Images of desire: food-craving activation during fMRI

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Food craving (defined as an intense desire to eat a specific food) is of interest because it is extremely common and because it influences obesity or nutritional status. It has also been suggested that food craving may be the evolutionary source for cravings of all kinds including cravings for drugs and alcohol. Yet, little is known about the functional neuroanatomy of food craving. We report here the first functional magnetic resonance imaging (fMRI) study to explicitly examine food craving. A two-part technique was used to produce the food cravings. Threshold was reduced through a diet manipulation (monotonous diet) and cravings were triggered during blood oxygenation level-dependent (BOLD) fMRI sessions by having subjects imagine the sensory properties of favorite foods (a cue-induction technique). Subjects were also asked to imagine the monotonous diet (which they did not crave). Diet condition had an activating effect on both behavioral (reports of craving) and fMRI measures. Craving-related changes in fMRI signal were identified in the hippocampus, insula, and caudate, three areas reported to be involved in drug craving. Thus, this work supports the common substrate hypothesis for food and drug cravings.

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Introduction

The most commonly used definition of food craving is that it is an intense desire to eat a specific food (Kozlowski and Wilkinson, 1987; Weingarten and Elston, 1990). There are two aspects of this definition that are important. One is that the desire be intense, something that we might go out of our way for. Intensity distinguishes food cravings from ordinary food choices. The other critical aspect of the definition is specificity. This serves to contrast food craving to hunger: When hungry, any of a wide variety of foods could be satisfying. However, there is a sensory memory or template that must be matched in order to satisfy a craving.

Food cravings are of nutritional interest because of their high prevalence and their nutritional impact. Surveys in the United States, Canada, and Great Britain using a definition similar to that described above consistently show that food cravings are extremely common (Pelchat, 1997; Weingarten and Elston, 1991). Close to 100% of young adult females and about 70% of young men report having experienced one or more food cravings at some time in the past year. Food cravings may contribute to obesity and eating disorders. They are widely believed to influence snacking behavior, compliance with dietary restrictions, binge eating, and lifetime prevalence of bulimia nervosa (Basdevant et al., 1993; Gendall and Joyce, 2001; Waters et al., 2001; Wurtman, 1988).

There are numerous theories on the basis for food cravings. Probably the most common, especially among laypersons (Weingarten and Elston, 1991), is that cravings arise in response to a nutrient or caloric deficit. However, it has been surprisingly difficult to demonstrate a relationship between nutritional need and food craving in a laboratory setting (Beauchamp et al., 1990; Weingarten and Elston, 1991). Further, in many cases, nutritional deprivation is confounded with dietary monotony. Pelchat and Schaeffer (2000) found that young adult subjects on a nutritionally adequate, single food, sweet (monotonous) diet (large quantities of a nutritional supplement beverage) experience large increases in food cravings as compared with a baseline (normal diet) period. Therefore, hunger or nutritional need is not a necessary condition for the production of food cravings, and food cravings are clearly a separate phenomenon from hunger. In addition to its bearing on mechanisms for food craving, a nutritionally adequate but monotonous diet was used as a tool to increase the probability of food cravings in this study.

Drug craving is viewed as central to maintenance and relapse of drug addiction (American Psychiatric Association, 1994). Thus, a more thorough understanding of craving could contribute to better comprehension of basic processes underlying addiction and to the design of more effective therapeutic interventions. Many lines of evidence suggest that there are similar neural substrates for food and drug rewards (Kelley and Berridge, 2002; Pelchat, 2002; Wise, 2004).
Indeed it is probably the case that drugs of abuse take over substrates for natural reward (Wise, 1996). Given that food craving may be the primal source for cravings of all kinds, it is surprising that so little is known about its brain organization.

There has been no previous functional imaging work that explicitly examines food craving in humans. However, several studies have focused on the pleasantness or desirability of food. Areas activated by food cues include orbitofrontal cortex (O’Doherty et al., 2000; Small et al., 2001; Wang et al., 2004), amygdala (Labar et al., 2001), parahippocampal gyrus (LaBar et al., 2001; Small et al., 2001), anterior fusiform gyrus (LaBar et al., 2001), insula (Gordon et al., 2000; Small et al., 2001; Wang et al., 2004), striatum (Small et al., 2001; Volkow et al., 2002a,b), and cingulate (Small et al., 2001). In these studies, hunger or satiety was the means of manipulating food desire. Hunger may make food craving more likely just as withdrawal can make drug craving more likely. However, just as withdrawal is not necessary for drug craving, hunger is not necessary for food craving. Further, hunger can introduce generalized activation not specific to the craving state. Because hunger and satiety-induced changes in food desirability are psychologically distinct from other influences on desire, they may be expected to have different neural substrates (Small, 2002). In this study, we attempt to identify neural correlates of food cravings that are independent of confounding effects of hunger.

There are a few studies that attempt to identify functional correlates of food pleasantness or incentive salience that are independent of hunger or satiety. In work using sensory specific satiety to manipulate palatability (Kringelbach et al., 2004; O’Doherty et al., 2000), a comparison of the response to foods eaten to satiety with response to other foods can provide information related to palatability independent of hunger. In such studies, differences in activation related to pleasantness were reported in orbitofrontal cortex. In a PET study, Arana et al. (2003) showed descriptions of highly desirable or of neutral foods to satiated subjects. Both amygdala and orbitofrontal cortex were activated by more desirable foods relative to less desirable foods. Another approach is to look at correlates of food pleasantness. In an [(11)C]raclopride binding study, Small et al. (2003b) reported that the amount of dopamine released in the dorsal striatum is correlated with food pleasantness. In a study using gustatory, retronasal olfactory, and flavor (combined gustatory and retronasal olfactory) stimuli, activity in anterior medial orbitofrontal cortex was correlated with rated stimulus pleasantness (Araujo et al., 2003). So, in four studies, orbitofrontal activity was related to food pleasantness or desirability. However, pleasantness and craving are not synonymous. It is possible to like a food without craving it, and subjects in these studies were not asked about food craving. So, in the current study, subjects were explicitly asked about cravings.

Although there are no functional magnetic resonance imaging (fMRI) studies specifically directed at understanding food cravings, there is a growing literature on the neural substrate of addictive drug craving. In light of evidence for common mechanisms, we used work on drug cravings to inform our predictions regarding the neuroanatomy of food craving. Cue-induction paradigms have been successfully used for producing drug craving during neuroimaging. Structures that show activation in conjunction with drug and alcohol craving include amygdala (Childress et al., 1999; Grant et al., 1996), anterior cingulate (Childress et al., 1999; Garavan et al., 2000; Maas et al., 1998), orbital frontal cortex (Wang et al., 1999), insula (Bonson et al., 2002; Breiter et al., 1997; Garavan et al., 2000; Hommer, 1999; Wang et al., 1999), hippocampus (Breiter et al., 1997; Schneider et al., 2001), caudate (Breiter et al., 1997; Hommer, 1999), and dorsolateral prefrontal cortex (Grant et al., 1996; Maas et al., 1998). We hypothesize that individuals receiving a monotonous diet will have greater food cravings and related activation in these candidate regions than individuals maintained on their normal diet.

### Materials and methods

#### Subjects

BOLD fMRI was performed on a sample of 20 healthy volunteers: 10 who received a monotonous diet (5 female, 5 male) and 10 who were maintained on their normal diet (5 female, 5 male). They had no history of illicit drug dependence and were not currently dieting to lose weight. Smokers were instructed to smoke as usual for the duration of the study. All of the subjects had completed at least some college. Informed consent was obtained before the study under an IRB-approved protocol, and subjects were paid for their participation (see Table 1 for more subject characteristics).

#### Diet manipulation

The monotonous diet (Pelchat and Schaeffer, 2000) consisted of a single, homogeneous, nutritionally complete food (vanilla-flavored Boost, Mead Johnson Nutritional). Boost is lactose-free, has 240 kcal in an 8-oz serving, and provides the recommended daily allowance of protein and 24 vitamins and minerals in four servings. The average number of cans consumed per day was 8.9 ± 0.8 and the number of cans ranged from 7 to 15.

Monotonous diet subjects were asked to consume Boost for 1.5 consecutive days. They were not permitted to consume anything else except water. They were permitted to brush their teeth with toothpaste. In earlier work, we had found large increases in average number of food cravings per day when subjects were on a consecutive days. They were not permitted to consume anything except water. They were permitted to brush their teeth with toothpaste. In earlier work, we had found large increases in average number of food cravings per day when subjects were on a consecutive days. They were not permitted to consume anything except water. They were permitted to brush their teeth with toothpaste. In earlier work, we had found large increases in average number of food cravings per day when subjects were on a consecutive days. They were not permitted to consume anything except water. They were permitted to brush their teeth with toothpaste. In earlier work, we had found large increases in average number of food cravings per day when subjects were on a consecutive days. They were not permitted to consume anything except water. They were permitted to brush their teeth with toothpaste. In earlier work, we had found large increases in average number of food cravings per day when subjects were on a consecutive days. They were not permitted to consume anything except water. They were permitted to brush their teeth with toothpaste. In earlier work, we had found large increases in average number of food cravings per day when subjects were on a consecutive days. They were not permitted to consume anything except water. They were permitted to brush their teeth with toothpaste. In earlier work, we had found large increases in average number of food cravings per day when subjects were on a consecutive days. They were not permitted to consume anything except water. They were permitted to brush their teeth with toothpaste. In earlier work, we had found large increases in average number of food cravings per day when subjects were on a consecutive days. They were not permitted to consume anything except water. They were permitted to brush their teeth with toothpaste. In earlier work, we had found large increases in average number of food cravings per day when subjects were on a consecutive days. They were not permitted to consume anything except water. They were permitted to brush their teeth with toothpaste. In earlier work, we had found large increases in average number of food cravings per day when subjects were on a consecutive days. They were not permitted to consume anything except water. They were permitted to brush their teeth with toothpaste. In earlier work, we had found large increases in average number of food cravings per day when subjects were on a consecutive days. They were not permitted to consume anything except water. They were permitted to brush their teeth with toothpaste. In earlier work, we had found large increases in average number of food cravings per day when subjects were on a consecutive days. They were not permitted to consume anything except water. They were permitted to brush their teeth with toothpaste. In earlier work, we had found large increases in average number of food cravings per day when subjects were on a consecutive days. They were not permitted to consume anything except water. They were permitted to brush their teeth with toothpaste. In earlier work, we had found large increases in average number of food cravings per day when subjects were on a consecutive days. They were not permitted to consume anything except water. They were permitted to brush their teeth with toothpaste. In earlier work, we had found large increases in average number of food cravings per day when subjects were on a consecutive days. They were not permitted to consume anything except water. They were permitted to brush their teeth with toothpaste. In earlier work, we had found large increases in average number of food cravings per day when subjects were on a consecutive days. They were not permitted to consume anything except water. They were permitted to brush their teeth with toothpaste. In earlier work, we had found large increases in average number of food cravings per day when subjects were on a

<table>
<thead>
<tr>
<th>Diet group</th>
<th>N</th>
<th>Percentage of female</th>
<th>Average age ± SE</th>
<th>Age range</th>
<th>Percentage of right handed</th>
<th>Percentage of smokers</th>
<th>Average Weight (lb) ± SE</th>
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</thead>
<tbody>
<tr>
<td>Monotonous</td>
<td>10</td>
<td>50</td>
<td>25.4 ± 1.5</td>
<td>22–37</td>
<td>80</td>
<td>30</td>
<td>166 ± 12</td>
</tr>
<tr>
<td>Normal</td>
<td>10</td>
<td>50</td>
<td>21.8 ± 1.1</td>
<td>18–29</td>
<td>90</td>
<td>20</td>
<td>163 ± 11</td>
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excluded from the study. Subjects were given an adequate amount of beverage to maintain their weight based on a 24-h diet recall and on standard tables for caloric requirements for height, weight, sex, and age. Subjects in the normal diet group were given two cans of Boost over the day-and-a-half before the scan (plus one more can right before the scan, see below) but were otherwise permitted to consume anything that they chose to eat.

All subjects were instructed to eat a normal or monotonous meal before scanning and were also given a can of Boost to drink before the scan. This ensured that subjects were not hungry and that the ND group was familiar with Boost. Subjects were asked to name two foods that they “really like” (hereafter, foods A and B). These food names were visually presented during imaging. Subjects were instructed that when they saw the name of a food they were to think about their favorite version of it and to focus on its taste, smell, and texture the whole time the word was on the screen. Participants were given a practice task and a chance to ask questions to ensure comprehension. The task was administered on a Macintosh Powerbook laptop computer using the PowerLaboratory platform (Chute and Westall, 1997).

Participants were placed in the scanner in a supine position, using a foam head holder to reduce motion. The craving task began with 20 s of dummy scan followed by a 20-s visual fixation block (star). Twenty-second visual fixations also occurred in the middle and at the end of the study. The remaining blocks were randomly divided between six 30-s liked food blocks (three blocks food A, three blocks food B) and six 30-s monotonous food blocks. Task duration was 7 min and 19 s. The reason for using food names instead of photographs was that food cravings are very idiosyncratic. Subjects differ in their ideal version of desired foods, and presentation of a nonideal representation reduces craving. The word-cue visualization technique allowed subjects to think of the most desirable version of their liked food. After the scan, a structured interview was used to assess participants’ ability to comply with instructions (e.g., Were you able to think about Boost the entire time the word “Boost” was on the screen?) and their level of desire and craving for the imagined foods (e.g., Did you experience any food cravings while you were in the magnet?).

Images were acquired at the Magnetic Resonance Imaging Center of The University of Pennsylvania on a 4-T GE Signa Scanner (Milwaukee, WI), employing a whole-head coil running the 5.4 release of the GE Signa scanner software. Structural imaging consisted of a sagittal T1-weighted localizer, followed by a T1-weighted acquisition of the entire brain in the axial plane (24 cm FOV, 256 × 256 matrix, resulting in voxel size of 0.9375 × 0.9375 × 4 mm). This sequence was used both for anatomic overlays of the functional data and for spatial normalization of the data sets to a standard atlas (Talairach and Tournoux, 1988). An automated shimming program was performed to adjust the background gradients in the field to make it more uniform within a manually chosen region of interest containing the anterior medial temporal lobes (Webb and Macovski, 1991). After shimming, pilot echoplanar images were obtained and visually inspected before fMRI acquisition to insure good image quality in ventral areas. Functional data were obtained using blood oxygenation level-dependent (BOLD) (Bandettini et al., 1992; Kwong et al., 1992) imaging performed in the axial plane using a multislice gradient-echo planar sequence with a field of view of 24 (frequency) × 15 (phase) and an acquisition matrix of 64 × 40 (22 slices, 4 mm thickness, no skip, TR = 2000, TE = 40, 90° flip angle). This sequence delivers an effective voxel resolution of 3.75 × 3.75 × 4 mm. The fMRI raw echo amplitudes were saved and transferred electronically for off-line reconstruction using IDL (Research Systems Inc., Boulder, CO). The images were corrected for residual geometric distortion (Jezzard and Balaban, 1995) based on a magnetic field map acquired with a 1 min reference scan performed immediately following acquisition of the T1 localizer (Alsop, 1995). This correction realigns the echoplanar images with the higher quality T1 images used for determining the transformation to the standard atlas.

Functional data were preprocessed using MeX, 3.3 (Sensor Systems, Inc., Sterling, VA). Images within each run were motion corrected (Woods et al., 1993) to the image occurring in the middle of the run. This corrects for any motion that might have occurred during an individual task condition (intrarun realignment). Realignment is made to the middle image to minimize the amount of transformation required for images in the last half of the run. The realignment algorithm consists of a rigid body six-parameter transformation, using a least squares cost function with scaling of intensity. Proportional scaling of each image to its mean can result in white matter activation artifact. Therefore, the images were globally scaled to the mean of voxels not found significantly correlated with the task (Andersson, 1997). This mask is created by thresholding an intermediate omnibus F-map (P > 0.001). This preliminary statistical analysis, identical to the model described below, is performed on a set of temporary images created by band pass filtering and smoothing the motion-corrected images. After this scaling procedure, the images were band-pass filtered (Butterworth, 6–80 s) and smoothed (8 mm FWHM, isotropic). The smoothing kernel was based on two times the in-plane resolution at which the data were acquired and was chosen to optimize sensitivity (Hopfinger et al., 2000) and account for between-subject differences in anatomy. Transformation to Talairach space (Talairach and Tournoux, 1988) occurred in two steps. The first transformation was created using a surface registration method (Pellizari et al., 1989). Contours were hand drawn on the reference image used in the intrarun realignment and on the T1 axial localizer. A least squares fitting algorithm then registered the raw functional image to the localizer. This step accounted for possible movement between the time of acquisition of the localizer image and the functional data. The second transformation was created by hand selecting commissural landmarks on the T1 localizer and using a polynomial Talairach transform with trilinear interpolation.

A multsubject statistical analysis was performed using a two-stage random-effects approach. The random-effects model takes into account intersubject variance in generating the group maps, permitting population-level inferences. In the first stage, a multiple linear regression procedure estimated the hemodynamic response to stimuli at each voxel for each subject. The design matrix included a boxcar waveform convolved with a sample hemodynamic response as implemented in SPM99 software (Friston et al., 1995). In the second stage, the first stage regression coefficients were treated as data and analyzed using paired t tests, contrasting the group of subjects at each voxel between two conditions (liked foods minus monotonous food). Contrasts were performed both within and between groups. Within-task contrasts were performed on the whole brain. Between-group comparisons for each contrast were restricted to voxels that had above-threshold responses for either group during their respective within-group contrasts. This conservative approach insured that between-task contrasts were limited to hypothesized regions showing reliable task-related activations. Resulting SPM{T} maps were transformed to the unit
normal distribution $\text{SPM}(Z)$. Because hypotheses were restricted to limbic and paralimbic regions (see Introduction) the significance threshold was set at an uncorrected value of $P < 0.001$ ($Z = 3.09$) based on peak height ($u$). Any effects observed outside these hypothesized regions were reanalyzed with a more rigorous corrected significance threshold of $P < 0.05$.

**Results**

All individuals understood instructions and successfully completed fMRI. All subjects reported being able to sustain thoughts about the specified foods all of the time or almost all of the time that the food names were on the screen. All of the subjects reported that they had been able to switch their thoughts quickly when a new food name appeared on the screen. All monotonous diet participants reported food craving while imagining both liked foods. Normal diet subjects did not consistently report cravings while imagining liked foods. Only 5 of the 10 normal diet participants (3 female, 2 male) reported craving while thinking about the liked foods. Further, three out of these five members of the normal diet group reported craving for only one, but not both of the liked foods. Therefore, the MD manipulation was effective at increasing the probability that subjects would experience food cravings while imagining liked foods in the magnet (Fisher’s exact test, $P = 0.035$). No subjects reported any cravings while visualizing the monotonous food. Therefore, the paradigm was successful at turning cravings on and off in correspondence to changes in stimulus conditions during the scan.

**Liking-specific patterns**

Liking-specific patterns of fMRI activation were identified by subtracting images acquired during monotonous food cues from images acquired during liked food cues. This was designed to isolate activation related to thinking about a liked food from activation related to thinking about food in general. Individuals receiving their normal diet did not produce any significant differences in activation. In contrast, the monotonous diet group showed pronounced differences in activation between the two conditions (Fig. 1 and Table 2). Thus, diet condition had an activating effect on both behavioral and metabolic measures. Areas of differential activation for the

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<th>Table 2</th>
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<td>Local maxima of blood oxygen level-dependent fMRI signal change while thinking about liked foods in normal diet and monotonous diet subjects</td>
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<td>Group and region</td>
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<td>Liking-specific activation</td>
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<td>Normal diet ($n = 10$) (liked &gt; Boost)</td>
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<tr>
<td>No significant activations</td>
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<td>Monotonous diet ($n = 10$) (liked &gt; Boost)</td>
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<td>L Fusiform gyrus</td>
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<td>R Amygdala</td>
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<td>Craving-specific activation</td>
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<td>Monotonous diet &gt; normal diet</td>
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<td>L Insula</td>
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<td>R Caudate nucleus</td>
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$^a$ Peak activation in which the difference in signal change exceeded $Z = 3.0$.

$^b$ Coordinates from the stereotaxic atlas of Talairach and Tournoux.
monotonous diet group were as follows: left fusiform gyrus, left parahippocampal gyrus, right amygdala, left caudate nucleus, right putamen, and bilateral cingulate gyrus.

Craving-specific activation

As only the monotonous diet group showed activation to liked versus monotonous food cues and because they reported more cravings in response to liked-food cues, they were contrasted with the normal diet group. The monotonous diet group showed greater activation in the left hippocampus, left insula, and right caudate nucleus (Fig. 2 and Table 2). Thus, only subjects in the monotonous diet group showed craving-specific activation in candidate limbic or paralimbic and basal ganglia areas.

Discussion

Craving-specific activation

Three areas were identified as showing greater craving-specific activation in the monotonous diet group: hippocampus, insula, and caudate. These areas are also activated during drug craving, and our results therefore support the hypothesis of a common circuitry for desire for natural and pathological rewards (Volkow et al., 2002a; Vorel et al., 2001). The results also modify our view of food-craving mechanisms in humans by placing emphasis on three structures that have received little attention in previous studies of hunger and satiety.

1. Hippocampus: Recent animal work has shown that stimulation of the ventral subiculum of the hippocampus is more effective at reinstating bar pressing for cocaine than is electrical stimulation of the medial forebrain bundle (despite the fact that the latter supports bar pressing for self-stimulation) (Vorel et al., 2001). This is interpreted as reflecting the incentive properties of hippocampal stimulation, suggesting that memory of the reinforcer may be more crucial than the actual reinforcement in triggering reward seeking behavior and may help explain why sensory cues are such potent triggers for cravings in humans (Fedoroff et al., 1997; Tuomisto et al., 1999).

2. Caudate: There has been increasing emphasis in the drug-craving literature on dorsal striatum which is involved in habit learning (White, 1996), and drug-craving-related brain activation has been reported for this area (Garavan et al., 2000). Although ventral striatum (which includes nucleus accumbens) has long been associated with motivation to eat, Volkow et al. (2002b) report significant increases in dopamine levels in the dorsal, but not ventral striatum in hungry subjects exposed to food stimuli. Further, Small et al. (2003b) have reported a significant decrease in raclopride binding potential in dorsal striatum in fasted subjects who have been allowed to eat their favorite meal to satiety. The decrease in binding potential was correlated with the rated pleasantness of the meal. The role of striatal dopamine in the acquisition of desire is also well documented (Robinson and Berridge, 1993). However, the role of reward mechanisms in the experience of craving is unclear (see hippocampus, above). Reward mechanisms, however, are much more clearly related to the establishment or maintenance of incentive salience for foods.

3. Insula: Insula is known to receive gustatory, olfactory, and visceral afferents, to be involved in taste memory (Levy et al., 1999) and has been implicated in the experience of emotion (Phan et al., 2002). So the observed activation in this region could (like hippocampal activation) represent the memory of the reinforcer. Craving-related activation in insula has been consistently reported in drug-craving studies (Bonson et al., 2002; Breiter et al., 1997; Garavan et al., 2000). Activation in insula has also been reported in studies that used other methodologies (e.g., hunger) to manipulate desire for food (Gordon et al., 2000; Small et al., 2001; Wang et al., 2004). So it is possible that this region (like the caudate, see above) plays a general role in desire for food.

Liking-related areas

The subtraction of images acquired during monotonous food cues from images acquired during liked food cues was designed to
isolate activation related to thinking about a liked food from activation related to thinking about food in general. However, the members of the monotonous diet group (the only subjects who showed significant activation in these images) were also experiencing cravings during these epochs. So the areas of significant activation in these subtraction images could reflect food liking, food craving, or both. We will discuss these areas of significant activation in the order that they appeared in Table 2.

1. Fusiform. Fusiform activation is more commonly associated with perception of emotional expression (Kanwisher et al., 1997) and is less commonly seen in association with appetitive variables. However, LaBar et al. (2001) did report differential activation in this area to food images when subjects were hungry versus not hungry.

2. Parahippocampal gyrus. Activity in the parahippocampal formation is associated with hunger in lean individuals (Del Parigi et al., 2002), and differential activation of this area has been reported in response to food (Small et al., 2001) or food images (LaBar et al., 2001) as level of hunger changed. Activity in parahippocampal gyrus is also correlated with cocaine craving (Breiter et al., 1997). The parahippocampal gyrus efferents to nucleus accumbens, amygdala, and hippocampus. It is thought to be involved in explicit memory and emotional memory (Breiter et al., 1997) and therefore to play a role in the affective evaluation of stimuli.

3. Amygdala. Differential activation in the amygdala has been reported when subjects are hungry versus not hungry (LaBar et al., 2001) and when sated subjects view the names of neutral versus preferred foods (Arana et al., 2003). So, two different ways of manipulating the value of food produce differential responding in the amygdala. Activity in the amygdala is also related to cue-induced cocaine craving (Childress et al., 1999; Grant et al., 1996). Over the years, it has been hypothesized that the amygdala is activated by negative emotion in particular or by emotional stimuli in general, that it responds to learned salience or to novelty (Zald, 2003). Recent work shows that the amygdala responds to the intensity rather than to the valence of gustatory (Small et al., 2003a) or olfactory (Anderson et al., 2003) stimuli. Perhaps its true function is to respond to the significance of stimuli to the organism.

4. Caudate. See above.

5. Putamen. The putamen seems to be involved in Pavlovian conditioning or prediction of reward (O’Doherty et al., 2004). Perhaps the observed activation is related to these functions.

6. Anterior cingulate. Regional cerebral blood flow in the anterior cingulate has been reported to be inversely proportional to the desirability of chocolate (Small et al., 2001), and cingulate activation has been reported to be associated with cue-induced cocaine craving (Childress et al., 1999; Garavan et al., 2000; Maas et al., 1998). Anterior cingulate has both cognitive (e.g., working memory or attention) and affective functions. The affective subdivision is involved in assessing the salience of emotional information and in regulating emotional responses and is connected to a number of other areas that showed liking- or craving-related activation in this study including, amygdala, insula, and hippocampus (Bush et al., 2000). Consistent with this view of anterior cingulate function, relative resting glucose metabolism in anterior cingulate predicted level of executive functioning or attention in a population that included cocaine addicts, alcoholics, and healthy individuals (Goldstein et al., 2004).

Given the prominent representation of orbitofrontal cortex activation in studies on functional correlates of food pleasantness that are independent of hunger or satiety, it might be surprising that we did not see food-craving-related activation of orbitofrontal cortex in our subjects. This could of course be due to difficulty in imaging ventral brain regions due to susceptibility artifacts, especially with a high-field magnet. It is also possible that orbitofrontal activation is related to thinking about food in general, whether it is liked or disliked. In that case, the activity would not have survived either of our subtractions.

In sum, this network of regions is involved in experience of affect or emotion, memory, higher level processing of chemosensory stimuli, and in the establishment of incentive salience. Brain areas showing food-craving-related activation in this study have all been reported to be activated in drug-craving studies. Therefore, this work is consistent with the common substrates hypothesis. Further, the prominent representation of memory and sensory integration structures in the current study supports the central role of sensory memory in the experience of food cravings (e.g., “It has to be chocolate ice cream, lemon pie won’t do”).

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