Increased sensitivity to food cues in the fasted state and decreased inhibitory control in the satiated state in the overweight

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ABSTRACT
Background: Flexibility of food reward–related brain signaling (FRS) between food and nonfood stimuli may differ between overweight and normal-weight subjects and depend on a fasted or satiated state.

Objective: The objective was to assess this flexibility in response to visual food and nonfood cues.

Design: Twenty normal-weight [mean ± SEM BMI (in kg/m²) = 22.7 ± 0.2; mean ± SEM age = 22.4 ± 0.4 y] and 20 overweight (BMI = 28.1 ± 0.3; age = 24.0 ± 0.7 y) participants completed 2 fMRI scans. Subjects arrived in a fasted state and consumed a breakfast consisting of 20% of subject-specific energy requirements between 2 successive scans. A block paradigm and a food > nonfood contrast was used to determine FRS.

Results: An overall stimulus × condition × subject group effect was observed in the anterior cingulate cortex (ACC) (P < 0.006, F(1,38) = 9.12) and right putamen (P < 0.006, F(1,38) = 9.27). In all participants, FRS decreased from the fasted to the satiated state in the cingulate (P < 0.005, t(39) = 3.15) and right prefrontal cortex (PFC) (P < 0.006, t(39) = 3.00). In the fasted state, they showed FRS in the ACC (P < 0.004, t(39) = 3.17), left insula (P < 0.009, t(39) = 2.95), right insula (P < 0.005, t(39) = 3.12), cingulate cortex (P < 0.004, t(39) = 3.21), and thalamus (P < 0.006, t(39) = 2.96). In the satiated state, FRS was limited to the left insula (P < 0.005, t(39) = 3.21), right insula (P < 0.006, t(39) = 3.04), and cingulate cortex (P < 0.005, t(39) = 3.15). Regarding subject group, in the fasted state, FRS in the ACC was more pronounced in overweight than in normal-weight subjects (P < 0.005, F(1,38) = 9.71), whereas in the satiated state, FRS was less pronounced in overweight than in normal-weight subjects in the ACC (P < 0.006, F(1,38) = 9.18) and PFC (P < 0.006, F(1,38) = 8.86), which suggests lower inhibitory control in the overweight.

Conclusion: FRS was higher in the overweight in the satiated state; however, when sufficiently satiated, the overweight showed decreased inhibitory control signalling, which facilitates overeating. This trial was registered in the Dutch clinical trial register as NTR2174.


INTRODUCTION

Understanding the integrative role of the central nervous system in energy and reward homeostasis has become increasingly important as the prevalence of obesity and obesity-related diseases is rising worldwide (1, 2). Previous observations suggest an overlap between the neurocircuitries regulating reward perception and energy homeostasis (3, 4), with homeostatic and reward circuitries acting in concert to regulate eating behavior. Disruption of the interaction between these circuitries might promote overeating and contribute to obesity (3).

Previous fMRI studies show that food cues (images, smells, and tastes) activate brain regions involved in the processing of reward and control (5–7), including the nucleus accumbens, striatum, ventral tegmental area, anterior cingulate, and prefrontal cortices (5–7). In line with the proposition that obesity is associated with a disruption of the reward circuitry in response to food, previous fMRI studies suggest that overweight/obese participants show greater brain signaling in response to food cues and anticipated reward compared with normal-weight participants (8–12), preprandially and postprandially (8, 10, 11, 13, 14). Even after diet-induced weight loss, formerly obese humans still exhibit an increased responsiveness to food cues in reward-related brain regions (15–18).

In general, the response to food stimuli was found to be decreased postprandially compared with preprandially (3, 19). However, only a few studies investigating food reward–related brain signaling (FRS) investigated both a pre- and postprandial state (1, 19–21). Most studies have been conducted in the fasted state because of the higher motivation to eat and increased incentive salience of food (10–12, 22–25). However, in the fasted state, the processes involved in food reward are intertwined with the homeostatic regulation of food intake and are thus difficult to decipher (26). Imaging studies conducted in the postprandial state argue that the excess energy intake in obesity is at least

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4 Abbreviations used: ACC, anterior cingulate cortex; FRS, food reward–related brain signaling; PFC, prefrontal cortex; V AS, visual analog scale.
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partly due to eating in the absence of hunger (nonhomeostatic eating) (13, 27). Therefore, we assessed the differences between overweight and normal-weight subjects regarding their FRS in response to food and nonfood stimuli in a fasted as well as a satiated state. The design furthermore controlled for subject-specific energy requirements and visual complexity. A similar subject-specific design was previously used in a positron emission tomography study by Tataranni et al (28). We hypothesized that FRS in the fasted state would be greater in overweight than in normal-weight subjects. This difference was hypothesized to remain, despite a decrease in salience from the fasted to the satiated condition.

SUBJECTS AND METHODS

This study was approved and registered under MEC09-3–085 by the Medical Ethical Committee of Maastricht University, Maastricht, Netherlands, and at the Central Committee on Research Involving Human Subjects, The Hague, Netherlands, under NL30898.068.09. The study was registered in the Dutch clinical trial register under number NTR2174.

Subjects

In total, 45 subjects were screened. Written informed consent was obtained from all subjects. Inclusion criteria were healthy male and female subjects, BMI (kg/m²) between 20 and 35, and right-handedness. Exclusion criteria were recent dieting, smoking, personal or familial history of a psychiatric disorder, or use of contraceptives. Because of the inclusion criteria, only 40 subjects were included, of whom 20 were lean (BMI: 20–25) and 20 were overweight (BMI: 25–35). Subject characteristics are summarized in Table 1. The research procedures were in accordance with the Helsinki Declaration. All subjects were informed on the purpose, procedures, and potential risks of the study before providing written informed consent.

Experimental set-up

To create fasted and satiated conditions, the subjects came to the university after an overnight fast of 10 h. The subjects were instructed not to drink any alcoholic beverages on the day before the test and not to eat or drink anything, except for water, after 2200 on the evening before testing. Subjects verbally confirmed their adherence to these instructions. The test day included 4 visual analog scale (VAS) questionnaires for assessing appetite profile and 2 fMRI scans, after which the tastiness of the food and nonfood pictures were assessed by using VAS questionnaires (Figure 1A). Breakfast, which was provided between the first and second fMRI scans, created the subsequent satiated condition. Breakfast consisted of typical Dutch breakfast items constituting a typical healthy breakfast, with 18% protein, 47% carbohydrate, and 35% fat. The breakfast provided 20% of subject-specific calculated daily energy requirements. Daily energy requirements were calculated individually for each of the subjects by multiplying basal metabolic rate by the appropriate physical activity factor derived from the Baecke screening questionnaire (mean ± SEM for all subjects: 1.7 ± 0.01) (29). The basal metabolic rate was calculated according to the equation of Harris-Benedict (mean ± SEM for all subjects: 7.4 ± 0.16 MJ/d) (30). Breakfast was offered immediately after the first scan and had to be consumed in full within 20 min, before the second scan.

TABLE 1

Characteristics of the subjects

<table>
<thead>
<tr>
<th>Subject characteristics</th>
<th>Normal weight</th>
<th>Overweight</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 10 M, 10 F)</td>
<td>(n = 10 M, 10 F)</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>22.4 ± 0.5</td>
<td>23.7 ± 1.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.7 ± 0.3</td>
<td>28.1 ± 0.5</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.76 ± 0.02</td>
<td>0.79 ± 0.01</td>
</tr>
<tr>
<td>TFEQ F1</td>
<td>4.7 ± 0.7</td>
<td>6.5 ± 0.6</td>
</tr>
<tr>
<td>TFEQ F2</td>
<td>4.2 ± 0.4</td>
<td>4.8 ± 0.5</td>
</tr>
<tr>
<td>TFEQ F3</td>
<td>5.1 ± 0.6</td>
<td>4.7 ± 0.8</td>
</tr>
<tr>
<td>DER (MJ)</td>
<td>12.2 ± 0.3</td>
<td>13.0 ± 0.5</td>
</tr>
</tbody>
</table>

1 All values are means ± SEMs. DER, daily energy requirement; TFEQ F1, F2, and F3, Three-Factor Eating Questionnaire Factors 1 through 3.

2 Significantly different from overweight, P < 0.0001.

3 Calculated according to the equations of Harris and Benedict and adjusted for the appropriate physical activity level assessed by the Baecke questionnaire.

VAS questionnaires

To determine the effect of the breakfast on the appetite profile, a VAS for the factors, hunger, fullness, satiety, desire to eat, and thirst were used. A VAS was administered 4 times: before the first scan and immediately after the first scan before breakfast, 20 min after the start of breakfast, and immediately after the second scan (Figure 1A). The mean of the first 2 questionnaires was used as the “fasted” measurement, and the mean of the last 2 questionnaires was used as the “satiated” measurement. To determine whether subjects were able to discriminate between the food and nonfood pictures, a VAS questionnaire assessing tastiness was used. These VAS questionnaires were administered after the completion of both fMRI scans. Food and nonfood pictures were shown in a randomized order with the VAS questionnaire beneath each picture. The VAS questionnaires consisted of 100-mm lines anchored with “not at all” at the far left and “extremely” at the far right. The questions asked were as follows: “How hungry are you?”, “How full do you feel?”, “How satiated do you feel?”, “How large is your desire to eat?”, “How thirsty are you?”, and “How tasty do you find the picture shown above?” Subjects were instructed to make a single vertical mark at the appropriate point between the 2 anchors on each scale to indicate their subjective feelings.

fMRI settings and paradigm

The subjects were scanned in a Siemens Magnetom Allegra MRI system (3 Tesla; Siemens AG, with the standard one-channel head coil. The subject’s position was confirmed with T1-weighted scout images. During the functional run, the subjects were presented with blocks of food and nonfood pictures. Both food and nonfood picture blocks comprised both natural and artificial objects (Figure 1C). Food and nonfood stimuli were previously validated (31); nonfood stimuli were carefully matched with the food stimuli (31). The photograph of each object was presented on a gray background, and the nonfood
items were matched for color, luminance, and visual complexity with the food items (31). All pictures were designed and photographed at the University of Kuopio (31). The paradigm consisted of 2 sequential cycles of 6 blocks and 3 blocks of each stimulus type (food and the nonfood items); each block contained 8 different pictures (Figure 1B). The stimuli were presented in a counter-balanced manner. The interstimulus interval was 16 s. To minimize activation related to eye movements during the interstimulus interval, the subjects were instructed to visually fixate a central cross on the screen. Each image was shown for 2 s. The computer that controlled the stimulus display was triggered by the scanning sequence. Paradigms composed of different pictures were used in the fasted and satiated states; the order of these different paradigms was counterbalanced between the subjects.

fMRI images were acquired throughout the session by using a T2*-weighted protocol to obtain a blood oxygen level–dependent T2* signal (repetition time = 2 s, echo time = 26 ms, flip angle = 90°, matrix = 96 × 96, field of view = 269, voxel size = 3 × 3 × 3.9 mm, and gap = 0.1 mm).

fMRI data preprocessing

All fMRI data were analyzed with BrainVoyager QX version 2.3 software (Brain Innovation BV). The first 2 volumes of each run were discarded for analysis because of T1 saturation effects. Preprocessing of the functional data included a slice scan time correction with cubic spline interpolation, 3-dimensional motion correction with trilinear interpolated motion estimation (for alignment) and subsequent windowed sinc interpolation (for final resampling), and temporal high-pass filtering for removal of low-frequency noise with a window of 4 cycles. In the data analysis after preprocessing, the motion-correction parameters were included as confound predictors in the general linear model by using the BrainVoyager Analysis-Predictor tool (21). Functional data were aligned to each subject’s own 1-mm isovoxel high-resolution T1-weighted anatomical scan, and a coregistered volume-time-course was created per run. The auto alignment was performed by using a 6-parameter affine alignment and was corrected manually under visual inspection, if necessary. Finally, all images were transformed into the Talairach coordinate system (32) by using the standard procedure in the BrainVoyager QX version 2.3 software (Brain Innovation BV) that resulted in a resolution of 3 × 3 × 3-mm voxels, which resulted in functional voxels of 27 mm3. Finally, to increase the signal-to-noise ratio, the volume-time courses were spatially smoothed with a 4-mm full-width-at-half-maximum isotropic Gaussian kernel. For the creation of the general linear model and for running the cluster-level threshold estimator tool, as discussed below, a mask was created. The 1-mm isovoxel high-resolution T1-weighted anatomical scan of each subject was used to segregate brain from head tissue (gray and white matter) in an automated way, followed by transformation into the Talairach coordinate system. The ventricles were removed from the resulting anatomical scans, and the group average was used to create a mask file. All statistical analyses were superimposed on a group-average anatomical brain image.

Data analyses

The data were analyzed by using BrainVoyager QX version 2.3, Microsoft Excel, and Statview version 5.0. VAS questionnaires were analyzed by using a 2-factor ANOVA including Bonferroni corrections. VAS questionnaires for appetite were analyzed for the difference between before and after the meal,
with baseline scores as a covariant taken into account. Tests were 2-sided, and differences were considered significant at $P < 0.05$.

To analyze brain activation, separate predictors for food and nonfood were created to be applied in general linear model analyses and to be used in the first-level analyses and subsequent second-level analyses. The onset and duration of each trial were defined as the onset and duration of the image presentation (16 s), and the trials were convolved with the standard canonical 2-gamma hemodynamic-response function. In addition, motion-correction parameters were added as confound predictors. On the basis of this modeling approach, the baseline estimation rests on remaining fixation times during each interstimulus interval. To investigate the conditions separately and to perform group contrasts of comparisons of fasted and satiated conditions, dummy coding was applied with BrainVoyager analysis–Predictor Tool software. An overall analysis of variances for the factor sex was performed; no effect of sex was observed in any reward-related brain area.

Regarding analyses for the complete subject group, whole brain responses were analyzed in a 2 (stimulus: food, nonfood) $\times$ 2 (condition: fasted, satiated) $\times$ 2 (group: normal weight, overweight) ANOVA. Furthermore, interaction group contrasts were used to compare differences in activations from the fasted to the satiated condition for the complete subject group in whole brain images.

To compare the subject groups, ANOVAs were conducted for the fasted and the satiated conditions in whole brain images by using the separate beta-maps for each subject of the relevant contrasts and adding the BMI category as the between-subject factor. Correlation analyses were conducted in the fasted and the satiated states by testing for a correlation between the $\beta$ estimates of relevant contrasts and the covariate BMI.

The resulting whole-brain statistical $F$, $t$, and $r$ maps were used to identify the resulting significant brain activation at a voxel threshold of $P = 0.01$. Thresholded maps were then submitted to a whole-brain correction criterion based on the estimate of the map’s spatial smoothness and on an iterative procedure (Monte Carlo simulation) for estimating cluster-level false-positive rates. After 1000 iterations, the minimum cluster size threshold that yielded a cluster-level false-positive rate ($\alpha$) of 5% was applied to the each separate statistical maps (33, 34). The Talairach Client (http://www.talairach.org) was consulted to obtain an anatomical label of each single voxel of each significant cluster (35). Excel was used to make an inventory on the quantity of each anatomical label of all the voxels within a cluster, to make a correct judgment on the anatomical localization of each significant cluster.

When testing our hypotheses, we focused on brain areas involved in the processing of reward and control, as introduced in the introduction (ie, the nucleus accumbens, striatum, ventral tegmental area, anterior cingulate, and prefrontal cortices).

**RESULTS**

The fasted state before the first scan was confirmed by low VAS scores for satiety and fullness and high scores for hunger, thirst, and desire to eat (Figure 2). Eating the subject-specific breakfast led to significantly decreased hunger, thirst, and desire to eat and to increased satiety and fullness for the remainder of the session (Figure 2; $P < 0.0001$). The change in VAS scores from the fasted to the satiated state was not significantly different between the subject groups for any of the appetite factors. The subjects were able to discriminate between food and nonfood pictures because they judged the food pictures to be significantly tastier compared with the nonfood pictures ($P < 0.0001$).

fMRI results are summarized in Table 2. Significant differences in activated areas indicate a consistently higher activation in response to food compared with nonfood cues; activation in response to nonfood cues was never higher compared with food cues. An overall stimuli (food, nonfood) $\times$ condition (fasted, satiated) $\times$ subject group (normal weight, overweight) effect was observed in the anterior cingulate cortex (ACC) [$P < 0.006$, $F_{(1,38)} = 9.12$] and the right putamen [$P < 0.006$, $F_{(1,38)} = 9.27$], which suggests a larger change in specific FRS from the fasted to the satiated condition in overweight than in normal-weight subjects, as will be further detailed below. Comparison of the

![Appetite profile](image)

**FIGURE 2.** Appetite profile assessed with visual analog scale questionnaires. Values are means $\pm$ SEMs. $n = 20$ per group. Visual analog scale questionnaire data were analyzed by using 2-factor ANOVA including Bonferroni corrections. Visual analog scale questionnaires for appetite were analyzed for the difference before and after the meal, with baseline scores as a covariant taken into account. Tests were 2-sided, and differences were considered significant at $P < 0.05$. The change in visual analog scale questionnaire scores from the fasted to the satiated state was not significantly different between the subject groups for any of the appetite factors. $^a$Significant difference between fasted and satiated states, $P < 0.0001$. $^b$Significant difference between NW and OW, $P < 0.05$. $n = 20$ per group. NW, normal-weight subjects; OW, overweight subjects.
<table>
<thead>
<tr>
<th>Statistical test</th>
<th>Cluster threshold</th>
<th>Anatomic label resulting clusters</th>
<th>Estimated BA</th>
<th>No. of voxels</th>
<th>Statistical value</th>
<th>$P$ value</th>
<th>$x$ $y$ $z$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stimuli × condition × subject group</strong></td>
<td>10</td>
<td>Anterior cingulate (bilateral)</td>
<td>24, 25, 32</td>
<td>748</td>
<td>$F_{(1,38)} = 9.12$</td>
<td>0.0054</td>
<td>2 10 -9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Putamen R</td>
<td>422</td>
<td>$F_{(1,38)} = 9.27$</td>
<td>0.0052</td>
<td>29 -8 9</td>
<td></td>
</tr>
<tr>
<td><strong>Stimuli × condition</strong></td>
<td>18</td>
<td>Cingulate gyrus (bilateral)</td>
<td>32</td>
<td>673</td>
<td>$t_{(39)} = 3.15$</td>
<td>0.0043</td>
<td>-1 13 42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Middle frontal gyrus (PFC) R</td>
<td>8</td>
<td>584</td>
<td>$t_{(39)} = 3.00$</td>
<td>0.0054</td>
<td>29 43 45</td>
</tr>
<tr>
<td>Fasted: F &gt; NF</td>
<td>31</td>
<td>Superior/middle/medial frontal gyrus (PFC) (bilateral)</td>
<td>8/9/10/46</td>
<td>29,069</td>
<td>$t_{(39)} = 3.17$</td>
<td>0.0043</td>
<td>2 13 45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insula L</td>
<td>13</td>
<td>1086</td>
<td>$t_{(39)} = 2.95$</td>
<td>0.0059</td>
<td>-13 7 -9</td>
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<td></td>
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<td>13</td>
<td>1558</td>
<td>$t_{(39)} = 3.12$</td>
<td>0.0044</td>
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<td>31</td>
<td>11,371</td>
<td>$t_{(39)} = 3.21$</td>
<td>0.0041</td>
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<tr>
<td></td>
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<td>Thalamus (bilateral)</td>
<td>940</td>
<td>$t_{(39)} = 2.96$</td>
<td>0.0058</td>
<td>2 -17 6</td>
<td></td>
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<tr>
<td>Fasted: stimuli × subject group</td>
<td>10</td>
<td>Anterior cingulate (ACC) L</td>
<td>32</td>
<td>1291</td>
<td>$F_{(1,38)} = 9.71$</td>
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<td>-13 19 12</td>
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<tr>
<td>Fasted: correlation F &gt; NF with BMI</td>
<td>8</td>
<td>Anterior cingulate (ACC) L</td>
<td>32</td>
<td>457</td>
<td>$r_{(38)} = 0.47$</td>
<td>0.0038</td>
<td>-13 16 12</td>
</tr>
<tr>
<td>Satiated: F &gt; NF</td>
<td>17</td>
<td>Insula L</td>
<td>13</td>
<td>1032</td>
<td>$t_{(39)} = 3.21$</td>
<td>0.0040</td>
<td>41 7 -6</td>
</tr>
<tr>
<td>Satiated: stimuli × subject group</td>
<td>11</td>
<td>Insula R</td>
<td>13</td>
<td>795</td>
<td>$t_{(39)} = 3.04$</td>
<td>0.0051</td>
<td>-40 4 -6</td>
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<tr>
<td></td>
<td></td>
<td>Anterior cingulate (ACC) (bilateral)</td>
<td>24, 31</td>
<td>$t_{(39)} = 3.15$</td>
<td>0.0042</td>
<td>-31 21 9</td>
<td></td>
</tr>
<tr>
<td>Satiated: correlation F &gt; NF with BMI</td>
<td>8</td>
<td>Superior frontal gyrus (PFC) (bilateral)</td>
<td>8, 9</td>
<td>1146</td>
<td>$F_{(1,38)} = 9.18$</td>
<td>0.0053</td>
<td>-7 37 -9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Superior frontal gyrus (PFC) (bilateral)</td>
<td>6, 9</td>
<td>958</td>
<td>$F_{(1,38)} = 8.86$</td>
<td>0.0058</td>
<td>-16 52 33</td>
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</table>

$^1n = 20$ per group. The Talairach Client (http://www.talairach.org) was consulted to obtain an anatomic label of each single voxel of each significant cluster (35). Microsoft Excel was used to make an inventory on the quantity of each anatomic label of all the voxels within a cluster, to make a correct judgment on the anatomic localization of each significant cluster; here, the peak voxel coordinates are given as a reference. Cluster threshold was based on the estimate of the map’s spatial smoothness and on an iterative procedure (Monte Carlo simulation) for estimating cluster-level false-positive rates. After 1000 iterations, the minimum cluster size threshold that yielded a cluster-level false-positive rate ($\alpha$) of 5% was applied to each separate statistical map (33, 34). ACC, anterior cingulate cortex; BA, Brodmann area; F > NF, food > nonfood contrast; L, left hemisphere; PFC, prefrontal cortex; R, right hemisphere.
fasted with the satiated state showed a decrease in FRS from the fasted to the satiated state in the cingulate \( P < 0.005, t_{(39)} = 3.15 \) and the right prefrontal cortex (PFC) \( P < 0.006, t_{(39)} = 3.00 \).

In the fasted state, the whole group of participants showed a specific FRS in response to the food > nonfood contrast in the PFC \( P < 0.004, t_{(39)} = 3.17 \), left \( P < 0.009, t_{(39)} = 2.95 \) and right \( P < 0.005, t_{(39)} = 3.12 \) insula, ACC \( P < 0.004, t_{(39)} = 3.21 \), and thalamus \( P < 0.006, t_{(39)} = 2.96 \). Only in the ACC was this signaling more pronounced in the overweight than in the normal-weight subjects \( P < 0.005, F_{(1,38)} = 9.71 \) (Figure 3A). Furthermore, the food > nonfood contrast activation in the ACC was positively associated with BMI \( P < 0.004, r_{(38)} = 0.47 \pm 0.002 \).

In the satiated state, the complete subject group’s specific FRS in reaction to the food > nonfood contrast was limited to the left \( P < 0.005, t_{(39)} = 3.21 \) and right \( P < 0.006, t_{(39)} = 3.04 \) insula and the ACC \( P < 0.005, t_{(39)} = 3.15 \). When satiated, signaling in the ACC was less pronounced in the overweight than in the normal-weight subjects \( P < 0.006, F_{(1,38)} = 9.18 \) (Figure 3A). At the same time, in the satiated state, less pronounced FRS in the overweight than in the normal-weight subjects was observed in the PFC \( P < 0.006, F_{(1,38)} = 8.86 \) (Figure 3B), which suggests a lower inhibitory control. In the satiated condition, the food > nonfood contrast was negatively associated with BMI in the left PFC \( P < 0.005, r_{(38)} = -0.45 \pm 0.002 \).

**DISCUSSION**

The current study assessed differences between overweight and normal-weight subjects in FRS between food and nonfood-stimuli comparing a fasted and a satiated state while subject-specific energy requirements were controlled for. We hypothesized that overweight subjects had a more pronounced FRS in the fasted state than did the normal-weight subjects, which may remain elevated compared with that in normal-weight subjects, despite a decreased salience from the fasted to the satiated condition.

![Figure 3](image-url)
Our results showed that overweight subjects had a more pronounced food-reward anticipating related brain signaling in the fasted state in the ACC than did the normal-weight subjects. This is in line with previous research (1, 36, 37). Führer et al (1) previously observed a significant interaction in activation pattern between the states of hunger and satiety and stimulation with food and nonfood images in the left ACC, in the superior occipital sulcus, and in the vicinity of the right amygdala.

The second part of our hypothesis, comparing the fasted and the satiated state, was only partly confirmed; we observed a decrease in FRS from the fasted to the satiated state in the cingulate and the right PFC, which was also observed in previous research (3). However, the results did not confirm our hypothesis regarding the difference between normal-weight and overweight subjects in the fasted and satiated state. In fact, the exact opposite was found: when sufficiently satiated, FRS was less pronounced in the overweight than in the normal-weight subjects in the ACC and the PFC. This suggests that the higher focus on food in the overweight subjects, which has been reported in the literature (3, 11, 23), may fade in a sufficiently satiated state achieved by providing a meal according to subject-specific energy requirements. Born et al (19) previously identified the cingulate cortex as a brain area specific for “wanting” signaling. We observed that a postprandial decreased FRS in the cingulate cortex in the overweight compared with that in the normal weight can be attributed to the provision of a meal meeting subject-specific energy requirements. In addition to wanting, the incentive salience concept by Berridge (25, 38–40) and Finlayson et al (41) introduces the component of “liking.” We did not find any differences between the normal-weight and overweight subjects in brain signaling in the insula—the area associated with liking (19). We thus speculate that liking for food does not change between a fasted and satiated state in a comparison of overweight and normal-weight subjects. This is in line with several studies reporting that individuals rate liking at a constant level across several food items, irrespective of weight status or satiety state (20, 42–46).

However, our results showed that postprandial brain signaling in the PFC was lower in the overweight than in the normal weight, which we speculate may imply less inhibitory control in the overweight when satiated. The PFC forms an important part of the circuitry in which associations between visual cues and the actions or choices they specify are formed, and it plays a central role in the inhibition of inappropriate behaviors (47–49). A previous positron emission tomography study by Tataranni et al (28) in lean subjects, which used a subject-specific design similar to ours, already showed that satiation was associated with an increased activity in the PFC. Other positron emission tomography studies in lean and obese subjects further indicated that the PFC may play an important role in the central regulation of eating behavior by sending inhibitory inputs (28, 36, 47–52). Gautier et al (50, 51) reported a larger increase in PFC activity from the fasted to the satiated state in obese than in lean men and women, whereas Le et al (49) showed the exact opposite. The most recent study in line with our results shows an association between obesity and a satiation-related reduction in PFC activity (53). In an earlier study, Le et al reported the same increase in PFC activity caused by satiety in postobese women as in lean women.

In obese women this increase was significantly lower than in both lean and postobese women (48). The lack of differences in PFC signaling between lean and postobese research participants may be due to functional differences in the PFC as a consequence of obesity and are reversible, thus flexible. Because research showed that the decreased inhibitory control, observed as decreased PFC signaling, in the obese could be reversible, neurofeedback methods to increase activity in the PFC may be a target for prevention in the future. Among the studies using fMRI, the Batterink et al (2010) and Frankort et al (2011) showed that, in a hungry state, BMI is negatively associated with activation in the PFC when subjects are required to inhibit responses to appetizing foods (13, 23). A similar inverse relation between BMI and PFC activation was found in the current study in the satiated state. No correlation between BMI and PFC activity was found in the hungry state, given that the PFC is an area necessary for control we presume that this control signaling is not necessary in the fasted state.

We did not observe an effect of sex in any of the reward-related brain areas, although previous neuroimaging studies have reported significant sex differences in brain activation during the physiologic conditions of hunger and satiety in response to flavor (54, 55), food pictures (37, 56), and pure tastes (57). The strengths of our study were the simultaneous investigation of obese and lean participants in a fasted and satiated state, the use of well-matched food and nonfood cues, and the use of meals meeting identical subject-specific energy requirements. One limitation of the current study was that subjects did not perform a task during scanning. Therefore, we were not absolutely sure that attention to the stimuli was paid throughout the entire experiment. Furthermore, the repetition of the measurement on the same day was also a limitation. In future studies, adding a task during the interstimulus interval and counterbalancing the conditions on different test days would eliminate these limitations.

In conclusion, FRS was higher in the overweight subjects in the fasted state. When sufficiently satiated, FRS is lower in the overweight than in those of the normal weight, but inhibitory control is decreased, facilitating overeating, which may result in eating in the absence of hunger.

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The authors’ responsibilities were as follows—MJM: conceived and conducted the experiment (including the fMRI), analyzed the data, and wrote the manuscript; JMB: advised on the setup of the paradigm, assisted the experiment fMRI and the fMRI preprocessing, and reviewed the manuscript; SGTL: assisted the experiment fMRI and reviewed the manuscript; KH: provided the food and nonfood pictures for the paradigm and advised on the setup of the paradigm; AH: assisted the fMRI preprocessing and data analyses; RG: advised on the setup of the fMRI paradigm, supervised the fMRI data analysis, and reviewed the manuscript; TCA: advised on the data analyses and reviewed the manuscript; and MSW-P: conceived and supervised the experiment, supervised the data analysis, and reviewed the manuscript. Top Institute Food and Nutrition did not influence the study design, implementation, analysis, or interpretation of data. None of the authors declared a conflict of interest.

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