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In vivo evidence of global and focal brain alterations in anorexia nervosa

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ABSTRACT

Brain alterations are known to be associated with anorexia nervosa (AN) and tend to be distributed across brain structures, with only a few reports describing focal damage. Magnetic resonance images of 21 anorexic patients with different disease duration and 27 control subjects were acquired and compared using voxel-based morphometry (VBM). Patients had a significant reduction of total white matter (WM) volume and focal gray matter (GM) atrophy in cerebellum, hypothalamus, caudate nucleus and frontal, parietal and temporal areas. The cerebellum was more affected in patients with longer disease duration, whereas the hypothalamic alterations were more pronounced in patients with shorter food restriction. A correlation with body mass index (BMI) and GM was found in the hypothalamus. Our data demonstrate a diffuse reduction of WM together with focal areas of GM atrophy in AN. The finding of a hypothalamic focal atrophy points to hormonal dysfunction and opens the possibility for a central dysregulation of homeostasis. The involvement of temporoparietal areas could account for body image distortion. Finally, the cerebellar GM atrophy confirms previous findings and seems to be a late consequence of AN that could play a role in the chronic phase of the disease.

1. Introduction

Anorexia nervosa (AN) is an eating disorder (ED) that predominantly affects women from adolescence to adulthood (sex ratio: 10/1 = F/M); its incidence and lifetime prevalence among females are 0.5-1% and 0.5%, respectively (DSM IV-TR, American Psychiatric Association, 2000).

Clinical features of AN are body image distortion and intense fear of becoming fat, with refusal of food and consequent severe emaciation (Cash and Deagle, 1997; Epstein et al., 2001; Seeger et al., 2002; Wagner et al., 2003). Because of self-starvation, anorexic patients could suffer from several physical consequences, such as anemia, osteoporosis, amenorrhea and other endocrine dysfunctions. Notably, cerebral alterations have been described as among these consequences. Cerebral alterations relative to controls have been demonstrated in post mortem investigations (Gagel, 1953; Martin, 1958) and in vivo by neuroimaging studies, using computed tomography (CT) (Enzmann and Lane, 1977; Kolhmeyer et al., 1983; Artmann et al., 1985; Dolan et al., 1988; Hoffman et al., 1989; Addolorato et al., 1998) and magnetic resonance imaging (MRI) (Golden et al., 1996; Katzman et al., 1996; Kingston et al., 1996; Swayze et al., 1996, 2003; Lambe et al., 1997; Inui et al., 2002; Miwa et al., 2004). The most frequently described macroscopic anatomical brain changes are cerebral and cerebellar gray matter (GM) and white matter (WM) atrophy and ventricular enlargement. These findings have been globally distributed over the brain, suggesting a diffuse cerebral vulnerability. However atrophy has also been reported in some discrete areas, including paracentral lobule (Inui et al., 2002), thalamus, midbrain (Husain et al., 1992), mammillary bodies (Kingston et al., 1996) and extra-striate body areas (Suchan et al., 2010). On the other hand, some authors have failed to find significant total and focal GM volumetric differences between anorexics and healthy controls (Swayze et al., 1996, 2003).

The inconsistency in findings can partly be explained by the reversibility of these lesions. Indeed, longitudinal studies have reported that both GM and WM abnormalities are partially reversible after body weight restoration (GM: Kingston et al., 1996; Katzman et al., 1997; Swayze et al., 1996, 2003; WM: Swayze et al., 2003).

Similar results have been reported for intracranial cerebrospinal fluid (CSF) volume. It has been found to be increased in the supratentorial ventricular compartments (Artmann et al., 1985; Kingston et al., 1996) and in the subarachnoid spaces (Krieg et al.,

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1988; Hentschel et al., 1995; Swayze et al., 2003), and restored by body weight gain (Golden et al., 1996; Swayze et al., 2003). These findings have been recently confirmed in both short (Castro-Fornieles et al., 2009) and long-term recovered patients (Wagner et al., 2006), although persistent total GM and bilateral anterior cingulate cortical decrease after recovery has also been observed (Mühlau et al., 2007). Based on these abnormal brain findings, recent studies focused on the cognitive performance in patients with AN; however, correlations between cerebral morphological abnormalities and cognitive performance in AN patients have tended to be weak (Palazidou et al., 1990) or absent (Lankenau et al., 1985; Laessle et al., 1989; Kingston et al., 1996). More interesting, a recent study suggested a morpho-functional interaction in the brain region implicated in body image processing, showing a focal alteration in the extrastriate body area in anorexic patients (Suchan et al., 2010). This result is very intriguing, suggesting a brain alteration that is likely more related to the etiopathogenesis or at least to the perpetuation of the disease than to the consequence of the disease.

Methodological differences, such as imaging techniques (i.e. CT and MRI) and morphometric methods for brain anatomy evaluation, used in the above-mentioned studies could explain some of the contradictory findings. These limitations may be overcome by voxel-based morphometry (VBM), an unbiased automated technique developed to characterize morphological brain differences across groups of subjects (Ashburner and Friston, 2000; Good et al., 2001a, 2001b).

The aim of the present study was to characterize brain abnormalities in AN using VBM in two groups of unrecovered AN patients with different disease durations.

2. Methods

2.1. Subjects

Twenty-one right-handed women with a diagnosis of restricting type AN, according to the criteria of the 4th revised edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR, American Psychiatric Association, 2000), were consecutively admitted to the Psychiatric Unit of the University of Torino, AOU S.Giovanni Battista, Torino, over a period of 4 months. They all were without periods of disease recovery. Exclusion criteria were a previous and/or actual alcohol or substance abuse and neurological disease. The whole sample was divided into two subgroup comprised 10 patients at their first presentation to the Psychiatric Unit for AN (patient group P1), while the second subgroup incorporated 11 patients followed by the Psychiatric Unit for more than 9 years (patient group P2). At the time of MRI all patients were in treatment with antidepressant drugs (selective serotonin reuptake inhibitors, SSRI), nutritional therapy and psychotherapy. All patients underwent a routine neuropsychological evaluation with the Wechsler Adult Intelligence Scale Revised (WAIS-R) (Wechsler, 1981).

Two groups of right-handed healthy women (C1 = 13 subjects; C2 = 14 subjects), age-matched with the two subgroups of patients, were also enrolled as normal controls with normal weight and without history of eating disorder (ED) or any psychiatric, neurological or medical illness. Demographic and clinical characteristics of patients and controls were compared using two-sided independent *t*-tests.

All subjects enrolled gave their written informed consent to the study. Procedures were approved by the ethics committee of the hospital.

2.2. Procedures

2.2.1. MRI data acquisition

Structural MRI scans were acquired on a 1 Tesla Impact Magnetom Imager (Siemens, Erlangen, Germany). Whole brain scans were obtained as high-resolution T1-weighted 3D MPRAGE (Magnetization Prepared Rapid Acquisition Gradient Echo), acquired in the sagittal plane (TR = 11.4 ms, TE = 4.4 ms, TI = 300 ms, FA = 15°, FOV = 256 × 192 mm; matrix = 256 × 192, voxel size = 1 × 1 × 1.4 mm, 128 sections).

2.2.2. VBM analysis

Image analyses were performed on a workstation. Images were first converted from DICOM to ANALYZE format with the MRIcro software package (MRIcro v1.39, Nottingham University; www.mricro.com). Subsequent analyses were performed using the Statistical Parametric Mapping software (SPM2, Wellcome Department of Imaging Neuroscience, http:/www.fil.ion.ucl.ac.uk/spm/), in MATLAB environment (Math Works Inc, Natick, MA, USA).

The optimized VBM protocol was applied to patients and controls (Ashburner et al., 1997; Ashburner and Friston, 2000; Good et al., 2001a, 2001b). Briefly, GM and WM study-specific templates were created; then the original MRI images were segmented into GM and WM in native space, and GM and WM partitions were normalized to the respective study-specific template. The obtained normalization parameters were finally applied to native MR images which were then segmented again. These normalized partitions were modulated to compensate for normalization-dependent volumetric distortions (Ashburner and Friston, 2000) and then smoothed with a 12-mm full width at half-maximum isotropic Gaussian kernel to render data normally distributed.

Global differences in GM, WM and CSF volumes were tested by comparing values computed from unnormalized partitions.

Statistical analysis to search for regional differences in GM and WM volumes between patients and normal controls was performed using the general linear model approach implemented in SPM2. First, local brain differences were examined in the whole sample (i.e. all patients and all normal controls) using age and total intracranial volume (TIV) (i.e. the sum of GM, WM and CSF compartments volumes) as confounding covariates. Then we performed a comparison between each subgroup of patients with its age-matched subgroup of normal controls (P1 versus C1 and P2 versus C2). In this second analysis only TIV was used as confounding covariate because age was matched across patients and controls. Moreover, we performed a comparison between the two subgroups of patients (P1 versus P2) in order to investigate differences between patients with shorter and longer disease duration; in this analysis TIV and age were used as confounding covariates.

Additionally, we searched for correlations between GM and WM volumes and BMI values and years of disease. Regressors for TIV and age were entered into the design as confounding covariates, in order to discard any possible global effect.

To obtain anatomical localization of significant voxels, we used the MRIcro software, and results were reported in the Talairach coordinates system with corresponding Brodmann areas.

3. Results

3.1. Characteristics of participants

The demographic and clinical characteristics of patients and control subjects are summarized in Table 1. Both patients [mean age = 29 years; standard deviation (SD) = 10.1; median = 27; mode = 21; age range = 19-54 years] and normal controls (mean age = 30.8 years, SD = 8,7, median = 34, mode = 23, range = 21-52 years) included were right-handed. Patients' and normal controls' BMI were significantly different both considering the overall group and subgroups; on the contrary BMI values from the two patient groups were not significantly different. Patients showed normal total, verbal and performance IQ scores, with no significant differences in subtest scores across groups.