Regional decrease in gray matter volume is related to body dissatisfaction in anorexia nervosa

Kunihiro Kohmura\(^a,b,⁎\), Yasunori Adachi\(^b,c\), Satoshi Tanaka\(^d\), Hirotou Katayama\(^b,e\), Miho Imaeda\(^a,f\), Naoko Kawano\(^g\), Kazuo Nishioka\(^a,h\), Masahiko Ando\(^i\), Tetsuya Iida\(^j\), Norio Ozaki\(^i\)

\(^a\) Department of Psychiatry, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan
\(^b\) Seichiryo Hospital, Nagoya, Aichi, Japan
\(^c\) Department of Clinical Oncology and Chemotherapy, Nagoya University Hospital, Nagoya, Aichi, Japan
\(^d\) Department of Psychiatry, Nagoya University Hospital, Nagoya, Aichi, Japan
\(^e\) Department of Neuropsychiatry, Faculty of Medical Sciences, University of Fukui, Yoshida-gun, Fukui, Japan
\(^f\) Sakura Clinic, Nagoya, Aichi, Japan
\(^g\) Institutes of Innovation for Future Society, Nagoya University, Nagoya, Aichi, Japan
\(^h\) National Hospital Organization Higashi Owari National Hospital, Nagoya, Aichi, Japan
\(^i\) Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Nagoya, Aichi, Japan
\(^j\) Department of Physical and Occupational Therapy, Nagoya University, Graduate School of Medicine, Nagoya, Aichi, Japan

A B S T R A C T

Anorexia nervosa (AN) is a psychiatric disorder, in which the prognosis for some patients is poor. The etiology and effective treatments for AN have not been established. We examined morphometric changes in the brain of AN and clarified how the changes were associated with symptoms and pathophysiology. We enrolled 52 participants: 7 with the restrictive type of AN, 13 with the binge-eating/purging type, 3 with eating disorder not otherwise specified, and 29 healthy controls. Participants underwent T1-weighted MRI. Group differences between patients and controls in gray matter volume (GMV) were analyzed using voxel-based morphometry. Age and body mass index (BMI) were considered covariates. Correlations between regional GMVs and drive for thinness and body dissatisfaction were examined. Patients had decreased GMV in the superior/middle temporal gyrus (STG/MTG), pulvinar, and superior frontal gyrus after correction for age and BMI, and in the STG/MTG, middle frontal gyrus, and cingulate after correction for age. A correlational group difference was detected for body dissatisfaction and GMV in the STG. Our findings suggest that decreased GMV in the STG is related to body dissatisfaction that could come from impaired visuospatial perception, together with GMV decreases in several regions, which may be involved in development of AN.

1. Introduction

Anorexia nervosa (AN), which is a psychiatric disorder that typically affects teenage females, is characterized by severe weight loss, relentless pursuit of thinness, a refusal to maintain body weight at 85% of the expected standard for age and height, food restriction, and strong fears of becoming fat (American Psychiatric Association, 2013, 2000). The prognosis of AN is poor for some patients, because patients with AN tend to be resistant to most medical treatments due to their poor understanding of their disease. The 10-year mortality rate of AN is about 5%, and the suicide rate is 56.9 times higher than in the general population (Abbate-Daga et al., 2013). Even after treatment, around 50% of patients become chronic sufferers of AN (Nielsen et al., 1998). Thus, clarification of the pathophysiological basis of AN and identification of effective treatments are critical, but have not been established.

Chronic starvation results in medical complications that affect every organ system in the body. In particular, severe brain alterations can be manifested as cognitive dysfunction and abnormalities in brain volume (Warren, 2011). Recently, a hypothesis has emerged that suggests that neurobiological alterations in AN can be separated into two categories, trait-related and state-related alterations (Kaye et al., 2009). Trait-related alterations correspond to premorbid and genetically determined changes that may contribute to vulnerability to developing AN. State-related alterations are secondary to malnutrition and may sustain and perhaps accelerate AN. The patient starts dieting, and extreme weight loss leads to neurobiological changes that exacerbate psychological symptoms such as denial, rigidity, anxiety, and obsessions, which then
result in an increase in pathological dieting (Kaye et al., 2009).

Drive for thinness and body dissatisfaction, which are the core symptoms of AN, are considered to appear in the context of a mismatch between the ideal body image and the real figures that patients see with their eyes (Hagman et al., 2015). A previous study revealed that healthy female adolescent dancers at high risk for AN tend to have body dissatisfaction and a strong drive for thinness, indicating that these changes were present before the onset of AN (Jones et al., 2014). McNamara et al. (2008) reported that negative emotional responses and fears increase when AN patients view pictures of food, and that these increases are related to body dissatisfaction. Thus, we assume that the drive for thinness and body dissatisfaction are involved in the pathophysiology of AN.

Neuroimaging techniques have recently been used to detect abnormalities in the brain of patients with AN. Many studies have been performed using magnetic resonance imaging (MRI), which identified higher cerebrospinal fluid (CSF) volumes in association with deficits in total gray matter volumes (GMVs) and white matter volumes (WMVs) in patients with AN (Joos et al., 2010; Suchan et al., 2010). voxel-based morphometry (VBM) is an automated technique based on voxel-wise statistical analysis of pre-processed structural MRI (Ashburner and Friston, 2000).

The VBM technique has led to a steady increase in studies assessing brain abnormalities in AN. However, findings from these studies have been inconsistent (Van den Eynde et al., 2012). According to the studies using VBM, regional GMV changes in acute AN have been found in a wide variety of areas including frontal (anterior cingulate cortex and frontopolar cortex), temporal (superior temporal gyrus (STG) and temporoparietal junction), parietal (precuneus and inferior parietal cortex), and occipitotemporal cortex (Castro-Fornieles et al., 2009; Joos et al., 2010; Suchan et al., 2010). A recent meta-analysis of seven VBM studies of AN revealed decreases in regional GMVs in the hypothalamus, caudate nucleus, lentiform nucleus, and the inferior parietal lobe (Titova et al., 2013). In contrast, many reports have suggested the absence of GMV loss in AN (e.g., Boghi et al., 2011; Brooks et al., 2011).

In this study, we hypothesize that GMVs decrease in patients with eating disorders, specifically extremely malnourished patients and especially those with AN. The first aim was to test this hypothesis by assessing patients with severe low body weight compared to previous studies. Second, we identified which regional GMVs were actually reduced in patients. Then, we evaluated the relationships between regional volume changes in the brain and clinical symptoms of drive for thinness and body dissatisfaction.

2. Methods

2.1. Participants

A total of 52 female participants were enrolled in the study: 7 with the restrictive type of AN (AN-R), 13 with the binge-eating/purging type of AN (AN-BP), 3 with eating disorder not otherwise specified (ED-NOS), and 29 age-matched healthy women in the normal weight range. Patients with lifetime diagnoses of posttraumatic stress disorder, bipolar disorder, major depressive disorder, schizophrenia, obsessive-compulsive disorder, substance use disorder, or borderline personality disorder were excluded. Written informed consent was obtained from all participants prior to enrollment in the study. Body mass index (BMI) was obtained at the time of MRI scanning.

2.2. Procedure and analysis of clinical data

Before entering the study, the participants were interviewed with the Structured Clinical Interview for DSM-IV axis I Disorders to screen for lifetime psychiatric diseases (First et al., 1994). In addition, the participants completed a battery of self-report questionnaires that included the Beck Depression Inventory (BDI) and the Eating Disorder Inventory II (EDI-II) (Tachi et al., 2007). The age of onset and the duration of the disease were obtained for the patient group. All participants underwent structural MRI and were asked to fast for at least 3 h before imaging.

Clinical data were analyzed using IBM SPSS Statistics Ver. 22. The Student’s t-test was performed to test for differences between the patient group and the control group in age and BDI, and the Mann-Whitney U test was used to analyze BMI. For drive for thinness and body dissatisfaction, which are derived from the EDI-II subscales, the Student’s t-test was used followed by Bonferroni correction for multiple testing to compare the two groups.

2.3. MRI data acquisition and image processing

MR images were obtained using one of three scanners for each participant. Each scanner was equipped with a standard single-channel head coil. Magnetization prepared rapid acquisition gradient echo was used to obtain 224 contiguous sagittal 3D T1-weighted images with (1) a Siemens TrioTim 3-T scanner: slice thickness of 1 mm, repetition time per echo time = 1570/2.19 ms, inversion time = 800 ms, flip angle = 15°, matrix size = 256 × 256 pixels, voxel size = 1 × 1 × 1 mm, (2) a Siemens Verio 3-T scanner: slice thickness of 1 mm, repetition time per echo time = 2500/2.48 ms, inversion time = 900 ms, flip angle = 8°, matrix size = 256 × 256 pixels, voxel size = 0.5 × 0.5 × 0.5 mm, and (3) Siemens Verio 3-T scanner: slice thickness of 1 mm, repetition time per echo time = 1570/2.22 ms, inversion time = 800 ms, flip angle = 15°, matrix size = 256 × 256 pixels, voxel size = 1 × 1 × 1 mm. Sampling periods lasted for more than 2 years to allow strict application of enrollment criteria. During the study period, our center replaced an old scanner with a new one. Therefore, we could not avoid using several scanners for the study. The first scanner was used for 14 participants in the patient group and 18 in the control group. The second scanner was used for two participants in the patient group and 11 in the control group. The last one was used for 7 in the patient group. We applied VBM8, a freely available software toolbox for VBM (http://dbm.neuro.uni-jena.de/vbm8/), implemented in SPM8 (Statistical Parametric Mapping; FIL, Institute of Neurology, UCL, London, UK; http://www.fil.ion.ucl.ac.uk/spm/). With the VBM toolbox, we performed non-linear normalization (non-linear only) with the DARTEL algorithm and performed segmentation into gray matter (GM), white matter (WM), and

| Table 1 |
|-----------------|-----------------|-----------------|-----------------|
| **Patient group (n = 23)** | **Control group (n = 29)** | **p** |
| Mean (SD) | Mean (SD) | |
| Age (years) | 28.5 (6.7) | 28.2 (7.0) | 0.884 |
| BMI (kg/m²) | 13.2 (1.5) | 21.5 (3.3) | < 0.001† |
| BDI | 25.3 (7.0) | 4.3 (4.5) | < 0.001† |
| Age of onset (years) | 18.0 (3.2) | – | – |
| Disease duration (years) | 10.5 (6.2) | – | – |
| EDI-II, Drive for Thinness | 9.6 (6.9) | 3.2 (4.3) | < 0.001*** |
| EDI-II, Body Dissatisfaction | 12.8 (4.2) | 8.8 (7.1) | 0.019*** |

BMI: Body Mass Index; BDI: Beck Depression Inventory; EDI-II: Eating Disorder Inventory II, significant group differences (Mann-Whitney U test, *p < 0.05; Student’s t-test, **p < 0.05; Student’s t-test, followed by Bonferroni correction, ***p < 0.05/2).
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