Reduction of gray matter density in the extrastriate body area in women with anorexia nervosa

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ABSTRACT

Body processing has been associated functionally to the so called extrastriate body area (EBA) which is located in the lateral occipital cortex. As body image disturbance is one of the main diagnostic criteria in anorexia nervosa (AN) this study aimed at looking for alterations in gray matter density in women with (AN) especially in the EBA. High resolution T1 images from 15 women with AN and 15 age matched healthy controls women were contrasted using voxel based morphometry (VBM). Additionally functional localizer scans were used to determine functionally the EBA of each participant. In general, total gray matter volumes did differ between groups. VBM results yielded evidence for a reduction of gray matter density in the left EBA. This reduction, which resulted from whole brain analysis, was localised within the activation cluster of the EBA localizer scan. The current results provide for the first time evidence for structural alterations in the EBA in patients with AN which might suggest that body image distortion is related at least in part to structural alteration in the EBA.

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1. Introduction

AN reflects a serious mental disorder that leads to death in approximately 10% of the cases [16]. Beyond low body weight, one of the main diagnostic criteria of AN is body image disturbance [1]. Though a large number of studies have demonstrated an inaccuracy in the estimation of the own body girth among females with AN (for reviews, see [4,5,25]), the underlying mechanisms of body image disturbance are unknown to date. Since previous research has demonstrated that patients with eating disorders are correct in the estimation of the width of various objects [2], it has been speculated that body image distortion seems not to be caused by a general sensory deficit. It might rather reflect a cognitive phenomenon based on dysfunctional information processing [38]. Alternatively, body image distortion has been discussed as being related to neglect and possible dysfunctions of the parietal, frontal and cingulate cortex [7,12]. Nevertheless, these hypotheses have not been empirically supported yet. More recent research using functional magnetic resonance imaging (fMRI) provided first evidence that body image disturbance in AN might be associated with dysfunctional body-image processing brain circuits. Uher et al. [32] found a reduced activation in the so called extrastriate body area (EBA) in females with anorexia nervosa. This area located in the occipito-temporal site of the visual cortex is specialized for the visual perception and processing of human bodies [18]. While results by Uher et al. yielded evidence for functional alterations in the EBA, structural alterations in this part of the brain have not been reported or analysed yet. Results from further studies using imaging techniques like single positron emission tomography yielded hyperperfusion of the medial prefrontal and anterior cingulate cortex [15,30] in AN which seem to be independent of weight [10].

Beyond these functional abnormalities, alterations in brain structures in AN have been reported by Mühlau et al. [14] used voxel based morphometry (VBM) on high resolution T1 images of women who recovered from AN. Region specific analysis yielded evidence for gray matter decrease in the anterior cingulate cortex (ACC). This study yielded additional evidence for the crucial involvement of the ACC in AN [10,15,30]. However, applying VBM to subjects with AN has to be considered cautiously because of the confounding effects of malnutrition that may also cause alterations in brain structures [7]. Control and matching of gray and white matter volume of the study groups is therefore of essential matter.

The present study aims to get further inside in the structural changes of AN patients, especially of...
women with AN before cognitive behavioural therapeutic intervention using VBM.

2. Methods

2.1. Participants

15 Women (mean age: 26.8 years; SD 8.4 years, all right-handers according to the Oldfield handedness scale [17] who met the criteria for AN as defined by the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders [2] participated in this study. The patients had a mean body mass index (BMI) of 16.0 kg/m²; SD = 1.3. Mean disease duration was 5.3 years (SD = 5) (see Table 1).

15 Female healthy controls without history of neurological or psychiatric diseases and a mean age of 29.5 years (SD = 8.2) and a mean BMI of 22 kg/m² (SD = 2.1) served as a control group (see Table 1).

Healthy controls and AN patients were comparable with respect to their age (t = −0.89; p > 0.05). Due to the nature of the disorder, participants with AN displayed significantly lower BMI compared to healthy controls (t = −8.5, p < 0.001).

All subjects gave written consent before the structural scans were acquired. The study was approved by the local ethic committee of the medical faculty of the Ruhr-University of Bochum.

2.2. Additional behavioural data

Additionally, the Contour Drawing Rating Scale [31] was applied to all participants. This scale uses standardized silhouettes and asks the question: “How do you look like?”

The silhouettes were also used for a rating of the body images from 10 external, female raters. The frontal images of all participating women were presented randomly three times in combination with the silhouettes on a computer screen. The raters had to match the image of the body with the scale of nine different female body contours provided by the Contour Drawing Rating Scale [31]. The median of raters had to match the image of the body with the scale of nine different female body contours provided by the Contour Drawing Rating Scale [31]. The median of the rating for every individual woman was subtracted from the self estimation of this woman, resulting in a difference score which represents the misrating of body image.

3. Scanning procedure and MRI protocol

3.1. Structural images

All high resolution T1-weighted 3D MR images (MPRAGE) were acquired on a Siemens (www.siemens.de; Erlangen, Germany) 1.5 T scanner. 112 sagittal slices with a resolution of 0.5 mm × 0.5 mm × 1.25 mm were acquired with a TR of 1900 ms and a TE of 3.9 ms.

3.2. Functional imaging

Functional imaging was done using the stimuli provided by Downing (http://www.bangor.ac.uk/~pss811/page7/page7.html). A block design was applied presenting each one image for 3 s in a block of 15 images followed by a fixation baseline of 45 s. Each block was repeated five times. 220 T2* images with a TR = 2200 ms were acquired.

3.3. Analysis

All analyses were performed on a PC using Matlab 7.0 (Mathworks Inc, Natick, MA, USA; http://www.mathworks.com/) and SPM5 software (Statistical Parametric Mapping; www.filion.ucl.ac.uk/spm). T1-weighted images were analysed using the VBM 5.1 toolbox provided by Christian Gaser (http://dbm.neuro.uni-jena.de/vbm.html). Images were analyzed using SPM5 by segmenting gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) from the normalized high resolution images. Prior information has been implemented by applying a Hidden Markov Random Field (HMRF) model. Resulting images were smoothed with a Gaussian kernel of 12 mm FWHM (see http://dbm.neuro.uni-jena.de/vbm/vbm5-for-spm5/).

A non-paired t-test was applied with no global normalization and no grand mean scaling. To avoid edge effects on the border between gray and white matter, voxels with a gray or white matter volume of <0.2 (maximum 1) were excluded. All contrasts were thresholded to p < 0.05 (FWE corrected) for multiple comparisons. Only clusters with a minimum of 12 voxels were included in the results. Anatomical labelling was performed as described elsewhere [27]. Additionally, the gray matter density was extracted from the clusters that differed between healthy controls and AN for correlation with additional scorings.

Functional images were analysed using SPM5 software (http://www.filion.ucl.ac.uk/spm/software/spm5/). After slice time correction, images were realigned to the first image of each subject. Afterwards all images were normalised to the standard brain of the Montreal Neurological Institute provided by SPM. Contrast between bodies and objects were calculated on the first level and fed into a second level analysis afterwards. All results were thresholded at p < 0.05 (false discovery rate corrected) with an extend threshold of eight contiguous voxels.

4. Results

4.1. Behavioural data

An ANOVA for repeated measures was applied to the self (CDR) and the objective ratings with group as between subject factor (see Fig. 1). Results yielded a significant interaction (F1,28 = 17.4;
the gray matter reduction and the percentage of signal changes in images of the EBA localiser using the cluster found in the VBM analysis. The fraction of gray matter/total brain volume differed significantly (using marsbar software 0.42; \( p = 0.38 \)) between these two variables. Additionally the percentage of signal changes (using marsbar software 0.42; http://marsbar.sourceforge.net/) were extracted from functional images of the EBA localiser using the cluster found in the VBM analysis as a region of interest. Correlation analysis yielded evidence for a strong trend towards a significant negative correlation between the gray matter reduction and the percentage of signal changes in this cluster (\( r = -0.47; p = 0.052 \)).

4.2. VBM analysis

Healthy controls and AN patients differed with respect to their BMI significantly (\( t = -8.5, p < 0.001 \)) and also with respect to their gray matter (\( t = -2.94; p > 0.01 \)), and brain volume (\( t = 1.8, p > 0.05 \), see Table 1). The fraction of gray matter/total brain volume differed not significantly (\( t = 1.1; p > 0.05 \)).

Imaging results of the non-paired t-test for the whole brain yielded significant differences in gray matter in the lateral occipital cortex (\( -48 -66 9; z = 4.9, k = 45 \)). This part of the occipital cortex has been referred to as the EBA [18] which was further supported by the result of the functional imaging data (see results below). Additionally a second focus of reduced gray matter has been found in the superior temporal gyrus (\( -56 -50 15; z = 5.9; k = 19 \)). No further significant differences have been observed.

Additionally a correlation analysis (one-sided) was performed using non-parametric spearman correlation coefficient for the gray matter density within the EBA and the body size misjudgement index of the AN subjects. Results yielded evidence for a strong trend towards a significant negative correlation (\( r = 0.38; p = 0.08 \)) between these two variables. Additionally the percentage of signal changes (using marsbar software 0.42; http://marsbar.sourceforge.net/) were extracted from functional images of the EBA localiser using the cluster found in the VBM analysis as a region of interest. Correlation analysis yielded evidence for a strong trend towards a significant negative correlation between the gray matter reduction and the percentage of signal changes in this cluster (\( r = -0.47; p = 0.052 \)).

4.3. Functional imaging analysis

Due to technical problems, two subjects had to be excluded from the AN group and one subject from the healthy control group. Results from contrasts of human bodies versus objects yielded activation in the left and right lateral occipital cortex covering functionally the EBA in both groups. The overlay of functional activations of both groups and additionally the significantly reduced gray matter in the EBA is illustrated in Fig. 2 (see also Table 2 for activation clusters). By simply comparing the coordinates from the VBM results and the functional localizer contrast it can easily be inferred that both results totally overlap.

5. Discussion

The major finding of the present study was that women suffering from AN displayed a significantly reduced gray matter volume in the left lateral occipital cortex functionally covering the EBA compared to age-matched healthy controls. Interestingly, this result was found in a whole brain analysis without the application of a region of interest analysis. While a functional localizer scan was additionally performed to localize the EBA, this activation cluster was not used as a region of interest to define the EBA in the VBM analysis. However, the overlay of activation from the localizer scans yielded evidence for a total overlap of functionally activated clusters related to activation of the EBA and reduction of gray matter exactly in this area. This is important as the EBA can be characterised as a functional unit, which has to be specifically activated by human bodies.

Beside the reduction of gray matter in the EBA, a second focus has been found in the superior temporal gyrus. It has been shown recently, that the posterior part of the superior temporal gyrus is involved in body processing [22]. This focus of gray matter reduction reflects additional evidence for disturbances in the system that is involved in body processing in AN. Other studies suggest that the superior temporal sulcus processes biological motion (e.g. [21]). Peelen et al. [19] discussed the possible involvement of the EBA in processing of biological motion. In general, the EBA is involved in the processing of static body representation which is also a part of the network responsible for processing biological motion. As reported by Vocks et al. [35] women with bulimia nervosa (BN), another prominent eating disorder, demonstrate deficits in processing of biological motion. Present results suggest that a similar deficit might be found in AN patients due to the reduction of gray matter found in the STS. It may be speculated whether the pattern found in BN is comparable to that of women with AN: body-motion perception is correlated with social insecurity and body avoidance and static body image perception is related to shape weight concerns. This has to be investigated in further studies using functional imaging techniques.

As described in several other studies (e.g., [28]), participants from both groups did differ with respect to their gray matter volumes, indicating that the reduction in brain mass seems to be a phenomenon of a generally reduced gray matter volume in AN due to malnutrition [7]. Fraction of gray matter and total brain volume did not differ significantly between groups yielding evidence for a focused gray matter reduction strongly associated with the underlying pathology. This pattern of brain alterations is at least in parts in contrast to findings in the literature. Reduction of gray and white matter has previously been reported in several studies [8,28] as well as the enlargement of the ventricle system [29]. Factors like duration of disease and BMI might play a crucial role for the different affection of these factors.

This present study further aimed at looking for association between alterations in the gray matter of AN patients and their dif-
difficulties in body processing, one major feature in AN. Behavioural data yielded evidence for an overestimation of body size in AN patients and an underestimation of body size in healthy controls if compared to the judgement of independent female raters. This is in accordance with results reported by Vocks et al. [36] and replicates the symptom of body image distortion in AN in the present study. This result further suggests a dissociation between perceptual and emotional processing of their own body in AN. Seeger et al. [24] reported amygdala activation of AN patients during the evaluation of their own body yielding evidence for fear related processes during the evaluation of the own body. Present results show additionally perceptual deficits in AN patients which are related to body size/shape mismatching, probably based on gray matter reduction in the EBA.

The finding of the focused gray matter reduction in AN patients if compared to healthy controls in the left EBA which functionally responds selectively to human bodies (for a review, see [18]) might provide an explanation for the aforementioned body size overestimation in AN. In general, correlation between EBA density and body size misjudgement yielded evidence for a strong trend towards a significant correlation between both variables. This trend suggests that body size misjudgement as assessed with the current approach is strongly associated with the reduced gray matter density of the left EBA and may possibly be explained by this reduction. The current approach has to be characterised as an attempt to assess body size misjudgement. Further studies using more elaborated paradigms should investigate this phenomenon in AN. In general, there are two components that cause body image distortion: perceptual disturbances and cognitive dissatisfaction with the own body as a result of social comparison [23]. Present results suggest that the women participating in this study showed perceptual deficits. Further research has to clarify whether the two aforementioned components of body image distortion can be separated and reflect different sub-forms of AN. The existence of such distinct sub-forms might also explain different patterns of brain alteration in AN like reduced white matter or enlarged ventricles. This is supported by results from Urgesi et al. [33] and Pitcher et al. [20] which yielded evidence for the critical role of the EBA in body form processing. Alteration in the EBA might therefore cause problems in body form processing as described in the results of the present experiment. In accordance with the data by Smeets and Kosslyn [26], the alteration in the EBA has been found on the left side.

Correlation between signal changes in the EBA elicited by the functional localizer and the reduction of gray matter exactly in this brain area yielded evidence for a nearly significant, negative correlation. At first sight, this result might be non-intuitive, high activation levels should correlate positively with high gray matter density. One explanation for this finding might be that this phenomenon reflects a compensation mechanism. Reduced gray matter density might be compensated by increased activity in exactly this part of the brain.

Interestingly, Moro et al. [13] recently introduced the term body form agnosia by showing that subjects with posterior brain lesions covering the EBA demonstrate deficits in body recognition. Reduction of gray matter density in the EBA in AN might explain the body size misjudgement in AN analogically to the findings by [13]. The development of tests to quantify this phenomenon is a challenge for the future and will give further insight in the pathology of AN. The present finding supports at least in parts the idea of a significant role of the EBA in the phenomenon of body size distortion in AN. Based on these findings, body size misjudgement might be explained by deficits in perceptual, visual processing in AN. This might support theories about body image distortion as published by Williamson and co-workers [38] suggesting that body image distortion is based on deficits in information processing. Additionally, in contrast to former theories that explained body image distortion in terms of neglect or related disorders which would reflect attentional processes [7,12], current results support the assumptions by Uhler et al. [32] and suggest that alterations in body-image processing brain circuits might be involved in this phenomenon.
remain. First, the causality is unclear. Future studies using a longitudinal design should focus on the question of whether the EBA volume reductions precede the onset of the AN and therefore might be of etiological relevance or whether they are a result of the disorder. It is known from post-traumatic stress disorder (PTSD) that the reduced volume of the hippocampus is caused by the traumatic, stressful experience. It is not clear if AN patients experienced something stressful comparable to that by PTSD patients. On the other hand, it is known that the increased or decreased use of specific parts of the brain might have a direct influence on its size. Maguire et al. [11] demonstrated alterations in the hippocampus of London taxi drivers. Additionally, Draganski et al. [6] demonstrated an increase in gray matter density after extensive juggling. As shown in these studies [3,6,11] the brain is flexible and reacts to specific stimulation. Therefore, it may be discussed whether the reduction of gray matter in AN reflects the result of body-related avoidance behaviour [23,34], probably negatively reinforced by the negative emotions like fear and disgust that patients with eating disorders generally experience when looking at their own body [37]. It may be speculated that this reduced exposure to the own body may cause the observed reduction of gray matter in the EBA. Based on these speculations, the question can be raised whether this volume reduction can be enhanced by body image interventions in which patients are repeatedly exposed to their own bodies [9,34].

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References
