Progress in Neuro-Psychopharmacology & Biological Psychiatry 51 (2014) 72–77

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

A tract-based spatial statistics study in anorexia nervosa: Abnormality in the fornix and the cerebellum

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ARTICLE INFO

Article history:
Received 30 September 2013
Received in revised form 29 December 2013
Accepted 13 January 2014
Available online 22 January 2014

Keywords:
Anorexia nervosa (AN)
Cerebellum
Diffusion tensor imaging (DTI)
Fornix
Tract-based spatial statistics (TBSS)

ABSTRACT

There has been an increasing interest in white matter abnormalities in patients with anorexia nervosa (AN). However, to date, there have been only a few diffusion tensor imaging (DTI) studies investigating AN, and the results are inconsistent. In this study, we employed tract-based spatial statistics (TBSS), a robust technique for whole-brain analysis of DTI data, to detect white matter abnormalities in AN patients compared with healthy controls. Seventeen women with AN and 18 age matched healthy women were included. The mean body mass index of patients was 13.6 kg/m^2 (controls: 19.9 kg/m^2). DTI data were acquired on a 3-Tesla magnetic resonance imaging system. Fractional anisotropy (FA) and mean diffusivity (MD) maps were calculated from the DTI data of each patient, and voxel-wise group comparisons of FA and MD were performed using TBSS. Compared with the healthy comparisons, the patients showed a significantly higher MD value in the fornix and lower FA value in the left cerebellum. We also found significant positive correlations between the mean FA value of the left cerebellar hemisphere cluster and BMI, as well as between the mean MD value of the cluster in the anterior body of the fornix and the duration of illness. The results suggest that the white matter abnormalities in the fornix and the cerebellum may be related to the pathophysiology of AN.

1. Introduction

Anorexia nervosa (AN) is a severe psychiatric disorder with high morbidity and significant lifetime mortality (Papadopoulos et al., 2009; Sullivan, 1995; Zipfel et al., 2000). The symptoms of AN are associated with refusal to maintain body weight at or above a minimally normal weight for age and height, intense fear of gaining weight or becoming fat and disturbance of body image based on the definitions provided in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).

Various neuroimaging techniques have been used to detect brain alterations in AN. Functional abnormalities have been detected by single-photon emission computed tomography (SPECT) (Matsumoto et al., 2006; Rodriguez-Cano et al., 2009), positron emission tomography (PET) (Frank and Kaye, 2005; Galusca et al., 2008), and functional MRI (fMRI). Previous studies using fMRI have revealed abnormal brain function in the cerebellum (Amianto et al., 2013a), the attention network (Sachdev et al., 2008), and limbic system (Ellison et al., 1998; Joos et al., 2011; Miyake et al., 2010; Vocks et al., 2010), including the reward system (Fladung et al., 2010).

Volumetric brain imaging studies have investigated gray matter (GM) and white matter (WM) volume abnormalities in patients with AN (Van den Eynde et al., 2011). GM volume reduction has been detected in the anterior cingulate cortex, frontal operculum, lateral occipital cortex, hypothalamus, precuneus, cerebellum, caudate nucleus and frontal, parietal and temporal areas (Amianto et al., 2013b; Boghi et al., 2011; Gaudio et al., 2011; Joos et al., 2010; Suchan et al., 2010). With regard to WM, although general volume reduction in AN was reported, a regional WM volume decrease was not detected (Boghi et al., 2011; Titova et al., 2013).

Diffusion tensor imaging (DTI) enables us to evaluate subtle microstructural abnormalities in WM that cannot be detected with a volumetric approach (Le Bihan et al., 2001). One of the most widely used measurements is fractional anisotropy (FA) (Mori and Zhang, 2006), which represents the degree of diffusional directionality (Klingberg et al., 2000). The FA value can be decreased by various conditions, whereas increases in the FA value are rarely reported (Alexander

Abbreviations: AN, anorexia nervosa; TBSS, tract-based spatial analysis; VBM, voxel-based morphometry; MRI, magnetic resonance imaging; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders; SCID-NP, Structured Clinical Interview for DSM-IV Axis I Disorders Non-patient Edition.

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http://dx.doi.org/10.1016/j.pnpbp.2014.01.009

et al., 2007). Mean diffusivity (MD) is also an indicator of white matter integrity, a scalar measure reflecting the magnitude of diffusion (Basser and Pierpaoli, 1996). Although DTI is applied to many psychiatric disorders (Agarwal et al., 2010), there are only few reports of DTI in regard to research about AN. One study reported WM alteration in the bilateral fimbria–fornix, superior and inferior fronto-occipital fasciculi, and posterior cingulum in AN patients relative to the control group (Kazlouski et al., 2011). However, another study reported WM alteration in the posterior thalamic radiation, which includes the optic radiation, and the left mediodorsal thalamus (Frieling et al., 2012). These inconsistent results might be due to the application of a voxel-based morphometry (VBM) approach for DTI data. VBM is a widely used, fully automated, whole-brain analysis method for structural MRI that does not require an a priori hypothesis for the search area. However, the methodological pitfalls of VBM-based analysis are considered to be more problematic when applied to DTI data, and there is a difficulty with white matter tract misregistration between subjects and smoothing kernel size (Jones et al., 2005). Tract-based spatial statistics (TBSS) is a voxel-wise image analysis method specialized for DTI data that solves the problem of misregistration and does not require smoothing (Smith et al., 2006). Until now, there has been no report on AN using TBSS.

Therefore, we investigated WM abnormalities in patients with AN using TBSS. Based on the previous findings, we hypothesized that there is disrupted WM connectivity in patients with AN and that it is one of the neural underpinnings of this disease. We expected a reduction of FA and/or increase of MD in patients with AN and an association with the pathophysiology of AN.

2. Methods

2.1. Subjects

Seventeen female patients with AN and 18 healthy age and sex matched comparison were recruited. Demographic data are shown in Table 1. The patients were recruited at the Kyoto Prefectural University of Medicine Hospital, Kyoto, Japan. All patients were diagnosed using the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I) (First et al., 1995). Four of them had current major depressive disorder (MDD) diagnosed by SCID-I, and one had MDD in the past. There was neither other nor past history. Six of the subjects were taking medication at scanning (Case 1, chlorpromazine, imipramine, mirtazapine, fluvoxamine, trazodone, flunitrazepam and risperidone; Case 2, olanzapine, cloxazolam, zolpidem and flunitrazepam; Case 3, quetiapine, valproic acid and risperidone; Case 4, estazolam and etizolam; Case 5, sertraline; and Case 6, zolpidem).

The exclusion criteria for patients were as follows: 1) significant physical diseases such as neurological diseases, diseases of the pulmonary, cardiac, renal, hepatic, or endocrine systems, and metabolic disorders; 2) DSM-IV diagnosis of mental retardation or pervasive developmental disorders based on clinical interview and psychosocial history; and 3) no obvious dehydration or obvious abnormality of electrolytes and complete blood count.

There was no history of psychiatric illness in the healthy comparisons (HC) as determined by the Structured Clinical Interview for DSM-IV Axis I Disorders Non-Patient Edition (SCID-NP). We confirmed that there was no psychiatric treatment history in any of their first-degree relatives. All of the participants were tested with the modified 25-item version of the Edinburgh Inventory (Oldfield, 1971), the eating disorder inventory-II (Garner, 1991; Tachi et al., 2007) and the Beck Depression Inventory-II (BDI-II) (Beck et al., 1961; Kojima et al., 2002) to assess handedness, severity of AN, and severity of depressive symptoms, respectively.

The Medical Committee on Human Studies of the Kyoto Prefectural University of Medicine approved all of the procedures. All participants provided written informed consent after receiving a complete description of the study.

Table 1
Clinical characteristics of patients with AN and healthy comparisons.

	Patients with AN (n = 17)	Healthy Comparisons (n = 18)	*p* value
	Mean ± SD	Mean ± SD	
Age, years	23.8 ± 6.68	26.2 ± 5.6	$p = .21$
BMI	13.6 ± 1.3	19.9 ± 2.0	$p = .000$
Total EDI score	77.8 ± 34.3	23.8 ± 11.1	$p = .000$
BDI-II	30.2 ± 12.8	6.1 ± 4.5	$p = .000$
Handedness, R/L	15/2	16/2	$p = .952$
Subtype (ANR/ANBP)	10/7	NA	NA
Duration of illness, years	4.93 ± 4.9	NA	NA

AN, anorexia nervosa; SD, standard deviation; BMI, body mass index; EDI-II, eating disorder inventory-II; BDI-II, Beck Depression Inventory-II; R, right; L, left; ANR, anorexia nervosa restricting type; ANBP, anorexia nervosa binge-eating/purging type; NA, not applicable.

2.2. Magnetic resonance imaging acquisition

MR images were obtained with a whole-body 3-Tesla MR system (Gyroscan Intera; Philips Medical Systems, Best, The Netherlands) with an eight-channel phased-array head coil. DTI data were obtained using a single-shot spin-echo echo-planar sequence with 32 Stejskal–Tanner motion-probing gradient orientations. The DTI protocol was as follows: $b = 1000$ s/mm^2, 60 axial slices with 2.0 mm thickness without gap, TR = 7181 ms, TE = 58 ms, flip angle = 90°, 112 × 110 matrix, and field of view (FOV) = 224 × 224 × 120 mm. One $b = 0$ image was obtained for each subject. Therefore, each subject had 33 volumes. A board-certified radiologist (H.I.) reviewed all scans and found no gross abnormalities in any of the subjects.

2.3. Image processing

All the DTI data processing was performed using the FMRIB Software Library (FSL version 4.1.4; http://www.fmrib.ox.ac.jk/fsl). All DTI source data were corrected for eddy current and head motions by registering each data point to the first $b = 0$ image with affine transformation. A voxel-wise statistical analysis of the FA data was performed using TBSS ver 1.2. First, FA images were created by fitting a tensor model to the raw diffusion data using FMRIB's Diffusion Toolbox (FDT). All subjects' FA data were aligned into a 1 mm^3 Montréal Neurological Institute (MNI) 152 space using the FMRIB's nonlinear image registration tool (FNIRT) by using a b-spline representation of the registration warp field. Next, the mean FA image was created from the all normalized FA images and thinned to create the mean FA skeleton, which represents the centers of all tracts common for the group. The skeleton was thresholded at FA ≥ 0.20 to ensure that gray matter regions were excluded from the analyses. Each subject's normalized FA and MD data were projected onto the skeleton, and the resulting skeletonized data were fed into voxel-wise cross-subject statistics.

2.4. Statistical analysis

For the analysis of demographic data, we used the Statistical Package for Social Sciences (SPSS for Windows, version 17.0, SPSS, Chicago, IL, USA). For the group comparison, Student's *t*-test was applied to the BMI, EDI and BDI. The Mann–Whitney *U* test was applied for the group comparison of age because it did not conform to normal distribution. Handedness and subgroup were statistically tested with the chi-square test.

Statistical analysis of imaging data was conducted on skeletonized FA and MD data. Voxel-wise permutation-based nonparametric inference was performed using FSL Randomize version 2.1 (Nichols and Holmes, 2002). For group comparisons, an analysis of covariance