

Articles

Structural brain changes in severe and enduring anorexia nervosa: A multimodal magnetic resonance imaging study of gray matter volume, cortical thickness, and white matter integrity

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ABSTRACT

Whole-brain T1-weighted imaging and diffusion tensor imaging was performed in 35 adult women with anorexia nervosa (AN) and 35 healthy controls. We conducted voxel-based group comparisons for gray matter volume (GMV), cortical thickness (CT), and fractional anisotropy (FA) values, using age and total intracranial volume as nuisance covariates. We then conducted the same group comparisons for these three measures, but this time also controlled for the following global pathological measures: total GMV, mean CT across the whole brain, and mean FA across the entire white matter skeleton. Compared with the healthy controls, AN patients had lower GMV and CT in widespread cortical regions, and smaller FA values in widespread white matter regions. After controlling for global parameters, almost all of the differences between the two groups disappeared, except for higher CT in the medial orbital gyrus and parietal operculum in the AN group. Structural brain changes in AN are likely to be composed of both global and region-specific changes. The former changes are likely to have a dominant impact, while the latter changes might in part explain the disease-specific pathophysiology of AN.

1. Introduction

Anorexia nervosa (AN) is an eating disorder characterized by persistent caloric restriction, fear and avoidance of weight gain, and distortion of body image (American Psychiatric Association, 2013). It is a severe psychiatric disease that frequently occurs among young women (Smink et al., 2012) and is associated with various physical complications (Westmoreland et al., 2016) and high mortality (Arcelus et al., 2011). However, the biological basis of its pathophysiology is unclear.

Brain magnetic resonance imaging (MRI) studies have been conducted using various imaging modalities to increase the biological understanding of AN. Compared with healthy controls (HCs), most of the reported brain structural changes observed in participants with AN were “decreased” changes. Regarding whole gray matter (GM)/white matter (WM), a meta-analysis demonstrated a 5.6% reduction in GM volume (GMV) and a 3.8% reduction in WM volume (WMV) (Seitz et al., 2014). As for regional changes, a meta-analysis reported GMV decreases in somatosensory areas including the inferior parietal lobule as well as

areas related to the reward system including the lentiform nucleus and caudate (Titova et al., 2013). However, results related to the specific areas of volume reduction have been inconsistent, and widespread local abnormalities have been reported (Van Den Eynde et al., 2012).

Since the mid-2010s, cortical thickness (CT) has also been studied. Several studies have reported cortical thinning in the superior/middle frontal gyrus, superior/inferior parietal gyrus, and precuneus (Bär et al., 2015; Bernardoni et al., 2016; Fuglset et al., 2016; Nickel et al., 2018).

Additionally, studies using diffusion tensor imaging (DTI) have been conducted to examine WM changes. A meta-analysis of DTI studies reported that the fractional anisotropy (FA), an indicator of WM integrity, was decreased in the fornix, cingulum, fronto-occipital tract (Monzon et al., 2016), thalamo-cortical tract, and occipital-parietal-temporal-frontal tract (Gaudio et al., 2019). In addition, a systematic review showed decreased FA in the left corona radiata and thalamus (Meneguzzo et al., 2019). Although the number of studies is increasing, results have been inconsistent within imaging modalities, and no convincing interpretations regarding the relationship between

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regional brain changes and AN pathophysiology have been presented. The widespread and inconsistent decreases reported in previous studies could be attributed not only to disease traits, but also to non-specific factors including malnutrition, dehydration, endocrine hormone changes, and neuronal apoptosis (Kaye et al., 2009; King et al., 2018).

Despite significant malnutrition, which drives brain structure to exhibit regional decreases, a few reports have suggested “increased” structural changes in AN. Increased GMVs have been reported in the orbitofrontal cortex (OFC), insula (Frank et al., 2013a, 2013b), and temporal cortex (Frank et al., 2013b), and increased CT has been demonstrated in the medial OFC and insula (Lavagnino et al., 2018).

Regarding the WM, studies have reported increased FA values in the anterior thalamic radiations; anterior superior longitudinal fasciculus (Travis et al., 2015); bilateral frontal, parietal, and temporal areas (Vogel et al., 2016); and the connection between the OFC and nucleus accumbens (Cha et al., 2016). Greater structural connectivity has also been reported in pathways between the insula, OFC, and ventral striatum (Frank et al., 2016).

However, because of the global brain atrophy that occurs in AN, these possible “increased” changes might have been underestimated in previous studies. To address this issue, several studies investigating GMV have applied total GMV corrections (Brooks et al., 2011; Fonville et al., 2014; Fujisawa et al., 2015; Gaudio et al., 2011). However, a similar approach has rarely been attempted for CT, and has not yet been attempted for WM. Because global brain structural changes are reportedly more prominent in participants with a lower body mass index (BMI) (Swayze et al., 2003), the consideration of global changes is critical when analyzing participants with severe and enduring AN.

We aimed to investigate these complex structural brain changes, including both the global changes associated with malnutrition and the specific regional changes possibly associated with disease-specific AN pathophysiology. To do this, we performed not only a standard group comparison, but also a group comparison after controlling for global changes—namely, whole GMV, mean CT across the whole brain, and mean FA across the entire WM skeleton.

2. Methods

2.1. Participants and clinical assessments

Thirty-five participants with AN and 35 age-matched HCs were included in this study; however, data for the DTI study were obtained from 32 participants with AN and 23 HCs because of mechanical setup problems. All participants were right-handed women, aged 20–55 years. The participants with AN were recruited from Kyoto University Hospital, and HCs were recruited by public advertisement. Participants with AN fulfilled the Diagnostic and Statistical Manual, 5th edition (DSM-5) criteria. Because the structured clinical interview for the DSM-5 does not have a Japanese translation, the clinical history of AN was confirmed using the Japanese version of the Structured Clinical Interview (SCID) for DSM-IV-TR Axis I Disorders (Takahashi et al., 2010). Clinical evaluation was performed using the Japanese version of the Eating Disorder Examination Questionnaire 6.0 (EDE-Q) (Fairburn, 2008; Nakai et al., 2015), and body weight was measured when MRI scans were performed. From the SCID overview and clinical records, none of the participants with AN were found to have comorbid psychiatric diagnoses. However, 12 participants with AN were prescribed psychotropic medications (i.e., antipsychotics, antidepressants, anxiolytics, or antiepileptics) to ameliorate mental symptoms associated with AN, such as anxiety, depression, and impulsivity. All participants with AN were outpatients and were not receiving any intensive nutritional therapy. The exclusion criteria for HCs were a history of any mental disorders as defined in the DSM-5, a history of neurological problems, and other medical illnesses affecting the central nervous system. This study was approved by the Committee on Medical Ethics of Kyoto University and was conducted in accordance with the Code of Ethics of the World Medical Association.

Written informed consent was obtained from each participant after offering a complete description of the present study.

2.2. MRI acquisition

All MRI data were acquired using a 3T whole-body scanner equipped with a 32-channel phased-array head coil (MAGNETOM Tim Trio, Siemens, Erlangen, Germany). The scanning parameters of the T1-weighted three-dimensional magnetization-prepared rapid gradient-echo (3D-MPRAGE) sequence were as follows: repetition time (TR) = 2000 ms; echo time (TE) = 3.4 ms; field of view (FOV) = 225 × 240 mm; matrix = 240 × 256; resolution = 0.9375 × 0.9375 × 1.0 mm; and 208 total axial sections without intersection gaps. The DTI scanning parameters were as follows: TR = 5640 ms; TE = 106 ms; FOV = 192 × 192 mm; 70 continuous axial slices with 2.0 mm thickness, 64 non-collinear volumes with $b = 1500 \text{ s/mm}^2$, and a volume with $b = 0 \text{ images}$, with a field map.

2.3. MRI data processing

2.3.1. Voxel-based morphometry (VBM)

T1-weighted images were preprocessed with CAT12 (Computational Anatomy Toolbox, <http://dbm.neuro.uni-jena.de/cat/>) using MATLAB R2014a. All images were segmented into GM, WM, and cerebrospinal fluid (CSF) and spatially normalized to the same stereotaxic space using the diffeomorphic anatomical registration through the exponentiated lie algebra (DARTEL) algorithm (Ashburner, 2007). Voxel values of the segmented and normalized GM images were modulated using Jacobian determinants obtained from nonlinear normalization steps. These preprocessing steps were performed using default parameters, except for the selection of the East Asian brain template in affine registration, which allowed for more suitable alignment considering the participant population of this study. The resultant GM images were smoothed using a Gaussian kernel of 8 mm full width at half-maximum, on which all analyses were performed.

2.3.2. Surface-based morphometry (CT)

For the surface-based morphometry analysis, T1-weighted images were preprocessed with CAT12 using MATLAB2014a. All images were segmented using surface and thickness estimations in the writing options. The images were smoothed using 15 mm kernels on which all analyses were performed.

2.3.3. Tract-based spatial statistics (TBSS)

All DTI data processing was performed using the FMRIB Software Library ver. 5.0.8 (<https://fsl.fmrib.ox.ac.uk/fsl>). All source data were corrected for eddy current distortion and head motion by registering the data to the first $b = 0$ image with affine transformation. TBSS version 1.2 was used for subsequent voxel-wise statistical analysis. FA maps were created for each participant using the FMRIB Diffusion Toolbox program. These images were aligned to standard space (FMRIB58_FA_1 mm) using the nonlinear image registration tool. The whole-brain WM skeleton image, which represents the center lines of fiber tracts common to all participants, was then created. The minimum threshold of the skeleton was set to 0.2 to include the major WM tracts. Each participant's normalized FA data were projected onto the skeleton, and all analyses were performed on the resulting skeletonized data.

2.4. Statistical analyses

2.4.1. Demographic and clinical characteristics

Differences in demographic and clinical characteristics between participants with AN and HCs were assessed using the Statistical Package for Social Sciences, version 22.0 (SPSS, Inc., Chicago, IL, USA). Age, BMI, years of education, and EDE-Q scores were compared between the two groups using the Student's *t*-test. For the EDE-Q scores, Bonferroni

correction was applied to correct for multiple comparisons. Effect sizes (Cohen's *d*) were also calculated.

2.4.2. Global brain measures

The GMV, WMV, CSF volume, mean CT across the whole brain (which is calculated within the software of CAT12 as “mean thickness value”), and mean FA values across the entire TBSS skeleton were obtained. In addition, the total intracranial volume (TIV) was calculated as the sum of the GMV, WMV, and CSF values. For the GMV, WMV, and CSF, analyses of covariance (ANCOVA) were conducted using TIV as a covariate, and Bonferroni correction was applied to correct for multiple comparisons. Group differences in the other global measures were assessed using the Student's *t*-test. Effect sizes were also calculated. For participants with AN, the group differences between medicated ($n = 23$ [$n = 21$ in DTI study]) and non-medicated ($n = 12$ [$n = 11$ in DTI study]) participants were also assessed.

2.4.3. VBM

Regional GMV differences between participants with AN and HCs were examined using the two-sample *t*-test in CAT12 VBM. In the first analysis, we compared the groups with age and TIV as nuisance covariates. In the second analysis, we added total GMV as an additional nuisance covariate to examine regional GMV changes that cannot be explained by global changes. The statistical threshold was set at $p < 0.05$, corrected for multiple comparisons by family-wise error (FWE) at the cluster level.

2.4.4. Surface-based morphometry

Regional CT differences between participants with AN and HCs were examined using the two-sample *t*-test in CAT12 surface-based morphometry. In the first analysis, we compared the groups with age as the nuisance covariate. In the second analysis, we added mean CT across the whole brain as an additional nuisance covariate to examine regional changes in CT that cannot be explained by global changes. The statistical threshold was set at $p < 0.05$, corrected for multiple comparisons by FWE at the cluster level.

2.4.5. TBSS

For group comparisons of FA values, voxel-wise permutation-based (10,000 permutations) nonparametric inference was performed using the FSL randomize function. In the first analysis, we compared the groups using an ANCOVA design in the general linear model framework, with age as the nuisance covariate. In the second analysis, we added the mean FA values across the entire WM skeleton as an additional nuisance covariate to examine regional changes in FA that cannot be explained by global FA changes. The statistical threshold was set at $p < 0.05$, corrected for multiple comparisons by threshold-free cluster enhancement (TFCE) (Smith and Nichols, 2009).

3. Results

3.1. Demographic and clinical characteristics

Table 1 shows the demographic and clinical characteristics. The AN and HC groups were not significantly different in age or years of education. The BMI was significantly lower in the AN group, and EDE-Q scores were significantly higher in the AN group than in the HC group. In the DTI study, comparisons were performed with 32 participants with AN and 23 HCs. There was no significant difference in age between the two groups (Supplementary Table 1).

3.2. Global brain measures

Table 2 shows the mean GM, WM, and CSF volumes in the whole brain. The mean CT and the mean FA value in the whole brain are also shown. Compared with the control group, the AN group showed a significant decrease in GMV (5.9%) and CT (3.4%). The mean WMV was 3.1% lower in the AN group, but no significant difference was found. The FA value was also significantly lower in the AN group. There were no significant differences in these global measures between the medicated and non-medicated AN participants (Supplementary Table 2). As *post-hoc* analyses, we conducted partial correlation analyses between the global measures and BMI, with age as the control variable. In the AN group, TIV-corrected GMV, TIV-corrected WMV, and CT had a positive correlation with BMI (TIV-corrected GMV: $r = 0.73$, $p < 0.001$; TIV-corrected WMV: $r = 0.64$, $p < 0.001$; CT: $r = 0.57$, $p < 0.001$), whereas TIV-corrected CSF had a negative correlation with BMI ($r = -0.78$, $p < 0.001$). For TIV-corrected GMV, TIV-corrected WMV, and TIV-corrected CSF, Bonferroni correction was applied to correct for multiple comparisons. In contrast, there was no significant correlation between the FA value and BMI ($r = 0.29$, $p = 0.12$) in the AN group. In the HC group, none of the global measures were significantly correlated with BMI.

3.3. VBM

In the first analysis, which applied age and TIV as nuisance covariates, participants with AN had significant GMV decreases in widespread regions, including the right precuneus, left angular gyrus, right cerebellum exterior, right middle frontal gyrus, left superior frontal gyrus, and bilateral middle temporal gyrus (Fig. 1, Table 3). No GMV increases were identified in AN.

In the second analysis, which applied age, TIV, and total GMV as nuisance covariates, there were no increased/decreased regions at the initial statistical threshold ($p < 0.05$, FWE-corrected at cluster level).

3.4. Surface-based morphometry

In the first analysis, which applied age as a nuisance covariate,

Table 1
Demographic and clinical characteristics.

	Anorexia nervosa $n = 35$ mean (SD)	Healthy controls $n = 35$ mean (SD)	Statistics	<i>p</i>	Cohen's <i>d</i>
Age (years)	36.3 (10.0)	36.0 (9.6)	$t(68) = 0.15$	0.884	0.04
BMI (kg/m ²)	14.2 (2.5)	21.0 (2.9)	$t(68) = 10.49$	< 0.001	2.51
Education (years)	14.4 (2.0)	15.3 (1.9)	$t(68) = 1.97$	0.053	0.47
Onset age (years)	20.7 (8.5)	–			
Illness duration (years)	15.7 (9.0)	–			
EDE-Q restraint	2.26 (1.96)	0.55 (0.81)	$t(45) = 4.79$	< 0.001*	1.14
EDE-Q eating concern	2.40 (1.88)	0.19 (0.40)	$t(37) = 6.79$	< 0.001*	1.62
EDE-Q shape concern	3.18 (1.77)	1.14 (1.05)	$t(55) = 5.86$	< 0.001*	1.4
EDE-Q weight concern	2.85 (1.81)	0.95 (0.98)	$t(52) = 5.46$	< 0.001*	1.31
EDE-Q global score	2.67 (1.70)	0.71 (0.71)	$t(46) = 6.31$	< 0.001*	1.51

BMI: body mass index, EDE-Q: global score of the Eating Disorder Examination Questionnaire 6.0; SD: standard deviation.

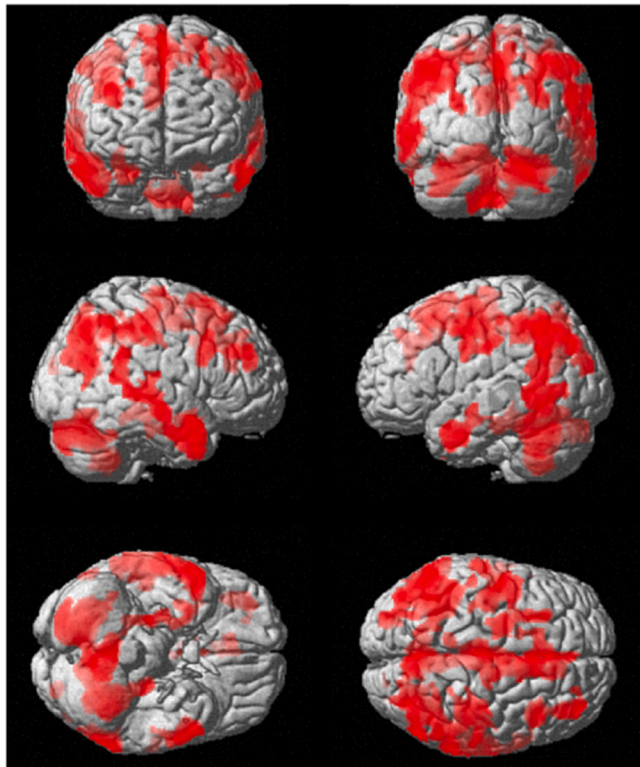
* $p < 0.05/5$ (Student's *t*-test, followed by Bonferroni correction).

Table 2

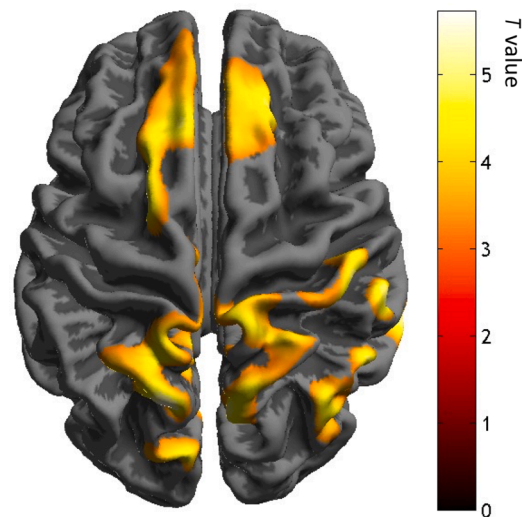
Whole brain tissue volumes, tissue volume ratios, cortical thickness, and FA values.

	Anorexia nervosa mean	SD	Healthy controls mean	SD		Statistics <i>p</i>	effect size
Gray matter (mL)	561.21	47.97	595.82	35.30	$F(1, 67) = 26.5$	$< 0.001^*$	$\eta_p^2 = 0.28$
White matter (mL)	462.94	41.76	477.90	36.89	$F(1, 67) = 8.4$	0.05	$\eta_p^2 = 0.11$
Cerebrospinal fluid (mL)	311.47	62.82	251.76	46.78	$F(1, 67) = 25.9$	$< 0.001^*$	$\eta_p^2 = 0.28$
Intracranial volume (mL)	1335.62	95.78	1325.48	87.51	$t(68) = 0.55$	0.59	$d = 0.11$
Cortical thickness (mm)	2.58	0.11	2.67	0.08	$t(68) = 3.62$	< 0.001	$d = 0.86$
FA value (whole brain)	0.42	0.03	0.45	0.02	$t(53) = 4.46$	< 0.001	$d = 1.15$

FA: fractional anisotropy, SD: standard deviation.

* $p < 0.05/3$ (Student's *t*-test, followed by Bonferroni correction).**Fig. 1.** Areas of gray matter volume reductions in participants with anorexia nervosa compared with healthy controls. The results are displayed on the brain surface (corrected for age and total intracranial volume; $p < 0.05$, corrected for multiple comparisons by family-wise error at the cluster level).

significant CT decreases were identified in widespread cortical regions: the bilateral parietal lobule, bilateral superior frontal gyrus, bilateral precuneus, right middle temporal gyrus, right postcentral gyrus, right

**Fig. 2.** Areas of cortical thickness reductions in participants with anorexia nervosa compared with healthy controls. The results are displayed on the brain surface (corrected by age; $p < 0.05$, corrected for multiple comparisons by family-wise error at the cluster level).

supramarginal gyrus, right angular gyrus, left cuneus, and left calcarine cortex (Fig. 2, Table 4). No CT increases were found in the AN group.

In the second analysis, which applied age and mean CT of the whole brain as nuisance covariates, there were no significant CT decreases, but a significant CT increase was identified in the medial orbital gyrus and parietal operculum ($p < 0.05$, FWE-corrected at cluster level) (Fig. 3, Table 5).

3.5. TBSS

In the first analysis, which applied age as the nuisance covariate, participants with AN had a significant decrease in FA in widespread WM

Table 3

Regions of gray matter volume differences between AN and HC (corrected by age and total intracranial volume).

Contrast	Region	<i>p</i>	Cluster size	Peak level MNI coordinates			<i>T</i> -value
				<i>x</i>	<i>y</i>	<i>z</i>	
HC>AN	Rt. precuneus	< 0.001	16,297	3	-69	46	6.31
	Lt. angular gyrus	< 0.001	7832	-38	-54	51	6.06
	Rt. cerebellum exterior	< 0.001	11,278	21	-69	-26	5.77
	Rt. middle frontal gyrus	0.001	1714	44	18	32	5.69
	Lt. superior frontal gyrus	< 0.001	4090	-26	-6	62	5.47
	Rt. middle temporal gyrus	< 0.001	4953	64	-16	-8	5.31
	Rt. cerebral white matter	0.005	1262	24	-26	-15	5.03
	Lt. middle temporal gyrus	0.007	1153	-52	0	-27	4.59
	No regions						
AN>HC							

AN: anorexia nervosa patients, HC: healthy controls, Lt.: left, MNI: Montreal Neurological Institute, Rt.: right.

* $p < 0.05$ family-wise error-corrected at cluster level.

Table 4
Regions of cortical thickness differences between AN and HC (corrected by age).

Contrast	Region	p	Cluster size	Peak level MNI coordinates			T-value
				x	y	z	
HC>AN	Lt. superior parietal lobule	< 0.001	1050	−16	−68	57	5.74
	Rt. middle temporal gyrus	0.017	158	66	−39	−4	4.98
	Rt. postcentral gyrus	< 0.001	347	49	−24	57	4.96
	Rt. precuneus	< 0.001	1121	6	−69	49	4.95
	Rt. supramarginal gyrus	0.013	166	60	−28	44	4.92
	Lt. superior frontal gyrus	< 0.001	665	−22	8	61	4.86
	Rt. angular gyrus	< 0.001	403	55	−52	40	4.8
	Rt. superior frontal gyrus	< 0.001	396	20	34	46	4.8
	Lt. precuneus	0.001	257	−7	−50	53	4.64
	Lt. cuneus	0.037	131	−8	−86	35	4.45
	Lt. calcarine cortex	0.004	209	−7	−68	10	4.1
	Rt. fusiform gyrus	0.029	139	34	−49	−8	3.69
	AN>HC						
	No regions						

AN: anorexia nervosa patients, HC: healthy controls, Lt.: left, MNI: Montreal Neurological Institute, Rt.: right.

* $p < 0.05$ family-wise error-corrected at cluster level.

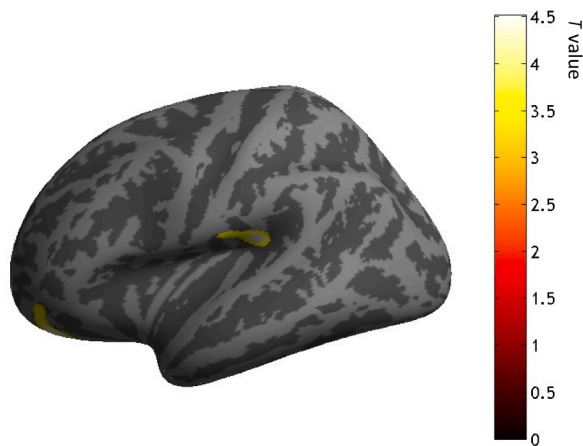


Fig. 3. Areas of cortical thickness (CT) increases in participants with anorexia nervosa compared with healthy controls (corrected by age and mean CT across the whole brain; $p < 0.05$, corrected for multiple comparisons by family-wise error at the cluster level). Increased CT was detected in the medial orbital gyrus and the parietal operculum.

Table 5
Regions of cortical thickness differences between AN and HC after controlling for global changes (corrected by age and mean cortical thickness across the whole brain).

Contrast	Region	<i>p</i>	Cluster size	Peak level			<i>T</i> -value
				MNI coordinates			
				<i>x</i>	<i>y</i>	<i>z</i>	
HC>AN	No regions						
AN>HC	Lt. medial orbital gyrus	0.032	117	−18	42	−18	4.43
	Lt. parietal operculum	0.012	144	−42	−33	17	4.39

AN: anorexia nervosa patients, HC: healthy controls, Lt.: left, MNI: Montreal Neurological Institute.

* $p < 0.05$ family-wise error-corrected at cluster level.

tracts (Fig. 4), encompassing all 20 major WM tracts defined by the John Hopkins University WM atlas (Hua et al., 2008). No FA increases were found in any WM regions in these participants.

In the second analysis, which applied age and mean FA values of the whole brain as nuisance covariates, no increased/decreased regions were identified with the initial threshold ($p < 0.05$, corrected for

multiple comparisons by TFCE).

4. Discussion

This study investigated global and regional structural brain changes, including the GMV, CT, and WM integrity, in severe and enduring AN using multimodal MRI. Globally across the brain, GMV, CT, and FA values were decreased in participants with AN. In the first analyses, which were uncontrolled for global measures, lower GMV and CT were found in widespread cortical regions in AN. Lower GMV was also identified in the cerebellum in this group. Moreover, FA values were reduced in widespread WM regions. In contrast, no regions had increased GMV, CT, or FA in the AN group. In the second analyses, which controlled for global changes in each structural brain measure, most of the aforementioned decreases disappeared, and there was increased CT in the medial orbital gyrus and parietal operculum.

The first finding of the present study was that brain structural changes in AN were mainly decreases, as expected. In GMV, there were reductions in the parietal lobe, temporal lobe, cerebellum, and frontal lobe (except for the frontal pole and inferior frontal gyrus). For CT, reductions in participants with AN were identified in similar regions as for GMV, but in more restricted areas; namely, the parietal lobe, superior frontal gyrus, and occipital lobe. The parietal lobe and superior frontal gyrus were the only two areas with both GMV and CT reduction in the AN group. A previous meta-analysis reported GMV reductions in the frontal lobe, temporal lobe, parietal lobe, occipital lobe, and brainstem in AN (Titova et al., 2013). Cerebellar volumes have also been reported as reduced in this disease (Amianto et al., 2013; Boghi et al., 2011). Furthermore, a decrease in CT has been reported in widespread brain regions, including the paracentral lobule, precuneus, superior frontal lobule, and superior parietal lobule (Nickel et al., 2018). Thus, our results are generally consistent with previous studies. The present study also showed decreased FA values in all major tracts, with no specific localization. Findings of WM abnormalities in AN have been inconsistent among previous studies, although FA decreases in various WM tracts have been reported. In studies with sample sizes similar to or larger than that of the present study, FA values were significantly decreased in the callosal body in AN in one study (von Schwanenflug et al., 2019), and there were no FA differences between AN and HC in another study (Pfuhl et al., 2016). Our findings of decreased FA values in widespread WM regions in AN were inconsistent with these previous results. These inconsistencies might be caused by differences in participants' ages and illness durations: the mean age was 16.1 years in the study by Pfuhl et al. while in the study by von Schwanenflug et al. it was 15.9 years, and illness duration was 1.2 years. In contrast, the mean age of our participants was 36.6 years, and mean illness duration was 15.7 years. Low FA

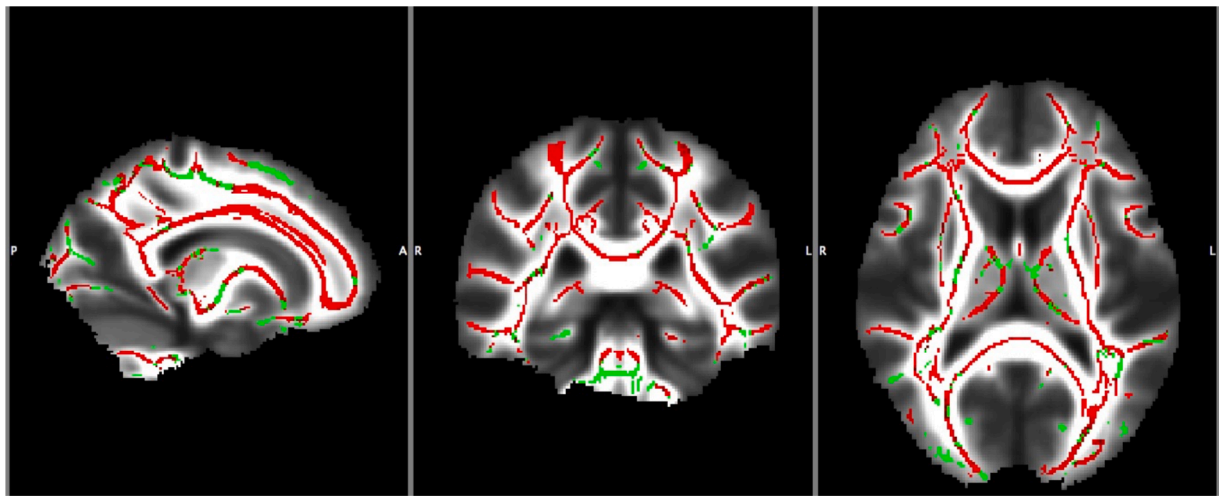


Fig. 4. Areas of fractional anisotropy (FA) reduction in participants with anorexia nervosa (AN) compared with healthy controls (corrected by age; $p < 0.05$, corrected for multiple comparisons by threshold-free cluster enhancement). The FA skeleton is shown in green, and the voxels where group differences were found are overlaid in red. Participants with AN exhibited widespread reductions in white matter tracts in the whole brain.

values are thought to reflect decreased axonal density and/or disrupted myelination (Jones et al., 2013). Considering the chronic nature of AN in our study's participants, the global reduction in FA might be explained by long-term malnutrition.

As for regional changes, after controlling for global pathological measures, increased CT of the left medial orbital gyrus and left parietal operculum was identified in AN in the present study. These were the only two regions that showed an increase in measured brain parameters using a conservative statistical threshold. Of the few reports of increased changes in AN, structural changes in the medial orbital cortex have been reported. Although our results differ in regard to left-right differences, higher CT in the right medial orbital cortex in current and recovered AN patients has been reported (Lavagnino et al., 2018). Moreover, increased GMV in the medial orbitofrontal cortex as well as the insula in AN patients has been reported (Frank et al., 2013a). Furthermore, a functional MRI study reported an abnormal response of the orbital frontal cortex during a taste reward task in AN patients (Frank et al., 2012). The orbital frontal cortex is considered to play a role in reward processing, decision making, and behavioral control. Therefore, the association between the pathophysiology of AN, such as the persistence of maladaptive eating behavior, and structural and functional changes in the orbital frontal cortex has been a primary focus of investigation (O'Hara et al., 2015). The parietal operculum has functional connectivity with the posterior insula (Limanowski et al., 2020), and both are considered important cortical regions for pain perception (Sawamoto et al., 2000). Galusca et al. reported increased serotonin receptor binding in several regions, including the parietal operculum, in lean and recovered restrictive AN patients (Galusca et al., 2008). To our knowledge, no other studies have specifically suggested a relationship between the parietal operculum and AN. This may be because no previous studies investigating CT have applied global measure corrections, and thus any possible disease-specific increases in CT have been masked. Alternatively, it may be because our study population consisted of participants with mostly severe and enduring AN, which is relatively unusual. Nevertheless, the possible involvement of the parietal operculum in AN pathophysiology should be further investigated.

Aside from the increased CT in the medial orbital gyrus and the parietal operculum, the between-group differences that were identified in the first set of analyses disappeared when global measures were entered as nuisance covariates in the second set of analyses. Several previous studies have also taken these global changes into account. Previous VBM studies with smaller sample sizes have conducted similar investigations using total GMV as a nuisance covariate, and reported

decreased volumes in the left cerebellum, bilateral parahippocampal gyrus, right anterior insula, left fusiform gyrus, and right posterior cingulate (Brooks et al., 2011); decreased volumes in the bilateral middle cingulate cortex, bilateral precuneus, bilateral inferior, and superior parietal lobules (Gaudio et al., 2011); and decreased volume in the bilateral inferior frontal gyrus (Fujisawa et al., 2015). However, in a study with a similar-sized sample to that of the present study, no local GMV reductions were identified in AN compared with HCs after controlling for differences in total GMV (Fonville et al., 2014). An increased volume has also been reported in the right dorsal prefrontal cortex after controlling for total GMV, but again the study had a smaller sample size (Brooks et al., 2011). We speculate that the differences between ours and previous studies might be caused by different sample sizes as well as different clinical characteristics; our patients mainly had severe and enduring AN. As for CT, a study that explored CT and gyrification patterns using graph theory tools adopted mean CT as a covariate, but reported no regional changes (Collantonio et al., 2019). For WM, we surveyed 10 cross-sectional studies in participants with AN that were discussed in a meta-analysis (Gaudio et al., 2019), but none of these studies controlled for mean FA values. Our results suggest that regional changes in previous studies might have been overestimated, and that global, rather than regional, changes might have a greater impact on structural changes in AN.

Although much attention has been paid to regional structural changes in the past, it is also necessary to consider global changes. The first issue that requires consideration concerns the factors that might influence global structural brain changes in AN. In the present study, the global measures of TIV-corrected GMV, TIV-corrected WMV, and CT were positively correlated with BMI in the AN group. Previous studies have also reported a positive correlation between BMI and total GMV (Nickel et al., 2018; Swayze et al., 2003), as well as BMI and total WMV (Swayze et al., 2003). However, Joos et al. reported no correlations between these factors (Joos et al., 2010). Thus, to date, findings regarding the relationship between BMI and tissue volumes have been inconsistent. As for CT and FA, the correlations between regional values and BMI have often been examined, but the correlations between these global values and BMI have not yet been sufficiently investigated. Studies in weight-recovered AN (wr-AN) patients may help address this issue. In adult wr-AN patients, GMV change has been shown to be reversible (Brodrick et al., 2021; Kaufmann et al., 2020; Nickel et al., 2018). Moreover, CT changes have been shown to be reversible for the most part, although decreases in the superior frontal cortex can persist (Kaufmann et al., 2020). Regarding WM integrity, reports include no FA

difference between wr-AN and HC groups (Bang et al., 2018.; Yau et al., 2013.) as well as reduced FA in the anterior corona radiata, external capsule, cerebellum (Shott et al., 2016), and corpus callosum (Nickel et al., 2019) in the wr-AN group. These results suggest the reversibility of most brain structures after weight recovery, although structural changes may persist in some restricted regions. In addition to BMI, other factors such as age of onset, duration of disease, and minimum lifetime weight are also thought to be influential factors for global changes, but further studies are required. The second issue that requires consideration concerns the magnitude of global brain structural changes. In the present study, patients with severe AN, with a mean BMI of 14.2, participated. In future studies, it will be necessary to explore the magnitude of global brain structural changes in patients with mild or moderate AN.

The major limitation of our study involves the possible effects of medication and comorbid psychiatric conditions. We confirmed that there was no difference in global tissue volume between the medication and non-medication groups; however, we were unable to assess the possible effects of each particular medication. As for possible psychiatric comorbidities, we screened for these using clinical records and SCID overviews, but this may not have been sufficient to exclude participants with psychiatric comorbidities. Finally, our study participants were relatively old (mean age 36.3), and had long disease durations (mean 15.7 years) and low BMIs (mean 14.2). Thus, the neuroimaging findings in our study might be specific to this particular patient population, and may not be generalizable to younger patients with milder AN severity.

In conclusion, our multimodal neuroimaging study revealed widespread structural changes encompassing both GM and WM in AN. However, most of these changes disappeared after controlling for global parameters, except for the increased CT of the left medial orbital gyrus and the left parietal operculum. Structural brain changes in AN are likely to be composed of both global and region-specific changes. The former changes are likely to have a dominant impact, while the latter changes might in part explain the disease-specific pathophysiology of AN.

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CRediT authorship contribution statement

Ryo Mishima: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Masanori Isobe:** Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Writing – review & editing. **Tomomi Noda:** Data curation, Investigation, Writing – review & editing. **Keima Tose:** Data curation, Investigation, Writing – review & editing. **Michiko Kawabata:** Data curation, Investigation, Writing – review & editing. **Shun'ichi Noma:** Conceptualization, Supervision, Writing – review & editing. **Toshiya Murai:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors have no conflict to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.psychres.2021.111393](https://doi.org/10.1016/j.psychres.2021.111393).

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