Effects of overfeeding on the neuronal response to visual food
cues¹–³

Marc-Andre Cornier, Sandra S Von Kaenel, Daniel H Bessesen, and Jason R Tregellas

ABSTRACT
Background: The regulation of energy intake is a complex process involving the integration of homeostatic signals and both internal and external sensory inputs. Environmental visual cues are one of the first and primary inputs signaling the potential availability of food.

Objective: We examined the effects of short-term overfeeding on the neuronal responses to food-related visual stimuli in thin individuals.

Design: Twenty-five thin individuals (13 women, 12 men) were studied. Functional magnetic resonance imaging (fMRI) was performed after 2 days of eucaloric energy intake and after 2 days of 30% overfeeding in a counterbalanced design. fMRI was performed while the subjects were presented with visual stimuli in 3 different categories: neutral control objects, foods of neutral hedonic value, and foods of high hedonic value. Measures of appetite were obtained by using visual analogue scales before and after meals.

Results: In the eucaloric state, pictures of foods of high hedonic value elicited greater activation of neuronal regions than did neutrally rated foods, which is consistent with visual processing and attention (inferior temporal visual cortex, posterior parietal cortex, premotor cortex, and hippocampus) and with activation of the hypothalamus. Two days of overfeeding led to significant attenuation of these responses. Overfeeding also resulted in reduced hunger ratings and increased satiety ratings.

Conclusion: These findings emphasize the important role of external food-related visual cues and suggest that there are interactions between external visual sensory inputs, energy balance status, and brain regions important in the homeostatic regulation of energy intake. Am J Clin Nutr 2007;86:965–71.

KEY WORDS Functional magnetic resonance imaging, fMRI, neuroimaging, hunger, satiety, thin persons, hypothalamus

INTRODUCTION
The pathophysiologic processes that underlie the increasing prevalence of obesity have not been clearly defined but likely involve faulty interactions between environmental factors, which favor positive energy balance, and weight regulatory systems in genetically susceptible persons. Persons who are genetically predisposed to thinness in the current environment may be able to sense and respond to excess energy intake more rapidly and accurately than do persons predisposed to obesity (1). Where and how does this “sensing” of energy balance occur? The regulation of energy intake is a complex process requiring the integration of multiple internal and external signals. A great deal has been learned about the homeostatic regulation of energy balance and the interactions with adiposity and gut signals (2, 3). Ultimately, however, the decisions of when to initiate food intake, of how much to consume, and of when to terminate a meal are affected by not only these homeostatic mechanisms but also by learned behaviors, cognitive factors, habits, social context, availability of food, and external sensory cues, such as visual, smell, and taste inputs (4).

A key signal to the initiation of a meal is the visual stimulus of the food. By seeing the food, we are aware of its availability and potential palatability, both of which affect the motivation to initiate food intake (5). The sight and visual characteristics of food have been shown to have a significant effect on the incentive to eat in primates and have been shown to be associated with the activation of specific brain regions (6, 7). In humans, however, published data are limited on the neuronal responses to visual food cues (8, 9).

In addition, reward systems are powerful modulators of feeding behaviors. Most mammals will eat beyond their needs when presented with foods that are highly palatable, and the rewarding effects of food in humans cannot be argued. There is likely an interaction between the homeostatic mechanisms of feeding and the reward or hedonic effects of food. For example, a food stimulus that may be pleasurable while hungry may lose its desirability when satiated (10). This relates to the concept of incentive or the reinforcing value of food. The hedonic preference for a food relates to the palatability or pleasantness of that food and is associated with the liking of food (11). The incentive or reinforcing value of a food corresponds with the motivational value of that food and the wanting of food (11). The liking and wanting of food work together to effect the reinforcing value of food and

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ultimately the behavior, eating. Neuroimaging studies have suggested that specific brain regions are activated in association with the pleasantness or repetitiveness of a stimulus (12-14).

We thus hypothesized that thin individuals, ie, individuals who adapt effectively to periods of positive energy balance, would be sensitive to food-related visual stimuli and that the response to these stimuli would be attenuated in the overfed state when the internal milieu should promote reduced food intake. The present study was designed to examine these hypotheses.

SUBJECTS AND METHODS

Subjects

Twenty-five thin [body mass index (BMI; in kg/m\(^2\)) < 24], right-handed, healthy individuals (13 women and 12 men) aged 25-45 y were recruited and screened (Table 1). Eligible subjects were free of metabolic, psychiatric, and eating disorders. The study was approved by the Colorado Multiple Institutional Review Board, and all subjects gave informed consent.

Study design and measurements

Subjects first underwent baseline assessments, including a 3-d diet diary, completion of the Three-Factor Eating Inventory (15), measurements of resting metabolic rate by hood indirect calorimetry (2900 metabolic cart; Sensormedics, Yorba Linda, CA), and body-composition measurement by dual-energy X-ray absorptiometry (DPX whole-body scanner; Lunar Radiation Corp, Madison, WI).

Subjects were then studied on 2 occasions (eucaloric and overfeeding) in a randomized crossover manner. In women, the study periods were performed during the follicular phase of their menstrual cycle. Each study period included a 3-d run-in diet phase, a 2-d controlled diet phase, and a study day. The run-in diet phase was done to ensure energy and macronutrient balance. Estimates of daily energy intake were made by using usual intake via a 3-d food diary, the Harris-Benedict equation, baseline resting metabolic rate plus an activity factor, and lean body mass. On one occasion (eucaloric), the subjects were maintained on the eucaloric diet for 2 more days. On another occasion, the subjects were overfed by 30% above eucaloric needs (overfeeding) for 2 d. The macronutrient compositions of the diets were kept stable at 50% carbohydrate, 30% fat, and 20% protein. The ratio of saturated to polyunsaturated fat and the fiber and cholesterol contents of the diets were identical. All food was prepared and provided by the General Clinical Research Center kitchen. Subjects arrived at the center every morning, where they were weighed, ate breakfast, and picked up the remainder of their daily meals in coolers. They were asked to return any uneaten food, which was then measured and incorporated into their next day of food. The subjects were asked to maintain their usual pattern of physical activity and were regularly questioned regarding activity and compliance. They were asked to not consume any alcoholic or calorie-containing beverages during the study period.

Functional magnetic resonance imaging

The subjects arrived at the Brain Imaging Center at the University of Colorado at Denver Health Sciences Center the morning after each controlled diet phase in an overnight fasted state. Imaging studies were performed with a GE 3.0-T magnetic resonance scanner equipped with high-speed gradients (300-μs rise time and maximum gradient strength of 24 mT/m) and echoplanar (EPI) capability. Anatomical imaging was performed first. fMRI data were then acquired by using an EPI T2* BOLD (blood oxygen level dependent) contrast technique (repetition time = 2000, echo time = 30, 64\(^2\) matrix, 240 mm\(^2\) field of view, 28 axial slices angled parallel to the planum sphenoidale, 4-mm thick, 0-mm gap). Functional imaging was performed while the subjects were presented visual stimuli by using a projector and screen system. The visual stimuli were from 3 different categories: neutral nonfood objects (O), foods of high hedonic value (H), and foods of neutral hedonic or utilitarian value (U). Examples of O included images of animals, trees, books, furniture, and buildings. Examples of H included images of waffles with whipped cream and syrup, chocolate cake, cookies, plate of eggs

<table>
<thead>
<tr>
<th>Subject characteristics(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong> ((n = 13))</td>
</tr>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
</tr>
<tr>
<td>Body fat (%)</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
</tr>
<tr>
<td>Restraint</td>
</tr>
<tr>
<td>Disinhibition</td>
</tr>
<tr>
<td>Hunger</td>
</tr>
</tbody>
</table>

\(^1\) All values are \(\bar{x} \pm SD\).

\(^2\) Significantly different from men, \(P < 0.05\).

### Table 1

Region of interest analyses showing areas of increased neuronal activation in response to neutral or utilitarian food images (U) as compared with neutral nonfood objects (O) in the eucaloric state (EU) and hedonic (H) compared with utilitarian (U) food images in the EU compared with overfed (OF) conditions

<table>
<thead>
<tr>
<th>Local maxima coordinates(^1)</th>
<th>(x)</th>
<th>(y)</th>
<th>(z)</th>
<th>(t)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EU, U &gt; O</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insula, left</td>
<td>-39</td>
<td>-3</td>
<td>-3</td>
<td>1.74</td>
<td>0.047</td>
</tr>
<tr>
<td>Dorsolateral prefrontal cortex, left</td>
<td>-45</td>
<td>39</td>
<td>9</td>
<td>2.43</td>
<td>0.011</td>
</tr>
<tr>
<td><strong>EU &gt; OF, H &gt; U</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior visual cortex, right</td>
<td>39</td>
<td>-51</td>
<td>-12</td>
<td>2.40</td>
<td>0.012</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>6</td>
<td>0</td>
<td>-15</td>
<td>1.78</td>
<td>0.044</td>
</tr>
</tbody>
</table>

\(^1\) Stereotactic coordinates in Montreal Neurological Institute space.
and bacon, and pastries. Examples of U included images of bagels, fruit, bread, and cereal. Two runs each lasting 8 min were performed with each run consisting of a block design with 5 blocks of pictures of H, 5 blocks of U, and 5 blocks of O.

Behavioral measurements

Measures of appetite were made during each controlled diet period. Before and after each meal, the subjects rated their hunger, fullness, and prospective consumption on visual analogue scales (VASs) as described by Rolls and Bell (16, 17). Hunger was rated on a 100-mm line preceded by the question, “How hungry do you feel right now?” and anchored by “not at all hungry” and “extremely hungry” on the right. Fullness was rated by the question, “How full do you feel right now?” with the anchors “not at all” and “extremely.” Prospective consumption was rated by using the question, “How much food do you think you could eat right now?” anchored by “nothing at all” and “a large amount.”

Calculations and statistical analyses

Functional images were analyzed with SPM2 (Wellcome Department of Imaging Neuroscience, London, United Kingdom). After discarding the first 4 scans from each run for saturation effects, images were motion-corrected, normalized to standard space, spatially smoothed with an 8 full-width-half maximum kernel, and evaluated by using the general linear model in a random effects analysis. To generate the random effects model in SPM2, statistical parametric maps were first generated for each subject by using the general linear model to describe the variability of the data on a voxel-by-voxel basis. Hypotheses expressed in terms of model parameters are assessed at each voxel with univariate statistics, yielding an image whose voxel values comprise a statistical parametric map. The model consisted of a hemodynamic response function-convolved boxcar function. Additionally, a high-pass filter was applied to remove low-frequency fluctuation in the BOLD signal. A second-level analysis was performed to incorporate both within-subject and between-subject variance, thus allowing inference to the population. Accordingly, each individual subject’s data for each condition of interest, both within and across feeding conditions, were summarized with one parametric map (accounting for within-subject variance) and were then assessed across subjects (accounting for between-subject variance), thereby implementing a random effects model. Second-level contrasts of interest (t tests) were used to evaluate specific hypotheses. Data were corrected for multiple comparisons with the false discovery rate technique, thresholding at $P = 0.05$.

In addition to the whole-brain analyses used to evaluate the main effects of stimulus type, region-of-interest analyses were used to evaluate responses in less-powered comparisons (namely, the effect of eating conditions) in the hypothalamus, insula, dorsolateral prefrontal cortex (DLPFC), and inferior visual cortex. Regions of interest for the insula, DLPFC, and inferior visual cortex consisted of 20-mm diameter spheres centered on the local maxima for the conditions of interest. Because of its smaller size, a 10-mm sphere was used for the hypothalamus. The

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FIGURE 1. Neuronal activation in response to visual stimuli of foods of high hedonic value compared with foods of neutral hedonic value in the eucaloric state. Robust activation is noted in the inferior temporal visual and premotor cortices as well as in the hypothalamus. Mean ($\pm$SEM) BOLD (blood oxygen level dependent) responses are shown for the hypothalamus and inferior visual cortex.
TABLE 3
Regions of increased neuronal activation in response to hedonic (H) compared with neutral or utilitarian (U) food images, from whole-brain analyses in the eucaloric (EU) state

<table>
<thead>
<tr>
<th>EU, H &gt; U</th>
<th>Local maxima coordinates 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Premotor cortex (BA6), right</td>
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</tr>
<tr>
<td>Inferior visual cortex, left</td>
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</tr>
<tr>
<td>Inferior visual cortex, right</td>
<td>36</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>6</td>
</tr>
<tr>
<td>Parietal cortex, right</td>
<td>21</td>
</tr>
<tr>
<td>Hippocampus, left</td>
<td>-27</td>
</tr>
<tr>
<td>Hippocampus, right</td>
<td>24</td>
</tr>
</tbody>
</table>

1 Stereotactic coordinates in Montreal Neurological Institute space.

mean response for all voxels in each region of interest was determined by using the Marsbar toolbox (18) in SPM2. For Figures 1 and 2, functional results were overlaid onto the group average T1-weighted anatomical images. Mean BOLD responses shown are % signal change, relative to the global mean. Coordinates shown in the tables and figures are in standard stereotactic space as defined by the Montreal Neurological Institute standard brain (Internet: http://mni.mcgill.ca/); x is the distance in mm to the right (+) or left (−) of the midline; y is the distance in mm anterior (+) or posterior (−) to the anterior commissure; and z is the distance in mm superior (+) or inferior (−) to a horizontal plane through the anterior and posterior commissures.

RESULTS
Study participants
The subjects’ characteristics are summarized in Table 1. The subjects were lean by definition with a mean BMI of 21.5 ± 1.6. Although the men had a higher mean body weight and lower percentage of body fat than did the women, BMI and total fat mass did not differ significantly between the sexes. Although overall, the participants were considered to be unrestrained eaters, the women had greater restraint scores than did the men.

Eucaloric state
First we describe the neuronal responses to visual stimuli while the subjects were in energy balance (EU). Images of foods of neutral hedonic value or utilitarian foods compared with neutral nonfood objects (EU, U > O) resulted in modest activation of the left insula and left dorsolateral prefrontal cortex (Table 2). When visual stimuli of foods of high hedonic value were compared with utilitarian foods (EU, H > U), however, dramatic differences in neuronal activation were seen, as shown in Figure 1 and Table 3. Robust activation of bilateral inferior temporal visual cortices, right posterior parietal cortex, and premotor cortex was observed, as well as activation of the hippocampus. In addition, there was significant activation of the hypothalamus in response to these hedonic food visual cues.

Overfed state
Overfeeding (OF) resulted in significant reductions in premeal hunger and prospective consumption ratings and significant increases in postmeal satiety ratings as measured by visual analogue scales (Figure 2). As measured by fMRI, 2 days of overfeeding attenuated the activation described in the eucaloric conditions. Specifically, Figure 3 and Table 2 show that overfeeding was associated with reduced hypothalamic activity (EU > OF, H > U). In addition, the robust visual-attention response to the visual stimuli of hedonic foods was also diminished with overfeeding (EU > OF, H > U). No effect of eating condition was observed in the comparison of utilitarian foods with neutral nonfood objects (EU > OF, U > O).

DISCUSSION
The present study was performed to examine the central response to food-related visual cues during states of energy balance and short-term positive energy balance in individuals screened to be resistant to weight gain and obesity. The data show that thin individuals have a robust response to food-related visual cues, and the greater the salience of the stimuli, the greater the attention is placed toward these cues. In addition, there appears to be communication between these external visual cues and the homeostatic regulation of food intake as seen by hypothalamic activation in response to visual food stimuli. Furthermore, these thin individuals quickly and appropriately sense the positive energy balance associated with overfeeding, which is associated...
with significant attenuation in the neuronal responses to external food cues, including a reduction in hypothalamic activity.

How then can these data be interpreted? First, we see that basic food-related visual cues activate the insular cortex. Although usually considered the primary taste cortex, the insula has also been shown to be a brain region important in the regulation of feeding behaviors (12, 14, 19). The insula has been shown to be activated by visual food-related stimuli and the mere thought of food (8, 9, 20, 21) and may relate to the memory of the rewarding effects of food (21, 22). As in the present study, the insula has been shown to be activated with hunger but not with satiation or overfeeding (23). In addition, we see that food-related visual cues activate the DLPFC. The DLPFC has been implicated as a brain region important in working memory, attentional control, and goal-directed behavior with the left hemisphere associated with approach as opposed to withdrawal on the right (24). Interestingly, acute satiation has been found by others to be associated with activation of the left DLPFC (25). It appears, therefore, that after a period of energy balance and an overnight fast, visual food cues may be associated with activation of the memory of the rewarding effects of food and goal-directed behavior potentially preparing the individual for ingestion.

Second, when the visual food cues are made more salient through the use of images of foods of high hedonic value, robust activation of visual processing and attention-related cortical regions is observed (26). It may be that when food is available and appears to be highly palatable and calorically dense, attention and motivation to eat is heightened. In addition, we see significant hypothalamic activation in response to these visual food cues, which suggests an interaction between external sensory inputs and homeostatic mechanisms. This could be interpreted as when desirable food is seen, ie, when food is available and of high incentive value, the gain on the homeostatic or autonomic drive to eat is changed, promoting increased hunger and food intake. Although a great deal of evidence supports hypothalamic regulation by nutrients, these data are the first to demonstrate direct regulation of hypothalamic activity by visual food stimuli in humans. Animal data suggest that after visual cortical activation, visual pathways include activation of the amygdala and orbito-frontal cortex before reaching the hypothalamus (4, 27). Although we did not see activation of these specific intermediate sites, we did see bilateral hippocampus activation as a potential route of signaling between the visual cortex and hypothalamus.

Third, 2 d of positive energy balance as produced by 30% overfeeding has a dramatic effect on the neuronal response to visual food cues in thin individuals. Overfeeding results in diminished activation in cortical regions associated with visual processing and attention, which suggests that the salience of the food cues is reduced after overfeeding. In addition, reduced hypothalamic activation in response to overfeeding may reflect interactions between visual cues and the homeostatic status of the individual. In a state of positive energy balance, the “gain” on the homeostatic regulation of energy balance is changed, promoting a return to energy balance. Neuronal activation in response to other food-related stimuli, for example, taste and smell, has also

FIGURE 3. The effects of overfeeding on neuronal response to visual stimuli of foods of high hedonic value compared with foods of neutral hedonic value. Reduced activation of the visual cortex and hypothalamus is noted. Mean (±SEM) BOLD (blood oxygen level dependent) responses are shown for the hypothalamus in the eucaloric and overfed conditions.
been shown to be affected by acute satiation supporting the concept that the metabolic state affects the response and processing of external food-related stimuli (4, 14, 28, 29). Although we are not aware of any studies reporting the effects of short-term positive energy balance on the hypothalamic response to food-related stimuli in humans, studies have shown that acute satiation results in reduced hypothalamic activation (23, 25). It may be that the changes in corticolimbic activation with alterations in homeostatic state drive the hypothalamic response. On the other hand, the hypothalamus may integrate homeostatic and nonhomeostatic signals directly (4, 30).

As previously discussed, the regulation of energy intake is a complex process ultimately processed by the integration of internal and external sensory inputs. It has been hypothesized that the regulation of food intake follows the structure of motivated behavior (31). First, visceral and external sensory inputs are processed and integrated with reward and memory systems leading to an “incentive value” of the goal. Behavior is then initiated following the interaction of the internal state, such as state of energy balance or hormonal changes, and the incentive value of the goal, ie, food. This motivated ingestive behavior is the outcome of the integration of stimulatory and inhibitory neural circuits. Once food intake has been initiated, functions of reward and aversion, as well as learning and memory, are critical in this integrative process. As food intake continues, several feedback signals are at work leading to potential continuation versus termination of feeding (31). Our data are consistent with this concept. The metabolic state of the organism (eucaloric or overfeeding) affects the incentive value of the available food. In a state of energy balance and after an overnight fast when individuals are hungry, greater attention is placed toward food items of higher potential reward, ie, a state of increased wanting for food. This is then associated with increased hypothalamic activation or activation of the homeostatic mechanisms associated with food intake. This could be interpreted as when we see food we turn on the signals that drive us to eat. In turn, when there is no food around, these signals are attenuated, or when the organism does not need more food (overeating), these signals are attenuated or inhibited.

In conclusion, our data show that thin individuals who have been screened to be resistant to weight gain and obesity have a robust response to food-related visual cues, and that the greater the salience of the stimuli, the greater is the attention placed toward these cues. In addition, communication appears to exist between external visual cues and the homeostatic regulation of food intake as was seen by hypothalamic activation in response to visual food stimuli. Overfeeding results in attenuation of the response to foods of high hedonic value, including reduced activation of the hypothalamus. These findings emphasize the important role of external visual cues in the regulation of energy intake and suggest that there is an interaction between external visual sensory inputs, energy balance status, and brain regions important in the homeostatic regulation of energy intake.

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The contributions of the authors were as follows—M-AC: helped to design the study, acquire the data, analyze and interpret the data, and draft and finalize the manuscript; SSVK: helped to acquire the data and critically revise the manuscript; DHB: helped to design the study, interpret the data, and critically revise the manuscript; JRT: helped to design the study, analyze and interpret the data, and draft the manuscript and performed the statistical analysis. None of the authors had a personal or financial conflict of interest.

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