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Voxel-based morphometry in eating disorders: Correlation of psychopathology with grey matter volume

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ABSTRACT

Twenty-nine adult female patients with eating disorders (17 with bulimia nervosa, 12 with restrictive anorexia nervosa) were compared with 18 age-matched female healthy controls, using voxel-based morphometry. Restrictive anorexia nervosa patients showed a decrease of grey matter, particularly affecting the anterior cingulate cortex, frontal operculum, temporoparietal regions and the precuneus. By contrast, patients with bulimia nervosa did not differ from healthy controls. A positive correlation of "drive for thinness" and grey matter volume of the right inferior parietal lobe was found for both eating disorder groups. The strong reduction of grey matter volume in adult patients with restrictive anorexia nervosa is in line with results of adolescent patients. Contrary to other studies, this first voxel-based morphometry report of bulimic patients did not find any structural abnormalities. The inferior parietal cortex is a critical region for sensory integration of body and spatial perception, and the correlation of "drive for thinness" with grey matter volume of this region points to a neural correlate of this core psychopathological feature of eating disorders.

1. Introduction

The lifetime prevalence of anorexia nervosa (AN) is 0.9%, and that of bulimia nervosa (BN) is 1.5% in women (Hudson et al., 2007). The core psychopathology of these eating disorders (ED) consists of preoccupation with food and body shape, drive for thinness (DT) and disturbances of eating behaviour. It typically affects female adolescents and young adults in a critical phase of psychosexual development. The aetiology is multidimensional and only partially understood. AN is divided into a restrictive type (AN-R) and a binge-eating/purging type.

Brain imaging has disclosed functional and structural abnormalities in patients with ED (Frank et al., 2004), the most consistent findings being a decreased brain mass and increased cerebrospinal fluid (CSF) space in AN (Frank et al., 2004). A large cranial computed tomography (CCT) study demonstrated increases in CSF spaces in AN, and to a lesser extent in BN patients (Krieg et al., 1989). The latter finding was substantiated by further investigations (Hoffman et al., 1989; Kiriike et al., 1990).

Subsequent structural imaging studies in AN mostly used a region of interest (ROI) approach and found abnormalities in a variety of areas, including the mesial temporal lobe, thalamus and brain stem (Neumarker et al., 2000; Giordano et al., 2001; Connan et al., 2006; Husain et al., 1992). A study of adolescent AN patients described whole brain grey matter (GM) and white matter (WM) decreases (Katzman et al., 1996). Adult AN patients showed decreased WM in temporoparietal regions and trends for GM decrease, when investigated with a semiautomated tissue segmentation method (Swayze et al., 2003). WM and GM correlated with the body mass index (BMI). Castro-Fornieles et al. (2009) used a voxel-based morphometrical (VBM) approach in 12 adolescent AN patients and reported structural changes of temporoparietal regions, including the precuneus, and the midcingulate cortex (MCC). In this patient group, whole brain GM and CSF showed significant deviations, whereas WM did not (Castro-Fornieles et al., 2009). With weight restoration these deviations returned to normal — though less in the MCC (Castro-Fornieles et al., 2009). Other authors (Kerem and Katzman, 2003) also reported GM decreases in adolescent AN patients and incomplete reversibility following weight normalization. In adult ED populations, VBM

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analyses have been reported for recovered patients only (Muhlau et al., 2007; Wagner et al., 2006).

This study investigated symptomatic adult patients with ED using VBM — which allows whole brain analyses without a priori decisions on ROIs. AN-R and BN patients were chosen in order to study two poles of ED (Fairburn et al., 2003). These subgroups share core features like a strong DT and preoccupation with shape and weight, but differ in the degree of malnutrition, hormonal disturbances, impulsive eating and purging behaviour.

Based on the findings summarized above, we expected an increase of CSF in the AN-R group paralleled by a decrease in global GM and WM, the former being more affected. We hypothesized the GM reduction to be more pronounced in temporoparietal and cingular regions (Castro-Fornieles et al., 2009). We assumed GM and WM deviations to be stronger in AN-R compared to BN, and correlated with BMIs.

In addition, we correlated central psychopathological features of eating disorder pathology with local GM volume, focussing on DT and bulimia, which can be assessed by subscales of the Eating Disorder Inventory (EDI) (Paul and Thiel, 2005). DT is a core and transdiagnostic symptom of ED, which can be viewed as a continuum (Fairburn and Harrison, 2003). DT sharply distinguishes ED groups from healthy controls (HC), more than body dissatisfaction does (Garner, 1991). Furthermore, AN patients are underweight, and body dissatisfaction is (therefore) less pronounced, compared to BN patients (Garner, 1991; Ruuska et al., 2005). Therefore, we focussed the analysis on DT. Associations of the subscale "bulimia" with GM volume concerned the BN group only.

Based on previous reports of deviations of the parietal cortex in ED (Frank et al., 2004; Wagner et al., 2003; Uher et al., 2004; Bailer et al., 2004; Goethals et al., 2007) and its association with body image distortion (Frank et al., 2004; Wagner et al., 2003; Delvenne et al., 1999; Castro-Fornieles et al., 2009), we hypothesized a correlation of DT with parietal GM volume in the whole ED group. Based on functional magnetic resonance imaging (fMRI) data (Uher et al., 2004), we hypothesized a correlation of DT with GM volume of the anterior cingulate cortex (ACC) in both ED groups. Thirdly, due to experimental data (Uher et al., 2004; Uher et al., 2005), we expected a negative correlation of GM of the dorsolateral prefrontal cortex and bulimic symptoms.

2. Materials and methods

2.1. Subjects

Twenty-nine patients (17 with BN, 12 with AN) were recruited from the services of the Department of Psychosomatic Medicine and Psychotherapy, University of Freiburg. Inclusion criteria were a diagnosis of AN-R or BN according to the Diagnostic and Statistical Manual of Mental Disorders — Fourth Edition (DSM IV), duration of illness of at least 1 year, and an age of 18 or more. All patients were female. Apart from one AN-R patient, who was being treated with sertraline, 75 mg/day, none was on regular psychotropic medication. One AN inpatient reported inconstant bulimic phases and another use of laxatives. These would qualify as AN-B/P (though DSM IV indicates that AN-R do not *regularly* engage in such behaviour, and there are still questions on the validity of subtyping the disorder (Peat et al., 2009)). Furthermore, EDI-"bulimia" subscales were low for these patients. As it was the intention to capture a pole of the continuum of ED rather than completely distinct groups, we decided to include them in our analysis. Five ED subjects and four HC were left-handed. Exclusion criteria were metallic implants, psychosis, severe medical illness, claustrophobia, neurological disease and antipsychotic medication. Eighteen female age matched HC were recruited by local advertisement and screened for a history of abnormal eating habits, neurological and psychiatric disease.

2.2. Procedure and analyses of clinical data

Participants were asked to eat the last meal 3 h before imaging. They completed self-report questionnaires, including the EDI (Paul and Thiel, 2005), the Beck Depression Inventory (BDI) (Beck et al., 1995) due to strong comorbidity of ED with depression (Joos et al., 2009) and the Multiple Choice Verbal Comprehension Test (MWT-B) (Merz et al., 1975) to estimate crystalline verbal intelligence. *t*-values of the EDI are reported, i.e. 50 representing the mean of a healthy population and ± 10 one standard deviation. After complete description of the study to the subjects, written informed consent was obtained. The study had been approved by the University of Freiburg Ethical Committee.

After assessing normal distribution of behavioural data of ED groups, ED groups and HC were compared by a one way analysis of variances (ANOVA), and Tukey–Kramer-Tests post-hoc. The alpha significance level was conventionally set at $P<0.05$ (two-sided). Correlation analyses used Pearson coefficients.

2.3. MRI data acquisition and image processing

MRI data were acquired on a 3 T whole-body system (TRIO, Siemens Erlangen, Germany) using an eight channel head coil. Scanning parameters for the T1-weighted 3D MPRAGE (Magnetization Prepared Rapid Acquisition Gradient-Echo Imaging) included: repitition time (TR) = 2200 ms, echo time (TE) = 4.91 ms, inversion time (TI) = 1000 ms, flip angle = 12°, matrix 512×512 pixel, 160 slices of 1 mm, field of view (FOV) = 256×256 cm^2.

Images were firstly segmented into GM, WM and CSF using SPM8 (Wellcome Trust Centre for Neuroimaging, Institute of Neurology, UCL, London UK — http://www.fil.ion.ucl.ac.uk/spm). Then, GM segments were further normalized to the population template generated from all the images using a diffeomorphic registration algorithm (Ashburner, 2007). This non-linear warping technique minimizes structural variation between subjects. A separate 'modulation' step (Ashburner and Friston, 2000) was used to ensure that the overall amount of each tissue class remained constant after normalisation. After this step, the values of each voxel represent a measure of the local volume of that tissue class. A Gaussian smoothing kernel of 12-mm FWHM was applied, similar to other VBM studies in ED (Wagner et al., 2006; Muhlau et al., 2007; Castro-Fornieles et al., 2009).

2.4. Whole brain tissue volume

After segmentation, the values of all voxels of a given tissue segment were added to estimate the volume. As in related studies (Muhlau et al., 2007), we analysed the fraction of each tissue segment relative to the total intracranial volume (TIV). TIV was computed by adding the volumes of each tissue segment. Student's *t*-tests (two-sided) were used to compare HC with ED groups (*df* 28, 33, respectively). Correlation analyses of BMIs with tissue fractions used Pearson coefficients.

2.5. Voxelwise analyses

With respect to VBM, GM volume reductions of AN-R (compared to HC) were studied using *t*-tests (one-sided, *df* 28). Considering the lack of VBM reports in BN up to now, we studied GM volume reductions as well as increases (compared to HC; *df* 33). A multiple regression model was used to test for changes in GM with BMIs and the EDI subscales DT and "bulimia". Since we expected a similar association of DT with GM volume in both patients groups – which are by definition characterised by different weights and therefore likely different GM volume levels – we used a regression model that allowed a different offset of the regression slope for each group. Voxels with an at least 20% probability of belonging to the GM segment entered