BRAIN RESEARCH

Research Report

Hunger and satiety in anorexia nervosa: fMRI during cognitive processing of food pictures

Stephanie Santel[a], Lioba Baving[b], Kerstin Krauel[a], Thomas F. Münte[c,*], Michael Rotte[d]

[a]Department of Child and Adolescent Psychiatry, University Magdeburg, Germany
[b]Department of Child and Adolescent Psychiatry, University Kiel, Germany
[c]Department of Psychology, University Magdeburg, P.O. Box 4120, D-39016 Magdeburg, Germany
[d]Department of Neurology II and Center for Advanced Imaging, University Magdeburg, Germany

ARTICLE INFO

ABSTRACT

Neuroimaging studies of visually presented food stimuli in patients with anorexia nervosa have demonstrated decreased activations in inferior parietal and visual occipital areas, and increased frontal activations relative to healthy persons, but so far no inferences could be drawn with respect to the influence of hunger or satiety. Thirteen patients with AN and 10 healthy control subjects (aged 13–21) rated visual food and non-food stimuli for pleasantness during functional magnetic resonance imaging (fMRI) in a hungry and a satiated state. AN patients rated food as less pleasant than controls. When satiated, AN patients showed decreased activation in left inferior parietal cortex relative to controls. When hungry, AN patients displayed weaker activation of the right visual occipital cortex than healthy controls. Food stimuli during satiety compared with hunger were associated with stronger right occipital activation in patients and with stronger activation in left lateral orbitofrontal cortex, the middle portion of the right anterior cingulate, and left middle temporal gyrus in controls. The observed group differences in the fMRI activation to food pictures point to decreased food-related somatosensory processing in AN during satiety and to attentional mechanisms during hunger that might facilitate restricted eating in AN.

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* Corresponding author. Fax: +49 391 6711914.
  E-mail address: thomas.muente@medizin.uni-magdeburg.de (T.F. Münte).

Abbreviations:
ACC, anterior cingulate cortex
AN, anorexia nervosa
ANOVA, analysis of variance
BA, Brodmann area
BDI, Beck Depression Inventory
BMI, body mass index
BOLD, blood oxygenation level
dependency
CFT 20, Culture Fair Intelligence Test
DSM, Diagnostic and Statistical
Manual
EPI, echo-planar imaging
fMRI, functional magnetic
resonance imaging
FWHM, full width at half maximum
HC, healthy controls
IPL, inferior parietal lobe
MNI, Montreal Neurological Institute
OFC, orbitofrontal cortex
ROI, region of interest
RT, reaction time
SSRI, selective serotonin reuptake
inhibitor
TFEQ, Three Factor Eating
Questionnaire

1. Introduction

Anorexia nervosa (AN) is a mental disorder that occurs mainly in adolescent and young adult females with first onset peak at age 14 (Foreyt and McGavin, 1988). According to DSM-IV (American Psychiatric Association, 1994), AN is characterized by self-induced body weight of at least 15% below expected, a fear of gaining weight, body image distortion, and an endocrine disorder resulting in amenorrhea. Cognitive preoccupation with food, often in an obsessive manner, is a clinically observed phenomenon that has also been demonstrated in experimental designs. In Stroop-like tests, AN patients showed increased interference to food words (Channon et al., 1988; Perpina et al., 1993). In memory tasks involving food stimuli, recognition of food items in AN patients was comparable with healthy control (HC) subjects in a hungry state. In HC subjects, memory for food words was decreased in a satiated relative to a hungry state. AN patients, however, showed high recognition for food words, irrespective of being hungry or satiated (Morris and Dolan, 2001; Pietrowsky et al., 2002). Healthy persons assign positive emotional valence to food stimuli that is enhanced by hunger (Lozano et al., 1999). AN patients, who are preoccupied with food irrespectively of hunger, however, report negative valence of food stimuli (Bossert et al., 1991; Vaz et al., 1998). So far, the influence of hunger states on valence ratings of food in AN has not been investigated.

Neural correlates of the processing of visual food stimuli in eating disorders have been investigated in sophisticated studies by Uher et al. (2003, 2004). They found that patients with eating disorders (AN and bulimia nervosa) relative to healthy persons showed decreased activation in inferior parietal lobe (IPL) and occipital cortex and increased activation in medial prefrontal cortex when viewing food pictures. It is unclear, however, how these brain activations would be modulated by hunger and satiety because subjects have been tested in a state intermediate between hunger and satiety and, furthermore, some patients apparently had fasted longer than healthy controls.

Previously, activation of the IPL has been associated with appetitive and food-related behavior (MacKay et al., 1992; Wang et al., 2002). Specifically, Tataranni et al. (1999) have found a relation of this region to satiation. Therefore, we expected that, in a satiated state, AN patients would show weaker IPL activation to food stimuli than controls.

Food is a highly salient stimulus because of its biological relevance (LaBar et al., 2001; Morris and Dolan, 2001), which may explain why healthy subjects have previously been found to exhibit enhanced responses to food stimuli in visual areas of the occipital cortex (Killgore et al., 2003; LaBar et al., 2001; Simmons et al., 2005) similar to salient stimuli of other classes (Bradley et al., 2003; Lang et al., 1998). Activation of secondary visual areas (fusiform gyrus, parahippocampal gyrus) was greater in healthy participants when hungry compared to satiated (LaBar et al., 2001). Uher et al. (2003, 2004) found diminished occipital activation in response to food stimuli in their eating disorders group relative to the HC group. Specific comparisons of AN patients with healthy subjects revealed increased occipital activation in one study (Uher et al., 2004) and decreased occipital activation in the other (Uher et al., 2003). In light of the increased salience of food during hunger in healthy persons, we expected that hungry AN patients would show weaker occipital activation to food stimuli than hungry controls.

Uher et al. (2003, 2004) reported increased activation to visual food stimuli in medial prefrontal cortex in AN patients. This area is commonly associated with cognitive control mechanisms (Fuster, 1993; Stuss and Benson, 1986). We assumed that such control processes should be engaged particularly in AN patients when viewing food in a hungry state and thus expected stronger medial prefrontal activation to food in hungry AN patients than hungry controls.

The current study thus explores neural correlates of AN-specific cognitions to food by investigating the differential impact of hunger and satiety in two separate sessions.

2. Results

2.1. Demographic data

All 13 AN patients and 10 control subjects were female and within an age range of 13 to 21 (for means and standard deviations see Table 1). The groups did not differ in age or intelligence as determined with the Culture Fair Intelligence Test (CFT 20; Weiß, 1998).

All patients had a lowest ever body mass index (BMI) below the 10th age-related percentile; none had a BMI higher than the 25th percentile at the time of testing. As expected, BMI of patients was lower than that of controls (see Table 1). Time since first onset of AN was within a range of 3 to 62 months (median: 8 months), with the majority of patients ($n=10$) suffering from first episode AN of less than a year.

As expected, the AN group scored significantly higher on symptoms of depression than the healthy group, as determined with a modified version of the Beck Depression Inventory (BDI; Beck et al., 1961, German version: Hautzinger et al., 1995) (see Table 1).

Table 1 – Sample characteristics: means and standard deviations (SD)			
	Anorexia patients ($n=13$)	Control subjects ($n=10$)	p value
	Mean (SD)	Mean (SD)	
Age (years)	16.1 (2.0)	16.8 (2.6)	>.40
IQ	116.4 (9.4)	112.4 (16.0)	>.40
BMI (kg/m^2)	16.0 (1.7)	20.5 (1.9)	<.001
BDI[a]	18.1 (9.0)	5.8 (4.2)	<.01
TFEQ			
Scale 1: dietary restraint[b]	15.1 (5.2)	3.6 (4.0)	<.001
Scale 2: disinhibition[c]	3.1 (2.8)	6.0 (2.8)	<.05
Scale 3: hunger[d]	2.6 (3.3)	6.5 (3.1)	<.01

[a] Possible scores ranged from 0 to 63, with higher scores indicating more severe symptoms.
[b] Possible scores ranged from 0 to 21, with higher scores indicating stronger dietary restraint.
[c] Possible scores ranged from 0 to 16, with higher scores indicating stronger disinhibition of eating.
[d] Possible scores ranged from 0 to 14, with higher scores indicating stronger experienced hunger.

The patient group scored significantly higher on the scale "dietary restraint" and lower on the scales "disinhibition" and "hunger" of the Three Factor Eating Questionnaire (TFEQ; Stunkard and Messick, 1985, German version: Pudel and Westenhöfer, 1989) (see Table 1).

2.2. Hunger ratings

Self-reported hunger scores of both patients and HC subjects were significantly higher in the hungry than in the satiated condition (HUNGER STATE: $F_{(1,21)}=98.2$, $p<.001$; see Table 2). Hunger scores of AN patients were significantly lower than those of HC subjects (GROUP: $F_{(1,21)}=7.8$, $p<.05$). There was a trend towards an interaction (HUNGER STATE×GROUP: $F_{(1,21)}=3.4$, $p=.078$) indicating that this group difference in hunger ratings was significant in the hungry (GROUP: $t_{(21)}=3.4$, $p<.05$) but not in the satiated condition.

2.3. Valence ratings of stimuli

AN patients rated food stimuli as significantly less pleasant than did controls (GROUP: $F_{(1,21)}=6.8$, $p<.05$) (see Table 2). There was a trend towards an interaction effect (HUNGER STATE×GROUP: $F_{(1,21)}=3.8$, $p<.066$), indicating that hunger led to a stronger positive rating of food stimuli in controls ($t_{(9)}=1.5$, $p=.16$) but had no influence on the ratings of food stimuli in AN patients ($t_{(12)}=-0.8$, $p>.41$). Ratings of non-food stimuli were not affected by hunger state or study group (all $p>.1$). There were no effects or interactions in reaction times (RT) (all $p>.1$).

2.4. fMRI Data

2.4.1. Group comparisons

Group comparisons for the contrasts 'food > non-food' revealed that AN patients showed diminished activation compared with HC subjects in the left inferior parietal lobe (IPL; BA 40) when satiated (see Fig. 1a; Table 3). An ROI analysis confirmed this group difference ($T=3.07$; $p<.005$, see Fig. 1b). The individual beta values of this IPL activation peak voxel showed a negative correlation with the TFEQ scale "dietary restraint" ($r=-0.443$; $p<.05$, see Fig. 2a) and positive correlations with the TFEQ scale "disinhibition" ($r=0.512$; $p<.05$, see Fig. 2b) and BMI values ($r=0.672$; $p<.01$, see Fig. 2c). The correlations indicate that, with stronger dietary restraint, weaker disinhibition of eating, and lower BMI values, there was diminished IPL activation.

When hungry, AN patients compared with controls showed diminished activation in the right lingual gyrus (BA 17 and 18) (see Fig. 3a; Table 3). Again, this result was confirmed by ROI analysis ($T=3.46$; $p<.005$, see Fig. 3b). The beta values of peak lingual gyrus activation also showed a negative correlation with the TFEQ scale "dietary restraint" ($r=-0.545$, $p<.01$, see Fig. 2d) and a positive correlation with the TFEQ scale "disinhibition" ($r=0.517$, $p<.05$, see Fig. 2e). The correlations show that increased dietary restraint and decreased disinhibition of eating are associated with significantly weaker activation in right lingual gyrus when viewing food.

Table 2 – Mean hunger ratings before the session and mean valence ratings of stimuli during the experiment

	Anorexia patients (n=13)		Control subjects (n=10)	
	Satiated	Hungry	Satiated	Hungry
Hunger rating[a]	5.15 (1.77)	10.77 (2.74)	5.80 (3.05)	14.00 (1.41)
Valence rating[b]				
Food	1.54 (0.44)	1.51 (0.40)	2.23 (0.34)	2.48 (0.40)
Non-food	2.02 (0.49)	2.01 (0.47)	1.72 (0.36)	1.72 (0.27)

Standard deviations in parentheses.
[a] Possible scores range from 3 to 15, with higher scores indicating stronger feelings of hunger.
[b] Possible scores ranged from 1 to 3, with higher scores indicating more positive ratings.

2.4.2. Group level activations

Table 3 further presents the activations that were observed in response to food pictures for the AN group and for the HC group separately in the satiated and the hungry state as well as in the contrast 'satiated>hungry'. Fig. 4 shows the global maxima observed in the hungry and satiated states for the AN and the HC group separately.

Fig. 5a presents the right middle occipital gyrus (BA18) activation that was found in the contrast 'satiated>hungry' in the AN group, which was significant in the ROI analysis ($T=3.31$; $p<.005$, see Fig. 5b).

The small activation clusters in the middle portion of right anterior cingulate gyrus (ACC; BA32), left lateral orbitofrontal cortex (OFC; BA11) and left middle temporal gyrus (BA21) that were found in the HC group for the contrast 'satiated>hungry' are presented in Fig. 6a. These activations were also significant in the ROI analyses (ACC: $T=3.46$, $p<.005$; OFC: $T=3.53$, $p<.005$; middle temporal gyrus: $T=3.74$, $p<.005$; see Fig. 6b).

The differences between satiated and hungry states that were observed in the AN patient group were absent in the HC group and vice versa. For both groups, no brain regions were more strongly activated in the hungry than in the satiated condition.

2.5. Possible confounding factors

The beta values of peak IPL activation in the satiated session and of peak lingual gyrus activation in the hungry session did not correlate significantly with individual BDI scores, age of participants or the duration of the disorder (all $p>.2$).

3. Discussion

In accordance with our first hypothesis, satiated AN patients showed weaker inferior parietal (BA 40) activation to food stimuli than satiated controls. Similar fMRI results have been shown previously (Uher et al., 2003, 2004) but without reference to hunger or satiety. Additionally, the present study demonstrates for the first time that activation in IPL was correlated with specific behavioral and physical symptoms of AN: there was decreased IPL activation in participants with stronger

dietary restraint, weaker disinhibition of eating and lower BMI values.

The postcentral gyrus of the IPL (BA 1, 2, 3) contains primary somatosensory neurons for body parts that are involved in eating, e.g. lips, teeth, tongue, etc. (Heimer, 1995). Caudally to the postcentral gyrus, BA 40 of the IPL contains secondary and tertiary somatosensory areas (Deuchert et al., 2002; Hagen and Pardo, 2002). This area is closely interconnected with the insula, i.e. the primary taste cortex, and receives both somatosensory and gustatory projections (Cerf-Ducastel et al., 2001; Yoshimura et al., 2004). Possibly, a decrease of activation in this area, as observed for our AN patients when viewing food pictures in the satiated state, is related to a decrease in gustatory perception or imagination of taste in response to visual food stimuli. Such decreased somatosensory–gustatory responsiveness may facilitate fasting, which is a core symptom of restrictive AN, and could also explain why patients with AN rate food stimuli as less pleasant than healthy persons. This argument is corroborated by opposite findings in obese subjects, in whom increased bilateral IPL activity compared to lean subjects was reported (Karhunen et al., 1997; Wang et al., 2002).
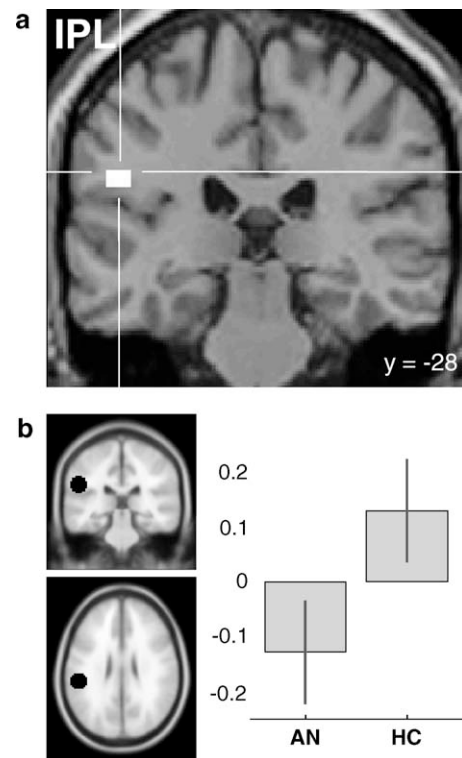

Fig. 1 – (a) Statistical map for the comparison of 'food>non-food' activation for AN patients<Controls in the satiated condition ($p<.001$, uncorrected). The map shows significant inferior parietal lobe (IPL) activation. All images are in neurological convention, i.e. right=right. (b) ROI based group comparison within the area of the left IPL. On the left side, the reconstructed ROI projected on the coronar and axial anatomic background (MNI reference brain), on the right side, the effects of interest based on the mean (box) and standard error (bar) for patients (AN) and controls (HC).

Table 3 – Comparison of brain activations for the contrast 'food > non-food' at $p < .001$, uncorrected (HC = healthy control; AN = anorexia nervosa, BA = Brodmann area)

Contrasts and brain region	BA	Side	Talairach coordinates			Cluster size (voxels)	Z
			x	y	z		
AN patients (n=13) < HC subjects (n=10)							
Satiated							
Inferior parietal lobule	40	L	−50	−28	26	14	3.63
Hungry							
Lingual gyrus	17, 18	R	12	−82	−8	17	3.53
AN patients (n=13)							
Satiated							
Inferior occipital gyrus and cerebellum (declive)	18	R	27	−91	−6	307	5.32
	–	R	30	−77	−21		3.18
Lingual gyrus and cerebellum (declive)	18	L	−18	−96	−3	202	4.48
	–	L	−18	−86	−21		4.05
Hungry							
Cuneus	18	L	−24	−93	−2	7 [a]	3.65
Fusiform gyrus	19	R	24	−79	−14	14	3.50
Satiated > Hungry							
Middle occipital gyrus	18	R	18	−93	13	4	3.42
HC subjects (n=10)							
Satiated							
Cuneus and middle occipital gyrus	17	R	18	−93	0	99	4.14
	19	R	30	−90	10		3.40
Cuneus and inferior occipital gyrus	17	L	−12	−99	0	88	3.88
	17	L	−12	−91	−8		3.84
Hungry							
Lingual gyrus and fusiform gyrus	17, 18	R	21	−91	−3	341	4.76
	19	R	33	−71	−17		3.44
Lingual gyrus	17	L	−15	−96	−3	186	4.12
Satiated > Hungry							
Anterior cingulate gyrus	32	R	15	19	27	6	3.40
Lateral orbitofrontal cortex	11	L	−33	40	−12	4	3.30
Middle temporal gyrus	21	L	−48	−10	−15	8	3.22

Only those clusters are reported that were either >10 voxels or survived the ROI analysis.
[a] Left cuneus: ROI analysis: T=3.12; $p < .005$, corrected.

In line with our second hypothesis, hungry AN patients showed weaker occipital activation to food stimuli than hungry control subjects. Others (Uher et al., 2003, 2004) also reported diminished responses of visual brain areas to food in patients with eating disorders than in healthy subjects. Our data show that in AN patients this effect is specific to hunger and does not occur in the satiated state. Furthermore, the occipital activation found in the group comparison in the current study also correlated significantly with measures of AN symptomatology.

As the strength of activation in primary and secondary visual areas is correlated to the salience of visual stimuli (Bradley et al., 2003; Lang et al., 1998; Moratti et al., 2004), we postulate that the observed group difference in visual responses in the hungry condition to food stimuli represents the subjective salience of food stimuli during hunger. In line with previous studies (Killgore et al., 2003; LaBar et al., 2001), both patients and healthy subjects showed an increased response in the occipital cortex to food compared to non-food (Fig. 4). In the patient group, however, activation of visual areas by food stimuli was significantly smaller when hungry than when satiated, whereas for

controls, there was no significant difference. Research of the last decade has shown that attentional modulation influences the degree of activation in sensory cortex. The intensity of attention to a stimulus correlates directly with the strength of activation in the relevant sensory cortex (Gazzaley et al., 2005; Jäncke et al., 1999a,b). The current data suggest that in the hungry condition AN patients focused less of their attention on the food stimuli. In daily life, such attentional mechanisms might support anorectic persons in resisting food and maintaining fasting. During the satiated state, such suppression of attention to food may not be necessary, thus explaining why AN subjects showed more occipital activation in the satiated than in the hungry state.

Previous behavioral findings have shown that hunger does not increase cognitive occupation with food stimuli in AN, whereas it does in controls (Morris and Dolan, 2001; Pietrowsky et al., 2002). Such findings support our interpretation of avoidant cognition in AN in the hungry state.

In the healthy group, we observed significantly stronger activation to food stimuli in the satiated compared with the hungry session in the left lateral OFC, the middle portion of
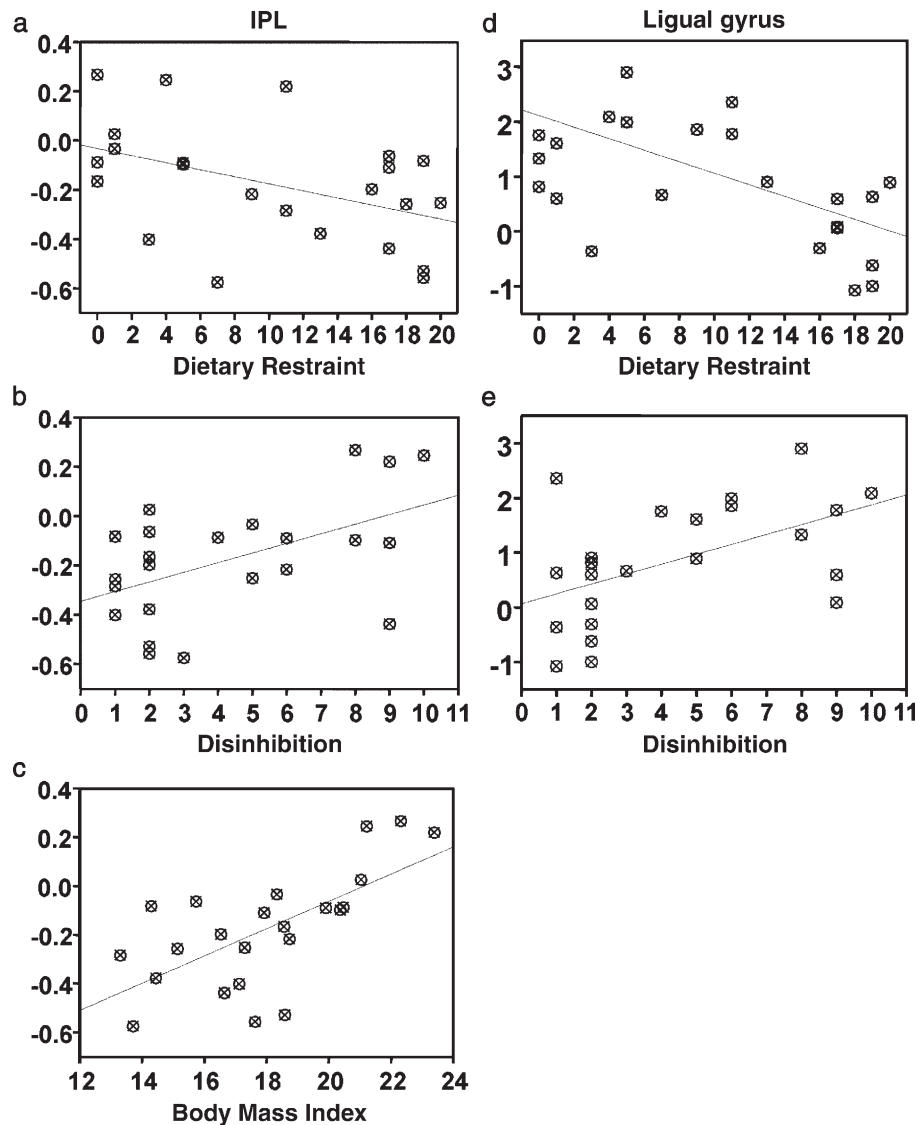
Fig. 2 – Scatterplots for significant correlations between symptom-related demographic data and beta values of group comparison activation maximum voxels for the contrast 'food > non-food'. (a) Negative correlation of TFEQ scale 1 "dietary restraint" with IPL activation. Beta weights at voxel $X=50$, $Y=28$, $Z=36$. (b) Positive correlation of TFEQ scale 2 "disinhibition" and IPL activation. Beta weights at voxel $X=50$, $Y=28$, $Z=36$. (c) Positive correlation of BMI (kg/m^2) with IPL activation. Beta weights at voxel $X=50$, $Y=28$, $Z=36$. (d) Negative correlation of TFEQ scale 1 "dietary restraint" with lingual gyrus activation. Beta weights at voxel $X=12$, $Y=82$, $Z=-8$. (e) Positive correlation of TFEQ scale 2 "disinhibition" with lingual gyrus activation. Beta weights at voxel $X=12$, $Y=82$, $Z=-8$.

the right ACC, and the left middle temporal gyrus. The lateral OFC has been associated with appetitive behavior, with visual presentations of food in primates and with taste and smell in humans (De Araujo et al., 2003b; O'Doherty et al., 2000). Furthermore, it is responsive to food cues during satiety (Hinton et al., 2004; Small et al., 2001) and has been suggested to underlie termination of eating (Small et al., 2001). It is also known for its role in evaluating reward value of food stimuli (Killgore et al., 2003). Activation of the middle portion of the ACC is related to both hedonic properties of food intake and pleasant food stimuli (De Araujo et al., 2003a; De Araujo and Rolls, 2004). Middle temporal gyrus activity has also been associated with perception of emotional stimuli (Mourao-Miranda et

al., 2003). As this pattern of activation was absent in the AN group, it is possible that, due to altered cognitive processing of food stimuli, AN patients are less responsive to the diverse pleasant aspects of food stimuli which would also find support in the pleasantness rating data.

Different from our expectations and some previous fMRI studies with AN patients (e.g. Nozoe et al., 1993; Uher et al., 2003, 2004), our results do not confirm findings of enhanced frontal lobe activation to food stimuli in AN. This may be related to differences in experimental procedures. Uher et al. (2003, 2004) instructed subjects to think of how hungry the food and non-food pictures made them feel, whereas in the present study, subjects were asked to rate stimuli for pleasantness. According to Phan et al. (2004), activity in
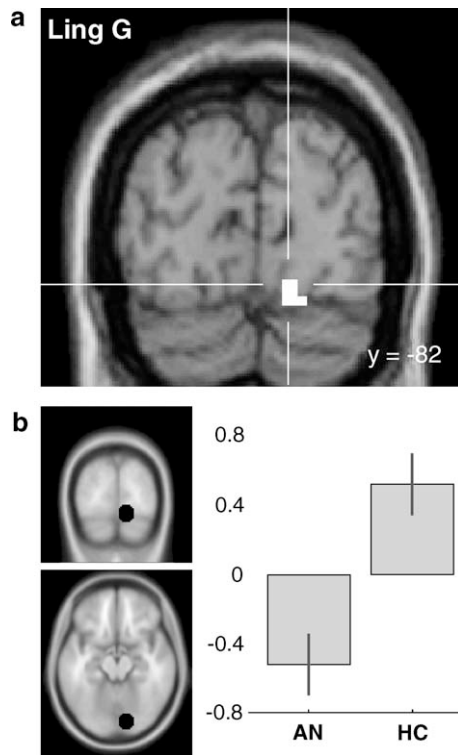
Fig. 3 – (a) Statistical map for the comparison of 'food >
non-food' activation for AN patients < Controls in the hungry
condition (p<.001, uncorrected). The map shows significant
right lingual gyrus (Ling G) activation. (b) ROI based group
comparison within the area of the right lingual gyrus. On the
left side, the reconstructed ROI projected on the coronar and
axial anatomic background (MNI reference brain), on the right
side, the effects of interest based on the mean (box) and
standard error (bar) for patients (AN) and controls (HC).

medial prefrontal cortex is especially pronounced in self-
related assessments. Furthermore, as Uher et al. (2003, 2004)
pointed out, the task that their subjects performed was
biased to food stimuli, whereas in the present study, there
was no such bias. Therefore, in our study, performance-
related activation in the prefrontal cortex (decision-making,
control mechanisms) is likely to have been comparable
during food and non-food presentation, thus canceling out
prefrontal activation in the contrast 'food>non-food'.

3.1. Strengths and limitations

A further important research question that was not
addressed by our study is how high- and low-caloric food
affects brain activations in AN patients. Different activa-
tions have been observed both in a study with AN subjects
(Ellison et al., 1998) and in healthy subjects dependent on
calorie content of food (Killgore et al., 2003).

As four patients were taking SSRI medication, it cannot
be excluded that this medication had effects on brain
activation. However, effects of SSRI on brain activations are
to be expected in midbrain, striatum, amygdala and further
subcortical areas (Linden, 2006). Furthermore, as SSRIs are

effective in the treatment of anorectic symptomatology
(Kaye et al., 2001), any effects of SSRI on brain activation
should have lessened rather than created differences
between the groups.

As is the case with other psychiatric disorders, patients
with anorexia nervosa show some heterogeneity for example
with regard to comorbid depression, duration of the disease,
and age. While some of this heterogeneity is also present in
our current sample, we could demonstrate that these factors
did not correlate with the degree of fMRI activations.

The following conclusions can be drawn from the present
results: both on behavioral and on brain activation levels, AN
patients seem to be less responsive to the pleasant aspects of
food stimuli that are highly appetizing to healthy subjects.
Overall, our findings can be interpreted in terms of altered
cognitive processing of visual food stimuli in AN patients,
which may facilitate fasting, a core symptom of restrictive AN.
The hypothesized mechanisms underlying this facilitation of
fasting may be decreased somatosensory processing in the
satiated state (as shown by decreased IPL activation) and
decreased attention to food stimuli in the hungry state (as
evident in reduced occipital activation).

4. Experimental procedures

4.1. Participants

The study group consisted of 13 patients with the restricting
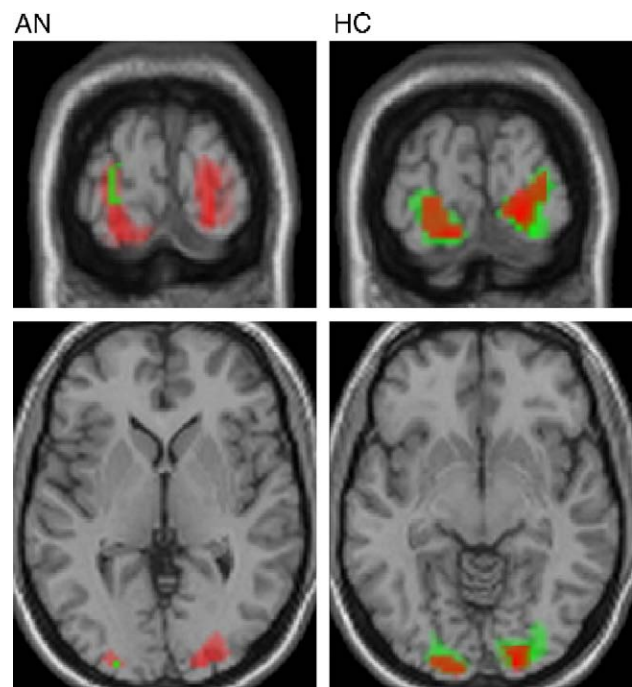type of anorexia nervosa (DSM-IV: 307.1) and 10 healthy

Fig. 4 – Group statistical maps of global maxima for
'food>non-food' activation for patients (AN, left panel) and
controls (HC, right panel) separately in both the satiated
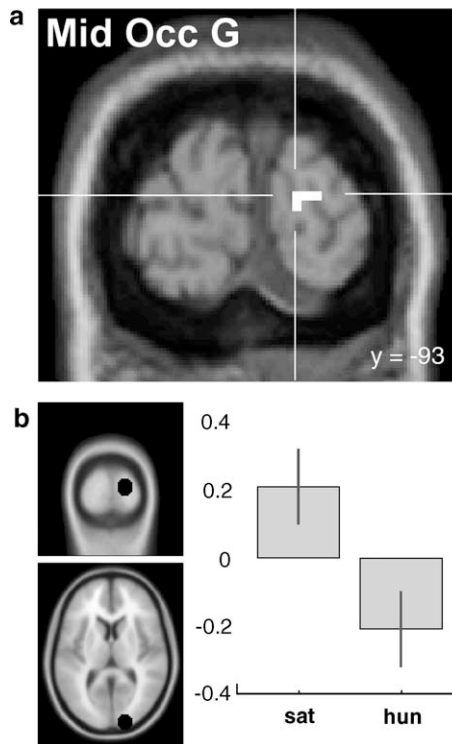(white/red) and hungry (black/green) conditions (p<.001,
uncorrected).

Fig. 5 – (a) Statistical map for the comparison of 'food >
non-food' activation for satiated > hungry in the AN patient
group (p < .001, uncorrected). The map shows significant right
middle occipital gyrus (Mid Occ G) activation. (b) ROI based
group comparison within the area of the right middle
occipital gyrus. On the left side, the reconstructed ROI
projected on the coronar and axial anatomic background
(MNI reference brain), on the right side, the effects of interest
based on the mean for satiated patients (sat) and hungry
patients (hun).

control subjects. Of originally 14 patients, one patient was
excluded because of non-compliance with instructions. Of
originally 13 healthy control subjects, one control subject was
excluded because of compliance problems and two dropped
out because they called in sick for the second session.

Most patients (n=9) were inpatients of the Department of
Child and Adolescent Psychiatry at the University of Magde-
burg. Additional patients and control subjects were recruited
by local advertisement.

All participants completed the Culture Fair Intelligence
Test (CFT 20; Weiß, 1998) and the Three Factor Eating
Questionnaire (TFEQ; Stunkard and Messick, 1985, German
version: Pudel and Westenhöfer, 1989).

All participants were examined for psychiatric disorders
by an experienced clinical psychologist with the structured
clinical interview DIPS, following DSM-IV criteria. Underage
participants and their parents were interviewed separately
with the child version (Unnewehr et al., 1998), whereas
adult participants and a close relative were examined with
the adult version (Margraf et al., 1991). Seven patients were
suffering from comorbid major depressive disorder at the
time of testing (mild: n=4, moderate: n=1, severe: n=2).

There was no other psychiatric or neurological comorbidity,
in particular no evidence for obsessive-compulsive disorder
or anxiety disorders. Four AN patients with current
depression were taking antidepressant medication (selective
serotonin reuptake inhibitors [SSRIs]). All healthy partici-
pants were free of psychoactive medication, had no
psychiatric or neurological disorders, and did not show
subclinical symptoms of eating disorders.

Additionally to the clinical interview, depressive symptoms
were assessed by a version of the Beck Depression Inventory
(BDI) (Beck et al., 1961, German version: Hautzinger et al., 1995)
that was slightly modified to be suitable not only for young
adults but also for teenagers (i.e. items regarding issues of
aging and sexual activity were reframed).

Written informed consent was given by all participants
and by parents of all underage participants. The study was
carried out in accordance with the ethical standards of the
Helsinki Declaration and had been approved by the
institutional review board of the University of Magdeburg,
Faculty of Medicine. Subjects were reimbursed for their
participation in the study with a voucher of 6 per hour.

4.2.   Stimuli

Stimuli consisted of 320 color photographs of high-caloric
sweet and savory food and of 320 color photographs of
objects of use (tools, make-up items, pencils etc., further on
referred to as non-food). Care was taken that pictures of the
two stimulus categories differed as little as possible on
luminance, color distribution, and visual complexity, for
example, non-food pictures were created as variable and
colorful as food pictures. Each stimulus was shown only
once. Stimuli were projected with an LCD projector onto a
screen fitted to the head coil at an eye distance of 35 cm.

4.3.   Procedure

The paradigm consisted of two 30-minute sessions
(satiated, hungry). Each session started at 8 a.m., and
participants were instructed to have breakfast prior to one
session and to abstain from eating for 12 h before the
other. The order of sessions was counterbalanced between
participants. Prior to each session, participants answered
items controlling for compliance with instructions regarding
food intake and rated their degree of hunger by judging
their agreements to three hunger-related statements on a
five-point Likert scale. Higher scores (range 3 to 15) in-
dicated stronger feelings of hunger. Most patients (n=9)
were inpatients of the clinic, for whom compliance with
instructions was confirmed by clinical staff. Subjects
received standardized instructions to rate as quickly as
possible for each picture whether they found it pleasant,
neutral, or unpleasant and to keep looking at each picture
for as long as it was presented. In order to rate the stimuli,
subjects used three buttons with their dominant hand. All
subjects were given at least 20 practice trials outside the
scanner and were familiarized with scanning procedures
and safety regulations. High resolution structural imaging
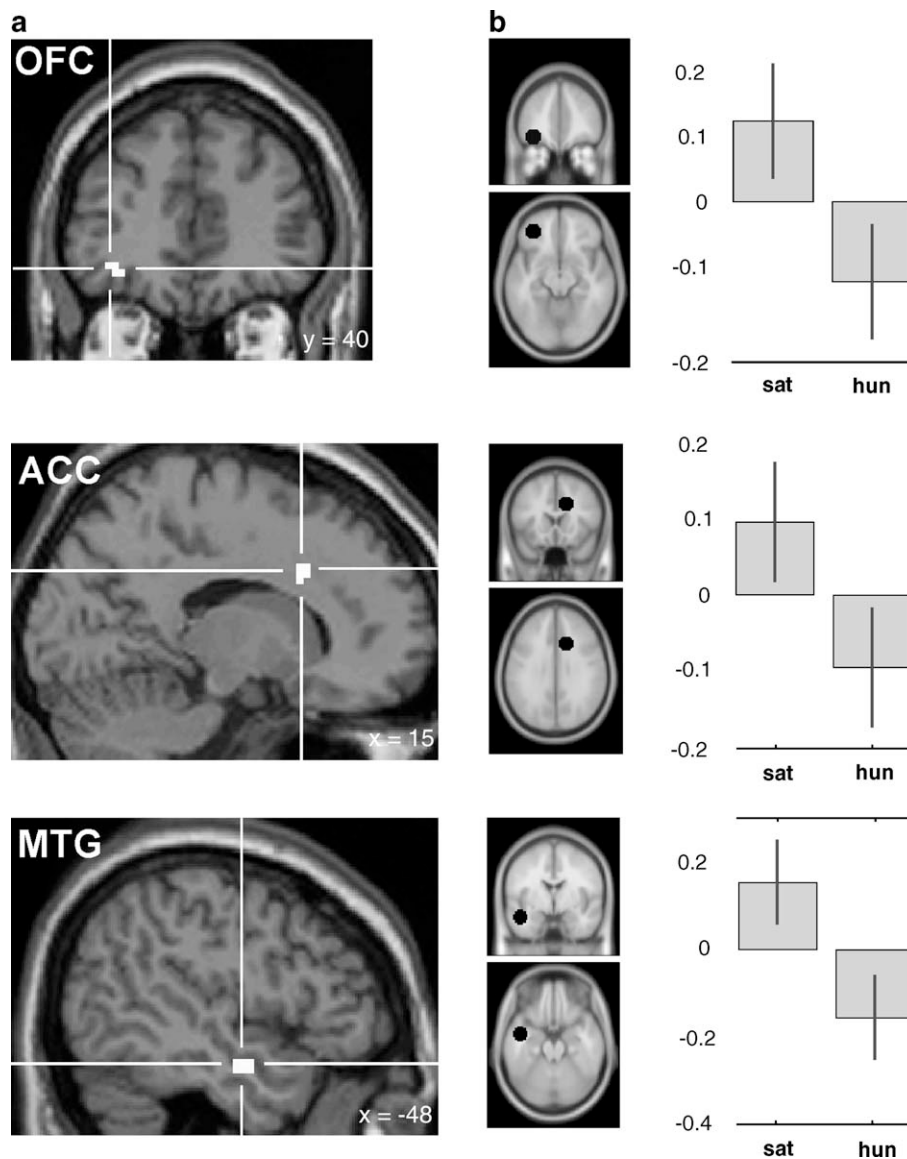assured that no subject had any gross structural brain
abnormalities.

Fig. 6 – (a) Statistical map for the comparison of 'food > non-food' activation for satiated > hungry in the healthy group (*p* < .001, uncorrected). The map shows significant activation of left lateral orbitofrontal cortex (OFC), middle portion of right anterior cingulate cortex (ACC), and left middle temporal gyrus (MTG). (b) ROI based group comparisons within the areas of the left lateral OFC (top panel), right ACC (middle panel), and left MTG (bottom panel). On the left side in each panel, the reconstructed ROI projected on the coronar and axial anatomic background (MNI reference brain), on the right side, the effects of interest based on the mean (box) and standard error (bar) for satiated controls (sat) and hungry controls (hun).

4.4. Design

In each session, two stimulus categories (food, non-food) were presented. All sessions consisted of four runs with a blocked design stimulus presentation. Within each run, participants were presented with eight consecutive blocks (40 s duration) each containing 10 stimuli (3.5 s, inter-stimulus interval fixation cross of 0.5 s) of one stimulus category. The first block presented ten stimuli of one condition and was followed by the second block presenting ten items of the other condition. After every two consecutive blocks, a baseline condition (fixation cross) was shown for 30 s. The following two blocks always presented conditions in the opposite order

to the previous two blocks. Two runs began with a block of food items, whereas the other two began with a block of non-food items. The order of the four runs was counterbalanced between participants.

4.5. Image acquisition

Data acquisition was performed on a neuro-optimized GE 1.5 T Signa Horizon LX system equipped with a standard birdcage head coil. Each session started with a set of structural images consisting of a high resolution rf-spoiled GRASS sequence (60 slices, 2.8 mm thickness). Functional imaging consisted of 23 slices aligned to the anterior and

posterior commissure (5 mm thickness with 1 mm gap). Images were acquired using an echo-planar T2* weighted gradient echo sequence EPI (TR=2000 ms, TE=40 ms, 64^2 matrix, flip angle $\alpha=80°$, field of view=20) consisting of 222 volumes each and coverage of the whole head.

4.6. Data analysis and statistics

4.6.1. fMRI
Data were analyzed using the Statistical Parametric Mapping Package (SPM99, http://www.fil.ion.ac.uk/spm). For individual subjects, after discarding the first four volumes to allow for T1 equilibration effects, functional images of the four runs were realigned. The resulting images were resliced into the MNI coordinate space using the provided EPI template (resulting in isometric 3 mm voxels) and spatially smoothed (10 mm full-width half-maximum [FWHM]). The data were high-pass filtered and temporally smoothed with a 4 s FWHM Gaussian kernel. Images of the four runs of one session were then combined by fixed level analysis using a boxcar function corrected for temporal delay of the BOLD response. In order to accommodate for movement artifacts, realignment parameters were treated as additional predictors in the model. This fixed level analysis resulted in individual images for the T contrasts 'food>non-food' (significance threshold $p<.001$, uncorrected). In a random effects analysis, one sample t tests resulted in images for these contrasts on a group level (e.g. 'AN: food>non-food[satiated]'). Two-sample t tests created images for group comparisons (e.g. 'HC>AN: food>non-food [satiated]'), and repeated measures t tests resulted in images for session comparisons (e.g. ''AN: [food>non-food (satiated)]>[food>non-food(hungry)]') within the two participant groups (significance threshold $p<.001$, uncorrected). Additionally, for any activation clusters with less than 10 voxels and for activation clusters found in the group comparisons, region of interest (ROI) analyses were performed. ROIs were defined as spheres with a 10 mm radius (approximately 150 voxels) around the cluster peak activation voxel. Only those clusters that survived these ROI analyses at a threshold of $p<.005$, corrected are reported.

4.6.2. Correlations of fMRI levels with AN symptomatology
For areas significantly differentiating between anorectic patients and healthy controls, individual beta weights were extracted to disentangle the contribution of each group to the observed signal change. Beta weights were derived from the peak voxel of the contrast of interest and were correlated with AN-specific measures of eating behavior, i.e. TFEQ scores, and of BMI.

4.6.3. Hunger ratings
Hunger ratings given before the session were analyzed using a 2×2 ANOVA with hunger state as within subjects factor and group as between subjects factor.

4.6.4. Valence ratings
Ratings from trials with reaction times (RT) longer than 2 standard deviations above the individual RT mean were excluded from the analysis. No more than 5% of reactions

per subject were excluded by this procedure. Mean valence rating scores were calculated, with higher scores indicating higher pleasantness. A 2 (food, non-food)×2 (hunger, satiety)×2 (AN, HC) ANOVA was performed.

4.7. Possible confounding factors

To control for possible confounding factors, the individual beta values that were extracted from the group comparison peak activation voxels were also correlated with individual BDI scores for depressiveness, with age and with duration of AN in months.

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