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Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals

Yvonne Rothemund,[a,*] Claudia Preuschhof,[b] Georg Bohner,[c] Hans-Christian Bauknecht,[c] Randolf Klingebiel,[c] Herta Flor,[d] and Burghard F. Klapp[a]

[a]*Center for Internal Medicine and Dermatology, Department of Psychosomatic Medicine, Charité — University Medicine, Charité Platz 1, 10117 Berlin, Germany*
[b]*Berlin Neuroimaging Center, Department of Neurology, Charité — University Medicine, Schumannstr. 20/21, 10117 Berlin, Germany*
[c]*Department of Neuroradiology, Charité — University Medicine, Charité Platz 1, 10117 Berlin, Germany*
[d]*Department of Clinical and Cognitive Neuroscience, University of Heidelberg, Central Institute of Mental Health, J5, 68159, Mannheim, Germany*

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The neural systems regulating food intake in obese individuals remain poorly understood. Previous studies applied positron emission tomography and manipulated hunger and satiety to investigate differences in appetitive processing between obese and normal-weight individuals. However, it is not known whether manipulation of stimulus value may yield different neural activity in obese as compared to control subjects when intrinsic physiological states are kept constant. We used functional magnetic resonance imaging to investigate 13 obese and 13 normal-weight subjects and manipulated food motivation by presenting visual food stimuli differing in their caloric content and energy density.

In contrast to controls, obese women selectively activated the dorsal striatum while viewing high-caloric foods. Moreover, in the high-calorie condition body mass index (BMI) predicted activation in the dorsal striatum, anterior insula, claustrum, posterior cingulate, postcentral and lateral orbitofrontal cortex.

The results indicate that in obese individuals simple visual stimulation with food stimuli activates regions related to reward anticipation and habit learning (dorsal striatum). Additionally, high-calorie food images yielded BMI-dependent activations in regions associated with taste information processing (anterior insula and lateral orbitofrontal cortex), motivation (orbitofrontal cortex), emotion as well as memory functions (posterior cingulate).

Collectively, the results suggest that the observed activation is independent of the physiological states of hunger and satiation, and thus may contribute to pathological overeating and obesity. Some of the observed activations (dorsal striatum, orbitofrontal cortex) are likely to be dopamine-mediated.

Keywords: Obesity; fMRI; Reward system; Striatum; Body mass index

* Corresponding author. Fax: +49 30 450 553 989.
E-mail address: yvonne.rothemund@charite.de (Y. Rothemund).
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Introduction

Obesity shows an increasing prevalence and is associated with increased risk for numerous health conditions and heightened mortality (Flegal et al., 2002, 2005). While there is a growing body of literature delineating mechanisms of food intake in the normal-weight population (Small et al., 1999; Tataranni et al., 1999; Gordon et al., 2000; LaBar et al., 2001; Killgore et al., 2003; Hinton et al., 2004; Wang et al., 2004a; St-Onge et al., 2005), the neural systems regulating eating behavior in obese individuals remain poorly understood. Recent approaches emphasized the similarity between obesity and drug addiction (Wang et al., 2001, 2004b; Volkow et al., 2002). Similar to drug addicts, obese individuals show significantly reduced dopamine (DA) D_2 receptor availability in the striatum, which is negatively correlated with BMI (Wang et al., 2001). Dopamine modulates reward circuitry and motivational processing (cf. Schultz et al., 1998), and is known to regulate food intake (cf. Kishi and Elmquist, 2005) based on the rewarding properties of food such as palatability (Martel and Fantino, 1996) and fat (Rolls et al., 1999; De Araujo and Rolls, 2004). The dorsal striatum relates to food motivation (Volkow et al., 2002), maintains caloric requirements for survival (Szczypka et al., 2001) and has been implicated in stimulus–response habit learning (Mishkin et al., 1984; Vanderschuren et al., 2005) whereas the ventral striatum is involved in the mediation of the rewarding properties of food (Hernandez and Hoebel, 1988; Richardson and Gratton, 1996; Bassareo and Di Chiara, 1999; Kelley, 2004).

Previous imaging studies on obesity investigated neural correlates of hunger and satiation (Karhunen et al., 1997; Gautier et al., 2001; Del Parigi et al., 2002, 2005). In these studies, participants were food-deprived and either received a liquid meal or observed food cues alternating with neutral pictures following the fast (cf. Karhunen et al., 1997). Regions that were activated in obese

Table 1
Characteristics of study sample

Characteristics	Normal-weight group ($n=13$)	Obese group ($n=13$)	T or Z value	P
Age, mean (SD), years	29 (5.6)	31 (9.4)	$t(24)=-0.71$	ns
≥12 years of education	11	5	$Z=-2.29$	0.02
BMI, mean (SD)	20.9 (1.7)	36.3 (4.8)	$t(24)=-10.8$	<0.001
Handedness (right)	10	13	$Z=-1.81$	ns
Current medication	None	None	Does not apply	Does not apply
Last food ingestion, mean (SD), h	4.0 (1.4)	3.3 (1.2)	$t(24)=1.39$	ns
Amount of calorie intake prior to scanning, mean (SD), kcal	318.9 (151.9; range=36.0–571.1)	377.2 (231.5; range=107.1–891.4)	$t(24)=-0.76$	ns
Time since suffering from obesity, mean (SD), years	Does not apply	17.2 (8.9)	Does not apply	Does not apply

BMI, body mass index; ns, not significant.

but not in normal-weight individuals comprised parietal, temporal and prefrontal cortices, cingulate cortex, hypothalamus, nucleus accumbens (NA) and amygdala, midbrain, insula, and orbitofrontal cortex (OFC; Karhunen et al., 1997; Matsuda et al., 1999; Gautier et al., 2001; Del Parigi et al., 2002, 2005). Summarizing previous studies, the physiological state "hunger" recruits a network of regions, which have been associated with reward and emotion processing, perception of internal states, goal-directed behavior, and classical conditioning (Hugdahl et al., 1995). It is important to note that in these previous studies the stimuli were kept constant whereas physiological states such as hunger and satiation were manipulated. However, it is not known whether obese and normal-weight individuals differ in appetitive processing concerning solely food motivation but not physiological states.

Therefore, using functional magnetic resonance imaging (fMRI), we assessed whether food motivation following visual presentation of food cues differs in obese and normal-weight individuals when intrinsic states were kept constant but stimulus value was manipulated. We hypothesized that striatal activation following food-cue stimulation should be greater in obese than in normal-weight subjects when hunger/satiation are kept constant. Stimulus value manipulation was expected to result in differential activation of reward-processing regions, particularly the striatum, with high-calorie stimuli yielding greater regional brain activation than low-calorie stimuli and eating-related utensils. Furthermore, activation was expected in connected dopaminergic regions such as OFC and amygdala.

Methods

Participants

Thirteen female obese, right-handed (Oldfield, 1971) and 13 normal-weight female subjects (10 right-handed) participated in this study. Table 1 compares the characteristics of the normal-weight control and the obese subjects. Both groups did not suffer from current or past severe pain, stroke, epilepsy or other neurological illnesses, diabetes, substance abuse or addiction, hypertension, claustrophobia or any psychiatric illness. Control subjects did not suffer from current or past eating disorders and were required to have a BMI of 18.5 to 24.0. Obese individuals did not suffer from any current or past eating disorder other than hyperphagia leading to obesity. They were included in the study if their BMI was greater than 31 corresponding to at least grade 1 obesity according to WHO criteria. Binge-eaters were excluded. Both groups were normal-sighted or had corrected to normal vision. Both groups were required to be neither hungry nor just satiated. None of the subjects had been eating in the 1.5-h period before scanning. All subjects were asked to indicate whether they were hungry or not prior to scanning. Hungry subjects were excluded. The mean amount of calorie intake prior to scanning was determined by an Internet-based database (http://www.freeweightlosscenter.com/cc.htm). Most of the volunteers were recruited through newspaper advertisements and reimbursed with € 20 for participation in the study. Written informed consent was obtained from all participants. The study was approved by the local Human Subjects Committee and adhered to the Human Subjects Guidelines of the Declaration of Helsinki.

Psychometric evaluation and stimulus materials

Prior to scanning demographic data of the subjects were obtained. Subjects were asked to observe the pictures during scanning paying full attention. Visual stimuli were presented in a block design similar to that described previously (Killgore et al., 2003). The stimulus material consisted of 40 slides of three food-related categories, high- and low-calorie foods, eating-related utensils, and neutral but similarly complex items that served as control stimuli. Pictures[1] were taken from the International Affective Picture System (Lang et al., 2005) and from commercial photography web sites. High-calorie pictures included images of items such as hamburgers, pancakes etc. Low-calorie foods consisted of different types of fruits, vegetables and other low-calorie foods, whereas items such as forks, spoons, etc., constituted the category of eating-related utensils. Pictures in the control condition comprised pictures such as flowers, rocks, etc. Each condition consisted of two stimulation periods of 34.87 s with the experimental and control condition alternating. All three categories differed significantly from each other with respect to caloric content ($F(2,27)=33.9$; $p<0.004$). Food categories were built based on both caloric content and energy density and included images with approximately similar masses of food. High-calorie

[1] IAPS numbers of pictures that were included in the present study: 5201, 5220, 5700, 7320, 5000, 5001, 5010, 5200, 7289, 7230, 7470, 7330, 7291, 7460, 7080, 7035, 7450, 7010, 7004, 7000, 7472, 7480, 7284, 7350, 7430, 7475, 5593, 7281, 7235, 7009, 7233, 7285, 5731, 5260, 7402, 7351, 7352, 7282, 7283, 7481, 7041, 7025, 5611, 5020, 5270, 5250, 5594.

items contained food items with an average of 395 kcal and an approximate energy density of ≥4 kcal/g whereas low-calorie items displayed food images with an average of 179 kcal and an approximate energy density of 1.5 kcal/g. Each block consisted of 10 randomized pictures of one caloric category. Each stimulus was presented for 3000 ms with an interstimulus interval (ISI) of 487 ms. The presentation of the visual stimuli was synchronized with the MR scanner pulses using the Software 'Presentation' (Neurobehavioral Systems, Inc., Albany, CA, USA) running on a personal computer (PC). The PC was connected to a beamer which was placed behind a diminishing lens. The pictures were then back-projected onto a screen fixed to the head coil. A mirror, also mounted to the head coil allowed for comfortable viewing of the stimuli. Directly after scanning, subjects indicated on a visual analogue scale (VAS) how much each of the pictures stimulated their appetite. The VAS ranged from 0, representing no stimulation of appetite, to 100, indicative of very strong stimulation of appetite. In addition, they had to complete a recognition test. Five pictures from each calorie category were randomly mixed with 5 novel pictures from the same category. To control for sufficient attention during the experiment, participants had to indicate whether the picture had been seen during scanning or whether it was a new picture.

Data acquisition and analysis

FMRI measurements were carried out on a 1.5 T scanner (Siemens Magnetom Vision, Erlangen, Germany) with a standard head coil. Head motion was minimized using a vacuum pad. Subsequent to the scout spin echo scan, 133 functional volumes approximately parallel to the bicommissural plane were acquired using a T2*-weighted echo planar imaging sequence (TR= 3487 ms, TE=40 ms, flip angle=90°, FOV=192 mm, matrix 64×64, 26 3-mm sagittal slices; interslice gap 0.9 mm, in-plane resolution 3×3 mm). Thereafter, structural 3D data sets were obtained using a T1-weighted sagittal (3-D-magnetization prepared rapid gradient echo sequence) (TR/TE 11.4/4.4 ms, flip angle 15°, FOV=256 mm, voxel size 1 mm^3, no gap).

Imaging data were analyzed using SPM2 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, University College London, UK). The first three functional volumes were discarded from the analysis to allow for magnetic saturation effects. Scans were slice-time corrected to the first slice, realigned, normalized and spatially smoothed by a Gaussian kernel (full width at half maximum=10 mm). Images were resliced to 2×2×2 mm within stereotactic space and a high-pass frequency filter (147 s) was applied to remove low-frequency drifts. Parameters for motion artifacts were determined using six parameters for rigid body transformation and translation. Anatomical and functional images were coregistered and normalized to the standard coordinate space of the Montreal Neurological Institute (MNI). For anatomical verification of activated regions, Talairach coordinates for maximum voxels were determined using the WFU pickatlas (Maldjian et al., 2003) and confirmed by use of an additional brain atlas (Lancaster et al., 1997). Time series were modeled using box car regressors for every condition as the reference paradigm and convolved with the hemodynamic response function. Contrast images for each condition and for differences between conditions were computed for each subject. Group SPM contrast maps were computed by using these contrast images and employing a random effects analysis (Friston et al., 1999) within the general linear model (Friston et al., 1995). Within-group analysis was performed using one-sample *t*-tests. Between-group analysis was conducted by computing analyses of covariance (ANCOVA) with "time-since-last-meal" as covariate to exclude confounding effects of this variable on brain activation. In order to exclude that the caloric content of the last meal prior to scanning influenced the observed brain activation, simple linear regression analyses were computed for each of the three calorie conditions (high, low, utensil) with the kilocalorie content of the last meal as covariate of interest. Furthermore, individual contrasts were entered into a simple linear regression model with the BMI as the covariate of interest. Separate regression analyses were conducted for each of the three conditions. The results were considered statistically significant for *t*-values thresholded at $p<0.001$ (uncorrected) with a minimum cluster size of 5 continuous voxels. A small volume correction was applied in a priori areas of interest. Results are reported for cluster-level corrected *t*-values at $p<0.05$ (corrected). In each group percentage of signal change related to the three main conditions (high, low, utensil) was computed for structures of interest defined by using the WFU pickatlas (Maldjian et al., 2003) including activated peak voxels. The percentage of signal change was compared with regard to each main condition between groups by using a *t*-test for independent samples. When left-handed subjects were excluded from the analyses, similar results were obtained. Therefore, these subjects were included in all analyses.

Statistical analysis

Differences between the two groups concerning age, BMI, last food ingestion, amount of calorie intake prior to scanning, and attention scores were computed using two-tailed independent samples *t*-tests. Differences between the three stimulus categories (high, low, utensil) regarding caloric content were computed using a one-way analysis of variance (ANOVA). Differences between obese and normal-weight subjects regarding stimulus ratings were calculated employing an ANOVA for repeated measures. *P*-values less than 0.05 were considered statistically significant. The software package SPSS 13.0 was used for all statistical analyses.

Results

Ratings

Postscanning appetite ratings showed main effects of stimulus category (high, low, utensil) [$F(2,48)=50.8$; $p<0.001$] but not for group [$F(1,24)=2.3$; $p=0.14$] or the group by category interaction [$F(2,48)=1.42$; $p=0.25$]. In both groups low-calorie foods were rated most appealing ($M_{contr}=53.6$; $SD_{contr}=25.2$; $M_{ob}=40.8$; $SD_{ob}=18.8$) followed by high-calorie foods ($M_{contr}=43.1$; $SD_{contr}=20.7$; $M_{ob}=31.5$; $SD_{ob}=22.7$) and eating-related items ($M_{contr}=6.3$; $SD_{contr}=5.8$; $M_{ob}=6.4$; $SD_{ob}=7.4$). Both groups did not differ in the postscanning recognition test [$t(24)=1.07$; $p=0.29$]. The overall recognition was significantly above chance in both controls [$M=71.9\%$, $SD=6.8$; $t(12)=11.7$; $p<0.001$] and obese subjects [$M=68.5\%$, $SD=9.4$; $t(12)=7.05$; $p<0.001$] indicating that both groups were sufficiently attentive during the fMRI experiment.

Imaging data

Between-group comparison

Both groups were compared in their regional brain activation patterns in response to viewing high-calorie foods relative to blocks of neutral control stimuli (e.g. waterfalls, fields) (high-calorie condition), low-calorie foods relative to neutral stimuli (low-calorie condition) and eating-related utensils relative to the neutral control stimuli (utensil condition).

High-calorie condition (HC). The obese compared to the control group showed activations in the right putamen, left caudate body, left anterior insula (BA 13), left hippocampus, and in the left parietal lobule (Fig. 1; Table 2). Contrasting normal-weight vs. obese did not yield any activation difference.

Low-calorie condition (LC). Obese subjects compared to the control group showed activations in the left superior frontal (BA 6, BA 8), right middle and inferior frontal gyrus (BA 45), middle occipital gyrus (BA 19), and left superior temporal gyrus (BA 41) (Fig. 1; Table 2). The opposite comparison did not reveal differences between the two groups.

Utensil condition (UC). Contrasting obese vs. control subjects resulted in activations of the left middle frontal gyrus (BA 10), left cuneus, and right inferior parietal lobule (BA 40). The opposite comparison revealed a differential activation peak in the vicinity of the right caudate body (Fig. 2; Table 2).

High-calorie vs. low-calorie

Both groups were compared in their regional brain activation patterns in response to viewing high-calorie foods relative to blocks of low-calorie food items. This comparison yielded activation in the bilateral putamen (Table 2).

Within-group comparisons

Within the obese group, regional brain activation patterns are reported in response to viewing high-calorie foods relative to blocks of neutral control stimuli (HC), low-calorie foods relative to neutral stimuli (LC) and eating-related utensils relative to the neutral control stimuli (UC). Likewise, results are presented for the control group.

Obese group

HC. Centers of activations were found in the bilateral para-hippocampal gyrus (BA 27) and hippocampus extending towards the putamen, in the left OFC (BA 11), bilateral fusiform gyrus (BA 19, BA 37), and right BA 18 (Fig. 3; Table 3).

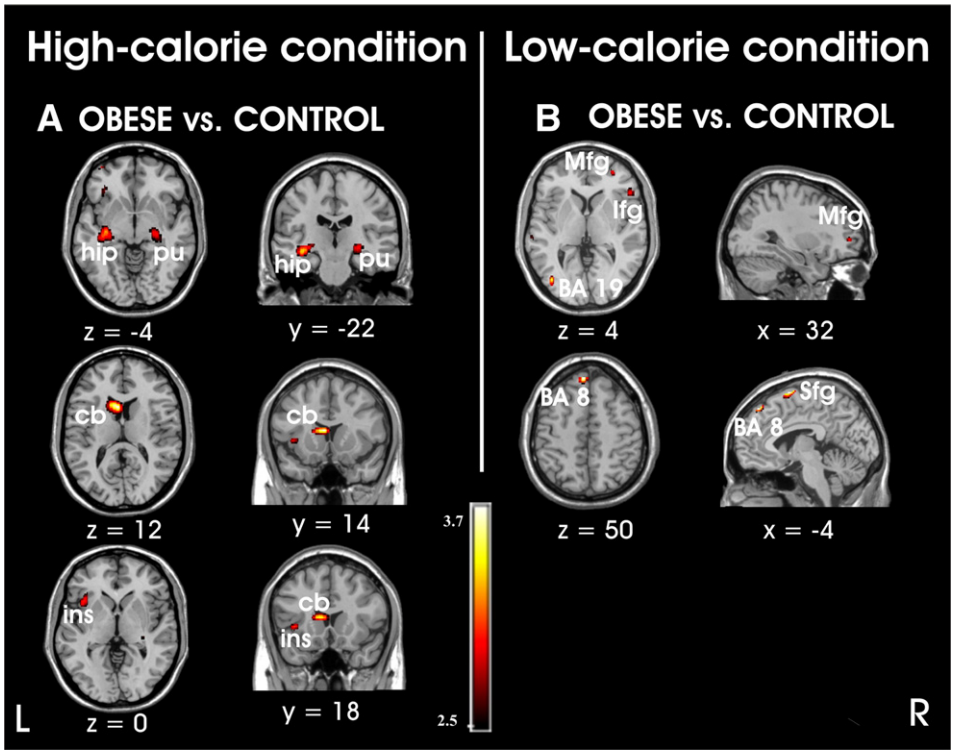

Fig. 1. Between group comparison for the high- and low-calorie condition (HC, LC). (A) In the HC, comparing the obese and the normal-weight group while controlling for "time of last meal prior to scanning" led to activation in the right putamen, left caudate body, left anterior insula (BA 13), left hippocampus, and left parietal cortex (not shown here). (B) In the LC, the comparison of obese and control subjects revealed activations in the left superior frontal gyrus (BA 8, 6), right middle frontal gyrus, left middle occipital gyrus (BA 19), right inferior frontal and left superior temporal gyrus (not shown here). The results of the group analyses were superimposed on the MNI template "colin" in neurological convention (right is right). Displayed are *x*, *y* and *z* (MNI) coordinates. For display purposes, statistic images correspond to $p<0.005$. The comparisons normal-weight vs. obese group yielded no activation in both HC and LC, and are therefore not displayed here. Abbreviations: hip=hippocampus, pu=putamen, cb=caudate body, ins=insula, Mfg=middle frontal gyrus, Ifg=inferior frontal gyrus, Sfg=superior frontal gyrus, BA=Brodmann area.

Table 2
Between-group comparisons contrasting differences in the high- and low-calorie and utensil condition

	Comparison	Region	Hem	BA	*T* contrasts	MNI coordinates
Obese vs. controls	High vs. neutral	Caudate body	L		3.69	−4, 14, 12
		Putamen	R		2.96	28, −22, −4
		Anterior insula	L	13	3.07	−38, 18, 0
		Hippocampus	L		3.46	−34, −20, −10
		Parietal lobule	L		3.00	−28, −38, 40
	Low vs. neutral	Superior frontal gyrus	L	8	3.24	−4, 44, 50
			L	6	3.24	−2, 10, 68
			L		3.14	−2, 2, 72
		Middle frontal gyrus	R		2.91	32, 50, 4
		Inferior frontal gyrus	R	45	2.90	54, 26, 2
		Middle occipital gyrus	L	19	3.12	−40, −76, 2
		Superior temporal gyrus	L	41	2.93	−50, −32, 14
	Utensil vs. neutral	Middle frontal gyrus	L	10	3.41	−36, 44, 12
			L	10	3.27	−32, 52, −4
		Cuneus	L		4.02	−20, −76, 30
		Inferior parietal lobule	R	40	2.93	38, −54, 46
	High vs. low	Putamen	R		3.77	26, −22, −4
			L		3.85	−26, −22, −2
Controls vs. obese	Utensil vs. neutral	Vicinity of caudate body	R		2.95	18, 30, 2

For all contrasts activated anatomic region, right or left (R, L) hemisphere (Hem), approximate Brodmann areas (BA), *t*-values, and coordinates of the local maxima of significance within the Montreal Neurological Institute (MNI) coordinate system are displayed.

LC. The obese group showed activations in the right fusiform gyrus (BA 37) and bilateral middle occipital gyrus (BA 18) (Fig. 3; Table 4).

UC. Activations were found in the bilateral fusiform gyrus (BA 37), left middle and inferior occipital gyrus, right inferior frontal gyrus (BA 47), and middle temporal gyrus (BA 22) (Fig. 3; Table 4).

High-calorie vs. low-calorie. High-calorie foods relative to blocks of low-calorie foods did not result in activated suprathreshold clusters.

High-calorie vs. utensil. Comparing high-calorie foods vs. blocks of eating-related utensil yielded activation in the left lingual gyrus (BA 17; Table 4).

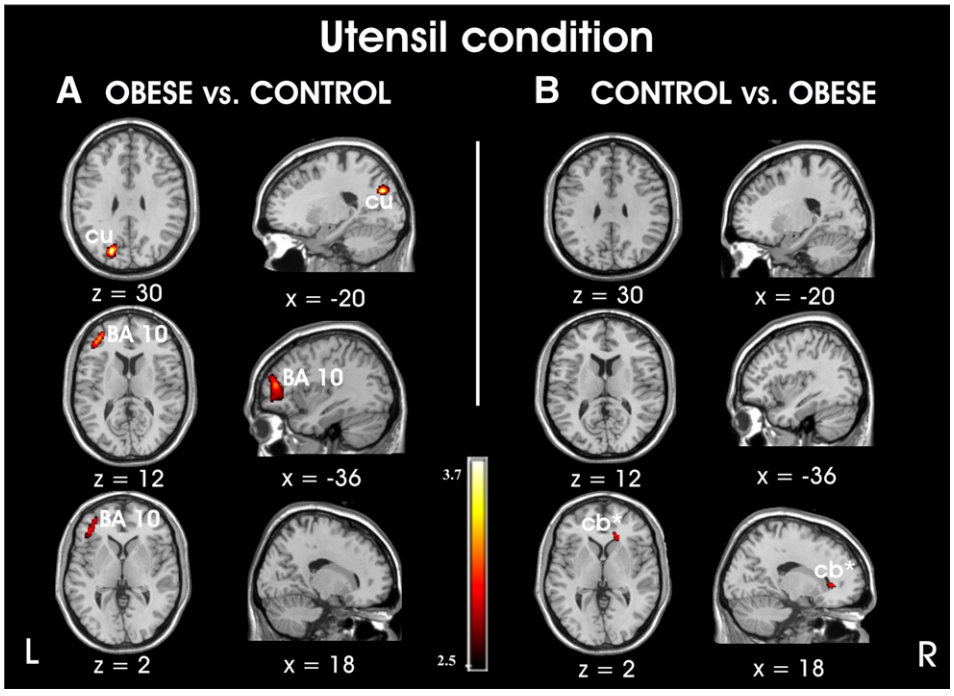

Fig. 2. Between group comparison for the utensil condition (UC). (A) Comparing the obese and normal-weight control subjects in the UC resulted in activations of the left middle frontal gyrus (BA 10), left cuneus, and inferior parietal cortex (not shown here). (B) Comparing normal-weight and obese group yielded activation in the vicinity of the right caudate body. Again, MNI coordinates (*x*, *y*, *z*) are displayed. Other conventions as in Fig. 1. Abbreviations: cu = cuneus, cb* = vicinity of caudate body.

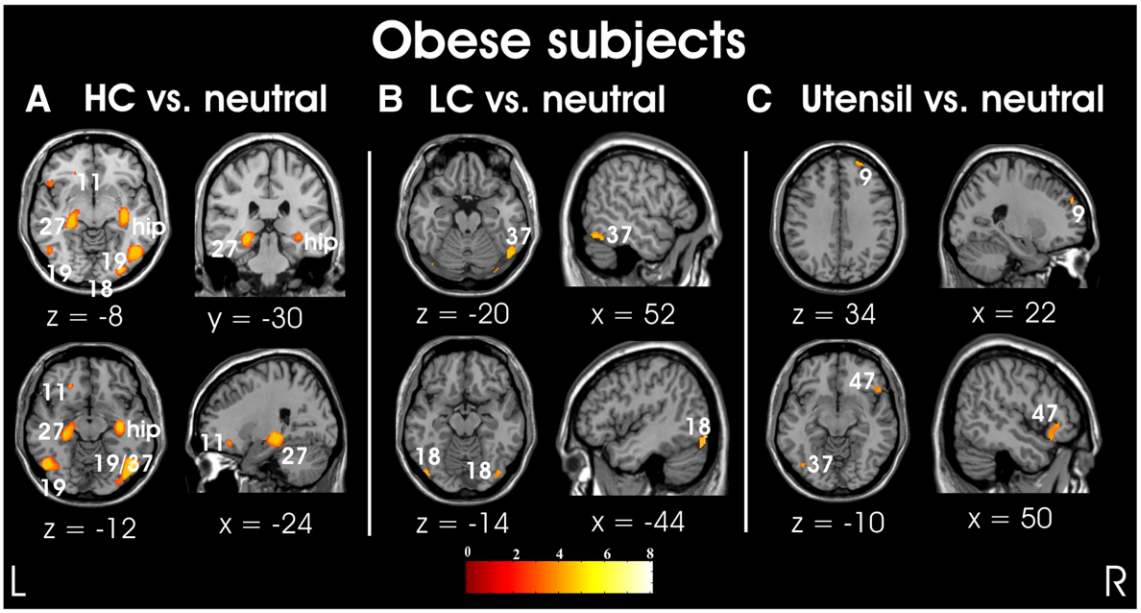

Fig. 3. Obese group: Within group comparison for HC, LC and UC. (A) In the HC, centers of activation were found in the bilateral parahippocampal gyrus (BA 27) and hippocampus extending towards the putamen, in the left orbitofrontal cortex (OFC) (BA 11), bilateral fusiform gyrus (BA 19, BA 37), and right BA 18. (B) The LC yielded activation in the right fusiform gyrus (BA 37) and bilateral middle occipital gyrus (BA 18). (C) The UC led to activation in the bilateral fusiform gyrus (BA 37), left middle and inferior occipital gyrus (not shown here), right superior (BA 9) and inferior frontal gyrus (BA 47), as well as in the middle temporal gyrus (BA 22, not shown here). Abbreviations: HC, high-calorie condition, LC, low-calorie condition, UC, utensil condition, hip=hippocampus. Numbers indicate Brodmann areas. Other conventions as in Fig. 1.

Normal-weight group

HC. At the given significance level of $p<0.001$ no significant activation was observed. Amygdala activation was only found in individual subjects, but did not reach statistical significance at the group level.

LC. This condition yielded activation in the right inferior temporal gyrus (Fig. 4; Table 5).

UC. Controls showed bilateral activation of the middle frontal gyrus in the vicinity of BA 46 (Fig. 4; Table 5).

High-calorie vs. low-calorie. This comparison did not result in suprathreshold cluster activation.

High-calorie vs. utensil. In the control group, this comparison did not result in activated clusters.

Table 6 displays the percentage of signal change for structures of interest in both the normal-weight controls and the obese group for the three main contrasts.

Regression analyses

Regional brain activation patterns in response to viewing high-calorie foods vs. neutral stimuli (HC), low-calorie foods vs. neutral stimuli (LC), and eating-related utensils vs. neutral stimuli (UC) were correlated with the BMI of the combined sample.

HC. The BMI was positively correlated with the BOLD signal change in the right ($r=0.56$, $p=0.003$) and left ($r=0.52$, $p=0.006$) putamen and the right caudate body ($r=0.53$, $p=0.005$), the right anterior insula ($r=0.55$, $p=0.004$), the right claustrum ($r=0.52$, $p=0.007$), the right posterior cingulate cortex ($r=0.56$, $p=0.003$), the left lateral globus pallidus ($r=0.50$, $p=0.009$), the right postcentral gyrus (vicinity of BA 2) ($r=0.54$, $p=0.004$) as well as the right lateral OFC (BA 47) ($r=0.52$, $p=0.006$) (Fig. 5; Table 7). Within the obese group, the BMI was also correlated with the BOLD signal change in the left globus pallidus ($r=0.76$, $p=0.003$) and right lateral OFC (BA 47) ($r=0.71$, $p=0.007$).

Table 3
Obese group contrasting within-group differences in the high-calorie condition

	Comparison	Region	Hem	BA	*T* contrasts	MNI coordinates
Obese group	High vs. neutral	Fusiform gyrus	L	19	8.08	−46, −66, −16
			R	37	7.26	46, −64, −14
			R	19	7.26	44, −74, −16
		Middle occipital gyrus	R	18	5.99	30, −88, −4
		Hippocampus	R		5.76	34, −20, −8
		Parahippocampal gyrus	L	27	5.05	−26, −30, −8
		Lateral OFC	L	11	3.89	−24, 34, −12

OFC, orbitofrontal cortex. Other conventions as in Table 1.

Table 4
Obese group contrasting within-group differences in the low-calorie and utensil condition

	Comparison	Region	Hem	BA	T contrasts	MNI coordinates
Obese group	Low vs. neutral	Fusiform gyrus	R	37	4.06	52, −60, −20
		Middle occipital gyrus	R	18	3.96	40, −82, −16
			L	18	3.84	−44, −80, −14
	Utensil vs. neutral	Middle occipital gyrus	L		4.89	−38, −86, 4
		Fusiform gyrus	R	37	4.23	40, −52, −24
			L	37	3.88	−54, −58, −22
		Middle temporal gyrus	R	22	4.22	64, −44, 2
		Inferior frontal gyrus	R	47	3.92	50, 24, −10
			R	47	3.79	54, 32, 0
		Superior frontal gyrus	R	9	4.27	22, 54, 34
		Inferior occipital gyrus	L		3.80	−40, −70, −8
	High vs. utensil	Lingual gyrus	L	17	4.25	−8, −94, −4

Conventions as in Table 1.

LC. At the SPM significance level of $p<0.001$ there was no significant correlation of the BMI with BOLD signal change.

UC. The BMI was significantly positively correlated with BOLD signal change in the middle frontal gyrus (BA 10) ($r=0.55$, $p=0.004$) (Table 7).

Caloric content of last meal

For all three conditions (*HC*, *LC*, *UC*), no significant correlation between caloric content of the last meal and BOLD signal change was found, indicating that the variable "kilocalorie content" did not influence the fMRI outcome.

Lateralization

The results indicated some lateralization of the findings. However, when a less strict threshold was applied (*t*-values thresholded at $p<0.01$, uncorrected) bilateral activation of most above-mentioned regions was observed. Therefore, these results are not displayed.

Discussion

This study used fMRI to investigate the neural correlates of appetitive processing in obese individuals. We provide evidence that obese and normal-weight individuals differ substantially in their neural activation related to cue-induced food motivation. In obese as compared to normal-weight women high-calorie food stimuli differentially activated the dorsal striatum (caudate nucleus and putamen, cf. Nieuwenhuys et al., 1991), a part of the habit learning system, which has previously been linked to a lowered DA D_2 receptor availability in obese (Wang et al., 2001) and drug-addicted individuals (Volkow et al., 1996, 1997; Volkow and Wise, 2005; Heinz et al., 2004; Martinez et al., 2004). There is evidence for functionally different roles of the ventral and dorsal striatum with the latter involved in food motivation following visual presentation of food (and excluding food consumption) in food-deprived normal-weight subjects (Volkow et al., 2002). A positron emission tomography study by Small et al. (2003) provides additional proof for a role of the dorsal but not the ventral striatum in feeding in normal-weight individuals. However, in our study normal-weight control subjects did not show any striatal activation subsequent to food stimulation. This difference most likely reflects that neither obese nor control subjects in our study were hungry but had had their last meal on average 4 h prior to scanning whereas Volkow et al. (2002) induced a state of hunger by food-depriving their subjects for 16–20 h prior to scanning. Additionally, their food stimuli involved smell and taste, which might intensify the motivational value of the

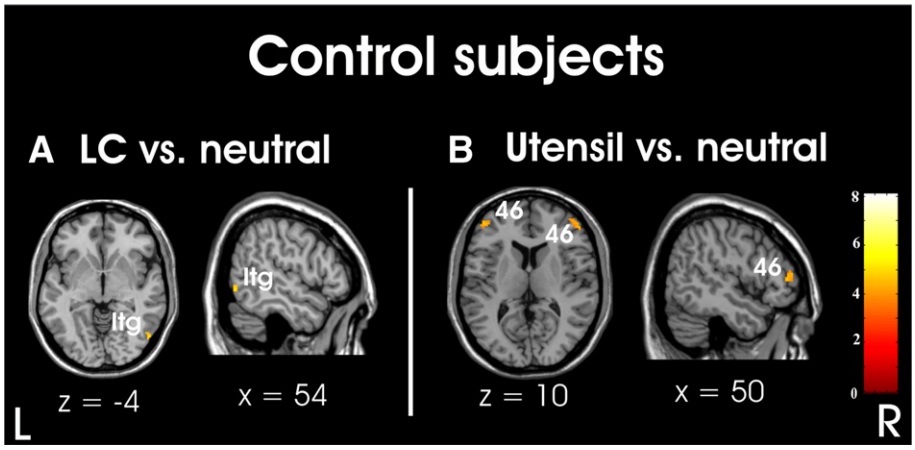

Fig. 4. Control group: Within group comparison for LC and UC. (A) In the LC, activations were found in the right inferior temporal and right inferior occipital gyrus (BA 19). (B) The UC led to bilateral activation of the middle frontal gyrus in the vicinity of BA 46. Abbreviations: LC, low-calorie condition, UC, utensil condition, Itg = inferior temporal gyrus. Numbers indicate Brodmann areas. Other conventions as in Fig. 1.

Table 5
Control group contrasting within-group differences in the low-calorie and utensil condition

	Comparison	Region	Hem	BA	T contrasts	MNI coordinates
Control group	Low vs. neutral	Inferior temporal gyrus	R		3.85	54, −70, −4
	Utensil vs. neutral	Middle frontal gyrus	R	46	4.50	50, 46, 10
			R		4.44	44, 52, 16
			L	46	4.01	−44, 48, 10

Conventions as in Table 1.

stimulus. The obese subjects in our study had had their last meal approximately 3 h prior to scanning and showed activation of the dorsal striatum following presentation of the high-calorie food cues. This result suggests that in obese individuals, the dorsal striatum, the activation of which has been linked to a role in obtaining sufficient energy in both animals (Szczypka et al., 2001) and food-deprived humans (Volkow et al., 2002), remains active even in the state of sufficient energy supply. It seems likely that learning processes such as classical conditioning may have influenced the anticipation and predictive representation of the motivational value of the stimulus (O'Doherty et al., 2002, 2006), because striatal and taste-related activation was only found following stimulation with high-calorie stimuli, which are known to increase the reward value of food and to be relevant for appetite in primates (Rolls et al., 1999; De Araujo and Rolls, 2004). The finding also suggests that hyperphagia, i.e. pathological overeating, may compensate for the decreased activation in the DA-dependent circuits. Furthermore, recent evidence from addiction research underlines a role of the dorsal striatum in cue-induced drug craving (Volkow et al., 2006) and drug seeking (Vanderschuren et al., 2005).

Correlation with BMI

Additional support for this interpretation comes from our finding that the activation of the dorsal striatum during the high-calorie condition was increased in proportion to the BMI. This complements results from Wang et al. (2001) who found DA D_2 availability in the striatum to be negatively correlated with BMI. In the HC, BMI-dependent activation was found in the lateral globus pallidus, a structure of the basal ganglia that has been linked to a role in the release of free fatty acids (Gunion et al., 1984), and thus to eventual binding to adipose cells. Further BMI-dependent activations were found in the anterior insula (primary taste cortex), the claustrum, a subcortical structure with extensive anatomical connections to sensory and association cortices and a suggested function in multimodal processing (Crick and Koch, 2005), the posterior cingulate cortex, a region associated with processing of emotionally relevant stimuli and memory-related function (Maddock et al., 2003; Fink et al., 1996), the postcentral gyrus which has been linked to an enhanced resting activity in obese subjects (Wang et al., 2002), and the lateral OFC (secondary taste cortex) associated with the processing of taste information (Rolls, 1990) and the mediation of hedonic responses to tastants (Scott et al., 2005). Human imaging studies also suggest a role of the OFC in the evaluation of the reward value of stimuli and responses in goal-directed behavior, and thus a role in rapid stimulus-reinforcement association learning (Elliott et al., 2000; Rolls, 2000, 2004; Saper et al., 2002). Activation of the OFC was also found in human imaging studies on appetitive behavior (Killgore et al., 2003; Holsen et al., 2005). In contrast to our findings, Killgore and Yurgelun-Todd (2005) described an inverse relationship of BMI and activation of the OFC when subjects were viewing high- and low-calorie foods and a positive correlation of OFC activation and BMI in the utensil condition. This apparent difference is probably caused by the differing range of BMI included in the two studies. While Killgore and Yurgelun-Todd (2005) included only 13 data points ranging from approximately 19 to 28, we computed a regression analysis based on 26 data points (range = 18.6–46.4) and hence a larger variance. When a regression analysis was computed only for the normal-weight subjects in our study, we found results comparable to those previously reported. However, BMI-dependent activations or deactivations were not found in the low-calorie condition whereas the utensil condition yielded BMI-dependent activation in the middle frontal gyrus (BA 10) which is associated with episodic memory retrieval (Cabeza et al., 2002) and working memory (Zhang et al., 2003).

Previous imaging studies

It is difficult to relate our findings to previous neuroimaging studies on food motivation in obese individuals as these studies investigated hunger and satiation and applied stimulation paradigms with *constant stimuli* such as a liquid meal after a prolonged fast (Gautier et al., 2000, 2001; Del Parigi et al., 2002, 2005) or a portion of food alternating with pictures of landscapes (Karhunen

Table 6
Percentage of signal change at structures of interest for the three conditions high-calorie, low-calorie, and utensil condition

Region	% signal change control group			% signal change obese group			*p*		
	Condition			Condition			Condition		
	HC	LC	UC	HC	LC	UC	HC	LC	UC
Caudate body	−0.27	−0.08	0.31	0.08	0.06	0.11	0.06	ns	ns
Putamen	−0.15	−0.09	0.17	0.02	0.09	0.06	ns	ns	ns
Insula	−0.026	−0.16	0.09	0.03	0.03	0.02	ns	ns	ns
Hippocampus	−0.11	−0.02	0.04	0.23	−0.03	0.03	0.02	ns	ns

HC, high-calorie condition; LC, low-calorie condition; UC, utensil condition.

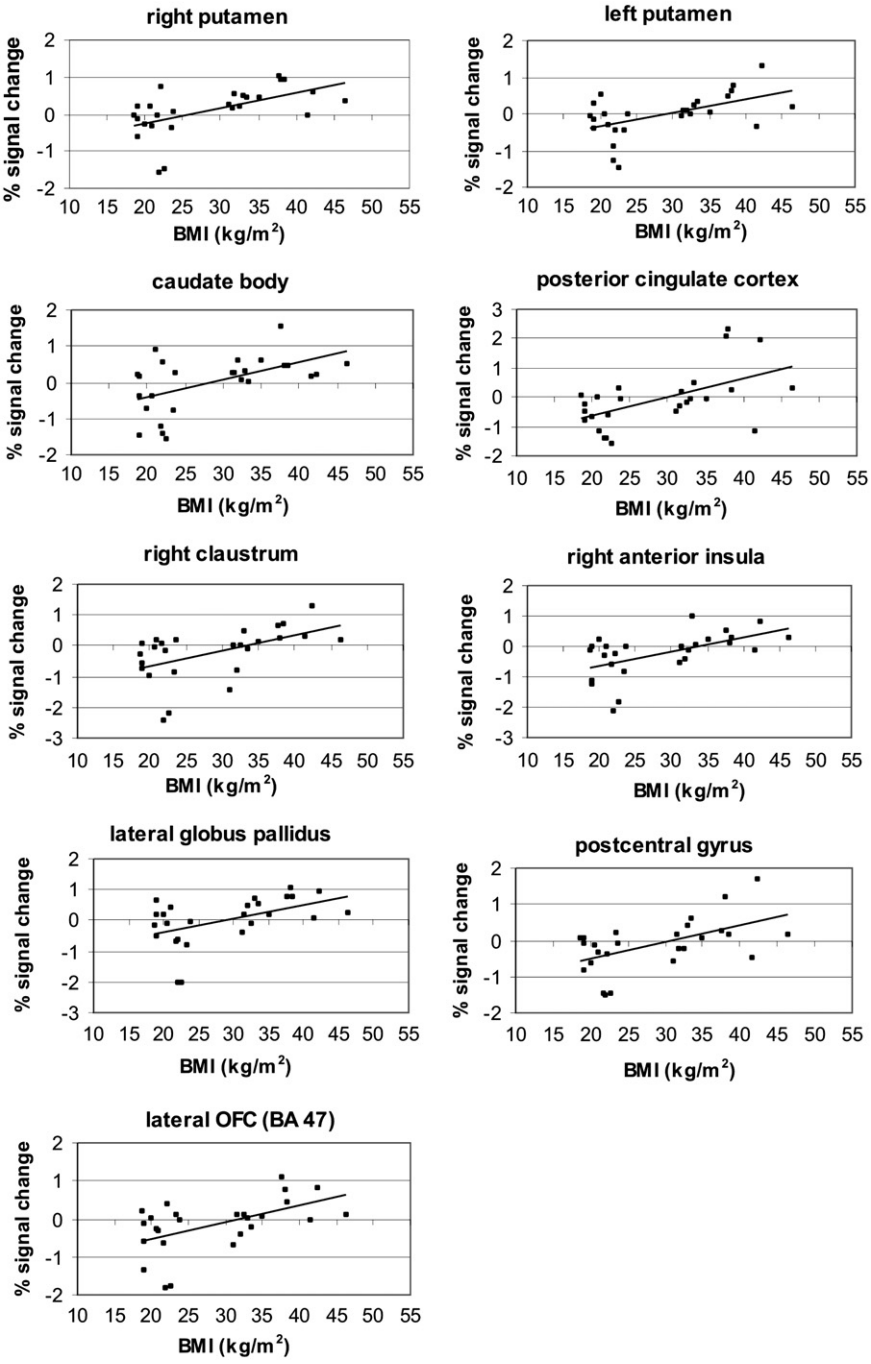

Fig. 5. Linear regression between activations during the high-calorie condition and BMI. Regression analysis revealed that BMI predicts activation in the bilateral putamen, right caudate body, right posterior cingulate cortex , right claustrum, right primary taste cortex (anterior insula), left lateral globus pallidus, right postcentral gyrus, and right lateral OFC during the HC. Abbreviations: BMI = body mass index, HC = high-calorie condition, OFC = orbitofrontal cortex. Other conventions as in Fig. 1.

et al., 1997). These previous data indicate differential patterns of neural activity in obese compared to normal-weight individuals in parietal and temporal cortices (Karhunen et al., 1997; Gautier et al., 2001; Del Parigi et al., 2005), cingulate cortex (Gautier et al., 2001; Del Parigi et al., 2002, 2005), hypothalamus (Matsuda et al., 1999; Gautier et al., 2001), prefrontal cortex, NA and amygdala (Gautier et al., 2001), midbrain, insula, and OFC (Del Parigi et al., 2005). However, independent of intrinsic state, we also found activity in insula, parietal and frontal regions with enhanced activation in obese compared to normal-weight individuals.

Surprisingly, we did not find consistent amygdala activation during the food conditions as expected from earlier studies (Gautier et al., 2001; Killgore et al., 2003). However, this finding is in accordance with studies reporting habituation effects of the amygdala subsequent to repeated visual stimulus presentations (Breiter et al., 1996; Wright et al., 2001; Holsen et al., 2005).

Table 7
BMI-dependent regions of activity

Condition	Region	Hem	BA	T contrasts	MNI coordinates
High-calorie condition	Putamen	R		3.28	34, −18, −8
		L		3.01	−30, −22, −2
	Caudate body	R		3.08	4, 12, 12
	Anterior insula	R	13	3.20	38, 16, 0
	Claustrum	R		2.95	36, 4, −10
	Posterior cingulate cortex	R	31	3.32	2, −40, 42
	Postcentral gyrus	R	[a]	3.17	32, −32, 42
		R		3.05	24, −38, 46
	Lateral OFC	R	47	3.02	30, 32, −8
	Lateral globus pallidus	L		2.85	−24, −16, −8
Utensil condition	Middle frontal gyrus	R	10	3.22	32, 54, −6

Other conventions as in Table 1.
[a] Vicinity (7 mm) of BA2.

Both control and obese subjects rated the low-calorie foods as more palatable and, thus as more likely to increase their appetite. This dissociation of valence ratings and physiological responses has also been observed in alcoholics (Grusser et al., 2002) and might be related to the view that alcohol or high-calorie foods are not desirable in the respective group but evoke still a strong affective and motivational response.

Limitations of the study and conclusion

This study has several limitations. First, three of the control subjects were left-handed which might have influenced stimulus processing. However, group analyses that excluded these subjects yielded similar results. Second, the educational background differed in the two groups, which might have influenced food preference and perhaps appetite ratings as lower formal education may be related to less knowledge about nutrition facts such as fat. However, high-calorie items yielded the best recognition scores in both groups. Third, individual food preferences were not accounted for, which might have biased the selection of appealing food stimuli. However, none of the food cues elicited an aversive reaction as indicated by scores larger than zero on the VAS measuring stimulation of appetite. Furthermore, DA D_2 receptor availability was not measured in the study participants.

In conclusion, our results support the notion that obesity and drug addiction have a partially common neural substrate and imply that treatment approaches similar to those applied in drug addicts might be successful. Furthermore, we provide fMRI evidence that in obese individuals food stimulation restrained to vision is sufficient to activate those parts of the reward system, which have been associated with a lowered DA D_2 receptor availability. We suggest that this dopamine-mediated stimulus–response-learned behavior is independent of the physiological states of hunger and satiation, and thus may contribute to pathological overeating and obesity.

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