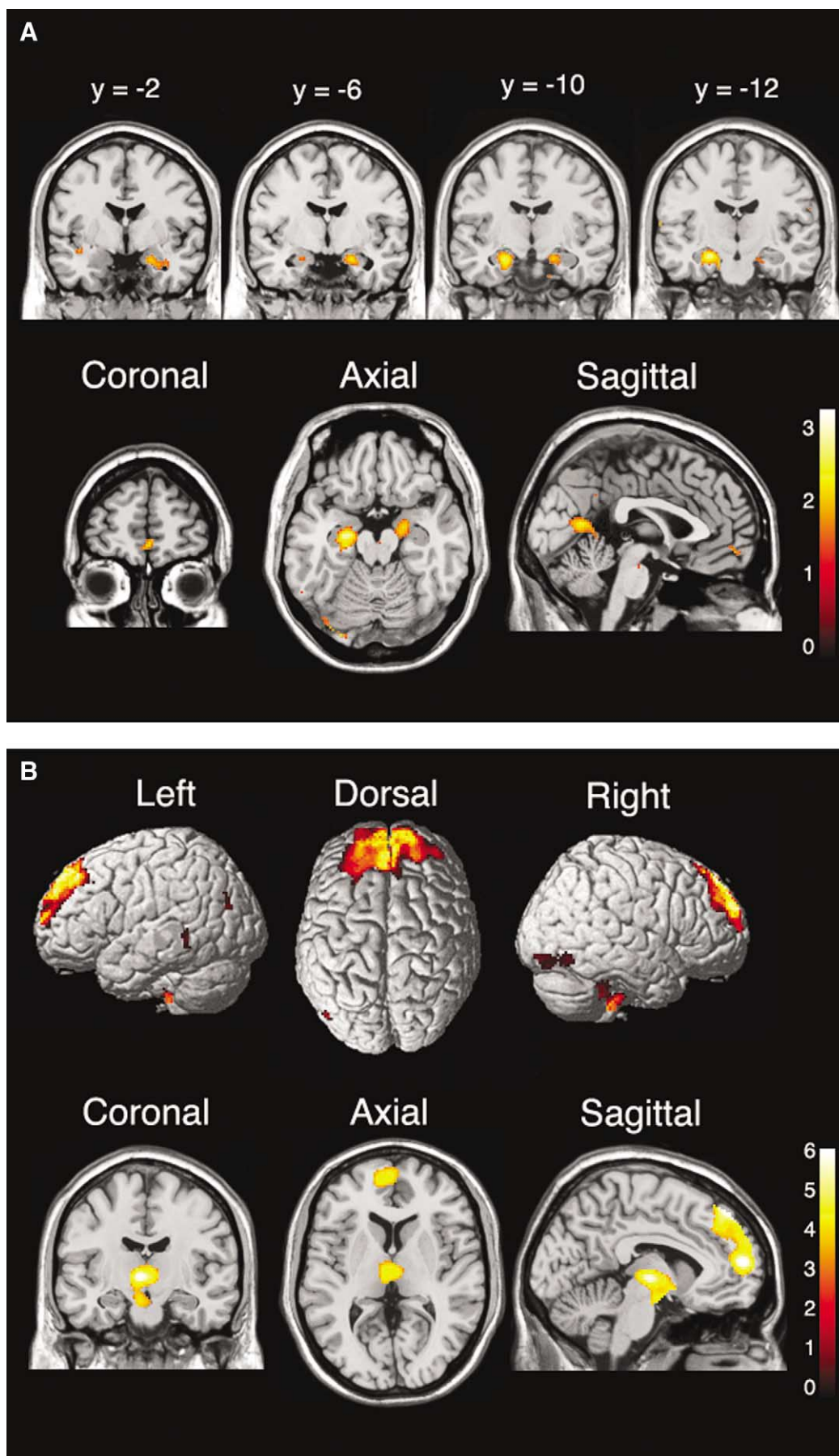
Three visual activation tasks were presented over separate scanning runs: (1) low-calorie foods, (2) high-calorie foods, and (3) nonedible food-related utensils. The order of presentation of the three tasks was counterbalanced across subjects. All stimuli were professional quality full-color photographs obtained from commercial stock photography Web sites. Low-calorie photographs included images depicting freshly prepared garden salads, whole-grain cereals, fresh vegetables, and fruits. High-calorie photographs included images such as french fries, ice cream sundaes, cheeseburgers, hot dogs, chocolate chip cookies, barbecued chicken, strawberry shortcake, and pasta with meat sauce. A third task depicted food-related utensils, such as colorful photographs of forks and spoons, dishes, placemats, chopsticks, and tableware, with no edible items present in the picture. Each of these paradigms lasted for 150 sec, consisting of two 30-sec stimulation periods, which alternated with three control blocks of equal duration. Control block images consisted of photographs of visually interesting objects that are generally not consumed as food in modern western cultures (e.g., rocks, shrubs, bricks, trees, and flowers). These photographs were selected as control stimuli because they required similar complex visual object analysis and were similar to the food stimuli in the variety of colors, textures, and shapes presented. Ten photographs were presented per block (2500-ms stimulus presentation with a 500-ms interstimulus interval). The stimuli were presented from a Macintosh computer using the Psyscope software program (Macwhinney, Cohen, and Provost, 1997) and were back-projected onto a screen placed at the foot of the scanning bed. The stimuli were easily viewed via a mirror mounted on the head coil. Participants were instructed to view each series of photographs and to try to remember them for a recognition test upon completion of the scanning session. Subjects were not informed of the food-related content of the photographs. Following completion of the imaging protocol, subjects exited the scanner room and immediately completed three postscan recognition tests on a personal computer. Each recognition test presented all 20 of the previously seen category specific photographs (i.e., low-calorie foods, high-calorie foods, or nonfood utensils) randomly intermixed with 20 novel distractor photographs from the same task category. Subjects

made a key-press response indicating whether each photograph had been seen previously (old) or had not been seen in the scanner (new). The percentage correct, including correct identifications and correct rejections, was calculated for each subject.

Each of the stimulus photographs was rated on an 11-point scale for motivational salience [i.e., subjects were asked to “please rate how each photo affects your appetite according to the following scale.” Scores had a potential range from -5 (highly aversive) to $+5$ (highly appealing)]. Ratings were available for a subset of the total sample ($n = 9$). These data clearly showed that the high-calorie foods ($M = 2.58$, $SD = 1.32$) were rated as significantly more appealing than the low-calorie foods ($M = 1.65$, $SD = 1.46$), dining utensils ($M = 0.43$, $SD = 0.68$), or control stimuli [$M = -0.34$, $SD = 0.69$; $F(3, 24) = 21.21$, $p < .0001$]. Moreover, Bonferroni-corrected multiple comparison tests revealed that high-calorie food pictures were rated as significantly more “appealing” than low-calorie foods across individual subjects ($t = 2.34$, $P < .05$). The construct of “motivational salience” was, therefore, defined operationally by the objective ratings of the appetitive appeal of the food categories.

Image processing and analysis

Functional images were corrected for motion in SPM99 using an intrarun realignment algorithm that uses the first image as a reference. Head motion exceeding 1 mm in any direction was used as an exclusionary criterion. No subject had motion exceeding this threshold in the present study. BOLD fMRI data were convolved into three-dimensional space and smoothed using an isotropic gaussian kernel. Given our interest in examining large regions, such as the prefrontal cortex, and the fact that our voxels were nonisotropic with a 7-mm thickness in the z axis, we chose to use a relatively large smoothing kernel [full width half maximum (FWHM) = 10 mm]. Images were resliced to $2 \times 2 \times 2$ mm within stereotaxic space using sinc interpolation. A statistical parametric map was generated for each subject using the general linear model within SPM99 (Friston et al., 1995a,b) with a 6-sec time-shifted box-car waveform employed as the reference paradigm. Employing a fixed-effects approach, group SPM contrast maps were created to determine the mean suprathreshold activation for the low-calorie food, high-calorie food, and utensil conditions relative to the control conditions. The SPM $\{t\}$ maps were displayed on an average template brain in the standardized coordinate space of the Montreal Neurological Institute (MNI) within SPM99. A conjunction analysis was performed to determine the regions that were significantly activated during both the high- and low-calorie conditions. Linear contrasts were then conducted between the low-calorie and high-calorie conditions, using masks created during the initial group maps, to isolate the cerebral regions that were uniquely involved in processing foods of differing energy value. To reduce Type I error, the group SPMs and all contrasts



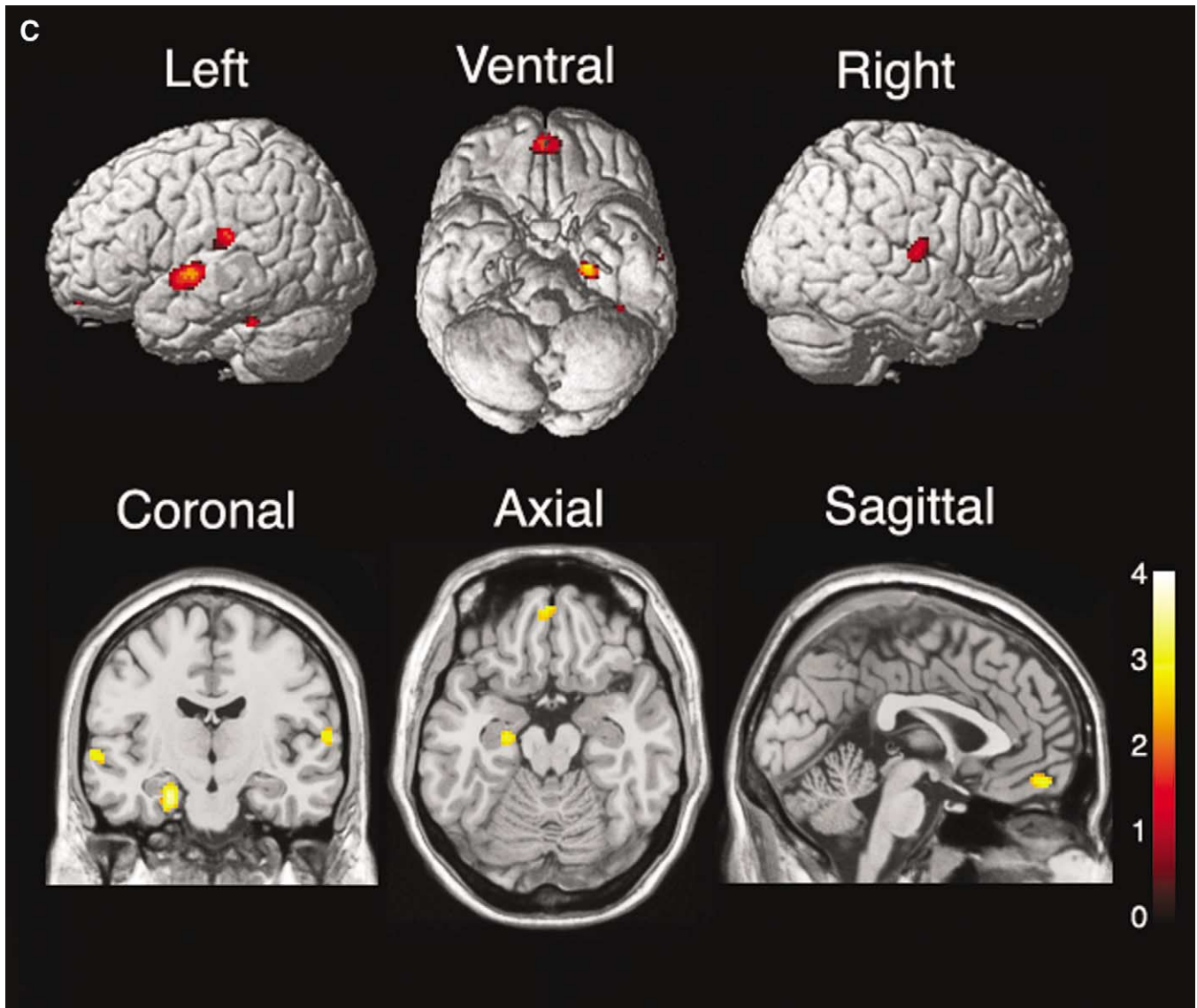


Fig. 1 (continued)

were set to an *a priori* threshold of $P < .005$, uncorrected, with a minimum cluster-size threshold set at 20 contiguous voxels.

Results

Behavioral performance data

The mean percentage of items correctly recognized during the posttest was significantly above chance for the low-calorie

($M = 84.0$, $SD = 8.4\%$; $t_{12} = 14.5$, $P < .001$), high-calorie ($M = 86.0$, $SD = 10.7\%$; $t_{12} = 12.1$, $P < .001$), and utensil conditions ($M = 86.2$, $SD = 6.6\%$; $t_{12} = 19.8$, $P < .001$), indicating that the subjects were effectively attentive and engaged in all three tasks during scanning. A repeated-measures analysis of variance (ANOVA) on the recognition scores indicated no significant difference in the memory performances for the three tasks [$F(2, 24) = 0.25$, $P = .78$], suggesting that the difficulty level of the paradigms was similar.

Fig. 1. Group statistical parametric maps of activated regions during presentation of food stimuli differing in calorie value (all images are in neurological orientation, i.e., right = right and left = left; the color bar at the right of each figure reflects the suprathreshold value of the SPM{t} statistic for the analysis). (a) Conjunction analysis shows the regions of suprathreshold ($P < .005$, uncorrected) activation in common for both high- and low-calorie food perception, including bilateral amygdala, anterior hippocampus, and medial prefrontal cortex. (b) A direct contrast between high-calorie foods and the control stimuli yielded significant activation ($P < .0005$, uncorrected) within the dorsolateral and medial prefrontal cortex, thalamus, and hypothalamus. (c) When low-calorie foods were directly contrasted with the control condition, regions of significant activation ($P < .005$, uncorrected) were observed along the superior temporal gyrus, postcentral gyrus, parahippocampal gyrus, and orbitofrontal gyrus.

Table 1

Foci of maximally activated brain regions surviving low-calorie and high-calorie conjunction analysis

Regions of activation	Brodmann's area	x	y	z	z score
L. Insula		-38	1	-10	3.17
L. Amygdala/hippocampus		-22	-12	-15	4.14
L. Post-central gyrus	40	-63	-23	16	4.80*
L. Cerebellum		-34	-36	-22	3.50
L. Fusiform gyrus		-44	-47	-16	3.26
L. Inferior occipital gyrus	18	-26	-86	-14	3.78
R. Medial frontal gyrus	10	4	54	-8	3.37
R. Amygdala		22	-5	-17	3.42
R. Transverse temporal gyrus	42	61	-17	12	3.00
R. Superior temporal gyrus	21	61	-48	10	4.02
R. Precuneus	7	4	-51	36	2.83
R. Posterior cingulate	23	2	-60	14	3.63

Note. L, left hemisphere. R, right hemisphere. Atlas coordinates are from the standard atlas of Talairach and Tournoux (1988), such that *x* reflects the distance (in millimeters) to the right or left of midline, *y* reflects the distance anterior or posterior to the anterior commissure, and *z* reflects the distance superior or inferior to the horizontal plane through the AC–PC line. Only regions with *z* scores significant beyond $P < .005$ (uncorrected) are reported.

* *P* values with an asterisk (*) reflect voxels that survived whole-brain correction for multiple comparisons ($P < .05$).

Neuroimaging data

High-calorie and low-calorie conjunction analysis

We first determined which cerebral regions were activated in response to presentations of food stimuli relative to control stimuli, regardless of the calorie content. To test for regions common to high- and low-calorie foods, the two experimental conditions were entered into a conjunction analysis using SPM99, with the significance threshold set at $P < .005$ (uncorrected) and a minimal spatial extent of 20 contiguous voxels. As evident in Fig. 1a, the regions activated in common by the two categories of food stimuli included bilateral amygdala/hippocampus, left insula, right inferior medial prefrontal cortex, and posterior cingulate, as well as several other regions that were not hypothesized but which are listed in Table 1 for completeness and to obviate bias in reporting. The tables present data for uncorrected activations reaching the *a priori* threshold ($P < .005$ or $P < .0005$), as well as indicating those values that remained significant even following whole-brain statistical correction for multiple comparisons at $P < .05$.

High-calorie food condition

We evaluated the activation maps produced by each condition separately. As evident in Fig. 1b, the perception of high-calorie food stimuli (e.g., french fries and ice cream) relative to the control condition (e.g., rocks and flowers) resulted in significant activation across a distributed network of cortical and subcortical regions often implicated in attention, motivation, emotional experience, and the inhibition of emotion. Due to the large spatial extent of activation

evident during the high-calorie condition at our *a priori* threshold of $P < .005$, we chose a more conservative post hoc threshold of $P < .0005$ (uncorrected). With this threshold, the high-calorie food condition yielded extensive activation of bilateral regions of medial and dorsolateral prefrontal cortex, including the medial, superior, and middle prefrontal gyri. Significant bilateral regions of activation were also evident in the medial dorsal thalamus, hypothalamus, corpus callosum, and the cerebellum. Table 2 lists the foci of maximal activation for the entire brain during the high-calorie perception condition.

Low-calorie food condition

Relative to blocks of nonfood control stimuli (e.g., rocks and flowers), presentation of photographs of low-calorie foods (e.g., salads and cereal) yielded significant ($P < .005$, uncorrected) activation in regions commonly described as primary gustatory cortex, including the bilateral superior and transverse temporal gyri, and inferior left hemisphere somatosensory cortex (see Fig. 1c). There was also a significant region of activation within the inferior medial prefrontal/orbitofrontal cortex and the left parahippocampal gyrus. Table 3 lists the local maxima and atlas coordinates for activated regions during the low-calorie food condition.

Food-related utensil condition

To provide a complex visual stimulation comparison condition, subjects were exposed to blocks of photographs

Table 2

Foci of maximally activated brain regions in response to high-calorie foods

Regions of activation	Brodmann's area	x	y	z	z score
L. Superior frontal gyrus	8	-24	41	40	5.61*
L. Amygdala		-20	-1	-20	3.81
L. Parahippocampal gyrus		-36	-3	-18	3.66
L. Thalamus		-4	-12	1	5.45*
L. Middle temporal gyrus	21	-63	-43	0	3.58
L. Middle temporal gyrus		-48	-75	24	3.85
M. Corpus callosum		2	11	16	4.51*
M. Cerebellum		0	-77	-31	4.20
R. Brainstem		8	-29	-41	4.53*
R. Cerebellum		40	-42	-28	4.06
R. Middle occipital gyrus	37	51	-66	-7	4.33

Note. L, left hemisphere; M, midline; R, right hemisphere. Atlas coordinates are from the standard atlas of Talairach and Tournoux (1988), such that *x* reflects the distance (in millimeters) to the right or left of midline, *y* reflects the distance anterior or posterior to the anterior commissure, and *z* reflects the distance superior or inferior to the horizontal plane through the AC–PC line. Only regions with *z* scores significant beyond $P < .0005$ (uncorrected) are reported.

* *P* values with an asterisk (*) reflect voxels that survived whole-brain correction for multiple comparisons ($P < .05$).

Table 3

Foci of maximally activated brain regions in response to low-calorie foods

Regions of activation	Brodman's area	x	y	z	z score
L. Superior temporal gyrus	21	-61	-6	-1	3.89
L. Parahippocampal gyrus	28	-22	-17	-19	3.63
L. Post-central gyrus	40	-63	-24	18	3.22
L. Anterior cerebellum		-38	-40	-22	3.37
L. Lingual gyrus		-18	-72	-5	3.10
M. Orbitofrontal gyrus	11	0	52	-16	3.07
R. Transverse temporal gyrus		65	-9	10	3.34

Note. L, left hemisphere; M, midline; R, right hemisphere. Atlas coordinates are from the standard atlas of Talairach and Tournoux (1988), such that *x* reflects the distance (in millimeters) to the right or left of midline, *y* reflects the distance anterior or posterior to the anterior commissure, and *z* reflects the distance superior or inferior to the horizontal plane through the AC–PC line. Only regions with *z* scores significant beyond $P < .005$ (uncorrected) are reported. No voxels in this analysis survived whole-brain correction for multiple comparisons ($P < .05$).

of common dining-related utensils (e.g., dishes and forks) that alternated with blocks of the nonfood control stimuli (e.g., rocks and flowers). This paradigm was expected to elicit activation of brain regions associated with visual processing of utilitarian objects commonly associated with eating, while avoiding motivationally significant activation that would be expected for actual food stimuli. As shown in Fig. 2a, relative to the control condition, visual perception of the utensils yielded significant ($P < .005$, uncorrected) activation in lateral visual processing areas, including large bilateral activations in the middle and inferior occipital gyri and smaller regions of activation within the right cerebellum and bilateral anterior prefrontal cortex (see Table 4).

Subtraction analyses

To determine the unique patterns of activation produced by each calorie condition relative to the other, the high-calorie and low-calorie conditions were subjected to two contrasting subtraction analyses in SPM99. Each analysis was masked using the regions of suprathreshold activation obtained from the initial group maps (i.e., high-calorie – low-calorie subtraction masked to include only voxels that were active during the high-calorie condition). For the high-calorie – low-calorie subtraction, Fig. 2b shows that the resulting activation map was quite similar to that found for the high-calorie vs. control contrast discussed earlier and shown in Fig. 1b. Relative to low-calorie foods, high-calorie food pictures yielded significantly ($P < .005$, uncorrected) greater BOLD signal change in medial and dorsolateral prefrontal cortex bilaterally and significantly greater bilateral activation within the thalamus. Lateralized activation was evident in the cerebellum, medulla, and middle occipital gyrus on the right. Table 5 presents the foci of greatest activation for the suprathreshold regions during the high-to-low subtraction. Conversely, to determine the regions that were uniquely activated in response to the low-calorie

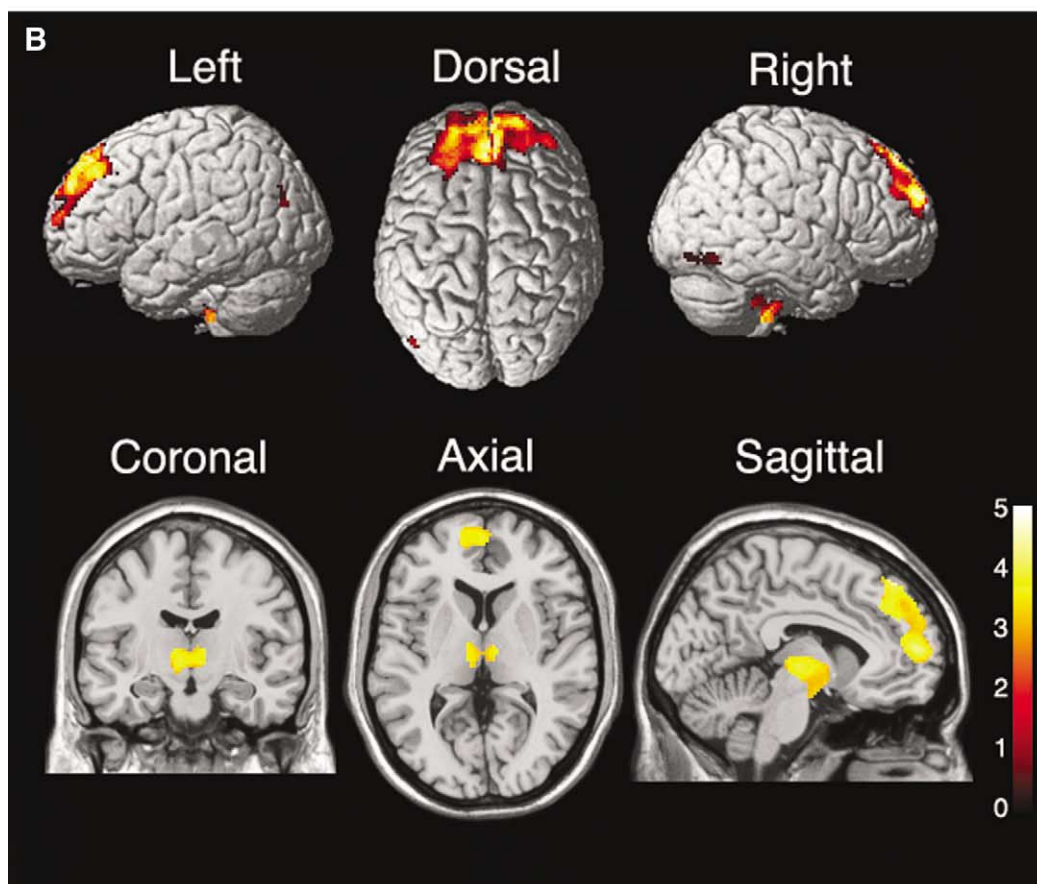
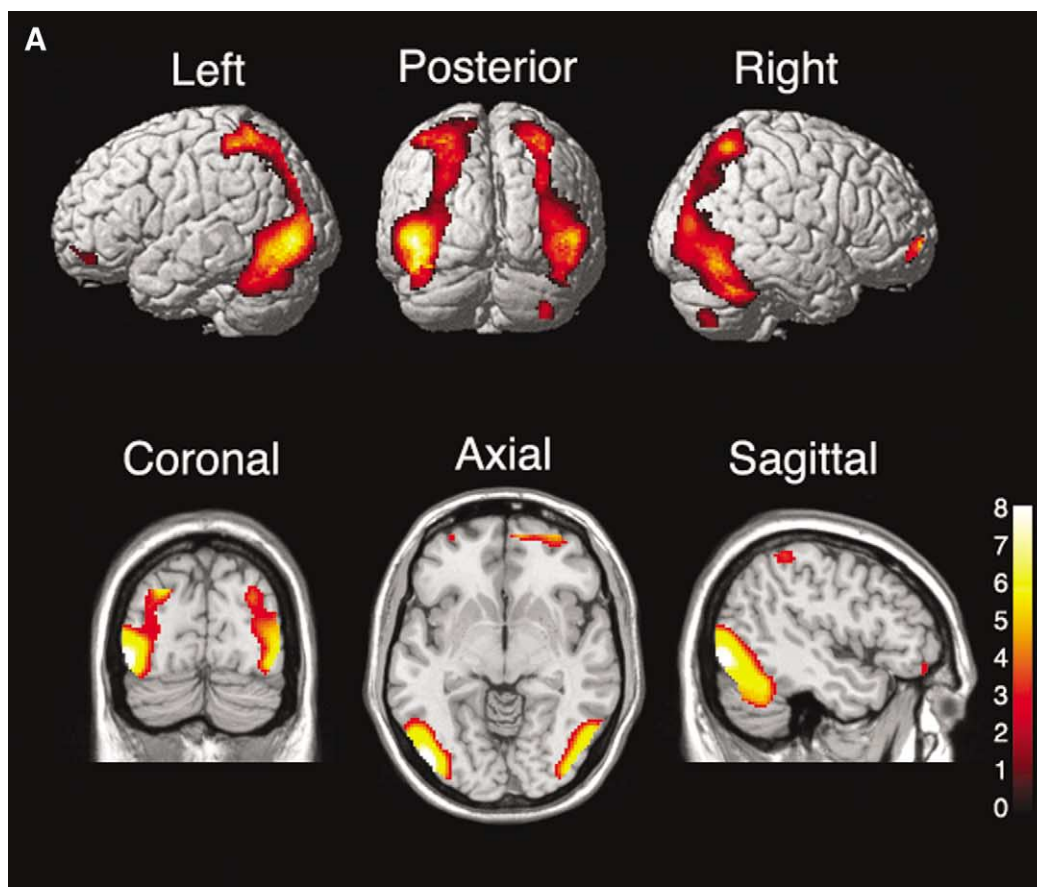
foods relative to the high-calorie foods, a low-calorie – high-calorie subtraction analysis was undertaken, again masking the activation map to include only those regions previously observed as active during the low-calorie condition. Figure 2c shows bilateral activation within inferior medial prefrontal/orbitofrontal cortex and left lateralized activation within the left lingual gyrus and the left middle temporal gyrus (see Table 6).

Discussion

In this fMRI investigation, several brain regions were activated consistently across all food conditions, regardless of caloric content, whereas other regions responded specifically to the caloric content of the food items. To our knowledge, this is the first reported fMRI study in healthy individuals to examine how the brain responds to the visual presentation of foods that differ according to caloric content and presumably, therefore, in motivational salience. Whereas a previous fMRI study manipulated the internal motivational state (i.e., hunger) of subjects while holding the stimulus value (i.e., food images) constant (LaBar, Gitelman, Parrish et al., 2001), the present study manipulated caloric content of the food images without manipulating the internal physiological state of the subject.

Nonspecific food activation

As shown in Fig. 1a, the amygdala, hippocampus, perirhinal cortex, and a small region of ventromedial prefrontal cortex were significantly more active across both food conditions relative to the control condition, regardless of the energy value of the foods. These findings are consistent with studies in primates that suggest that the amygdala and the ventral prefrontal cortex, especially the orbitofrontal regions, are important to the visual evaluation of food stimuli (Rolls, 1984, 1999; Wilson and Rolls, 1993). Rolls has suggested that the amygdala contributes to early stages of visual processing by evaluating novel stimuli to determine their value as reinforcers and potential as food sources (Rolls, 1992, 1999). The amygdala, however, does not appear to respond to rewarding stimuli specifically but appears rather to activate in response to a broad range of biologically relevant stimuli, presumably to facilitate associative conditioning of stimulus–reinforcement relationships (Rolls, 1999). Although it is difficult to classify subnuclei of the amygdala due to the limited spatial resolution and inherent error associated with spatial normalization, the observed stereotaxic coordinates are suggestive of activation within the basolateral complex. This is potentially important, as the basolateral complex of the amygdala appears to be important for evaluating the immediate reward value of objects in relation to the current needs of the organism (Baxter and Murray, 2002). Further research with higher resolution techniques will be necessary to verify which subnuclei are actually involved.



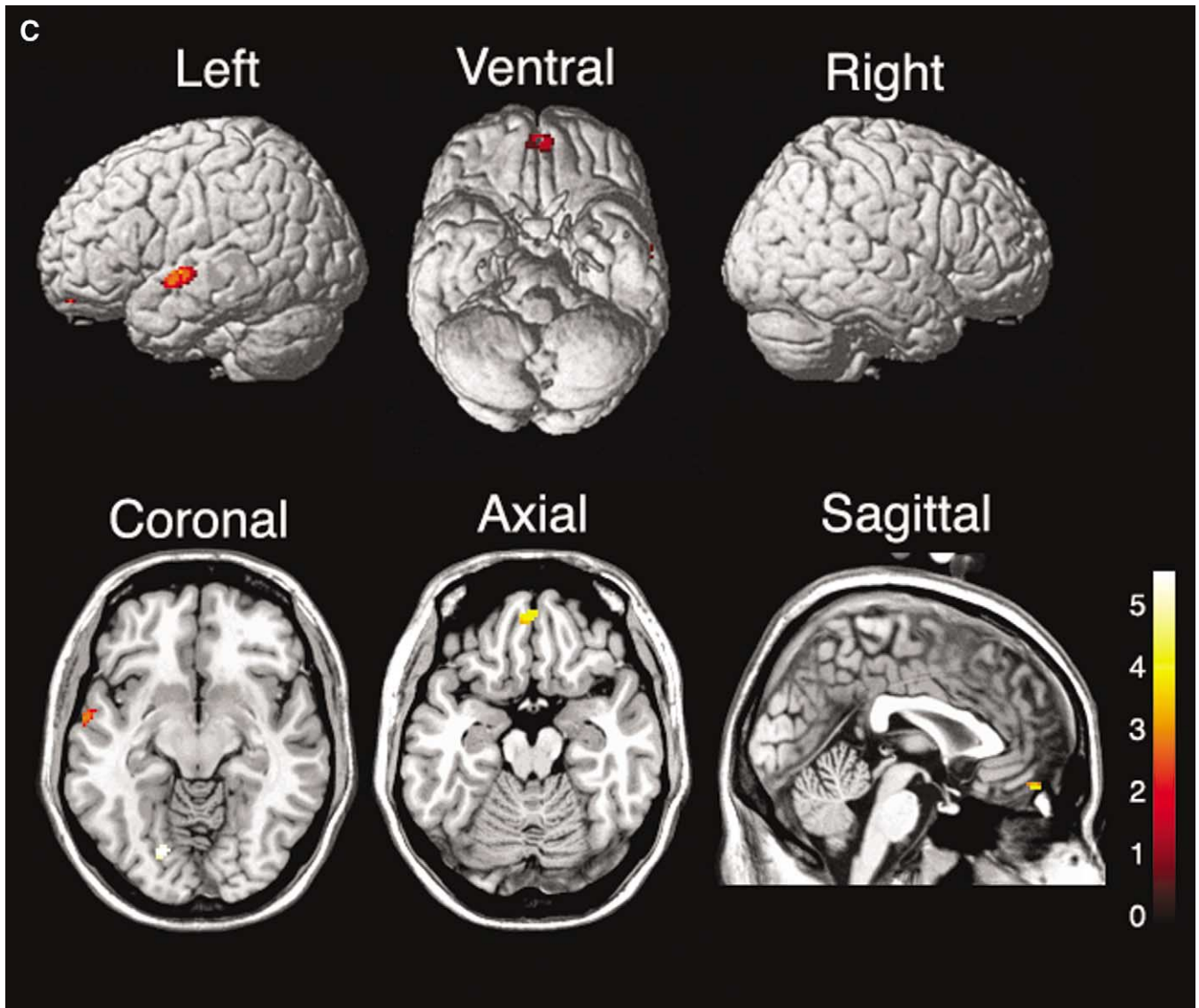


Fig. 2 (continued)

Calorie specific activation

In contrast to the general responsiveness of the amygdala/hippocampal region to both classes of food stimuli, we found several brain regions that were differentially activated by the calorie content of the stimuli. Visual presentations of high- and low-calorie foods were each associated with different patterns of regional activation. Visual presentation of high-calorie foods yielded significantly greater BOLD signal change than presentation of visually similar low-calorie

foods across a distributed network of brain regions involved in emotion, motivation, response selection, and behavioral regulation. Specifically, high-calorie food stimuli were associated with significant clusters of activation within the medial and dorsolateral prefrontal cortex, as well as medial dorsal thalamus, hypothalamus, corpus callosum, and cerebellum. Given the similarity in visual appearance between the high- and low-calorie food stimuli, the differential responsiveness of limbic and prefrontal regions to the two

Fig. 2. Group statistical parametric maps of significantly activated regions ($P < .005$, uncorrected) during the control condition and the masked subtraction analyses (all images are in neurological orientation, i.e., right = right and left = left; the color bar at the right of each figure reflects the suprathreshold value of the SPM {t} statistic for the analysis). (a) A direct contrast between the nonedible utensil condition and the control condition yielded significant activation within visual object processing areas including the middle and inferior occipital gyri, and some small areas within the inferior prefrontal cortex. (b) Subtraction of the low-calorie contrast from the high-calorie contrast (i.e., high – low) yielded significant activation within dorsolateral and medial prefrontal cortex, bilateral thalamus, hypothalamus, corpus callosum, brainstem, and cerebellum. (c) Subtraction of the high-calorie contrast from the low-calorie contrast (i.e., low – high) yielded significant activation within the left lingual gyrus, left middle temporal gyrus, and a small region of orbitofrontal cortex.

Table 4

Foci of maximally activated brain regions in response to food-related utensils

Regions of activation	Brodman's area	x	y	z	z score
L. Middle frontal gyrus	11	-42	50	-14	3.37
L. Inferior occipital gyrus		-46	-78	-1	>8.00*
R. Medial frontal gyrus		12	60	-6	5.22*
R. Middle occipital gyrus		53	-66	-3	6.28*
R. Posterior cerebellum		36	-70	-39	3.45

Note. L, left hemisphere; R, right hemisphere. Atlas coordinates are from the standard atlas of Talairach and Tournoux (1988), such that *x* reflects the distance (in millimeters) to the right or left of midline, *y* reflects the distance anterior or posterior to the anterior commissure, and *z* reflects the distance superior or inferior to the horizontal plane through the AC–PC line. Only regions with *z* scores significant beyond $P < .005$ (uncorrected) are reported.

* *P* values with an asterisk (*) reflect voxels that survived whole-brain correction for multiple comparisons ($P < .05$).

food conditions suggests a differential activation of conditioned cephalic phase responses, due presumably to prior conditioning histories with each class of food items (Powley, 1977; Powley and Berthoud, 1985).

There are at least two separable neural systems within the prefrontal cortex, the orbitofrontal and medial prefrontal systems, which each contribute to feeding, guidance of complex goal-directed behavior, and the control of mood and affect (Ongur and Price, 2000; Price, 1999). Consistent with the primary reinforcing nature of food, visual presentations of food stimuli with high energy content and reward value were associated with increased activation of the medial prefrontal cortex, medial dorsal thalamus, and hypo-

Table 5

Foci of maximally activated brain regions during a cognitive subtraction of low-calorie activation from high-calorie activation (i.e., high – low)

Regions of activation	Brodman's area	x	y	z	z score
L. Superior frontal gyrus		-26	52	29	4.82*
L. Thalamus		-6	-16	1	3.78
L. Middle temporal gyrus		-46	-76	24	3.93
R. Medulla		2	-33	-40	3.84
R. Posterior cerebellum		32	-42	-33	3.68
R. Middle occipital gyrus		50	-68	-7	3.53
R. Cerebellum		2	-75	-33	3.18

Note. Regions are masked to include only voxels exceeding threshold in the high calorie analysis. L, left hemisphere; R, right hemisphere. Atlas coordinates are from the standard atlas of Talairach and Tournoux (1988), such that *x* reflects the distance (in millimeters) to the right or left of midline, *y* reflects the distance anterior or posterior to the anterior commissure, and *z* reflects the distance superior or inferior to the horizontal plane through the AC–PC line. Only regions with *z* scores significant beyond $P < .005$ (uncorrected) are reported.

* *P* values with an asterisk (*) reflect voxels that survived whole-brain correction for multiple comparisons ($P < .05$).

Table 6

Foci of maximally activated brain regions during a cognitive subtraction of high-calorie activation from low-calorie activation (i.e., low – high)

Regions of activation	Brodman's area	x	y	z	z Score
L. Middle temporal gyrus		-57	-2	-7	3.31
L. Lingual gyrus		-18	-72	-5	5.47*
R. Medial frontal gyrus	11	4	52	-18	3.58

Note. Regions are masked to include only voxels exceeding threshold in the Low Calorie analysis. L, left hemisphere; R, right hemisphere. Atlas coordinates are from the standard atlas of Talairach and Tournoux (1988), such that *x* reflects the distance (mm) to the right or left of midline, *y* reflects the distance anterior or posterior to the anterior commissure, and *z* reflects the distance superior or inferior to the horizontal plane through the AC–PC line. Only regions with *z* scores significant beyond $P < .005$ (uncorrected) are reported.

* *P* values with an asterisk (*) reflect voxels that survived whole-brain correction for multiple comparisons ($P < .05$).

thalamus. These findings are consistent with models that posit a medial prefrontal network that receives afferent projections from the medial dorsal nucleus of the thalamus and influences autonomic and endocrine function via efferent projections to the hypothalamus and brainstem (Price, 1999). Other neuroimaging studies have demonstrated activation of the anterior medial prefrontal cortex when individuals make evaluative judgments (Zysset, Huber, Ferstl, and von Cramon, 2002) and during self-referential cognition (Gusnard, Akbudak, Shulman, and Raichle, 2001; Lane, Fink, Chau, and Dolan, 1997). The present activation patterns are consistent with the medial prefrontal activity found in these other studies, suggesting that visual images of high calorie foods yield activation in cortical regions important for evaluating the potential biological relevance of the stimulus and current affective state and needs of the individual.

High-calorie foods also yielded significant activation within adjacent dorsolateral prefrontal cortex, consistent with evidence implicating this region in the anticipation of reward and monitoring of behavioral consequences (Critchley, Mathias, and Dolan, 2001; Watanabe, 1996). Surprisingly, we observed no activation within the vicinity of the corpus striatum during the high-calorie condition. This is inconsistent with the model of the medial prefrontal network thought to mediate motivated or appetitive behavior, which is hypothesized to include the ventromedial caudate and putamen in addition to the aforementioned medial prefrontal, diencephalic, and brainstem structures (Ongur and Price, 2000). It is possible that the lack of striatum activation may have been due to the artificial circumstances posed by the scanning environment and lack of access to the actual food stimuli, which may have lead to behavioral inhibition. Specifically, one function of the medial prefrontal system appears to be the inhibition of unrewarded or inappropriate behavioral responses (Price, 1999; Reiman et al., 1997), and the prefrontal cortex is believed to operate as a feeding-suppressor under some circumstances (Nozoe et al., 1995).

It is possible that some of the activation observed in medial and dorsolateral prefrontal cortex in the present study may have also operated to inhibit activation within striatum and motor cortex given the context of viewing photographs of food stimuli in the MRI scanner, an environment where behavioral responses were clearly inappropriate and were unlikely to lead to immediate goal attainment or reward satisfaction. In fact, it is possible that the greater prefrontal activation in response to high-calorie relative to low-calorie foods may have been due to inhibitory processes in response to the general belief that high-calorie foods are unhealthy or should be avoided. This would be consistent with studies showing prefrontal activation during inhibitory (e.g., no/no-go) tasks (Liddle, Kiehl, and Smith, 2001) and the position that prefrontal activation may be involved in the inhibition of food intake (Del Parigi et al., 2002).

Interestingly, presentation of low-calorie foods yielded a pattern of cerebral activation that was clearly distinct from that of the high-calorie foods. Most notably, low-calorie foods activated the superior temporal gyri bilaterally and the somatosensory cortex and parahippocampal gyrus on the left, as well as a region of the ventromedial orbitofrontal cortex that was not active during high-calorie food perception. The orbitofrontal cortex has been shown to respond to visual presentations of food stimuli in primates and is believed to be important as a convergence zone for visual, olfactory, and taste representations as well as for its role in evaluating the reward value of food stimuli (Critchley and Rolls, 1996; Rolls, 1994, 1999, 2000). Furthermore, the orbitofrontal cortex receives afferent input from a variety of visual, somatosensory, gustatory, and olfactory nuclei in addition to receiving direct innervation from limbic regions such as the amygdala and surrounding cortex (Ongur and Price, 2000; Price, 1999). Several of these regions were activated simultaneously in conjunction with the orbitofrontal cortex during the low-calorie condition. It is evident from the low-calorie versus control contrast in Fig. 1c and the low-calorie – high-calorie subtraction in Fig. 2c that low-calorie foods were associated with significant activation in several somatosensory regions, particularly those associated with gustatory cortex, including inferior postcentral and superior temporal gyri, as well as perirhinal cortex. As it has been shown that the orbitofrontal cortex is richly interconnected with the limbic system, particularly the amygdala and perirhinal cortex; this network may serve to integrate affective, visceral, and primary sensory information (Price, 1999). Furthermore, these regions appear to be activated during actual taste stimulation, although discrete areas within these regions may be activated differentially to pleasant and unpleasant tastes (O'Doherty, Rolls, Francis, Bowtell, and McGlone, 2001). Our findings suggest that visual presentation of low-calorie food activates this visceral/sensory processing system to a greater extent than similar presentations of high-calorie foods. It is possible that the relatively lower reward value of the low-calorie foods compared to the high-calorie foods may have yielded less ef-

fective classical conditioning of cephalic phase responses to these stimuli throughout a lifetime of encountering such foods, thus reducing the magnitude of activation within medial and dorsolateral prefrontal regions when such images were presented during our study. It is possible that with reward associations of lesser strength, the low-calorie foods may have required more extensive integrative processing across the orbitofrontal-somatosensory-limbic network to evaluate the potential somatic sensations and reward value of the stimuli.

Several recent studies have implemented functional neuroimaging techniques to clarify the neurobiology of food-related processing within the brain. In general, these studies have compared cerebral responses of healthy subjects to that of obese subjects or patients with eating disorders. A recent SPECT study (Naruo et al., 2000) found that in comparison to healthy and nonbingeing anorexic controls, patients with binge/purge behavior showed significantly greater right-hemisphere prefrontal and parietal activation while imagining food (Naruo et al., 2000). Similarly, other SPECT studies have found that nonbingeing obese women show increased right parietal and temporal cortex activation to the sight of food (Karhunen et al., 1997), whereas obese binge eaters show significant rCBF increases in the left frontal and prefrontal regions, and regional activation is correlated with feelings of hunger (Karhunen et al., 2000) and serum leptin concentrations (Karhunen et al., 1999). The present investigation differed from these studies, as we included only healthy normal-weight subjects and did not manipulate the degree of hunger. However, our findings provide an important foundation for further study of food-related brain responses in individuals with eating disorders.

Two studies have used PET to examine cerebral responses to in vivo presentation of foods differing in caloric content (Gordon et al., 2000, 2001). Following an overnight fast, healthy female subjects showed reduced blood flow within the left temporoinular cortex and no regions of increased rCBF during the high-calorie relative to the low-calorie food presentation (Gordon et al., 2000). In contrast, female anorexic patients were found to have increased rCBF bilaterally within the medial temporal lobes and occipitotemporal regions during the high-calorie food perception condition (Gordon et al., 2001). Those findings stand in contrast to our present demonstration of significant regional activation during presentation of low- and high-calorie foods. These discrepancies may be due to methodological differences associated with PET and SPECT techniques used in the aforementioned studies relative to the use of BOLD fMRI in the present study. Furthermore, the studies by Gordon et al. included only a limited number of food stimuli (two in each condition), which were presented in vivo rather than as photographic representations. Interestingly, an fMRI study by LaBar and colleagues (LaBar, Gitelman, Parrish et al., 2001) contrasted brain activation in response to photographs of food, tools, and Gaussian-blurred objects, with the aim of comparing cerebral re-

sponses to food-related visual stimuli in the same subjects when hungry and satiated. The findings indicated activation patterns similar to those found in the present study, particularly the amygdala activation observed during the conjunction analysis. However, because they did not differentiate among their stimuli according to caloric content, the results of the two studies are not directly comparable. Nevertheless, the similarity in brain responses observed in these two fMRI studies suggests that the amygdala plays an important role in the evaluation of visually presented food stimuli.

To control for activation due to contextual cues associated with situations associated with food consumption exclusive of the actual food content, the current study included a control condition that presented photographs of food-related utensils, such as forks, spoons, tableware, placemats, and so on, obtained from the same stock photography sources. The utensil condition showed no significant activation within the limbic or prefrontal regions where activation was observed during the high- and low-calorie food conditions, but did yield a clear pattern of activation within the occipitotemporal junction consistent with previous work showing that this region is important for visual processing of common objects (Grill-Spector, Kourtzi, and Kanwisher, 2001) and tools (Martin, Wiggs, Ungerleider, and Haxby, 1996; Tranel, Damasio, and Damasio, 1997). The presently observed group differences, therefore, do not appear to be due to methodological factors such as simple alternation of object categories between conditions, visual analysis of familiar or interesting objects, or to the less “naturalistic” appearance of the prepared foods relative to the control stimuli, as these were held constant across conditions.

Several technical and methodological issues should be considered when interpreting the present findings. Brain regions, including the amygdala, mesiotemporal tissue and areas of the basal forebrain, present special challenges for fMRI studies because of the difficulty in resolving their location and in obtaining signal from these regions. As has been noted by Parrish and colleagues, many investigations applying fMRI techniques do not include a discussion of signal to noise and its implications for the interpretation of neuroimaging data (Parrish, Gitelman, LaBar, and Mesulam, 2000). For example, the location of the amygdala on the anteriomedial edge of the temporal lobes places it adjacent to the sinuses where the air–water interface creates a field inhomogeneity that causes in-plane distortion of EPI images (LaBar, Gitelman, Mesulam, and Parrish, 2001). This distortion is often severe, resulting in pixel compression and displacement. Additionally, the inhomogeneity causes signal loss due to through plane dephasing. These factors make it difficult to visualize and measure signal within the amygdala and surrounding area. We have recently demonstrated increased signal to noise through the application of a use of a matched-warp EPI techniques (Rohan, Killgore, Eskesen, Renshaw, and Yurgelun-Todd, 2001). Additionally, our group statistical maps showed significant activation in these regions under some conditions

(e.g., high-calorie condition and conjunction analysis), attesting to the robustness of the finding and supporting our ability to detect signal within the amygdala. However, lack of activation in these regions during some conditions may reflect either true reductions in activation or just poor signal due to field inhomogeneities. Replication will be necessary to address this issue. In addition, the finding of activation within the corpus collosum was unexpected, although a recent study has reported corpus collosum activation during conditions that elicit interhemispheric transfer of information (Tettamanti et al., 2002). Alternatively, such activation may simply be due to poor resolution due to local field potentials which typically integrate activity across several millimeters (Logothetis, Pauls, Augath, Trinath, and Oeltermann, 2001) and field inhomogeneity near the anterior regions of the lateral ventricles leading to bleeding over of activation from adjacent regions such as the cingulate gyrus or head of the caudate nucleus, which are well within the resolution imposed by our 10-mm smoothing kernel.

Methodological and design issues may also influence the interpretation of these findings. In order to obtain a more naturalistic assessment of typical brain function in response to food stimuli, we did not ask subjects to fast prior to the study, although none of the subjects had eaten within the 90 min preceding the scan. Because the manipulation of internal physiological or motivational state was not the aim of the present study, hunger was not systematically controlled. All subjects provided a detailed list of all foods consumed in the hours leading up to the study, and statistical analysis of regional voxel counts and signal intensity indicated that these measures were not significantly correlated with the number of calories consumed or time since the last meal, thus these were not included as covariates in the present analysis. However, since some studies have shown that longer duration of fasting is associated with increased activation within the amygdala and prefrontal cortex (LaBar et al., 2001; Morris and Dolan, 2001), this issue deserves further exploration. Finally, our study only included female subjects. Recent investigations suggest that there may be sex differences in the responses of the brain to hunger and satiety (Del Parigi et al., 2002). Given that circulating hormones may significantly influence appetite and eating behavior (Wiesner et al., 1999), and that many eating disorders are more prevalent in women (Garfinkel et al., 1995; Gøtestam, Eriksen, Heggstad, and Nielsen, 1998; Halmi, Falk, and Schwartz, 1981), it will be important for future studies to examine sex differences in brain responses to food stimuli and whether these responses vary over the menstrual cycle in women. With due consideration given to the aforementioned technical and methodological issues, we believe that the present study contributes to our understanding of the neurobiological systems involved in processing the motivational salience of food stimuli in healthy individuals and provides additional insight into the neural systems that may be affected in patients with a dysregulation of eating behavior.

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