Effect of satiety on brain activation during chocolate tasting in men and women[1–3]

Paul AM Smeets, Cees de Graaf, Annette Stafleu, Matthias JP van Osch, Rutger AJ Nievelstein, and Jeroen van der Grond

ABSTRACT

Background: The brain plays a crucial role in the decision to eat, integrating multiple hormonal and neural signals. A key factor controlling food intake is selective satiety, ie, the phenomenon that the motivation to eat more of a food decreases more than does the motivation to eat foods not eaten.

Objective: We investigated the effect of satiation with chocolate on the brain activation associated with chocolate taste in men and women.

Design: Twelve men and 12 women participated. Subjects fasted overnight and were scanned by use of functional magnetic resonance imaging while tasting chocolate milk, before and after eating chocolate until they were satiated.

Results: In men, chocolate satiation was associated with increased taste activation in the ventral striatum, insula, and orbitofrontal and medial orbitofrontal cortex and with decreased taste activation in somatosensory areas. Women showed increased taste activation in the precentral gyrus, superior temporal gyrus, and putamen and decreased taste activation in the hypothalamus and amygdala. Sex differences in the effect of chocolate satiation were found in the hypothalamus, ventral striatum, and medial prefrontal cortex (all $P < 0.005$).

Conclusions: Our results indicate that men and women differ in their response to satiation and suggest that the regulation of food intake by the brain may vary between the sexes. Therefore, sex differences are a covariate of interest in studies of the brain's responses to food. *Am J Clin Nutr* 2006;83:1297–305.

KEY WORDS Functional MRI, functional magnetic resonance imaging, brain, satiation, satiety, satiety response, sex differences

INTRODUCTION

The brain plays a crucial role in the decision to eat, integrating multiple hormonal and neural signals that convey information about the body's nutritional status (1). Among the many factors that influence the decision to start or stop eating, such as social context, the amount of food left, and dietary restraint, the volume and energy content of the food consumed are most important. As more food is ingested, the feeling of fullness becomes stronger and the motivation to eat decreases (2, 3). However, when a certain food is eaten, its pleasantness and the motivation to eat more of it decrease gradually, even though the stomach is not yet full (4). In this case, one is still motivated to consume other foods, particularly those with different sensory characteristics; ie, one is not satiated per se, but is satiated to the specific food that was consumed. This phenomenon has been termed *selective satiety* (5). Another widely used and closely related term, introduced by Rolls et al (6), is *sensory-specific satiety*. This term is also used to refer to what we defined above as selective satiety, but is usually more specific, referring to selective satiety of one of the senses, eg, olfactory sensory-specific satiety. Following the definitions of Blundell, we use the term *satiation* when referring to the process of becoming satiated, which ends with meal termination, and the term *satiety* when referring to the subsequent state of being satiated (7). Sensory-specific satiation for odor and taste have been shown to have neural correlates in the orbitofrontal cortex (8, 9).

Although sex differences in eating behavior have often been described (10–14), sex differences in the brain activation associated with food stimuli are undocumented. Most neuroimaging studies investigating the effects of food stimuli use either men or both men and women. For a better understanding of the regulation of food intake, it might be important to differentiate between men and women. In the present study, we examine the effect of satiation with chocolate on the brain activation associated with chocolate taste in both men and women.

SUBJECTS AND METHODS

Subjects

Twenty-four healthy normal-weight volunteers participated [12 men, mean age 21.3 ± 2.8 y, mean body mass index (BMI; in kg/m^2) 21.5 ± 1.6, and 12 women, mean age 20.5 ± 1.4 y, mean BMI 22.0 ± 1.4). Subjects were recruited through an advertisement put up at various locations in the University Medical

[1] From the Image Sciences Institute (PAMS, MJPvO, and JvdG) and the Department of Radiology (RAJN), University Medical Center Utrecht, Utrecht, Netherlands; the Department of Food and Chemical Risk Analysis, TNO Quality of Life, Zeist, Netherlands (PAMS, CdG, and AS); and the Department of Radiology, Leiden University Medical Center, Leiden, Netherlands (MJPvO and JvdG).

[2] Supported by the Dutch Ministry of Education, Culture and Science and the Dutch Ministry of Health, Welfare and Sport.

[3] Reprints not available. Address correspondence to PAM Smeets, University Medical Center Utrecht, Image Sciences Institute, Heidelberglaan 100, room Q0S.459, 3584 CX Utrecht, The Netherlands. E-mail: paul@isi.uu.nl.

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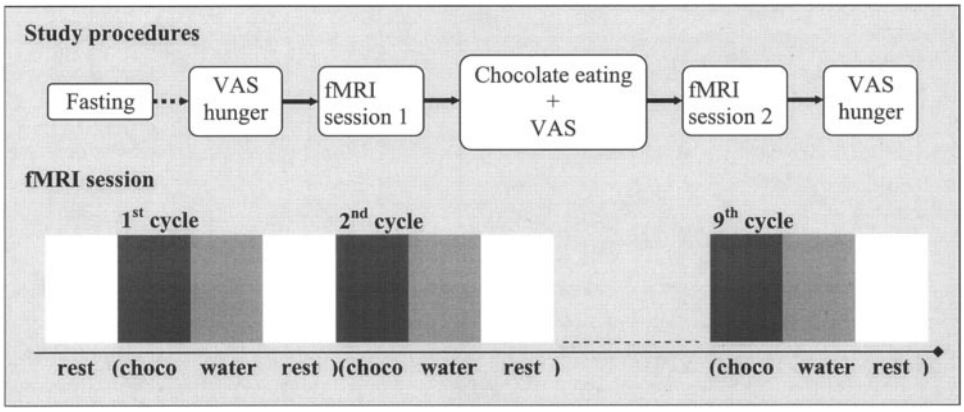

FIGURE 1. Summary of study procedures and visual representation of the functional magnetic resonance imaging (fMRI) block design. Choco, administration of chocolate milk; VAS, visual analogue scale; water, administration of water.

Center Utrecht. We used a Health and Lifestyle Questionnaire to assess general health and aspects of lifestyle relevant to the study and the Dutch Eating Behavior Questionnaire (15) to assess eating behavior (restrained eating in particular). The main purpose of these questionnaires was to screen for subjects who would in any way be unwilling to consume a large amount of chocolate, eg, because they were consuming a medically prescribed diet or were concerned with their weight. Exclusion criteria included a BMI <19 or >25; being under 18 or over 28 y of age on the study day; smoking; a history of alcohol consumption or current alcohol consumption of >28 units/wk; a history of medical or surgical events that may significantly affect the study outcome, such as metabolic or endocrine disease or any gastrointestinal disorder; irregular eating habits; following a weight-reduction diet or a medically prescribed diet; restrained eating [for men, a score >2.50, and for women, a score >3.50 on the Dutch Restrained Eating Questionnaire (15)]; use of medication (except aspirin, paracetamol, or contraceptive pills); claustrophobia; diabetes; and metal implants or metal objects on the body that cannot be removed (eg, piercing, hearing aid, or brace). Written informed consent was obtained from all subjects according to the Declaration of Helsinki, and the study protocol was approved by the Medical Ethical Committee of the University Medical Center Utrecht, Utrecht, The Netherlands.

Experimental procedures

The study procedures are summarized in **Figure 1**. The subjects were instructed to fast overnight from 2200 (no food or beverages, except water). In the morning, the subjects were scanned twice: before eating bittersweet chocolate until satiety (ie, fasted) and after (ie, satiated). During both scans, chocolate milk was administered (0.1 mL/s) followed by water (0.2 mL/s, to wash away the chocolate taste) and a rest period: 3 blocks of 30 s each, repeated 9 times. Stimuli were administered at room temperature (23 °C). To achieve chocolate satiety, the subjects were satiated with bittersweet chocolate because this is a food with a strong taste that requires chewing, which leads to prolonged and enhanced sensory stimulation. Hence, it was expected that a relatively small amount would induce chocolate satiety, circumventing overall satiety due to filling of the stomach (volume effect). After eating the chocolate, the subjects rinsed their mouths with tap water to remove chocolate residues, which might otherwise have affected their subsequent taste experience in the scanner. Chocolate milk was used as a stimulus during scanning because it has a chocolate flavor and is relatively easy to administer.

Scans were performed on a 1.5-T Philips Gyroscan ACS-NT system (Philips Medical Systems, Best, The Netherlands) by using a multislice 2D single-shot EPI sequence [repetition time/echo time (TR/TE) = 2500/45 ms, flip angle = 90°, 24 interleaved slices, $4 \times 4 \times 4$ mm^3 voxels). In addition, an anatomical T_1-weighted volume was acquired (TR/TE = 30/4.6 ms, flip angle = 30°, 48 axial slices, $1 \times 1 \times 2$ mm^3 voxels). So that we could assess their general motivation to eat, the subjects filled out a set of 4 visual analogue scales (VASs, range: 0 to 100 mm) before the first and after the second scan session on which they reported their feelings of general hunger, fullness, general desire to eat, and prospective food consumption (16). For every subject, the scores of these 4 scales were averaged to obtain a single general hunger score. To keep the subjects alert in monitoring the chocolate's taste and their motivation to eat during chocolate eating, palatability and desire to eat more chocolate were assessed after every 2 pieces of chocolate eaten (≈13 g) with 2 other VASs.

Data processing and analysis

Functional magnetic resonance imaging (fMRI) data were preprocessed and analyzed with the SPM2 software package (Wellcome Department of Imaging Neuroscience, London, United Kingdom) implemented in MATLAB 6.5 (The Mathworks Inc, Natick, MA). The functional volumes of every subject were realigned to the first volume of the first run, globally normalized (resampling to $2 \times 2 \times 2$ mm^3), and spatially smoothed with a gaussian kernel of 10 mm full width at half maximum. A statistical parametric map was generated for every subject by fitting a boxcar function to each time series, convolved with the canonical hemodynamic response function and its temporal derivative. Data were high-pass filtered with a cutoff of 128 s. Both the chocolate milk and the water delivery blocks were modeled. The response to water, however, was neglected in further analyses, because water delivery only served to wash away the preceding chocolate taste. To regress out motion-related activations, the motion-correction parameters from the realignment procedure were added to the model as covariates.

Within-subject analyses

For every subject, parameters were estimated for 6 comparisons (usually referred to as *contrasts*), yielding 6 contrast images: 2 for tasting chocolate milk in the hungry state versus rest (activation termed *taste hungry* and deactivation termed *taste hungry neg*), 2 for tasting chocolate milk in the satiated state versus rest (activation termed *taste satiated* and deactivation termed *taste satiated neg*), and 2 contrast images assessing the effects of satiation on taste activation. For the last 2 contrast images, 1 assessed the positive effects of satiation, ie, areas where the taste activation in the satiated state was greater than that in the hungry state (termed *taste satiated minus taste hungry*), and 1 assessed the negative effects of satiation, ie, areas where the taste activation in the hungry state was greater than that in the satiated state (termed *taste hungry minus taste satiated*). In the last analysis, taste-specific activations unaffected by satiation, ie, activations common to both states that were not of interest here, are expected to subtract out (eg, motor activations related to tongue movement and swallowing). This is because taste activations in the 2 states are compared within 1 subject. By *activation* we refer to fMRI signal increases, and by *deactivation* to fMRI signal decreases.

Between-subject analyses

Group analyses were performed by using the contrast images. Our main analysis involved subtraction of activation maps in the fasted and the satiated state. Because the main aim of this study was to study differences in taste activation due to satiation with chocolate, areas of taste deactivation were disregarded during the analyses by means of masking. Mask images were created by performing one-sample *t* tests on the taste hungry neg and taste satiated neg contrast images of men, women, and both men and women. The resulting *t*-maps were thresholded at $P = 0.05$ (uncorrected for multiple comparisons) and converted to exclusive binary mask images. The following analyses were performed:

1) Effects of satiation on taste activation in men and women. Voxels where satiation resulted in fMRI signal increases were tested for by putting the taste satiated minus taste hungry contrast images of men and women into a one-sample *t* test, masked for deactivation during hunger. Similarly, voxels where satiation resulted in fMRI signal decreases were tested for by putting the taste hungry minus taste satiated contrast images of men and women into a one-sample *t* test, masked for deactivation during satiety. T-maps were thresholded at $P = 0.005$ (uncorrected for multiple comparisons).

2) Sex differences in the effect of satiation on taste activation. Voxels with a differential effect of satiation on taste activation in men and women were tested for by comparing the taste satiated minus taste hungry and taste hungry minus taste satiated contrast images of men and women by using two-sample *t* tests. In this analysis, a positive effect of satiation that is greater in men than in women is equivalent to a negative effect of satiation that is greater in women than in men.

3) Region of interest (ROI) analysis. In addition to the whole-brain analyses outlined above, we performed the same tests confined to 4 a priori ROIs: the hypothalamus, the amygdala, the insula, and the orbitofrontal cortex. All of these regions have been implicated in taste processing, and the hypothalamus and amygdala are areas showing sex differences in response to emotional stimuli (1, 17–20). ROIs were analyzed by using the WFU Pickatlas tool (21), which confines the analysis to a volume of interest and uses SPM's small volume correction. The hypothalamic ROI was defined as an 8-mm sphere centered on Montreal Neurological Institute coordinates (0, −4, −8) and the amygdala ROI as two 8-mm spheres centered on Montreal Neurological Institute coordinates (−20, −4, −20) and (20, −4, −20). For the insula ROI, we used the mask image supplied with the WFU Pickatlas tool. The orbitofrontal cortex ROI consisted of a mask containing all orbital gyri and was generated by use of the software package MARINA (Bender Institute of Neuroimaging, University of Giessen, Giessen, Germany), which uses the anatomical parcellation of the brain published by Tzourio-Mazoyer et al (22).

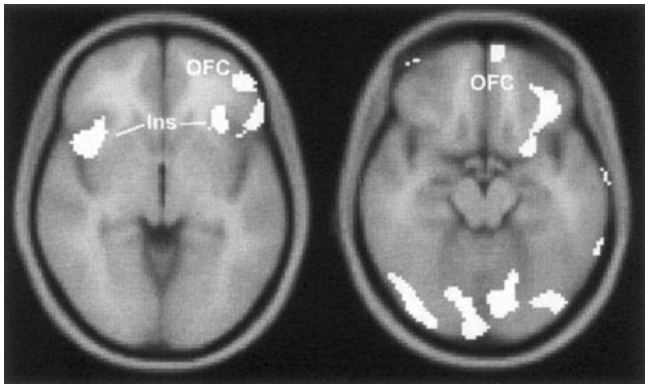

FIGURE 2. T-value maps of the brains of 2 subjects tasting chocolate milk overlaid on axial anatomical slices in neurologic orientation (ie, left is left). Images were obtained with the use of magnetic resonance imaging. The T-value maps are thresholded at $T = 4.79$ ($P = 0.05$, family-wise error-corrected for multiple comparisons). Taste activations were assessed by statistical parametric mapping. This figure shows our ability to measure significant taste activations in the insula (Ins) and orbitofrontal cortex (OFC).

4) Subjective ratings. Mean (general) hunger scores were calculated for every subject by averaging the VAS scores of general hunger (100 minus fullness), general desire to eat, and prospective food consumption. The effect of chocolate satiation on the mean hunger score and the general desire to eat was calculated by subtracting the score in the fasted state from that in the satiated state. Similarly, the decrease in chocolate palatability and the desire to eat more chocolate were calculated by subtracting the score in the fasted state (after the first 2 pieces of chocolate) from that in the satiated state (after the last piece of chocolate eaten).

Sex differences in these VAS scores and in the effect of satiation on them were tested for with a two-sample *t* test. Also, Pearson's correlation coefficients were calculated between these VAS scores (mean general hunger score, general desire to eat, palatability, and desire to eat chocolate) and the amount of chocolate eaten and between the effect of satiation on these scores and the amount of chocolate eaten. These analyses were done with SPSS statistical software (version 12.0.1; SPSS Inc, Chicago, IL). *P* values < 0.05 (two-sided) were considered significant.

RESULTS

Our ability to measure significant taste activations in single subjects in the insula and orbitofrontal cortex is shown in **Figure 2** ($P < 0.05$ corrected for multiple comparisons). The latter is an

TABLE 1
Brain regions affected by satiation with chocolate in men[1]

Region	Effect of satiation	Cluster size[2]	Peak voxel location[3]			z Score	SD[4]
			x	y	z		
Whole brain							
L ventral striatum–globus pallidus	pos	197[5]	−20	−8	−4	3.83	0.15
L ventral striatum–globus pallidus	pos	197[5]	−16	−2	0	3.39	0.26
L putamen	pos	197[5]	−35	−6	2	3.35	0.22
L precentral gyrus	pos	136	−34	−16	38	3.69	0.37
L dlPFC–superior frontal gyrus	pos	34	−14	12	66	3.55	0.28
R orbitofrontal cortex	pos	81	22	32	−4	3.47	0.34
L medial OFC–anterior cingulate	pos	63	−6	26	−4	3.33	0.28
L anterior insula	pos	112[5]	34	4	10	3.23	0.37
L dorsal striatum–putamen	pos	112[5]	−24	6	8	3.19	0.28
L cuneus	pos	48	−8	−80	20	3.21	0.40
L precentral gyrus	pos	72	−40	−8	36	3.17	0.53
L superior occipital gyrus	pos	92	−20	−90	16	3.09	0.44
L inferior parietal lobule	neg	29	−54	−34	54	3.24	0.57
L superior parietal lobule	neg	47	−42	−46	62	3.18	0.58
mPFC–superior frontal gyrus	neg	40	0	26	46	2.95	0.47
Insula ROI							
L anterior insula	pos	16	−34	4	10	3.23	0.37
R anterior insula–frontal operculum	pos	26	38	12	10	2.96	0.41
Orbitofrontal cortex ROI							
L medial OFC–anterior cingulate	pos	16	−6	26	−4	3.33	0.28

[1] Effects of satiation were tested for by performing *t* tests on the difference between taste activation in the fasted state and that in the satiated state for all brain voxels by using statistical parametric mapping. dlPFC, dorsolateral prefrontal cortex; L, left; mPFC, medial prefrontal cortex; neg, decreased taste activation after satiation; OFC, orbitofrontal cortex; pos, increased taste activation after satiation; R, right; ROI, region of interest.

[2] Reported clusters were thresholded at $P < 0.005$ with a cluster threshold of $K > 20$ voxels for the whole brain and $K > 10$ voxels for ROIs.

[3] Voxel coordinates are in the Montreal Neurological Institute (MNI) space (23).

[4] The SD was calculated by taking the square root of the residual variance, ie, the variance in the data that is not explained by the model that was fitted to the data.

[5] A cluster of significant voxels that contains more than one peak voxel or encompasses more than one anatomical location.

area that can be difficult to image by using fMRI because of signal loss caused by the air in the nasal cavity and sinuses.

Effect of satiation on taste activation in men and women

Brain regions in men and women in which chocolate satiation affected taste activation are tabulated in **Table 1** and **Table 2**, respectively. In men, chocolate satiation was associated with increased taste activation in the posterior part of the left ventral striatum (globus pallidus and putamen), left precentral gyrus, dorsolateral prefrontal cortex, left dorsal striatum (putamen), anterior insula, and the orbitofrontal and medial orbitofrontal cortex (anterior cingulate). Decreased taste activation was observed in somatosensory areas (inferior and superior parietal lobules) and the medial prefrontal cortex (medial part of the superior frontal gyrus, just anterior of the supplementary motor area). Selected activations are shown in **Figure 3**. Men showed no effect of satiation in the amygdala or hypothalamus.

In women, chocolate satiation was associated with increased taste activation in the precentral gyrus (bilaterally, but predominantly on the right), right superior temporal gyrus, and ventral striatum (putamen). Decreased taste activation was observed in the hypothalamus and amygdala. Selected activations are shown in **Figure 4**. Women showed no effect of satiation in the insula or orbitofrontal cortex.

Sex differences in the effect of chocolate satiation on taste activation

Brain regions that are differentially affected by chocolate satiation in men and women are tabulated in **Table 3**. Sex differences in the effect of chocolate satiation were found in the hypothalamus (a region showing a negative effect of satiation on taste activation in women, *see* Table 2 and Figure 4), ventral striatum (a region showing a positive effect of satiation on taste activation in men, *see* Table 1 and Figure 3), and medial prefrontal cortex (medial frontal gyrus, a region with a negative effect of satiation on taste activation in men, *see* Table 1 and Figure 3). No significant differences between the sexes were found in the insula, amygdala, or orbitofrontal cortex.

Subjective ratings

VAS scores and the amount of chocolate eaten are summarized in **Table 4**. On average, the men ate more chocolate than did the women ($P < 0.05$) and reported to be hungrier than the women were at the start of the experiment ($P < 0.05$). However, the decrease in the general hunger score due to chocolate eating did not differ between the sexes, nor did the scores relating to general desire to eat (Table 4). The scores of chocolate palatability and desire to eat chocolate and the decreases therein also did not differ significantly between men and women. In both sexes, the

TABLE 2
Brain regions affected by satiation with chocolate in women[1]

Region	Effect of satiation	Cluster size[2]	Peak voxel location[3]			z Score	SD[4]
			x	y	z		
Whole brain							
R precentral gyrus	pos	475[5]	44	−14	48	3.47	0.42
R precentral gyrus	pos	475[5]	56	−2	32	2.98	0.62
R superior temporal gyrus	pos	63	66	−30	12	3.29	0.31
R ventral striatum–putamen	pos	38	30	−16	−6	3.21	0.34
R superior temporal gyrus	pos	41	54	−10	8	2.90	0.79
L precentral gyrus	pos	18	−42	−16	48	2.81	0.50
Hypothalamus	neg	114	2	−4	−4	4.49	0.35
L amygdala	neg	92	−18	−6	−22	4.12	0.33
Amygdala ROI							
L amygdala	neg	65	−18	−6	−22	4.12	0.33
Hypothalamus ROI	neg	93	2	−4	−4	4.49	0.35

[1] Effects of satiation were tested for by performing *t* tests on the difference between taste activation in the fasted state and that in the satiated state for all brain voxels by using statistical parametric mapping. L, left; neg, decreased taste activation after satiation; pos, increased taste activation after satiation; R, right; ROI, region of interest.
[2] Reported clusters were thresholded at $P < 0.005$ with a cluster threshold of $K > 20$ voxels for the whole brain and $K > 10$ voxels for ROIs.
[3] Voxel coordinates are in the Montreal Neurological Institute (MNI) space (23).
[4] The SD was calculated by taking the square root of the residual variance, ie, the variance in the data that is not explained by the model that was fitted to the data.
[5] A cluster of significant voxels that contains more than one peak voxel.

decrease in the general desire to eat was smaller than the decrease in the desire to eat chocolate ($P < 0.05$). Correlations between the amount of chocolate eaten and (changes in) subjective ratings in men and women are shown in **Table 5**. In both men and women, the decrease in the desire to eat chocolate correlated positively with the amount of chocolate eaten (men, $r = 0.60$; women, $r = 0.62$; both $P < 0.05$), whereas the decrease in chocolate palatability did not. In women, there was a strong negative correlation between the general desire to eat in the fasted state and the amount of chocolate eaten ($r = -0.82$, $P < 0.01$). Thus, women who reported a higher general desire to eat at the start of the experiment subsequently ate a smaller amount of chocolate.

DISCUSSION

We investigated the effects of satiation with chocolate on the brain activation associated with chocolate taste and found that these are mostly different in men and women. Effects of satiation on brain activation have been shown for visual, olfactory, and gustatory food stimuli (8, 9, 24–27). In particular, it has been reported that brain activation in parts of the orbitofrontal cortex decreases after selective satiation (8, 9, 25). These studies used men or men and women. In our study, we examined men and women separately. In men, we found increased taste activation in parts of the orbitofrontal cortex in response to chocolate satiation, whereas in women we found no effects in the orbitofrontal cortex. O'Doherty et al (8) found decreased olfactory activation in part of the orbitofrontal cortex after satiation with bananas (the sex of the subjects was not reported). Kringelbach et al (9) found that similar parts of the orbitofrontal cortex showed decreased brain activation in response to tomato juice and chocolate milk after these were drunk to satiety. It should be noted that the method of analysis in both these studies was aimed at detecting activation decreases. In a positron-emission study in which subjects of both sexes were gradually satiated with chocolate, the

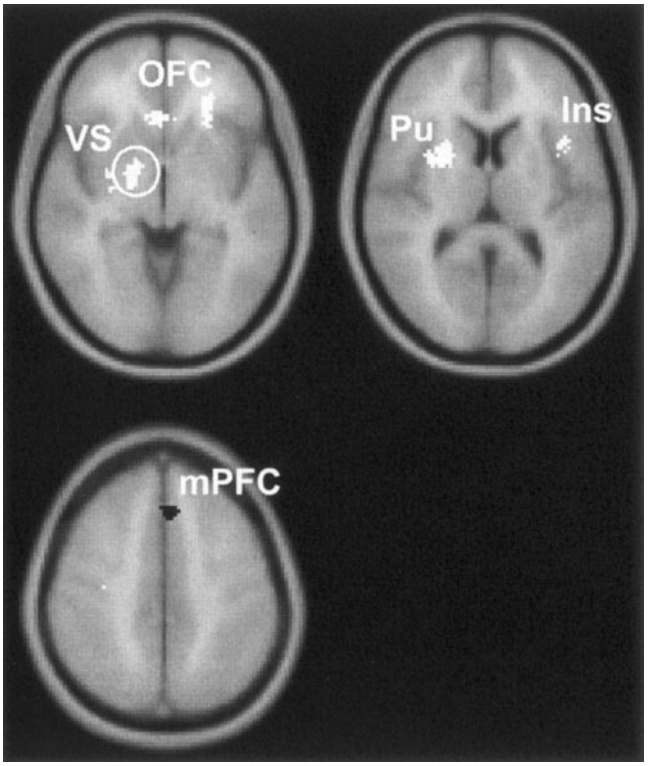

FIGURE 3. Brain regions in men ($n = 12$) where the taste activation in response to chocolate milk was affected by satiation with chocolate. Shown are T-value maps thresholded at $T = 3.11$ ($P = 0.005$ uncorrected for multiple comparisons) overlaid on axial sections of an average anatomical image in neurologic orientation (ie, left is left). Images were obtained with the use of magnetic resonance imaging. Regions with increased taste activation after satiation are shown in white; regions with decreased taste activation after satiation are shown in black. Differences in taste activation induced by satiation with chocolate were assessed by statistical parametric mapping. The figure is intended for visual inspection of some regions of the brain, including the insula (Ins), medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), putamen (Pu), and ventral striatum (VS). Details of all affected brain regions are shown in Table 1.

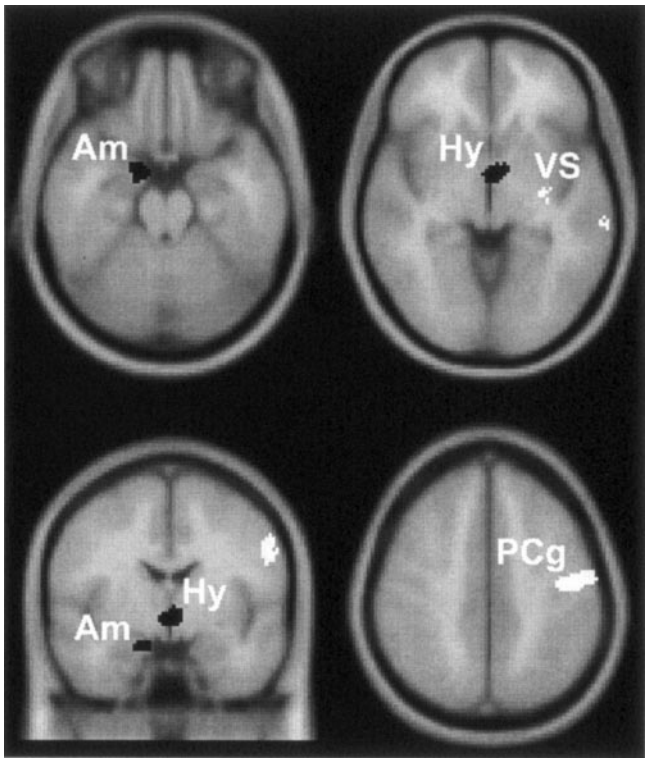

FIGURE 4. Brain regions in women ($n = 12$) where the taste activation in response to chocolate milk was affected by satiation with chocolate. Shown are T-value maps thresholded at $T = 3.11$ ($P = 0.005$ uncorrected for multiple comparisons) overlaid on sections of an average anatomical image in neurologic orientation (ie, left is left). Images were obtained with the use of magnetic resonance imaging. Regions with increased taste activation after satiation are shown in white; regions with decreased taste activation after satiation are shown in black. Differences in taste activation induced by satiation with chocolate were assessed by statistical parametric mapping. The figure is intended for visual inspection of some regions of the brain, including the amygdala (Am), hypothalamus (Hy), precentral gyrus (PCg), and ventral striatum (VS). Details of all affected brain regions are shown in Table 2.

decreasing reward value correlated with decreased activation in the caudomedial orbitofrontal cortex and increased activation in the caudolateral orbitofrontal cortex (25). This suggests that changes in orbitofrontal cortex activation after selective satiation relate to the decreased motivation to eat. Taken together, these and our findings warrant further investigation of the roles of the orbitofrontal cortex in the processing of food stimuli, looking at increases as well as decreases in activation and bearing sex in mind.

We found positive effects of satiation on taste activation in men in the ventral and dorsal striatum and in women in the ventral striatum. In men, effects of sensory-specific satiation with chocolate milk on taste activation in the ventral striatum (putamen) were found that were absent when the subjects were satiated with tomato juice (9). Moreover, Small et al (25) reported effects of satiation with chocolate in striatal regions (dorsal striatum, putamen, and caudate). This suggests that these striatal effects of satiation are specific to chocolate.

We found positive effects of chocolate satiation in the precentral gyrus (motor cortex) in both sexes. Other studies, with different methods, also showed effects of satiation on precentral gyrus activation (25, 27). In men, we observed decreased taste activation in response to satiation in somatosensory areas. This agrees with positron-emission data showing increased glucose metabolism in the somatosensory cortex of hungry subjects in response to the multimodal presentation of an attractive food (28). Another positron-emission study, which found enhanced resting state metabolism in the oral somatosensory cortex of obese subjects, suggested that this could indicate increased sensitivity to the rewarding properties of food (29). Similarly, in our study, satiation could have caused desensitization in somatosensory areas.

Amygdala

The amygdala is known to respond to both aversive and pleasant taste stimuli (30, 31). We found that amygdala activation in women decreased after chocolate satiation. This agrees with previous studies reporting decreased activation in the amygdala after odor-specific satiation (8) and smaller amygdala responses

TABLE 3
Brain regions that were differentially affected in 12 men and 12 women by satiation with chocolate[1]

Region	Cluster size[2]	Peak voxel location[3]			z Score	SD[4]
		x	y	z		
Whole brain						
Hypothalamus[5]	122[6]	−2	−4	−6	3.66	0.80
L ventral striatum–globus pallidus[7]	122[6]	−14	−2	−2	3.26	0.43
R medial frontal gyrus[8]	33	6	26	46	3.25	0.55
Hypothalamus ROI						
Hypothalamus	98	−2	−4	−6	3.66	0.80

[1] L, left; R, right; ROI, region of interest. Differential effects of satiation in men and women were tested for by comparing the effect of satiation with chocolate on taste activity during tasting chocolate milk for all brain voxels with a t test and statistical parametric mapping.
[2] Reported clusters were thresholded at $P < 0.005$ with a cluster threshold of $K > 20$ voxels for the whole brain and $K > 10$ voxels for ROIs.
[3] Voxel coordinates are in the Montreal Neurological Institute (MNI) space (23).
[4] The SD was calculated by taking the square root of the residual variance, ie, the variance in the data that is not explained by the model that was fitted to the data.
[5] Region with a negative effect of satiation on taste activation in women.
[6] A cluster of significant voxels that encompasses more than one anatomical location.
[7] Region with a positive effect of satiation on taste activation in men.
[8] Region with a negative effect of satiation on taste activation in men.

TABLE 4
Subjective ratings in and the amount of chocolate eaten by men and women[1]

Measure	Men ($n = 12$)	Women ($n = 12$)
VAS general hunger, fasted	78 ± 10	70 ± 8[2]
VAS general hunger, satiated	32 ± 20	25 ± 16
Decrease VAS hunger (fasted − satiated)	46 ± 22	44 ± 18
VAS general desire to eat, fasted	76 ± 18	70 ± 14
VAS general desire to eat, satiated	27 ± 21	25 ± 27
Decrease VAS general desire to eat (fasted − satiated)[3]	49 ± 27	45 ± 28
VAS palatability of chocolate, fasted	85 ± 13	84 ± 11
VAS palatability of chocolate, satiated	39 ± 27	22 ± 21
Decrease VAS palatability of chocolate (fasted − satiated)	46 ± 33	61 ± 21
VAS desire to eat chocolate, fasted	84 ± 14	79 ± 13
VAS desire to eat chocolate, satiated	8 ± 11	2 ± 3
Decrease VAS desire to eat chocolate (fasted − satiated)[3]	76 ± 20	77 ± 13
Amount of chocolate eaten (g)	157 ± 59	106 ± 48[2]

[1] All values are $\bar{x} \pm$ SD. Visual analogue scale (VAS) scores were taken before (fasted) and after (satiated) subjects ate bittersweet chocolate until they were satiated.
[2] Significantly different from men, $P < 0.05$ (two-sample t test).
[3] The decrease in the general desire to eat was significantly smaller than the decrease in the desire to eat chocolate in men (paired-sample t test, $P < 0.01$) and in women (paired-sample t test, $P < 0.05$).

to food-related visual stimuli in response to satiation (24). Amygdala activation has been linked to emotional intensity (18, 32) and, more generally, to the significance of the stimulus being evaluated (24, 33). Our findings in women agree with this: the taste of a liked food is more significant during hunger than during satiety and this is reflected in amygdala activation. In men, we found no effect of satiation on amygdala activation. Sex differences in amygdala response have been reported in the context of visual emotional stimuli (19, 30, 34), but not in the context of satiation.

Hypothalamus

The hypothalamus is important in the regulation of food intake (1, 17). In women, we found decreased taste activation in the hypothalamus in response to satiation. This could reflect the decrease in hunger, ie, the decreased motivation to eat chocolate. This hypothesis agrees with previous work suggesting that neuronal activity in the lateral hypothalamic area represents reward value (35) and that activity in the dorsomedial hypothalamus represents hunger (17).

Insula

The insula contains the primary taste cortex. In our study, taste activation in the anterior insula increased after satiation in men. Small et al (25) reported relative cerebral blood flow decreases with decreasing reward value of chocolate in the dorsal insula-operculum. In contrast, it was shown in macaques that the responsiveness of neurons in the insular gustatory cortex is independent of hunger (36). Also, the anterior insula responds in a similar way to the oral delivery of water in the thirsty and the satiated state (37). This suggests that more studies using different taste stimuli and motivational states are needed to further elucidate the functional neuroanatomy of the insula.

Sex differences

We found sex differences in the effect of satiation in the hypothalamus, ventral striatum, and medial prefrontal cortex. This adds to the growing number of studies reporting sex differences in stimulus processing in the brain, including responses to visual emotional stimuli (19, 34, 38, 39), sadness (40), odors (32), and extreme hunger and satiety (41). The sex differences we found suggest that satiation might work differently in men and women. There is supportive evidence for this from other fields that suggests that women are more affected than men by the hedonic value of food (42, 43).

Study design

We maximized chocolate satiety and minimized the amount of chocolate ingested by satiating subjects with small pieces of chocolate with a high cocoa content (52%). As intended, the decrease in the general desire to eat was smaller than the decrease in the desire to eat chocolate in both sexes. As in normal eating behavior, satiation with chocolate in our experiment involved not

TABLE 5
Pearson's correlation coefficients for the correlation between the amount of chocolate eaten and (changes in) subjective ratings in men and women[1]

	Correlation with the amount of chocolate eaten (g)		
Measure	Men ($n = 12$)	Women ($n = 12$)	Men and women ($n = 24$)
VAS general hunger, fasted	0.36	−0.69[2]	0.13
Decrease VAS general hunger (fasted − satiated)	0.34	−0.37	0.08
VAS general desire to eat, fasted	−0.03	−0.82[3]	−0.21
Decrease VAS general desire to eat (fasted − satiated)	−0.01	−0.33	−0.11
VAS palatability of chocolate, fasted	0.17	0.09	0.15
Decrease VAS palatability of chocolate (fasted − satiated)	0.12	0.19	0.00
VAS desire to eat chocolate, fasted	0.56	0.55	0.57[3]
Decrease VAS desire to eat chocolate (fasted − satiated)	0.60[2]	0.62[2]	0.53[3]

[1] Visual analogue scale (VAS) scores were taken before (fasted) and after (satiated) subjects ate bittersweet chocolate until they were satiated.
[2] Significant correlation, $P < 0.05$.
[3] Significant correlation, $P < 0.01$.

only satiation for a particular taste (chocolate) but also an inevitable concomitant increase in overall satiety because of the volume and energy content of the food ingested (3, 44). Thus, the observed effects of chocolate satiation on taste activation primarily reflect the decreased motivation to consume more chocolate, but also incorporate a decrease in the general motivation to eat.

We used solid chocolate for satiation and chocolate milk for tasting in the scanner. This approach presumes that satiation for solid chocolate extends to other chocolate substances. With the use of a similar approach with bananas and banana odor, effects of olfactory sensory-specific satiation were shown in the brain for the first time (8). Ideally, the same substance is used for satiation and testing. However, in fMRI paradigms, this precludes solid food stimuli.

Another source of variability that is part of every study of this kind lies in the differences in the taste experience of subjects. Some might find the chocolate taste to be stronger than others do; also, the effect of this strong taste on the subsequent tasting of chocolate milk likely varies between subjects. This could be assessed by obtaining taste intensity ratings. However, how differences in taste intensity experienced by subjects relate to their patterns of brain activity remains to be investigated.

In summary, we showed different effects of chocolate satiation on taste activation in men and women. Our results suggest that the sexes differ in their response to satiation. Therefore, sex differences are a covariate of interest in studies of the brain's responses to tasting food and the regulation of food intake.

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