

## Medial Prefrontal Cortex Activity Associated With Symptom Provocation in Eating Disorders

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**Objective:** The authors sought to identify neural correlates of eating disorders in order to contribute to the debate on the genesis and classification of eating disorders and provide endophenotypes for genetic research.

**Method:** Twenty-six female patients with eating disorders (10 with bulimia nervosa, 16 with anorexia nervosa) and 19 healthy female comparison subjects matched for age and education were presented with food and aversive emotional images while brain activity was recorded with functional magnetic resonance imaging.

**Results:** Women with eating disorders identified the food stimuli as threatening and disgusting. In response to these stimuli, the women with eating disorders had greater activation in the left medial orbitofrontal and anterior cingulate cortices and less activation in the lateral prefrontal cortex, inferior parietal lobule, and cerebellum, relative to the comparison group. In

addition, women with bulimia nervosa had less activation in the lateral and apical prefrontal cortex, relative to the comparison group. Between-group differences in response to nonspecific emotional stimuli were found in the occipital cortex, parietal cortex, and cerebellum.

**Conclusions:** A medial prefrontal response to symptom-provoking stimuli was identified as a common feature of anorexia and bulimia nervosa. This finding supports a conceptualization of eating disorders as being transdiagnostic at the neural level. The abnormal prefrontal reaction is associated with symptom-related material, whereas the occipital and cerebellar differences are nonspecific. An abnormal propensity to activate medial prefrontal circuits in response to inappropriate stimuli is common to eating, obsessive-compulsive, and addictive disorders and may account for the compulsive features of behavior in these conditions.

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Eating disorders comprise a spectrum of conditions, of which bulimia nervosa and anorexia nervosa are the major categories. Somatic symptoms (underweight, amenorrhea) are regarded as secondary to a core psychopathology, which is presumed to be encoded as long-standing alterations of cerebral neural circuits (1–3).

Evidence for a neural disturbance in eating disorders is compelling. The clinical syndrome can be reproduced by lesions in the right inferior prefrontal cortex (4, 5). Association with perinatal complications is also suggestive of a cerebral cause (6). Indirect evidence that eating disorders are neural diseases is inferred from neuropsychological, electrophysiological, neuropharmacological, structural neuroimaging, and functional neuroimaging investigations (3).

Functional neuroimaging studies in eating disorders have either investigated brain function at rest or under controlled disorder-specific conditions. Resting-state experiments have found global cerebral hypofunction (7), which is most pronounced in the anterior cingulate and frontal region (8, 9) and in the parietal lobe (7). In bulimia nervosa, parietal hypometabolism (7) and a loss of the normal right > left asymmetry of brain glucose metabolism (10) have been reported.

Controlled-condition experiments have used body shapes, eating, or food presentation to elicit symptom-related brain processes. In anorexia nervosa, perfusion of the frontal lobes (measured by single photon emission tomography [SPECT]) increased while subjects ate cake (11), and, in a functional magnetic resonance (fMRI) experiment, viewing high-caloric drinks elicited responses in the prefrontal cortex, anterior cingulate, insular cortex, and amygdala (12). A positron emission tomography (PET) study did not replicate these findings and reported food-related activity only in visual-associative cortices in seven anorexia nervosa patients who viewed high- versus low-caloric foods (13). Amygdala response to morphed images of subjects' bodies has been reported in three patients with anorexia nervosa (14). Data on bulimia nervosa are limited. One SPECT study that included five patients with bulimia nervosa showed that high basal frontal perfusion decreased with eating, a response pattern opposite to that seen in anorexia nervosa (15).

A summary of resting- and controlled-condition studies suggests that the same regions (prefrontal cortices, anterior cingulate) show diminished activity at rest but abnormally increased activity in response to food challenge. Some abnormalities (parietal hypometabolism at rest) are

TABLE 1. Demographic and Clinical Characteristics of Subjects in an fMRI Study of Neural Correlates of Eating Disorders<sup>a</sup>

Characteristic	Healthy Comparison Subjects (N=19)		Patients With Eating Disorders					
			All Patients (N=26)		Patients With Anorexia Nervosa (N=16)		Patients With Bulimia Nervosa (N=10)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	26.68	8.34	27.85	10.67	26.93	12.14	29.80	8.80
Education (years)	16.26	2.08	15.38	2.40	14.47*	2.42	16.50	1.84
Maudsley Obsessive-Compulsive Inventory score <sup>b</sup>	2.52	2.06	9.65***	6.12	10.00***	5.81	9.20**	7.13
Beck Depression Inventory score <sup>c</sup>	1.84	3.02	24.08***	13.51	25.80***	13.53	23.70***	12.77
Body mass index	22.41	2.98	18.59***	3.65	16.04***	1.64	22.43	2.37
Duration of eating disorder (years)			13.80	10.38	13.13	11.80	14.80	8.26
Hunger score <sup>d</sup>	2.42	1.17	2.00	1.30	1.67	1.23	2.40	1.35
Fasting time (hours) <sup>e</sup>	3.29	0.89	4.27*	1.82	4.10	1.86	4.50*	1.92

<sup>a</sup> Significant differences from the comparison group (analysis of variance, post hoc two-tailed t test) are noted.

<sup>b</sup> Possible scores range from 0 to 25, with higher scores indicating more severe symptoms.

<sup>c</sup> Possible scores range from 0 to 63, with higher scores indicating more severe symptoms.

<sup>d</sup> Rated on a scale from 1 to 7, with higher scores indicating a stronger feeling of hunger.

<sup>e</sup> Time between last meal and fMRI scan.

\* $p < 0.05$ . \*\* $p < 0.01$ . \*\*\* $p < 0.001$ .

common to anorexia nervosa and bulimia nervosa (7), while other (frontal reaction to eating) may differ between these diagnoses (15). These similarities and differences add to the debate on whether eating disorders constitute one entity with a spectrum of manifestations or are several separate syndromes (1, 2).

The propensity to specific attitudes (drive for thinness, fear of fatness) and behaviors (bingeing, restricting) is conceptualized as preferential activation of certain neural pathways and circuits. The functional relevance of neural circuits is inferred from activation patterns recorded in situations with a high probability of symptom manifestation. We used fMRI to investigate brain responses to food images in women with eating disorders and healthy female comparison subjects. Two general hypotheses were tested: 1) there will be activation patterns common to the whole eating disorders group, implying shared neural mechanisms, and 2) there will be responses specific to bulimia nervosa or anorexia nervosa, reflecting variations within the eating disorders spectrum. These differences should be specifically manifest in response to disease-specific material (food images), when symptom-related neural schemata are likely to be activated. To establish stimulus specificity, nonspecific emotionally salient stimuli were used in addition to food images.

## Method

### Participants

Patients with eating disorders were recruited from the inpatient (N=12) and outpatient (N=16) services of the South London and Maudsley Hospitals. Exclusion criteria were metallic implants, psychotropic medication other than antidepressants, claustrophobia, neurological disease, and axis I mental disease other than eating disorders. Affective and obsessive-compulsive symptoms are integral parts of eating disorders (1, 17), and their presence was not an exclusion criterion. Healthy women were recruited by local advertisement and were screened for abnormal eating habits and for neurological and psychiatric disease. Current and minimum past body mass index values were calculated. The Maudsley

Obsessive-Compulsive Inventory (18) and the Beck Depression Inventory (19) were used to measure severity of obsessive-compulsive and depressive symptoms.

After complete description of the study to the subjects, written informed consent was obtained, as approved by the South London and Maudsley Ethical Committee. Nine healthy participants and eight participants with anorexia nervosa were selected as comparison groups for recovered subjects in a parallel study, which is reported elsewhere (20).

### Stimuli

Custom-created color photographs depicted savory (e.g., pizza, rice, bread) and sweet (e.g., cake, chocolate) foods presented on plates. Photographs of nonfood items (stationery, household objects, flowers) were individually matched for color and visual complexity based on the ratings by five volunteers.

Emotional aversive photographs were selected from the International Affective Picture System (IAPS) (21) (IAPS numbers 2720, 2730, 3000, 3010, 3030, 3051, 3053, 3071, 3100, 3170, 3261, 9140, 9253, 9300, 9340, 9373, 9405) and contrasted with neutral stimuli matched for color and visual complexity (IAPS numbers 1600, 1670, 5201, 2250, 5390, 5780, 5982, 5990, 5991, 7010, 7020, 7090, 7100, 7150, 7235, 7550, 7950). A complete list of stimuli is available on request from the first author.

### Procedure

Participants were asked to eat a meal 3 hours before the experiment and to avoid smoking, eating, and drinking alcoholic or caffeine-containing beverages after the meal. Due to differential compliance, the time since the last meal was longer in the eating disorders group ("fasting time") (Table 1). After completing questionnaires and rating their feeling of hunger (Table 1), participants were scanned between 5:00 and 7:00 p.m. Food and non-food images were presented on a rear-projecting screen and viewed by means of a double-mirror periscope fitted to the head coil. Each image was shown for 2.5 seconds and was followed by a blank screen shown for 0.5 seconds. Ten food pictures in a 30-second block ("on" condition) were followed by 10 nonfood pictures ("off" condition). This sequence was repeated five times (with different stimuli) during the 5-minute experiment. Participants received the instruction: "You will be shown pictures of food and other objects. Look at each picture and think how hungry it makes you feel." An identical procedure was followed with aversive and neutral IAPS images with the following instruction: "You will be presented with a number of color pictures. Look at each of them and think what it makes you feel like." The order of the two exper-

TABLE 2. Ratings of Subjective Reactions to Stimuli Presented to Subjects During Scanning in an fMRI Study of Neural Correlates of Eating Disorders<sup>a</sup>

Stimulus and Subjective Reaction	Healthy Comparison Subjects (N=19)		Patients With Eating Disorders					
			All Patients (N=26)		Patients With Anorexia Nervosa (N=16)		Patients With Bulimia Nervosa (N=10)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Food stimuli								
Desire to eat	3.48	1.06	2.33**	1.28	1.70***	0.85	3.24	1.33
Pleasure	3.27	1.20	2.13**	1.14	1.96***	0.87	2.22	1.44
Fear	1.02	0.06	3.06***	1.91	3.80***	1.90	1.94*	1.43
Disgust	1.45	0.72	3.60***	1.82	4.21***	1.59	2.80	1.89
Nonfood stimuli								
Pleasure	2.66	1.42	2.46	1.50	2.65	1.51	2.16	1.50
Fear	1.14	0.37	1.32	0.45	1.36	0.50	1.26	0.37
Disgust	1.14	0.27	1.26	0.43	1.31	0.43	1.20	0.44
Aversive stimuli								
Pleasure	1.24	0.53	1.13	0.42	1.17	0.52	1.06	0.19
Fear	3.32	1.30	4.45**	1.31	4.57*	1.36	4.26	1.29
Disgust	5.12	1.15	6.23**	1.12	6.33**	1.05	6.08*	1.26
Neutral stimuli								
Pleasure	2.81	1.51	2.86	1.39	2.91	1.41	2.78	1.43
Fear	1.09	0.32	1.19	0.40	1.25	0.50	1.10	0.17
Disgust	1.07	0.32	1.04	0.13	1.06	0.16	1.00	0.00

<sup>a</sup> Stimuli were images presented on a rear-projecting screen and viewed by the subject during scanning by means of a double-mirror periscope fitted to the head coil. Food and nonfood stimuli consisted of color photographs of food on plates and of nonfood items matched for color and visual complexity with the food. Emotionally aversive stimuli consisted of photographs selected from the International Affective Picture System (IAPS) (21) and were contrasted with neutral stimuli from the IAPS that were matched for color and visual complexity with the aversive stimuli. Subjective reaction to the images was rated on numeric analogue scales ranging from 1 (not at all) to 7 (very much). Significant differences from the comparison group (analysis of variance, post hoc two-tailed t test) are noted.

\* $p < 0.05$ . \*\* $p < 0.01$ . \*\*\* $p < 0.001$ .

iments was counterbalanced between subjects. After the scanning, participants rated individual images from 1 (not at all) to 7 (very much) on numeric analogue scales for pleasantness, disgust, and fear. Food pictures were also rated for "desire to eat."

### Image Acquisition

Gradient echo echoplanar images were acquired on a 1.5-T neuro-optimized magnetic resonance system (GE Medical Systems, Milwaukee). One hundred  $T_2^*$ -weighted whole brain volumes were acquired in each experiment (repetition time=3 seconds, echo time=40 msec) in 16 near-axial 7-mm thick slices (0.7-mm interslice gap) depicting blood-oxygen-level-dependent (BOLD) contrast with an in-plane resolution of 3 mm.

### Data Analysis and Statistics

After motion correction (22), the estimated BOLD effect was modeled by two Poisson functions with hemodynamic delays of 4 and 8 seconds. This model has been extensively tested and shown to provide a fit equivalent to the physiological model of the BOLD effect. The least-squares model of the weighted sum of these two functions was compared with the signal in each voxel to obtain a goodness of fit statistic. The distribution of this statistic under the null hypothesis was calculated by wavelet-based resampling of the time series. Generic group activation maps, which depicted regions where the BOLD signal was significantly stronger in response to the active images (of food or aversive items) than to the control images (of nonfood or neutral items), were constructed by mapping the observed and randomized test statistics into standard space and computing and testing median activation maps. Between-group differences were established by cluster-level analysis with data randomization between groups to determine the sampling distribution of group differences under the null hypothesis. The probability of occurrence of any cluster in the observed data was computed by reference to the null distribution (23). In each experiment (food, aversive stimuli), four group comparisons were performed: eating disorders group and comparison subjects, anorexia nervosa subjects and comparison subjects,

bulimia nervosa subjects and comparison subjects, and anorexia nervosa subjects and bulimia nervosa subjects. To correct for repeated comparisons, a cluster-wise significance threshold was set at  $p \leq 0.001$ . At this level, the cumulative number of expected false positive clusters in all eight comparisons was less than one. Behavioral data were analyzed by using analysis of variance and post hoc two-tailed t tests (uncorrected).

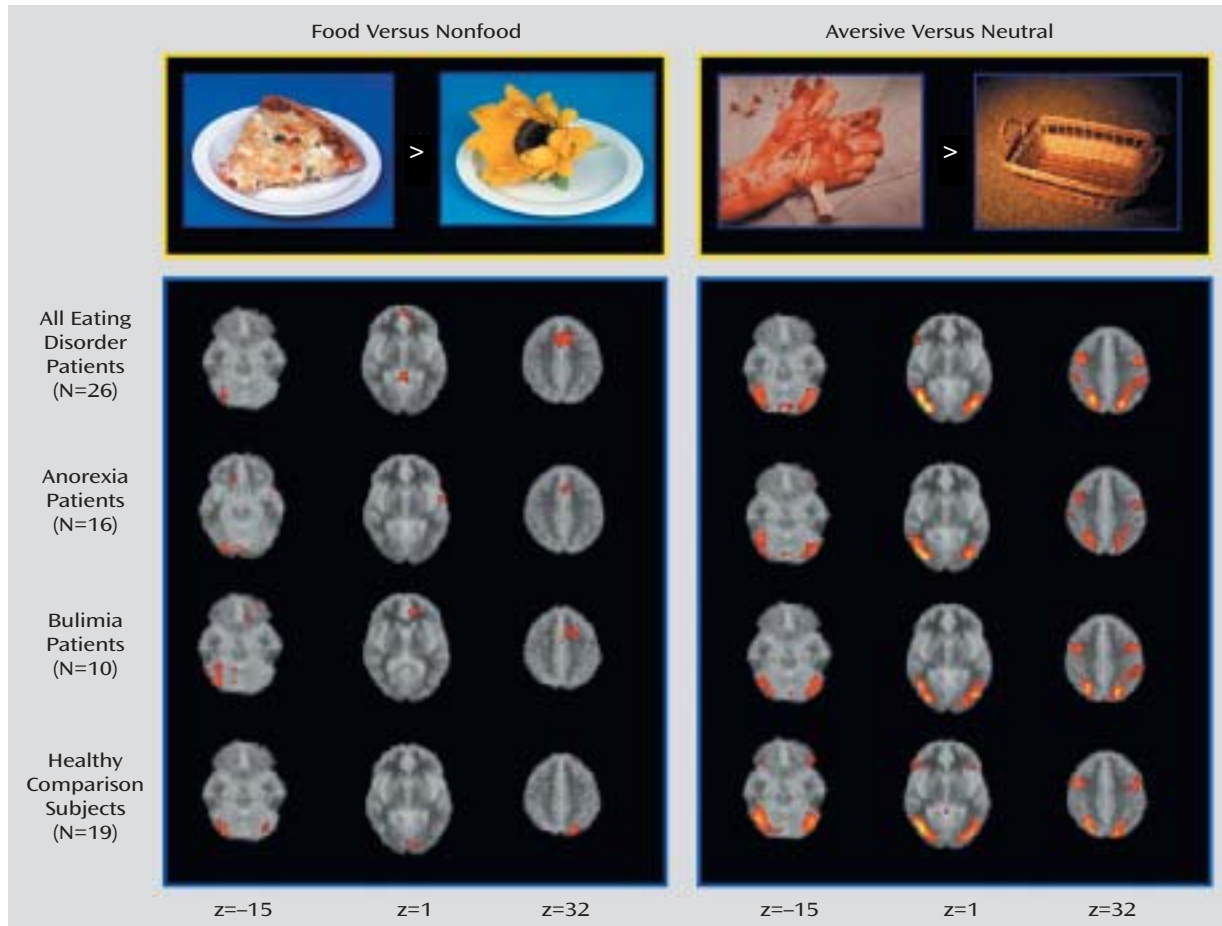
## Results

### Demographic and Behavioral Data

Of 43 patients with eating disorders who were assessed, nine declined to participate and eight were excluded because of past substance abuse ( $N=4$ ), claustrophobia ( $N=1$ ), and dental plates or metal implants ( $N=3$ ). The final study group consisted of 26 women with an eating disorder and 19 healthy comparison subjects. Ten participants fulfilled the DSM-IV criteria for bulimia nervosa and 16 for anorexia nervosa (nine with the restricting type and seven with the binge-eating/purging type). Ten participants (five with bulimia nervosa and five with anorexia nervosa) were taking antidepressant medication (selective serotonin reuptake inhibitors [SSRIs]). Although efforts were made to minimize delays between recruitment and the experiment, four of the 16 anorexia nervosa patients gained enough weight to be outside the diagnostic weight range at the time of scanning. Inclusion of patients who were taking medication and who had body weight outside the diagnostic range was addressed in the analysis.

The groups did not differ in age, gender (all female), or handedness (one comparison and one anorexia nervosa patient were left-handed). The anorexia nervosa group re-

**FIGURE 1. Examples of Stimuli and Generic Maps of Brain Activation in Response to Food and Aversive Images in Patients With Eating Disorders and Healthy Comparison Subjects<sup>a</sup>**



<sup>a</sup> Three representative axial slices are presented in radiological convention (right hemisphere is on the left-hand side of the image). The vertical position of each slice is determined by the z coordinate, which is given at the bottom of the figure. The depicted activations were associated with the active stimuli at the cluster-wise level of significance of  $p \leq 0.01$ .

ported significantly fewer years of education than the comparison group, whereas the bulimia nervosa group did not differ in education from the comparison subjects. Both patient groups scored significantly higher on self-report measures of obsessive-compulsive symptoms and depression (Table 1).

**Subjective Rating of Stimuli**

The participants with eating disorders rated food stimuli as significantly less desirable, less pleasant, more disgusting, and more fearful than did the comparison subjects; there were no differences in ratings of the nonfood stimuli (Table 2). Aversive stimuli were rated as more strongly negative by eating disorders subjects than by comparison subjects; there were no differences in ratings of the neutral stimuli (Table 2).

**Experiment 1: Food Versus Nonfood Stimuli**

**Generic group activation maps.** For the comparison group, activity in the left lateral prefrontal (Brodmann's area 10, 9), left parietal (Brodmann's area 7, 40), and bilat-

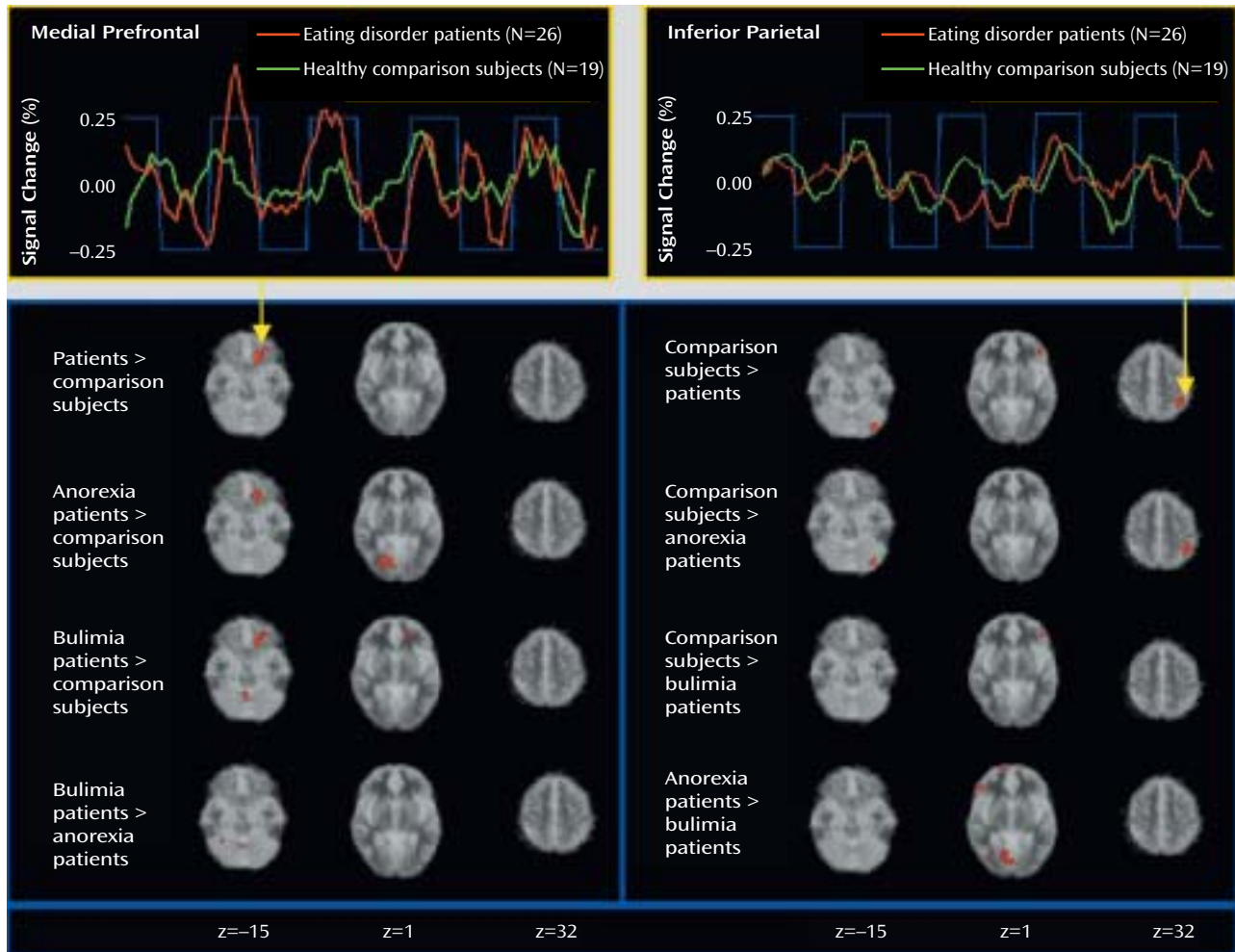
eral visual (Brodmann's area 17, 18) cortices and bilaterally in the cerebellum correlated with presentation of food stimuli at  $p \leq 0.01$  (Figure 1).

For the eating disorders group, food-related activity occurred in the anterior cingulate gyrus (Brodmann's area 24, 32) ( $p < 0.001$ ), posterior cingulate gyrus (Brodmann's area 23, 29, 30) ( $p < 0.001$ ), left orbitofrontal cortex (Brodmann's area 11) ( $p < 0.02$ ), left lateral prefrontal cortex (Brodmann's area 10), and right cerebellum (posterior lobe, declive). Activations in the anterior cingulate cortex and in the right cerebellum were similar in the bulimia nervosa and anorexia nervosa subgroups. Medial prefrontal activity was more extensive in the bulimia nervosa subgroup, whereas lateral prefrontal activation was detected only in the anorexia nervosa subgroup (Figure 1).

**Group comparisons.** In the eating disorders group, a left-sided cluster subsuming the medial orbitofrontal and anterior cingulate cortices was more active in response to food. This activation was significantly greater not only in the whole eating disorders group, relative to the compari-



FIGURE 2. Comparison of Brain Activation in Response to Food Stimuli and Time Series of Activation in Patients With Eating Disorders and Healthy Comparison Subjects<sup>a</sup>



<sup>a</sup> Differences in activation at a cluster-wise significance level of  $p \leq 0.001$  are shown in red in three representative axial slices. The vertical position of the slices is determined by the z coordinate, which is given at the bottom of the figure. Time series have been extracted from the medial prefrontal and inferior parietal clusters of activity in the composite patient group (N=26) and the healthy comparison group (N=19). After smoothing by a running average of five time points (15 seconds), time series have been plotted against the stimuli presentation paradigm (blue line).

son subjects, but also in the subgroups with bulimia nervosa and anorexia nervosa. Examination of time series revealed a strong reaction (0.5% change in BOLD signal) in this region in the eating disorders group, especially during the first three blocks of the paradigm (Figure 2). In addition, relative to the comparison group, the anorexia nervosa subgroup showed more activity in the lingual gyrus and the bulimia nervosa showed more occipital and cerebellar activity (Table 3, Figure 2).

The left lateral prefrontal cortex, left inferior parietal lobule, left occipital cortex, and posterior cerebellum were significantly less activated in the eating disorders subjects than in the comparison subjects. Responses in these regions in the comparison subjects averaged around 0.25% change in BOLD signal (the time series for the inferior parietal lobule is presented in Figure 2). Inferior parietal lobule and cerebellar activity were more diminished in the

anorexia nervosa subjects, whereas lateral prefrontal activity was decreased specifically in the bulimia nervosa subjects, relative to the comparison subjects and to the anorexia nervosa subjects (Table 3, Figure 2).

**Exclusion of confounding factors.** To address potential confounding factors that were related to inclusion of patients who were taking medication and patients who had gained weight, the group comparisons were repeated after exclusion of these participants. The diagnostically “pure” and medication-free group of 12 patients (five with bulimia nervosa, seven with anorexia nervosa) had significantly higher medial orbitofrontal and anterior cingulate activity and significantly lower lateral prefrontal, inferior parietal lobule, and left cerebellar activity than the comparison subjects. The group of 10 patients who were taking SSRI medication also showed higher orbitofrontal and

**TABLE 3. Comparison of Brain Activation in Response to Food Stimuli in 26 Patients With Eating Disorders and 19 Healthy Comparison Subjects<sup>a</sup>**

Comparison and Brain Region	Laterality	Brodmann's Area	Cluster Size (mm <sup>3</sup> )	Talairach and Tournoux Coordinates		
				x	y	z
Patients with eating disorders > comparison subjects						
Ventromedial prefrontal cortex	Left	11, 25, 32	3000	-16	28	-17
Comparison subjects > patients with eating disorders						
Lateral prefrontal cortex	Left	45, 46	900	-40	42	3
Dorsolateral prefrontal cortex	Left	44	660	-49	9	26
Inferior parietal lobule	Left	40	1440	-36	-42	48
Occipital cortex	Left	19	1620	-15	-72	33
Cerebellum (declive)	Left	—	840	-32	-74	-20
Patients with anorexia nervosa > comparison subjects						
Ventromedial prefrontal cortex	Left	11	1980	-13	29	-20
Occipital cortex: lingual gyrus	Right	19	3480	19	-72	-4
Comparison subjects > patients with anorexia nervosa						
Inferior parietal lobule	Left	40	720	-33	-47	44
Cerebellum (declive)	Left	—	600	-32	-73	-20
Patients with bulimia nervosa > comparison subjects						
Ventromedial prefrontal cortex	Left	11	4020	-17	35	-13
Occipital cortex: lingual gyrus	Left	19	660	-38	-60	-9
Cerebellum (vermis)	Right, left	—	1260	2	-54	-20
Comparison subjects > patients with bulimia nervosa						
Dorsolateral prefrontal cortex	Left	46/44	660	-46	23	26
Lateral prefrontal cortex	Left	45/44	600	-42	40	0
Patients with anorexia nervosa > patients with bulimia nervosa						
Apical prefrontal cortex	Right	10	840	13	64	-2
Lateral prefrontal cortex	Right	47	1380	47	36	-5
Occipital cortex: lingual gyrus	Right	18	3780	17	-72	1
Patients with bulimia nervosa > patients with anorexia nervosa						
Cerebellum	Right	—	1020	29	-57	-24

<sup>a</sup> Differences in activation at a cluster-wise significance level of  $p \leq 0.001$  are given.

lower lateral prefrontal activity, relative to the comparison subjects.

To investigate whether differences were related to depressive symptoms, a group of five eating disorders patients with Beck Depression Inventory scores below 14 (the cutoff value for mild depressive symptoms [19]) was selected. Relative to the comparison group, this nondepressed group had greater left orbitofrontal, bilateral medial prefrontal, and anterior cingulate responses and lower left parietal response.

Finally, three eating disorders patients (two with anorexia nervosa, one with bulimia nervosa) reported longer times (fasting times between 7 and 9 hours) than the other subjects since their last meal before the experiment. After exclusion of these three patients, there was no between-group difference in fasting time ( $p=0.36$ ), but the significance of the between-group differences in the medial and lateral prefrontal cortex, parietal cortex, and cerebellum was not diminished.

**Subtypes of anorexia nervosa.** Exploratory comparisons of the restricting and binge-eating/purging types of anorexia nervosa were conducted, although the numbers of subjects in the subgroups were small (nine with the restricting type, seven with the binge-eating/purging type). In reaction to food stimuli, left medial prefrontal activation was significantly higher in subjects with the restricting type than in the comparison subjects. In the binge-eating/purging subgroup, significantly different activation, relative to the comparison group, was right-sided and was

located in the lateral orbitofrontal cortex (Brodmann's area 47) and anterior orbitofrontal cortex (Brodmann's area 10).

When reactions to food were compared between the subgroups, the right anterior prefrontal (Brodmann's area 10; stereotaxic coordinates 11, 67, -7 [24]) and lateral orbitofrontal (Brodmann's area 47; coordinates 41, 26, -18) responses were stronger in patients with the binge-eating/purging type; there were no clusters significantly more activated in the patients with the restricting type.

**Experiment 2: Aversive Versus Neutral Stimuli**

**Generic group activation maps.** In response to aversive compared to neutral stimuli, there were two main symmetrical foci of activation: dorsolateral prefrontal activations (Brodmann's area 44, 45, 46) and occipital activations extending into the temporal and parietal cortices (Brodmann's area 18, 19, 7). This pattern was similar in all groups (Figure 1).

**Group comparisons.** Group differences in response to aversive emotional stimuli were located in the posterior cortices and in the cerebellum. Response in the right cerebellum was lower in both clinical groups than in the comparison group, whereas the left cerebellar reaction was significantly greater in patients with anorexia nervosa than in the comparison subjects. Greater activity in the visual occipital cortex and in the left inferior parietal lobule was characteristic of the bulimia nervosa patients. There were

**TABLE 4. Comparison of Brain Activation in Response to Aversive Stimuli in 26 Patients With Eating Disorders and 19 Healthy Comparison Subjects<sup>a</sup>**

Comparison and Brain Region	Laterality	Brodmann's Area	Cluster Size (mm <sup>3</sup> )	Talairach and Tournoux Coordinates		
				x	y	z
Patients with eating disorders > comparison subjects						
Inferior parietal lobule	Left	40	1200	-32	-47	40
Cerebellum	Left	—	1920	-14	-73	-24
Comparison subjects > patients with eating disorders						
Cerebellum	Right	—	1740	37	-60	-19
Patients with anorexia nervosa > comparison subjects						
Cerebellum	Left	—	3840	-18	-71	-26
Comparison subjects > patients with anorexia nervosa						
Cerebellum	Right	—	900	36	-63	-17
Patients with bulimia nervosa > comparison subjects						
Inferior parietal lobule	Left	40	1780	-35	-47	42
Occipital cortex	Right	17	1260	26	-72	25
	Left	17	3300	-22	-72	25
	Left	19	1690	-36	-76	-1
Comparison subjects > patients with bulimia nervosa						
Cerebellum	Right	—	3240	32	-51	-21
Patients with anorexia nervosa > patients with bulimia nervosa						
Cerebellum	Right	—	1620	15	-65	-27
	Right	—	2700	30	-49	-20
Patients with bulimia nervosa > patients with anorexia nervosa						
Occipital cortex	Right	17	1140	26	-73	17
	Left	17	4560	-24	-76	17
Cerebellum	Left	—	1080	-39	-61	-15

<sup>a</sup> Differences in activation at a cluster-wise significance level of  $p \leq 0.001$  are given.

no between-group differences in the frontal reaction to aversive emotional stimuli (Table 4).

## Discussion

Exploration of cerebral activity during presentation of food images has identified activations common to the whole eating disorders group and specific to subgroups with particular eating disorder diagnoses. An abnormal prefrontal reaction was specifically manifested in response to food stimuli, whereas differences in cerebellar, occipital, and parietal activity were present in reaction to both emotional and food images.

In response to food stimuli, patients with eating disorders recruited the medial orbitofrontal cortex and the anterior cingulate instead of the inferior parietal lobule and the left cerebellum, which were activated in the healthy comparison group. The finding of an increased medial prefrontal reaction to food was independently significant for both the anorexia nervosa and bulimia nervosa subgroups and therefore can be considered as a functional neural substrate common to these eating pathologies. The ventromedial prefrontal location of differential activity corresponds to locations where lesions are known to cause eating disorders-like syndromes (4, 5) and to neuroimaging data (8, 9, 11, 12, 15). The orbitofrontal and anterior cingulate cortices are a convergence zone for processing of emotional information and are consistently implicated in the pathogenesis of obsessive-compulsive and affective disorders (25, 26). Because there is phenomenological overlap (1, 17), comorbidity, and familial co-occurrence (27) of these disorders with eating disorders, common neural mechanisms are suspected. Since addiction-like

cue reactivity has been described in bulimia nervosa (28), another parallel comes from studies in drug addiction, which show anterior cingulate and orbitofrontal activations related to craving and compulsive drug-taking behaviors (16, 29). From these data, evidence converges on the anterior cingulate and the orbitofrontal cortex as major constituents in a dysfunctional network associated with compulsive and affective phenomena in a group of related disorders.

In our study, the patients with bulimia nervosa differed both from the patients with anorexia nervosa and from the comparison subjects by having decreased activation in the anterior and lateral prefrontal cortex in response to food. As the lateral prefrontal cortex is involved in suppressing undesirable behaviors (30), diminished activity in this region may account for the loss of control in the eating behavior of bulimic patients. Lateral and apical prefrontal activity has been retrospectively associated with good outcome in anorexia nervosa (20). In the future, frontal involvement in response to food may be evaluated as an outcome-modifying factor in bulimia nervosa.

Differences between groups in posterior cortical and cerebellar activation were present in reaction to both food and emotional stimuli. There are few data for comparison. Many neuroimaging studies have omitted the cerebellum or have used it as a baseline reference (11, 15). In this study, diagnosis-specific changes in cerebellar activations have been highlighted. As these activations were present in both the food and aversive emotional stimuli conditions, they are likely to be associated with nonspecific processes, such as attention and arousal.

The present findings are largely compatible with previous reports. In detailed comparisons, however, there are two notable differences. First, activation in the amygdala differentiated anorexia nervosa subjects from comparison subjects in a previous study from our laboratory (12), but in the present investigation there was no significant amygdala activation either in group maps or in between-group comparisons. Methodological differences, which might explain this difference in findings, include the type of stimuli (images of drinks labeled as high- or low-caloric were used previously) and the analytical procedures (more conservative in the current study). A more conclusive answer on the role of amygdala in eating disorders can be expected from studies with regionally optimized acquisition. Second, comparing anorexia nervosa and bulimia nervosa, we have found both common and differential components in frontal response to food stimuli, whereas an opposite pattern of frontal reaction to eating in anorexia nervosa and bulimia nervosa was reported by Nozoe et al. (15). In comparing the two studies' findings, different provocation paradigms (eating food versus seeing food) and neuroimaging methods (SPECT and fMRI) have to be taken into account. Most notably, Nozoe et al. chose to analyze regions of interest in only three of 35 axial slices; their findings may thus correspond to differential lateral prefrontal changes, while any common aspects of response in the ventromedial cortex may have been missed.

To our knowledge, the current study is the largest functional neuroimaging study in eating disorders to date and the first fMRI study in bulimia nervosa. A direct comparison of anorexia nervosa and bulimia nervosa patients allowed us to evaluate the similarities and differences of these groups. In addition to presentation of food images, a comparison paradigm was used to control for saliency and thus to differentiate between specific and nonspecific processes. Inclusion of subjects who were taking medication and of partially weight-recovered subjects was addressed in a confirmatory analysis by exclusion of the individuals with those characteristics.

Although the number of subjects in the current study is larger than in previous neuroimaging studies, it may not be large enough to explore the full eating disorders spectrum (e.g., subtypes of anorexia nervosa). The capacity of fMRI to detect signal changes is subject to regional differences in signal-to-noise ratio, and therefore the study procedures may be sensitive enough to detect differences in some brain regions but may lack power to do so in other regions (unpublished 2003 data of M. Brammer). Furthermore, fMRI explores paradigm-related changes in brain function but does not identify baseline differences, such as those reported in PET studies (13). The paradigm-related changes of activity reported here will therefore be best appreciated as deviations from a baseline, which itself is altered in eating disorders (7, 15).

The food paradigm was conceived as a symptom-provocation challenge, and the accompanying instruction was

biased toward food as opposed to control stimuli. Therefore, the resulting activations cannot be interpreted as pure reactions to food. Because the same procedure was applied for all participants, the group comparisons were not affected by this instruction bias.

In conclusion, an abnormal focus of food-related activity in the medial prefrontal region has been identified in a large number of eating disorders patients. This activity was specifically manifested in response to symptom-related material and was independent of the type of eating disorders, use of medication, presence of depressive symptoms, fasting time, and body-weight status. Distinct aspects of anorexia and bulimia nervosa were reflected in the activity of circuits comprising the lateral and anterior prefrontal cortices. The similarity of findings in eating, obsessive-compulsive, and affective disorders and in addiction raises the possibility of a common compulsion- and affect-related circuit that is based in the medial prefrontal cortex and activated by disease-specific stimuli in these various conditions.

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