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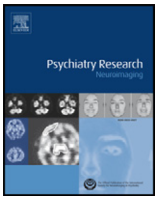

Amygdala hyperreactivity in restrictive anorexia nervosa

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ABSTRACT

Functional imaging studies had often investigated heterogeneous samples of anorexia nervosa (AN) patients with varying paradigms and methodologies that had resulted in divergent results. The present study aimed to examine these issues by studying a well-defined sample of restrictive AN patients with a disorder-specific paradigm which had been used previously. Subjects showed increased blood oxygen level dependent responses of the cingulate, frontal, insular and parietal cortices. Group comparisons demonstrated increased activity of the right amygdala in the sample of restrictive AN patients. Our results are in support of other recently published functional imaging studies and point to a pivotal role of the right amygdala in AN. Signals of the midcingulum were reduced in comparison to healthy controls. The constellation of increased activity of the amygdala and decreased activity of the cingulate cortex likely represents parts of a negative feedback loop of emotional processing. Disgust ratings correlated with the amygdala signal negatively, which points to the complex role of this structure within eating disorders.

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1. Introduction

Eating disorders (ED) are important psychosomatic illnesses affecting young females in a critical phase of psychosexual development (Fairburn and Harrison, 2003). Core pathologic features of anorexia nervosa (AN) consist of drive for thinness, disturbed eating behaviour, malnutrition and hormonal dysregulation. There is an ongoing debate on subtyping the disorder, as patients are heterogeneous in terms of personality characteristics, comorbid symptoms and long-term outcome (Ward et al., 2003), the most common distinction comprising restrictive (AN-R) and binge-eating/purging (AN-B/P) subtypes.

Structural cerebral studies demonstrated a decrease of cerebral grey matter in AN, including the cingulate cortex (Mühlau et al., 2007; Castro-Fornieles et al., 2009; Joos et al., 2010). Frontolimbic resting perfusion is reduced in AN, the anterior cingulate cortex (ACC) being particularly affected in AN-R (Naruo et al., 2001; Takano et al., 2001). A first functional magnetic resonance imaging (fMRI) study demonstrated increased blood oxygen level dependent (BOLD) responses of the left amygdala, insula and ACC in a sample of six AN patients using pictures of high caloric drinks as a paradigm (Ellison et al., 1998). The AN subtype was not reported. A further fMRI study of the same research group used visual food stimuli and investigated a heterogeneous AN patient sample, i.e. AN-R and AN-B/P patients (Uher et al., 2004). Increased ACC and orbitofrontal cortex (OFC) BOLD responses were reported (Uher et al., 2004). A limitation of the study was that one-third of patients were on psychotropic medication. A further study of an adolescent AN-R sample did not show increased frontolimbic perfusion, however (Santel et al., 2006). Further fMRI studies of AN had used body image stimuli — paradigms and methodologies varying greatly (Seeger et al., 2002; Wagner et al., 2003; Uher et al., 2005; Sachdev et al., 2008; Fladung et al., 2009; Miyake et al., 2010a; Vocks et al., 2010a), the salience of body image paradigms being a critical aspect (Uher et al., 2005).

The present study tried to further clarify frontolimbic dysfunction in AN, as there had only been two studies in adults using a disease-specific nutritional paradigm and one in adolescent patients, and by avoiding methodogical problems of former investigations: A clearly defined sample of AN-R patients was studied, in order to avoid heterogeneous samples, which differ with regard to psychopathological features, and possibly with regard to neural reactivity. A paradigm that had previously been applied in ED was used in order to be able to compare findings with earlier results (Uher et al., 2003, 2004). This aspect seems of importance, as many imaging studies investigate small numbers — and even in healthy controls there is variability of neural responses to food stimuli (Beaver et al., 2006). Stimuli variability was increased compared to previous studies (Uher et al., 2003, 2004) in order to minimize habituation effects, as amygdala responsiveness in particular shows habituation when the same

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emotional stimuli are repeated, as shown in healthy subjects (LaBar et al., 2001; Phillips et al., 2003; Ball et al., 2007). The instruction to the presentation of stimuli was held simple in order to reduce any cognitive interference with the emotional experience, as the latter might be influenced as well as neural activation patterns (Townsend et al., 2010). Similar to the study of Uher et al. (2004), we used a block design, which might be more effective with regard to amygdala response, compared to an event-related design (Sergerie et al., 2008).

2. Method and materials

2.1. Subjects

The participants comprised 11 female patients with AN-R, according to the Diagnostic and Statistical Manual of Mental Disorders — Fourth Edition (DSM IV) (American Psychiatric Association, 1994) and 11 healthy controls (HC). Duration of illness had to be more than 1 year and age above 18. Exclusion criteria were metallic implants, psychosis, severe medical illness, claustrophobia, and neurological disease. HC were matched according to age, education and handedness. Psychological characteristics were evaluated with the Eating Disorder Inventory (EDI) (Paul and Thiel, 2005), Beck Depression Inventory (BDI)(Beck et al., 1995) and multiple choice verbal comprehension test (Merz et al., 1975). After description of the study, written informed consent was obtained, as approved by the University of Freiburg Ethical Committee. In retrospect, one inpatient reported occasional vomiting during her hospital stay and another use of laxatives. As the EDI–Bulimia subscales (t-values of 46 and 60) were low, and DSM-IV indicates that AN-R patients should not *regularly* engage in such behaviour, we did not exclude them from our analysis. Apart from one AN-R patient, who was on sertraline 75 mg/day, none was on regular psychotropic medication.

2.2. Stimuli

Photographs depicting food and non-food items on white plates before a blue background were used, as previously described (Uher et al., 2003, 2004). In addition to a set of 20 picture pairs (kindly provided by R. Uher and colleagues), 30 pairs were created in order to increase variability, i.e. to show each picture only once. Food items consisted of savoury (e.g., potato fries, bread with cheese) and sweet (e.g., cake) foods. Photographs of non-food items (e.g., household objects) were carefully and individually matched for colour and visual complexity based on the ratings by five members of staff.

2.3. Procedure

The procedure was similar to the one used previously, including a block design (10 pictures for 2.5 s, 5 food blocks alternating with 5 non-food ones) (Uher et al., 2003, 2004). Instructions were as follows: “You will be shown pictures. Look at each picture attentively”. Pictures were rated after the scanning procedure on numeric analogue scales (1–7).

2.4. Image acquisition

FMRI was performed on a Siemens 3 T tim-TRIO (Erlangen, Germany), equipped with a 12-channel head coil. In order to limit head motion within the coil, foam padding was used. Functional images consisted of T2*-weighted echo-planar image (EPI) volumes (TR = 3000 ms, TE = 30 ms, flip angle = 70°, FOV = 192 mm, voxel size = 3 × 3 × 3 mm), which were processed with fully automated movement and distortion correction. This method assured reasonable signal detection in mesio-temporal and orbitofrontal regions. A total of 210 whole brain volumes were acquired for each run. Subsequently to the functional protocol, a T1-weighted anatomical data set was obtained using magnetization-prepare 180° radio-frequency pulses and a rapid acquisition gradient-echo (MPRAGE) sequence to serve as anatomical reference (TR = 2200 ms, TE = 4.91 ms, flip angle = 12°, FOV = 256 mm, voxel size 1 × 1 × 1 mm).

2.5. Data analysis and statistics

SPM 5 (Wellcome Department of Cognitive Neurology, London) was used to conduct statistical analyses, running with Matlab 7 (The Mathworks Inc., Natick, Massachusetts, USA). Prior to statistical analysis, several pre-processing steps were carried out on the functional images. The first 10 volumes of the functional run were discarded. Manual anterior commissure–posterior commissure reorientation of all anatomical and functional images was followed by realignment to the first scan to spatially correct for residual interscan movement artifacts. Both T1 anatomical images and the realigned functional scans were co-registered to the SPM T1 template in MNI (Montreal Neurological Institute) space. Subsequently, the functional images were spatially normalized (linear and nonlinear transformations) into the reference system of the MNI reference brain. MNI coordinates were transferred into Talairach coordinates using the Nonlinear Yale MNI to Talairach Conversion Algorithm (Lacadie et al., 2008). Finally, the normalized functional data were smoothed with a three-dimensional isotropic Gaussian kernel (8 mm full-width at half maximum, FWHM) to enhance signal-to-noise ratio and to accommodate for residual differences in functional neuroanatomy between subjects that persisted after normalization. To remove low-frequency artifacts in the time series, data were high-pass-filtered with a cut-off period of 128 s. A linear regression model (general linear model) was fitted to the fMRI data from all subjects. Significant hemodynamic changes for each condition were assessed using t-statistics. First level analysis results for participant- and condition-specific effects were subjected to full factorial second level analysis to identify predictive voxels across subjects.

Group activation maps (food versus non-food) used a height threshold of $p_{\mathrm{uncorr.}} < 0.001$ (>10 voxels). Clusters were considered statistically significant at $p_{\mathrm{clusterlevel}} < 0.05$, corrected for multiple comparisons across the whole brain.

Group comparisons used a height threshold of $p_{\mathrm{uncorr.}} < 0.01$ (>0 voxels), and clusters were considered statistically significant at $p_{\mathrm{clusterlevel}} < 0.05$, corrected for multiple comparisons across the whole brain. As there is increasing evidence of relevant cerebral regions for eating behaviour, a regions of interest (ROI) approach was used for group comparisons in addition, i.e. small volume correction (SVC), investigating the following regions: the medial and lateral OFC, amygdala, ACC, insula and parietal lobe (LaBar et al., 2001; Killgore et al., 2003; Uher et al., 2004; Santel et al., 2006; Führer et al., 2008; Schienle et al., 2009; Siep et al., 2009). Results were considered significant at $p < 0.05$, using the family-wise error rate (FWE) correction for multiple comparisons. In case of significant group differences, the BDI was introduced as a covariate, to address the potential influence of depressive comorbidity in ED (Joos et al., 2009). Correlation analyses of BOLD responses with emotional ratings (fear, disgust and pleasure) were carried out for the above-mentioned ROIs.

Clinical and behavioural data were analyzed using Student's t-tests.

3. Results

3.1. Sample characteristics

Clinical data are shown in Tables 1 and 2. AN-R patients experienced food stimuli very aversively (Table 2). Neutral stimuli were experienced slightly more fearfully by patients — however, ratings were still very low, i.e. near 1 (Table 2).

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