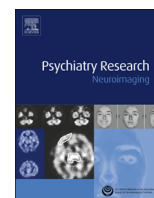




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Brain volumetric abnormalities in patients with anorexia and bulimia nervosa: A Voxel-based morphometry study

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ABSTRACT

Recent studies focussing on neuroimaging features of eating disorders have observed that anorexia nervosa (AN) is characterized by significant grey matter (GM) atrophy in many brain regions, especially in the cerebellum and anterior cingulate cortex. To date, no studies have found GM atrophy in bulimia nervosa (BN) or have directly compared patients with AN and BN. We used voxel-based morphometry (VBM) to characterize brain abnormalities in AN and BN patients, comparing them with each other and with a control group, and correlating brain volume with clinical features. We recruited 17 AN, 13 BN and 14 healthy controls. All subjects underwent high-resolution magnetic resonance imaging (MRI) with a T1-weighted 3D image. VBM analysis was carried out with the FSL-VBM 4.1 tool. We found no global atrophy, but regional GM reduction in AN with respect to controls and BN in the cerebellum, fusiform area, supplementary motor area, and occipital cortex, and in the caudate in BN compared to AN and controls. Both groups of patients had a volumetric increase bilaterally in somatosensory regions with respect to controls, in areas that are typically involved in the sensory-motor integration of body stimuli and in mental representation of the body image. Our VBM study documented, for the first time in BN patients, the presence of volumetric alterations and replicated previous findings in AN patients. We evidenced morphological differences between AN and BN, demonstrating in the latter atrophy of the caudate nucleus, a region involved in reward mechanisms and processes of self-regulation, perhaps involved in the genesis of the binge-eating behaviors of this disorder.

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1. Introduction

Anorexia nervosa (AN) and bulimia nervosa (BN), the two principal DSM-IV eating disorders (ED) diagnoses, are complex psychiatric disorders in which biological, psychological, socio-cultural and environmental factors interact and coexist in different stages of development (Sadock et al., 2009).

Recently, scientific research has focused on the study of the neurobiological basis of ED, aiming to identify biomarkers for the diagnosis and classification of these disorders, which are characterized by a high discrepancy between diagnostic criteria and clinical experience (Brooks et al., 2012). For this purpose, many

studies have used both structural and functional neuroimaging techniques to analyze the brain regions involved in the pathophysiology of ED (Sadock et al., 2009).

Observations of global cerebral and cerebellar atrophy in grey matter (GM) and white matter as well as ventricular enlargement in AN have led some authors to interpret these findings as representing a widespread cerebral vulnerability of this disorder (Artmann et al., 1985; Dolan et al., 1988; Krieg et al., 1988; Golden et al., 1996; Katzman et al., 1996; Lambe et al., 1997; Addolorato et al., 1998; Swayze et al., 2003; Chui et al., 2008).

Other studies, using a manual tracing approach on brain magnetic resonance imaging (MRI), have shown that some cerebral areas are particularly involved in AN, such as the thalamus, midbrain (Husain et al., 1992), paracentral lobule (Inui et al., 2002), hippocampus-amygdala complex (Giordano et al., 2001; Connan et al., 2006) and anterior cingulate cortex (ACC) (McCormick et al., 2008).

Voxel-based morphometry (VBM) is an unbiased automated technique based on high-resolution brain MRI sequences, and is

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widely used to measure structural differences across groups of subjects (Ashburner and Friston, 2000). A recent VBM study on AN patients found a significant reduction of total WM volume and focal GM atrophy in the cerebellum, hypothalamus, caudate nucleus, and frontal, parietal and temporal areas (Boghi et al., 2010). In another study, the authors found atrophy in the middle cingulate cortex, precuneus, and inferior and superior parietal lobules in restricting-type AN patients at an early stage of the disease, supporting the hypothesis of a regionally specific vulnerability in the areas that are involved in mental representation of self and body imagery (Gaudio et al., 2011). In recovered AN patients, a significant GM decrease in the ACC has been found, correlated with the lowest lifetime body mass index (BMI) (Muhlau et al., 2007). In another study, the authors found a volume reduction in the extrastriate body area in patients with AN which has been related to the body image distortion typical of this disorder (Suchan et al., 2010). In a recent work, Brooks and co-workers demonstrated a volumetric reduction of the insular cortex, parahippocampal and fusiform gyrus, cerebellum and posterior cingulate cortex in AN with respect to healthy controls. Moreover, the latter displayed an age-related volumetric decline of the dorsal-lateral prefrontal cortex that was absent in the patients, suggesting that restraint could spare the AN group from atrophy in this region (Brooks et al., 2011).

VBM longitudinal studies in AN patients have suggested the reversibility of structural brain abnormalities in individuals with ED after nutritional recovery (Wagner et al., 2006), in particular GM alterations (Castro-Fornieles et al., 2010). Conversely, other studies have shown that GM volume restitution was incomplete in subjects who had been previously severely affected by AN (Joos et al., 2011).

So far, only a few studies have focused their attention on brain changes in BN, finding that BN patients had decreased cortical mass, but that the decrease was less pronounced than in AN (Kriegel et al., 1989).

A recent VBM study, comparing AN and BN patients with controls, showed in AN a GM decrease in the ACC, frontal operculum, temporal-parietal regions and precuneus with respect to controls, while findings in BN did not show any difference from those in controls (Joos et al., 2010). Another study on AN and BN, which included long-term recovered patients, did not find differences with respect to controls except for an increased insular volume in BN (Wagner et al., 2006). A further study, which compared BN and binge-eating disorder patients, found that both had increased volume in the medial orbitofrontal cortex with respect to controls and BN displayed an enlargement of the ventral striatum, a brain structure involved in reward processes and self-regulation (Schäfer et al., 2010). However, the previous studies did not make direct comparisons between AN and BN, while in the majority of the current studies the authors included patients with symptoms of long duration.

The aim of the present study was to use VBM to characterize brain abnormalities of AN and BN patients who had received their first diagnosis of an ED, comparing the groups with each other and with healthy controls, in order to investigate those brain abnormalities which could be specifically linked to each ED diagnosis and to correlate them with clinical and demographic features.

2. Methods

2.1. Participants

All patients were recruited from the ED Pilot Centre of the Department of Neuroscience, San Giovanni Battista Hospital of Turin, between November 2010 and November 2011.

A total of 30 patients were enrolled in this study from outpatients of the ED Pilot Centre presenting a first diagnosis of ED: the group included 17 (15

restricting-type and 2 binge-purging) AN and 13 (11 purging-type and 2 not purging) BN. All patients were diagnosed by two psychiatrists specialised in ED (A.F. and G.A.D.) using the Structured Clinical Interview for Diagnosis (SCID) for DSM-IV-TR. An axis II assessment was also conducted using the SCID-II for DSM-IV-TR. A first assessment was performed by administering the SCID. After reviewing the diagnostic information, the psychiatrist made a final diagnosis of ED subtype and proposed the patient's participation in the research project.

The inclusion criteria for patients were as follows: female sex; age 16–30; right-handedness; a body mass index (BMI) of 15–18 for AN patients and 19–25 for BN patients; no past or present psychiatric or neurological diseases, no Axis II disorders, no past or present pharmacological medication, no drug or alcohol abuse; no personal or family history of diabetes; no past or present psychotherapy; symptoms of less than 2 years' duration.

All patients completed the Eating Disorders Inventory-2 (Garner, 1991) to assess eating problems and the Beck Depression Inventory (BDI) to exclude major depression symptoms. As determined by the SCID, no patients reported a previous ED diagnosis.

Fourteen healthy women were recruited as controls (CN) through local advertisements. They were interviewed by A.F. and G.A.D. using the SCID, to rule out past or present mental disorders or ED. The general inclusion criteria for controls were the same as for patients; the BMI was the same as for BN.

All patients and controls gave their written informed consent to the study. With juveniles, the written informed consent of their parents was obtained. The study was approved by the Ethical Committee of the San Giovanni Battista Hospital, Turin, in accordance with the Declaration of Helsinki.

2.2. MRI acquisition

MRI was acquired with a scanner at 1.5 T (Achieva, Philips). T1-Weighted 3D Turbo Gradient-Echo sequences (matrix=256 × 256; voxel size 1 × 1 × 1 mm³; number of slices: 190; TR: 7 ms; TE: 3 ms; TFE shots=89) were obtained with full brain coverage and isotropic voxels. Acquisition time was about 5 min.

2.3. VBM analysis

VBM was performed using the FSL-VBM 4.1 tool, part of the FSL software (FMRIB's Software Library, the University of Oxford).

For the VBM analysis, the steps below were followed (Good et al., 2001a):

- 1) Preparation of T1-weighted images in the correct format (compressed NIFTI)
- 2) Performance of the brain extraction using the BET-extraction FSL-tool on T1 images
- 3) Creation of the study-specific GM template at 2 × 2 × 2 mm³ resolution in standard MNI space
- 4) Non-linear registration of all the GM images on the template. The images were then modulated and smoothed with an isotropic Gaussian kernel of 7 mm FWHM (Full Width Half Maximum).
- 5) Use of FAST-segmentation and fslstats FSL-tools (www.fmrib.ox.ac.uk/fsl) to obtain total GM and total WM for each group.

Voxel-wise GLM analysis was carried out using permutation testing. FSL-Randomise 2.8 (www.fmrib.ox.ac.uk/fsl) with 5000 permutations was used, with the Threshold-Free Cluster Enhancement (TFCE) option. Age and BDI were used as confounding covariates. Global GM and WM were compared among groups, regional GM in ED vs. CN, AN and BN vs. CN and AN vs. BN. Finally, GM volume in each group was correlated with BMI, age, duration of disease and BDI.

Significant results ($p < 0.005$ uncorrected for multiple comparisons) with a cluster extent (K_e) > 60, were reported. Clusters surviving after correction for multiple comparisons were also looked at, using a corrected cluster size level of $p < 0.05$.

To obtain the anatomical localization of significant cluster peaks, the MRIcron software (www.mccauslandcenter.sc.edu/mricron/mricron) with AAL (Automated Anatomical Labelling) and Brodmann areas (BA) templates were used. The results were reported in the MNI coordinates system. In the figures, the result maps were reported in accordance with neurological convention (right is right). The SPSS 17™ software package (SPSS Inc., Chicago, IL, USA; www.spss.com) was used to compare global GM and WM and to make the statistical analysis on clinical and demographic data: we used ANOVA to compare means among groups, using Tukey's honestly significant difference (HSD) test for post hoc comparison when needed (threshold for significant results was $p < 0.05$).

3. Results

3.1. Characteristics of participants

The demographic and clinical characteristics of patients and controls are summarized in Table 1.

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