Psychiatry Research: Neuroimaging 279 (2018) 14–18

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Registration-based methods applied to serial high-resolution T1-weighted magnetic resonance imaging for the assessment of brain volume changes in anorexia nervosa of the restricting type

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ARTICLE INFO

Keywords:
Anorexia nervosa
Brain
Changes
Magnetic resonance imaging (MRI)
Registration-based methods
Volume

ABSTRACT

We aimed to determine whether variation in the body mass index (BMI)—a marker of anorexia nervosa (AN) severity—is associated with brain volume changes longitudinally estimated using registration-based methods on serial high-resolution T1-weighted magnetic resonance images (MRI). Fifteen female patients (mean age = 21 years; standard deviation [SD] = 5.7; range: 15–33 years) with the diagnosis of AN of the restricting type (AN-r)—according to the Diagnostic and Statistic Manual of Mental Disorders, 5th edition criteria—underwent T1-weighted MRI at baseline and after a mean follow-up period of 11 months (SD = 6.4). We used the brain boundary shift integral (BSI) and the ventricular BSI (VBSI) to estimate volume changes after registering voxels of follow-up onto baseline MRI. Very significant and strong correlations were found between BMI variation and the brain BSI, as well as between BMI variation and the VBSI. After adjustment for age at onset, duration of illness, and the BMI rate of change before baseline MRI, the statistical significance of both associations persisted. Registration-based methods on serial MRI represent an additional tool to estimate AN severity, because they provide measures of brain volume change strongly associated with BMI variation.

1. Introduction

Anorexia nervosa (AN) is a psychiatric disorder characterized by a relentless pursuit of thinness and a refusal to maintain the body weight at a minimally acceptable standard for age and height, an abnormal concern about gaining weight, and a disturbance in the way the body weight or shape are experienced, along with a persistent lack in recognizing the severity of the associated weight loss (American Psychiatric Association, 2000, 2013; Klein and Walsh, 2003). AN has the highest rate of mortality among psychiatric disorders, its average prevalence is approximately 0.3%, and up to 90% of patients with AN are young women (Hoek, 2006; Morris and Twaddle, 2007). AN can be subdivided into restricting (AN-r) and binge-eating/purging subtypes (American Psychiatric Association, 2000, 2013).

Studies using voxel-based morphometry (VBM) on T1-weighted magnetic resonance images—an established method to determine statistically significant differences of brain volume between groups of subjects, after normalizing (into the same stereotactic space) and segmenting the high-resolution images (Ashburner and Friston, 2000)—have found reversible brain volume loss in AN (Castro-Fornieles et al., 2009; Gaudio et al., 2011; Joos et al., 2010; Lazaro et al., 2013; Roberto et al., 2011), but it is still unclear to what extent the brain volume loss is completely reversible or represents a marker of illness severity (Van den Eynde et al., 2012).

Useful methods to longitudinally estimate brain volume variation on serial high-resolution T1-weighted magnetic resonance imaging (MRI) include registration-based methods, which can be broadly subdivided into linear registration methods, using up to 12 degrees of freedom to match (cf., register) voxels of follow-up onto baseline images; and non-linear registration methods, using viscous (i.e., fluid) models with hundreds of degrees of freedom to determine deformation fields or warping (Barkhof et al., 2011). So far, registration-based

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https://doi.org/10.1016/j.pscychresns.2018.06.014
Received 21 December 2016; Received in revised form 18 June 2018; Accepted 23 June 2018
Available online 09 July 2018
0925-4927/

methods have mostly been used to determine rates of cerebral atrophy in patients with dementia (Fox et al., 2001; Janssen et al., 2005).

To the best of our knowledge, no previous study assessed the usefulness of registration-based methods to determine rates of brain volume loss or recovery in patients with AN as these lose or recover weight. Therefore, the purpose of the present study was to determine to what extent variations in the body mass index (BMI) of patients with AN-r are associated with global brain volume changes longitudinally estimated by using registration-based methods applied to serial high-resolution T1-weighted MRI.

2. Methods

All procedures involving human participants included in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration or its later amendments.

2.1. Patient sample

Fifteen female patients (mean age = 21 years; standard deviation [SD] = 5.7; range: 15–33 years) with the diagnosis of AN-r—established in consensus by two psychiatrists, according to the Diagnostic and Statistic Manual of Mental Disorders, 5th edition (DSM-5) criteria (American Psychiatric Association, 2013)—were sequentially included for the present study. The age at onset and duration of AN (i.e., the elapsed time—in years—between age at onset of AN and the date of baseline MRI examination) were determined. To take into account weight variation before admission as a potential confound (Bomba et al., 2013), the BMI rate of change over approximately 6 months before baseline MRI was also calculated.

To be included in the present study, patients were required not to have any concomitant medical condition or psychiatric comorbidity apart from AN, not to be pregnant or lactating, nor to have any non-removable metal implant in the body or any other contraindication for MRI. To account for the confounding effect of hydration-related changes, we used the Smithline-Gardner formula to calculate serum osmolality values in mOsm per kilogram (kg) of solvent (Choy et al., 2016; Smithline and Gardner, 1976). All included patients had serum osmolality values ≥ 281 mOsm/kg and ≤ 298 mOsm/kg (mean = 288 mOsm/kg; SD = 5.5). These values indicate the unlikeliness of both excessive drinking and dehydration. Patients with AN of the binge-eating/purging subtype were excluded, because they are prone to develop hydroelectrolytic imbalance secondary to vomiting or an excessive use of laxatives.

At baseline, six (40%) of the 15 included patients were under treatment with antidepressant drugs, five (33%) patients were taking benzodiazepines, four (26.7%) patients were taking olanzapine, and four (26.7%) patients were not taking any psychotropic medication at all. At follow-up MRI, eight (53%) patients were under treatment with antidepressant drugs, five (33%) patients were taking benzodiazepines, three (20%) patients were taking olanzapine, and only three (20%) patients were free of any psychotropic medication. All (100%) included patients had regular sessions of psychotherapy during the entire duration of the study.

The weight and height of the patients were measured in order to assess the Quetelet's BMI, calculated as the weight in kilograms divided by the square of height in meters (Keys et al., 2014; Must and Anderson, 2006). The BMI value of all participants was ≤ 17.5 kg/m^2 at baseline, according to the clinical descriptions and diagnostic guidelines of the 'ICD-10 classification of mental and behavioural disorders' (World Health Organization, 1992). In addition, patients were classified as having mild (BMI ≥ 17 kg/m^2), moderate (BMI range: 16–16.99 kg/m^2), severe (BMI range: 15–15.99 kg/m^2), or extreme (BMI < 15 kg/m^2) AN, according to the DSM-5 criteria (American Psychiatric Association, 2013).

2.2. Magnetic resonance imaging protocol

MRI data were acquired using a scanner operating at 3 Tesla (Trio, A Tim System, Siemens, Erlangen, Germany) and equipped with a 12-channel radiofrequency head coil. Sagittal single-slab three-dimensional magnetization-prepared rapid gradient-echo T1-weighted images (T1-WI) were acquired (echo time = 3 ms, repetition time = 2300 ms, flip angle = 9°, inversion time = 900 ms, field of view = 240 mm, slice thickness = 1.2 mm, number of slices = 160, acquisition matrix = 256 × 256, voxel resolution = 1 × 1 × 1.2 mm, scanning time = 9:14 min). Patients were scanned at baseline and after a mean follow-up period of 11 months (SD = 6.4).

2.3. Image analysis

After applying the interactive and semi-automatic Medical Image Display and Analysis System software, more often called MIDAS (Freeborough et al., 1997), brain volume changes on T1-WI were assessed with the following linear registration methods: the brain boundary shift integral (BSI) and the ventricular BSI (VBSI), using 9 degrees of freedom, to express volume changes (in ml) as the amount (i.e., the integral) of shifting in the boundary between the brain and the cerebrospinal fluid over time (Freeborough and Fox, 1997). We also used a non-linear fluid registration method—voxel compression mapping—to illustrate specific examples of brain volume changes over time as a color overlay (Fox et al., 2001).

2.4. Statistical analysis

Associations between BMI variation and measures of brain volume change were tested using IBM SPSS 22.0 (https://www.ibm.com/analytics/data-science/predictive-analytics/spss-statistical-software).

Given that the continuous variables of interest had an approximately normal distribution, we used the Pearson's coefficient (r) to test correlations. We also used a linear regression analysis to adjust results for age at onset, duration of illness, and the BMI rate of change before baseline MRI. Statistical significance was considered when p-values were < 0.05.

3. Results

Table 1 summarizes characteristics of the included patients. The mean age at onset of AN was 17 years (SD = 3.8). The average BMI rate of change before baseline MRI was −0.09 kg/m^2/month (SD = 0.314, range: −0.61–0.59 kg/m^2/month).

At baseline MRI, the mean age of patients was 21 years (SD = 5.7), the mean duration of illness was 3 years (SD = 4.0), and the mean BMI was 14.3 kg/m^2 (SD = 1.42, range: 12–16.7 kg/m^2). Eleven (73.3%) patients had extreme AN, three (20%) patients had moderate AN, and one (6.7%) patient had severe AN.

At follow-up MRI, the mean BMI was 15.8 kg/m^2 (SD = 1.91, range: 12.5–18.6 kg/m^2). Six (40%) patients had extreme AN, five (33.3%) patients had mild AN, three (20%) patients had moderate AN, and one patient (6.7%) had severe AN.

During follow-up, three (20%) patients changed from extreme to moderate AN, two (13.3%) patients changed from extreme to mild AN, two (13.3%) patients changed from moderate to mild AN, one (6.7%) patient changed from extreme to severe AN, and one (6.7%) patient changed from severe to mild AN. Five (33.3%) patients with extreme AN were not found to have a change in the severity category during follow-up. Only one (6.7%) patient worsened from moderate to extreme AN during follow-up. In other words, all but one patient improved or maintained the severity category of illness at follow-up. Likewise, the mean BMI difference during follow-up was +1.5 kg/m^2 (SD = 2.00), indicating a slight improvement of illness severity.

Significant correlations were found between BMI variation and