

**Uher, R., Murphy, T., Brammer, M. J., Dalgleish, T., Phillips, M. L., Ng, V. W., Andrew, C. M., Williams, S. C., Campbell, I. C., and Treasure, J. (2004).** Medial prefrontal cortex activity is associated with symptom provocation in eating disorders. *American Journal of Psychiatry*, **161**, 1238-1246.

## **Medial prefrontal cortex activity is associated with symptom provocation in eating disorders**

Rudolf Uher, MUDr.

Tara Murphy, MSc.

Michael J. Brammer, Ph.D.

Tim Dalgleish<sup>1</sup>, Ph.D.

Mary L. Phillips, Ph.D.

Virginia W. Ng, MRCP

Christopher M. Andrew

Steven C.R. Williams, Ph.D.

Iain C Campbell, DSc.

Janet Treasure, FRC Psych

Institute of Psychiatry, King's College London, UK

<sup>1</sup> MRC Cognition and Brain Sciences Unit, Cambridge, UK

\* Address for correspondence:

Rudolf Uher, Eating Disorders Unit, Institute of Psychiatry PO59, King's College  
London, De Crespigny Park, London, SE5 8AF, UK

Phone: 0044 20 7848 0183

Fax: 0044 20 7848 0182

E mail: [r.uher@iop.kcl.ac.uk](mailto:r.uher@iop.kcl.ac.uk)

**Acknowledgements:** This study was supported by a grant QLK1-1999-916 from the European Commission Framework V program (<http://www.cordis.lu/life/home.html>) and the Nina Jackson Eating Disorders Research Charity. Rudolf Uher is supported by a Travelling Research Fellowship from the Wellcome Trust (065862).

Preliminary results from 18 participants were reported at the Human Brain Mapping conference in Brighton in June 2001 (abstract in Neuroimage; 13: S1022).

## **Abstract**

**Objective:** Identification of neural correlates will contribute to the debate on the genesis and classification of eating disorders and will provide endophenotypes for genetic research.

**Method:** 26 female patients with eating disorders (10 with bulimia nervosa, 16 with anorexia nervosa) and 19 female controls matched for age and education were presented with food and aversive emotional images while brain activity was being recorded by functional magnetic resonance.

**Results:** Women with eating disorders identified the food stimuli as threatening and disgusting. In response to these stimuli, left medial orbitofrontal and anterior cingulate cortices were more activated whereas the lateral prefrontal cortex, the inferior parietal lobule and cerebellum were less active than in the comparison group. In bulimia nervosa, there was an additional decrease in lateral and apical prefrontal activity. The between-group differences in response to non-specific emotional stimuli were in the occipital cortex, parietal cortex and cerebellum.

**Conclusions:** A medial prefrontal response to symptom provoking stimuli has been identified as a common feature of anorexia and bulimia nervosa, supporting the transdiagnostic concept in eating disorders at a neural level. The abnormal prefrontal reaction is associated with symptom-related material whereas the occipital and cerebellar differences are non-specific. It is proposed that 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.

**Introduction:**

Eating disorders (ED) comprise a spectrum of conditions, of which bulimia nervosa (BN) and anorexia nervosa (AN) are the major categories. Somatic symptoms (underweight, amenorrhoea) are regarded as secondary to a core psychopathology, which is presumed to be encoded as long-standing alterations of cerebral neural circuits (11;23;26).

Evidence for a neural disturbance in ED is compelling. The clinical syndrome can be reproduced by lesions in the right inferior prefrontal cortex (24;28). Association with perinatal complications is also suggestive of a cerebral cause (7). Indirect evidence for ED being neural diseases is inferred from neuropsychological, electrophysiological, neuropharmacological, structural neuroimaging and functional neuroimaging investigations (26).

Functional neuroimaging studies in ED have either investigated brain function at rest or under controlled disorder-specific conditions. Resting-state experiments have found global cerebral hypofunction (8), which is most pronounced in the anterior cingulate and frontal region (17;22) and in the parietal lobe (8). In BN, parietal hypometabolism (8) and a loss of the normal right>left asymmetry of brain glucose metabolism (29) have been reported.

Controlled condition experiments have used body shapes, eating or food presentation to elicit symptom-related brain processes. In AN, perfusion of the frontal lobes (measured by single photon emission tomography [SPECT]) increased when eating a cake (18) and, in a functional magnetic resonance (fMRI) experiment, viewing high-caloric drinks elicited responses in the prefrontal, anterior cingulate and insular cortices,

and in the amygdala (10). A positron emission tomography (PET) study did not replicate these findings and reported food-related activity only in visual-associative cortices in 7 AN patients viewing high- versus low-caloric foods (12). Amygdala response to morphed images of subjects' bodies has been reported in 3 patients with AN (21). Data on BN is limited: only one SPECT study included five patients with BN and found that high basal frontal perfusion decreased with eating, a response pattern opposite to that seen in AN (19).

A summary of resting and controlled-condition studies suggests that the same regions (prefrontal cortices, anterior cingulate) show diminished activity at rest but abnormally increase activity in response to food challenge. Some abnormalities (parietal hypometabolism at rest) are common to AN and BN (8), while other (frontal reaction to eating) may differ between these diagnoses (19). These similarities and differences add to the debate on whether ED are one entity with a spectrum of manifestations or are several separate syndromes (11;23).

The propensity to specific attitudes (drive for thinness, fear of fatness) and behaviors (bingeing, restricting) is conceptualised as preferential activation of certain neural pathways and circuits. Functional relevance of neural circuits is inferred from activation patterns recorded in situations with high probability of symptom manifestation. We used fMRI to investigate brain responses to food images in women with ED and healthy female controls (CO). Two general hypotheses were tested: there will be activation patterns common to the whole ED group, implying shared neural mechanisms, and secondly, there will be responses specific to BN or AN, reflecting variations within the ED spectrum. These differences should be specifically manifest in response to disease

specific material (food), when symptom related neural schemata are likely to be activated. To establish stimulus specificity, non-specific emotionally salient stimuli were used in addition to food.

## **Method**

### **Participants**

Patients with ED were recruited from the inpatient (10) and outpatient (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 ED. Affective and obsessive-compulsive symptoms are integral parts of ED (11;13) and their presence was not an exclusion criterion. Healthy women (CO) were recruited by local advertisement and screened for abnormal eating habits, neurological or psychiatric disease. Current and minimum past body mass index (BMI) were calculated. The Maudsley Obsessive-Compulsive Inventory (MOCI; 14) and the Beck Depression Inventory (BDI; 2) were used to measure obsessive-compulsive and depressive symptomatology.

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 AN have been selected as comparison groups for recovered subjects in a parallel study, which is reported elsewhere (25).

## **Stimuli**

Custom-created colour photographs included savoury (e.g. pizza, rice, bread) and sweet (e.g. cake, chocolate) foods presented on plates. Photographs of non-food items (stationary, household objects, flower) were individually matched for colour and visual complexity based on ratings by five volunteers.

Emotional aversive photographs were selected from the International Affective Picture System (IAPS No: 2720, 2730, 3000, 3010, 3030, 3051, 3053, 3071, 3100, 3170, 3261, 9140, 9253, 9300, 9340, 9373, 9405) and contrasted with neutral stimuli matched for colour and visual complexity (IAPS No: 1600, 1670, 5201, 2250, 5390, 5780, 5982, 5990, 5991, 7010, 7020, 7090, 7100, 7150, 7235, 7550, 7950; 15).

## **Procedure**

Participants were asked to eat a meal 3 hours before the experiment and avoid smoking, eating and drinking alcoholic or caffeine-containing beverages afterwards. Due to differential compliance, the time since the last meal was longer in the ED group ('Fasting time', Table 1). After completing questionnaires and rating their feeling of hunger (Table 1), participants were scanned between 5 and 7 p.m. Food and non-food images were presented on a rear-projecting screen and viewed via a double mirror periscope fitted to the headcoil. Each image was shown for 2.5 s followed by a blank screen for 0.5 s. Ten food pictures in a 30 second block ('on' condition) were followed by ten non-food pictures ('off' condition). This sequence was repeated 5 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 instruction: ‘You will be presented with a number of colour pictures. Look at each of them and think what it makes you feel like.’ The order of the two experiments was counterbalanced between subjects. After the scanning, participants rated individual images on 1 (not at all) to 7 (very much) 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 Tesla neuro-optimised MR system (GE Medical Systems, Milwaukee, USA). One hundred  $T_2^*$ -weighted whole brain volumes were acquired in each experiment (repetition time 3s, echo time 40ms) in 16 near-axial 7mm thick slices (0.7mm interslice gap) depicting blood oxygen level dependent (BOLD) contrast with an in-plane resolution of 3mm.

### **Data analysis and statistics**

Following motion correction (4), the estimated BOLD effect was modeled by two Poisson functions with haemodynamic delays 4 and 8 seconds. This model provides results, which are equivalent to the physiological model of the BOLD effect. The least-squares model of the weighted sum of these two functions was compared with 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, depicting regions where the BOLD signal was significantly stronger in response to the active images (food / aversive) than to the control images,

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 (5). In each experiment (food, aversive), four group comparisons were performed: ED and CO; AN and CO; BN and CO; AN and BN. 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 is less than one. Behavioral data were analyzed using ANOVA and post-hoc two-tailed t-tests (uncorrected).

## **Results**

### **Demographic and behavioural data**

Out of 43 patients with ED who were assessed, nine declined to participate and eight were excluded because of past substance abuse ( $n = 4$ ), claustrophobia ( $n = 1$ ), dental plates or metal implants ( $n = 3$ ). The final sample consisted of 26 women with an ED and 19 healthy controls. Ten participants fulfilled DSM-IV criteria for BN and 16 for AN (9 restricting subtype, and 7 binge-purge subtype). Ten participants (5 BN and 5 AN) were taking antidepressant medication (SSRI). Although efforts were made to minimise delays between recruitment and the experiment, 4 of the 16 AN patients gained enough

weight to be outside the diagnostic range at the time of scanning. Inclusion of patients with medication and body weight outside diagnostic range is addressed in the analysis.

The groups did not differ in age, gender (all females) or handedness (1 control and 1 AN patient were left-handed). The AN group reported significantly fewer years of education whereas the BN group did not differ in education from the healthy controls. Both patient groups scored significantly higher on self-report measures of obsessive-compulsive symptomatology and depression (Table 1).

### **Subjective rating of stimuli**

Participants with ED rated food stimuli as significantly less desirable, less pleasant, more disgusting and more fearful than CO; there were no differences in ratings of the non-food stimuli (Table 2). Aversive stimuli were rated as more strongly negative by ED than by CO; there were no differences in ratings of the neutral stimuli (Table 2).

## **EXPERIMENT 1: FOOD VERSUS NON-FOOD STIMULI**

### ***Generic group activation maps***

**Comparison group.** At  $p \leq 0.01$ , activity in the left lateral prefrontal (BA 10, 9), left parietal (BA 7, 40) and bilateral visual (BA 17, 18) cortices and bilaterally in the cerebellum correlated with presentation of food stimuli (Figure 1).

**Eating Disorders.** Food-related activity in the ED group was in the anterior cingulate gyrus (BA 24, 32;  $p < 0.001$ ), posterior cingulate gyrus (BA 23, 29, 30;  $p < 0.001$ ), left orbitofrontal cortex (BA 11;  $p < 0.02$ ), left lateral prefrontal cortex (BA 10) and right cerebellum (posterior lobe, declive). Activations in the anterior cingulate cortex and in

the right cerebellum were similar in BN and AN. Medial prefrontal activity was more extensive in the BN group whereas the lateral prefrontal activation was only detected in AN (Figure 1).

### ***Group comparisons***

In ED, a left-sided cluster subsuming the medial orbitofrontal and anterior cingulate cortices was more active in response to food. Compared to CO, this activation was significantly higher not only in the whole ED group but also in the subgroups of BN and AN. Examination of time-series revealed a strong reaction (0.5 % change in BOLD signal) in this region in ED, especially during the first three blocks of the paradigm (Figure 2). Additionally, the AN group showed more activity in the lingual gyrus and BN had more occipital and cerebellar activity than CO (Table 3, Figure 2).

The left lateral prefrontal cortex, the left inferior parietal lobule, the left occipital cortex and posterior cerebellum were significantly less activated in ED compared to CO. Responses in these regions in CO averaged around 0.25 % change in BOLD signal (time-series in the inferior parietal lobule is presented in Figure 2). The inferior parietal lobule and cerebellar activity were more diminished in AN, whereas the lateral prefrontal activity was decreased specifically in BN in comparison to CO and to AN (Table 3, Figure 2).

**Exclusion of confounding factors.** To address potential confounding factors due to inclusion of patients on medication and those who had gained weight, group comparison between ED and CO was repeated after exclusion of these participants. The diagnostically ‘pure’ and medication free group of 12 patients (5BN, 7AN) had

significantly higher medial orbitofrontal and anterior cingulate and lower lateral prefrontal, inferior parietal lobule and left cerebellar activity than controls. The group of 10 patients taking SSRI medication also showed higher orbitofrontal and lower lateral prefrontal activity compared to controls.

To investigate whether differences were due to depressive symptomatology, a group of 5 ED patients with BDI scores below 14 (cut-off value for mild depressive symptoms; (2) was selected. Compared to CO, this non-depressed group had greater left orbitofrontal, bilateral medial prefrontal and anterior cingulate responses and a decreased left parietal response.

Finally, some of the ED patients reported longer time since last meal before the experiment. This difference was entirely due to three patients (2 AN, 1 BN) who reported fasting times between 7 and 9 hours. After exclusion of these three patients, there was no between-group difference in fasting time ( $p = 0.36$ ) but the significance of between group differences in the medial and lateral prefrontal cortex, parietal cortex and in the cerebellum was not diminished.

### **Exploratory comparison of the restricting and binge/purge subtypes of AN.**

Although numbers in the subgroups were small (9 restrictors, 7 binge-purgers), exploratory comparisons were performed. In reaction to food stimuli, the left medial prefrontal activation was significantly higher in restrictors than in CO. In binge-purge subgroup, the significantly different activation was right-sided and located in the lateral orbitofrontal cortex (BA 47) and anterior orbitofrontal cortex (BA 10).

When reactions to food were compared between the subgroups, the right anterior prefrontal (BA 10; coordinates 11, 67, -7) and lateral orbitofrontal (BA 47; coordinates 41,26, -18) responses were stronger in binge-purgers; there were no clusters significantly more activated in restrictors.

## **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 (BA 44, 45, 46) and occipital activations extending into temporal and parietal cortices (BA 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 decreased in both clinical groups compared to controls, whereas the left cerebellar reaction was

significantly increased in AN. Increased activity in the visual occipital cortex and in the left inferior parietal lobule was characteristic for BN. There were no between group differences in the frontal reaction to aversive emotional stimuli (Table 4).

## **Discussion**

Exploration of cerebral activity during visual presentation of food has identified activations common for the whole ED group and specific for individual 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 ED 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 AN and BN and therefore can be considered as a functional neural substrate common to these eating pathologies. The ventromedial prefrontal location of differential activity corresponds to lesions causing eating-disorders-like syndromes (24;28) and to neuroimaging data (10;17-19;22). 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 (9;20). As there is a phenomenological overlap (11;13), comorbidity and familial cooccurrence (3) of these disorders with ED, common neural mechanisms are suspected. Since addiction-like cue reactivity has been described in BN (6), another parallel comes from studies in drug addiction, which show anterior cingulate and orbitofrontal activations related to craving and compulsive drug-taking behaviors (16;27). 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.

BN differed from both AN and CO 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 behaviours (1), diminished activity in this region may account for the loss of control in eating behaviour of bulimic patients. Lateral and apical prefrontal activity has been retrospectively associated with good outcome in AN (25). In future, frontal involvement in response to food may be evaluated as an outcome-modifying factor in BN.

The posterior cortical and cerebellar differences were present in reactions to both food and emotional stimuli. There is little data for comparison. Many neuroimaging studies have omitted the cerebellum or have used it as a baseline reference (18;19). In this study, diagnosis-specific changes in cerebellar activations have been highlighted. As these were present in both food and emotional conditions, they are likely to be associated with non-specific processes, such as attention and arousal.

The present findings are largely compatible with previous reports. In detailed comparisons however, there are two notable differences: Firstly, activation in the amygdala differentiated AN from controls in a previous study from our laboratory (10) 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 differential finding, include the type of stimuli (images of drinks labelled 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

ED can be expected from studies with regionally optimised acquisition. Secondly, comparing AN and BN, we have found both common and differential components in frontal response to food stimuli, whereas an opposite pattern of frontal reaction to eating in AN and BN was reported by Nozoe et al (19). 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 analyse regions of interest in only three axial slices out of 35; their findings may thus correspond to the differential lateral prefrontal changes while any common aspects of response in the ventromedial cortex may have been missed.

To our knowledge, this is the largest functional neuroimaging study in ED to date and the first fMRI study in BN. A direct comparison of AN and BN allowed us to evaluate the similarities and differences of these groups. In addition to the food, a comparison paradigm was used to control for saliency and thus to differentiate between specific and non-specific processes. Inclusion of subjects on medication and of partially weight-recovered subjects was addressed in confirmatory analysis by exclusion of concerned individuals.

Although the number of subjects is larger than in previous neuroimaging studies, it may not be sufficient to explore the full ED spectrum (e.g. subgroups of AN). The capacity of fMRI to detect signal changes is subject to regional differences in signal-to-noise ratio and therefore the study may be sensitive to detect differences in some brain regions while lacking the power to do so elsewhere (M. Brammer, unpublished data). Furthermore, fMRI explores paradigm-related changes in brain function, while it does not identify baseline differences, such as those reported in PET studies (12). The paradigm-

related changes of activity reported here will therefore be best appreciated as deviations from a baseline, which itself is altered in ED (8;19).

The food paradigm was conceived as a symptom-provocation challenge and the accompanying instruction was biased towards food as opposed to control stimuli. Therefore, the resulting activations cannot be interpreted as pure reaction to food. As 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 substantial sample of ED patients. This activity was specifically manifested in response to symptom-related material and was independent of the type of ED, medication, depressive symptoms, fasting time and body-weight status. Distinct aspects of anorexia and bulimia nervosa were reflected in the activity of circuits comprising 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-affect related circuit, based in the medial prefrontal cortex, and activated by disease-specific stimuli in these various conditions.

**Table 1:** Demographic and clinical characteristics.

	<b>HEALTHY CONTROLS n = 19</b>	<b>PATIENTS n = 26</b>	<b>ANOREXIA NERVOSA n = 16</b>	<b>BULIMIA NERVOSA n = 10</b>
Age	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 <sup>c</sup>	16.5 ± 1.84
MOCI (0-25)	2.52 ± 2.06	9.65 ± 6.12 <sup>a</sup>	10.00 ± 5.81 <sup>a</sup>	9.20 ± 7.13 <sup>b</sup>
BDI (0-63)	1.84 ± 3.02	24.08 ± 13.51 <sup>a</sup>	25.8 ± 13.53 <sup>a</sup>	23.7 ± 12.77 <sup>a</sup>
BMI	22.41 ± 2.98	18.59 ± 3.65 <sup>a</sup>	16.04 ± 1.64 <sup>a</sup>	22.43 ± 2.37
Duration (years)	-	13.80 ± 10.38	13.13 ± 11.8	14.80 ± 8.26
Hunger (1-7)	2.42 ± 1.17	2.00 ± 1.30	1.67 ± 1.23	2.40 ± 1.35
Fasting time*	3.29 ± 0.89	4.27 ± 1.82 <sup>c</sup>	4.10 ± 1.86	4.50 ± 1.92 <sup>c</sup>

\* Time since the last meal before scanning in hours.

Data is given as mean ± standard deviation. Significant differences from the control group (ANOVA, post hoc two-tailed t-test) are given: <sup>a</sup> p< 0.001; <sup>b</sup> p<0.01; <sup>c</sup> p<0.05

**Table 2:** Subjective rating of stimuli.

	<b>HEALTHY CONTROLS n = 19</b>	<b>PATIENTS n = 26</b>	<b>ANOREXIA NERVOSA n = 16</b>	<b>BULIMIA NERVOSA n = 10</b>
<b>FOOD STIMULI</b>				
Desire to eat	3.48 ± 1.06	2.33 ± 1.28 <sup>b</sup>	1.70 ± 0.85 <sup>a</sup>	3.24 ± 1.33
Pleasant	3.27 ± 1.20	2.13 ± 1.14 <sup>b</sup>	1.96 ± 0.87 <sup>a</sup>	2.22 ± 1.44
Fear	1.02 ± 0.06	3.06 ± 1.91 <sup>a</sup>	3.80 ± 1.90 <sup>a</sup>	1.94 ± 1.43 <sup>c</sup>
Disgust	1.45 ± 0.72	3.60 ± 1.82 <sup>a</sup>	4.21 ± 1.59 <sup>a</sup>	2.80 ± 1.89 <sup>c</sup>
<b>NON-FOOD STIMULI</b>				
Pleasant	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
<b>AVERSIVE STIMULI</b>				
Pleasant	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 <sup>b</sup>	4.57 ± 1.36 <sup>c</sup>	4.26 ± 1.29
Disgust	5.12 ± 1.15	6.23 ± 1.12 <sup>b</sup>	6.33 ± 1.05 <sup>b</sup>	6.08 ± 1.26 <sup>c</sup>
<b>NEUTRAL STIMULI</b>				
Pleasant	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

Data is given as mean ± standard deviation. Significant differences from the control group (ANOVA, post hoc two-tailed t-test) are reported: <sup>a</sup> p< 0.001; <sup>b</sup> p<0.01; <sup>c</sup> p<0.05

**Table 3:** Group comparisons of cerebral reactions to food stimuli.

Brain region	Laterality	Brodmann's area	Cluster size (mm <sup>3</sup> )	Coordinates		
				x	y	z
<b>ED &gt; CO</b>						
Ventromedial prefrontal	L	11,25,32	3000	-16	28	-17
<b>CO &gt; ED</b>						
Lateral prefrontal	L	45,46	900	-40	42	3
Dorsolateral prefrontal	L	44	660	-49	9	26
Inferior parietal lobule	L	40	1440	-36	-42	48
Occipital	L	19	1620	-15	-72	33
Cerebellum (declive)	L	-	840	-32	-74	-20
<b>AN &gt; CO</b>						
Ventromedial prefrontal	L	11	1980	-13	29	-20
Occipital: lingual gyrus	R	19	3480	19	-72	-4
<b>CO &gt; AN</b>						
Inferior parietal lobule	L	40	720	-33	-47	44
Cerebellum (declive)	L	-	600	-32	-73	-20
<b>BN &gt; CO</b>						
Ventromedial prefrontal	L	11	4020	-17	35	-13
Occipital: lingual gyrus	L	19	660	-38	-60	-9
Cerebellum (vermis)	R,L	-	1260	2	-54	-20
<b>CO &gt; BN</b>						
Dorsolateral prefrontal	L	46/44	660	-46	23	26
Lateral prefrontal	L	45/44	600	-42	40	0
<b>AN &gt; BN</b>						
Apical prefrontal	R	10	840	13	64	-2
Lateral prefrontal	R	47	1380	47	36	-5
Occipital – lingual gyrus	R	18	3780	17	-72	-1
<b>BN &gt; AN</b>						
Cerebellum	R	-	1020	29	-57	-24

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

**Table 4:** Group comparisons of cerebral reactions to aversive stimuli:

Brain region	Laterality	Brodmann's area	Cluster size (mm <sup>3</sup> )	Coordinates		
				x	y	z
<b>ED &gt; CO</b>						
Parietal– inferior lobule	L	40	1200	-32	-47	40
Cerebellum	L	-	1920	-14	-73	-24
<b>CO &gt; ED</b>						
Cerebellum	R	-	1740	37	-60	-19
<b>AN &gt; CO</b>						
Cerebellum	L	-	3840	-18	-71	-26
<b>CO &gt; AN</b>						
Cerebellum	R	-	900	36	-63	-17
<b>BN &gt; CO</b>						
Parietal – inferior lobule	L	40	1780	-35	-47	42
Occipital	R	17	1260	26	-72	25
Occipital	L	17	3300	-22	-72	25
Occipital	L	19	1690	-36	-76	-1
<b>CO &gt; BN</b>						
Cerebellum	R	-	3240	32	-51	-21
<b>AN &gt; BN</b>						
Cerebellum	R	-	1620	15	-65	-27
Cerebellum	R	-	2700	30	-49	-20
<b>BN &gt; AN</b>						
Occipital	R	17	1140	26	-73	17
Occipital	L	17	4560	-24	-76	17
Cerebellum	L	-	1080	-39	-61	-15

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

Figure 1: Examples of stimuli and generic group activation maps for food and aversive images.

- Figure 1 -

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  $p \geq 0.01$ .

Figure 2: Group comparisons of cerebral reaction to food stimuli and time series of activity.

- Figure 2 -

Activations differentiating between the groups at a significance level of  $p \geq 0.001$  are given 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 cluster of activity in the composite patient group (PATIENTS;  $n = 26$ ) and for the healthy comparison group (CONTROLS;  $n = 19$ ). After smoothing by a running average of five time points (15 seconds), time series have been plotted against the presentation paradigm (blue line).

## Reference List

1. Aron AR, Fletcher PC, Bullmore ET, Sahakian BJ, Robbins TW: Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nat.Neurosci.* 2003; 6:115-116
2. Beck A.T., Steer RA, Brown GK: BDI II Manual San Antonio, Texas, The Psychological Corporation, 2002
3. Bellodi L, Cavallini MC, Bertelli S, Chiapparino D, Riboldi C, Smeraldi E: Morbidity risk for obsessive-compulsive spectrum disorders in first-degree relatives of patients with eating disorders. *Am.J.Psychiatry* 2001; 158:563-569
4. Bullmore ET, Brammer MJ, Rabe-Hesketh S, Curtis VA, Morris RG, Williams SC, Sharma T, McGuire PK: Methods for diagnosis and treatment of stimulus-correlated motion in generic brain activation studies using fMRI. *Hum.Brain Mapp.* 1999; 7:38-48
5. Bullmore ET, Suckling J, Overmeyer S, Rabe-Hesketh S, Taylor E, Brammer MJ: Global, voxel, and cluster tests, by theory and permutation, for a difference between two groups of structural MR images of the brain. *IEEE Trans.Med.Imaging* 1999; 18:32-42

6. Carter FA, Bulik CM, McIntosh VV, Joyce PR: Changes in cue reactivity following treatment for bulimia nervosa. *Int.J.Eat.Disord.* 2001; 29:336-344
7. Cnattingius S, Hultman CM, Dahl M, Sparen P: Very preterm birth, birth trauma, and the risk of anorexia nervosa among girls. *Arch Gen.Psychiatry* 1999; 56:634-638
8. Delvenne V, Goldman S, DeMaertelaer V, Lotstra F: Brain glucose metabolism in eating disorders assessed by positron emission tomography. *Int.J.Eat.Disord.* 1999; 25:29-37
9. Drevets WC: Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Curr.Opin.Neurobiol.* 2001; 11:240-249
10. Ellison Z, Foong J, Howard R, Bullmore E, Williams S, Treasure J: Functional anatomy of calorie fear in anorexia nervosa. *Lancet* 1998; 352:1192
11. Fairburn CG, Harrison PJ: Eating disorders. *Lancet* 2003; 361:407-416
12. Gordon CM, Dougherty DD, Fischman AJ, Emans SJ, Grace E, Lamm R, Alpert NM, Majzoub JA, Rauch SL: Neural substrates of anorexia nervosa: a behavioral challenge study with positron emission tomography. *J.Pediatr.* 2001; 139:51-57

13. Halmi KA, Sunday SR, Klump KL, Strober M, Leckman JF, Fichter M, Kaplan A, Woodside B, Treasure J, Berrettini WH, Al Shabboat M, Bulik CM, Kaye WH: Obsessions and compulsions in anorexia nervosa subtypes. *Int.J.Eat.Disord.* 2003; 33:308-319
14. Hodgson RJ, Rachman S: Obsessional-compulsive complaints. *Behav.Res.Ther.* 1977; 15:389-395
15. Lang, P. J., Bradley, M. M., and Cuthbert, B. N. International Affective Picture System (IAPS) 1999; New York, NIMH Center for the Study of Emotion and Affection.
16. Maas LC, Lukas SE, Kaufman MJ, Weiss RD, Daniels SL, Rogers VW, Kukes TJ, Renshaw PF: Functional magnetic resonance imaging of human brain activation during cue-induced cocaine craving. *Am.J.Psychiatry* 1998; 155:124-126
17. Naruo T, Nakabeppu Y, Deguchi D, Nagai N, Tsutsui J, Nakajo M, Nozoe SS: Decreases in blood perfusion of the anterior cingulate gyri in Anorexia Nervosa Restricters assessed by SPECT image analysis. *BMC Psychiatry* 2001; 1:2
18. Nozoe S, Naruo T, Nakabeppu Y, Soejima Y, Nakajo M, Tanaka H: Changes in regional cerebral blood flow in patients with anorexia nervosa detected through single photon emission tomography imaging. *Biol.Psychiatry* 1993; 34:578-580

19. Nozoe S, Naruo T, Yonekura R, Nakabeppu Y, Soejima Y, Nagai N, Nakajo M, Tanaka H: Comparison of regional cerebral blood flow in patients with eating disorders. *Brain Res.Bull.* 1995; 36:251-255
20. Saxena S, Brody AL, Schwartz JM, Baxter LR: Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. *Br.J.Psychiatry Suppl* 1998;26-37
21. Seeger G, Braus DF, Ruf M, Goldberger U, Schmidt MH: Body image distortion reveals amygdala activation in patients with anorexia nervosa -- a functional magnetic resonance imaging study. *Neurosci.Lett.* 2002; 326:25-28
22. Takano A, Shiga T, Kitagawa N, Koyama T, Katoh C, Tsukamoto E, Tamaki N: Abnormal neuronal network in anorexia nervosa studied with I-123-IMP SPECT. *Psychiatry Res.* 2001; 107:45-50
23. Treasure J, Collier D: *Spectrum of Eating Disorders in Animal Models of Eating Behaviour and Body Composition Disorders* Edited by Owen JB, Treasure J, Collier D. Kluwer academic publishers B.V., 2001
24. Trummer M, Eustacchio S, Unger F, Tillich M, Flaschka G: Right hemispheric frontal lesions as a cause for anorexia nervosa report of three cases. *Acta Neurochir.(Wien.)* 2002; 144:797-801

25. Uher R, Brammer MJ, Murphy T, Campbell IC, Ng VW, Williams SC, and Treasure J. Recovery and chronicity in anorexia nervosa: brain activity associated with differential outcomes. *Biological Psychiatry* , *in press*

26. Uher R, Treasure J, Campbell I.C.: Neuroanatomical bases of Eating Disorders in *Biological psychiatry* Edited by D'Haenen HAH, den Boer JA, Willner P. Chichester, UK, John Wiley & Sons, 2002

27. Volkow ND, Fowler JS: Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. *Cereb.Cortex* 2000; 10:318-325

28. Ward A, Tiller J, Treasure J, Russell G: Eating disorders: psyche or soma? *Int.J.Eat.Disord.* 2000; 27:279-287

29. Wu JC, Hagman J, Buchsbaum MS, Blinder B, Derrfler M, Tai WY, Hazlett E, Sicotte N: Greater left cerebral hemispheric metabolism in bulimia assessed by positron emission tomography. *Am.J.Psychiatry* 1990; 147:309-312