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Comprehensive elucidation of resting-state functional connectivity in anorexia nervosa by a multicenter cross-sectional study

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Abstract

Background. Previous research on the changes in resting-state functional connectivity (rsFC) in anorexia nervosa (AN) has been limited by an insufficient sample size, which reduced the reliability of the results and made it difficult to set the whole brain as regions of interest (ROIs).

Methods. We analyzed functional magnetic resonance imaging data from 114 female AN patients and 135 healthy controls (HC) and obtained self-reported psychological scales, including eating disorder examination questionnaire 6.0. One hundred sixty-four cortical, subcortical, cerebellar, and network parcellation regions were considered as ROIs. We calculated the ROI-to-ROI rsFCs and performed group comparisons.

Results. Compared to HC, AN patients showed 12 stronger rsFCs mainly in regions containing dorsolateral prefrontal cortex (DLPFC), and 33 weaker rsFCs primarily in regions containing cerebellum, within temporal lobe, between posterior fusiform cortex and lateral part of visual network, and between anterior cingulate cortex (ACC) and thalamus ($p < 0.01$, false discovery rate [FDR] correction). Comparisons between AN subtypes showed that there were stronger rsFCs between right lingual gyrus and right supracalcarine cortex and between left temporal occipital fusiform cortex and medial part of visual network in the restricting type compared to the binge/purging type ($p < 0.01$, FDR correction).

Conclusion. Stronger rsFCs in regions containing mainly DLPFC, and weaker rsFCs in regions containing primarily cerebellum, within temporal lobe, between posterior fusiform cortex and lateral part of visual network, and between ACC and thalamus, may represent categorical diagnostic markers discriminating AN patients from HC.

Original Article

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Introduction

Anorexia nervosa (AN) is a psychiatric disorder characterized by food intake restriction leading to significantly lower body weight, intense fear of weight gain, and distorted body image (American Psychiatric Association, 2013). The standard mortality rate of AN is as high as 5.86, which is the highest rate among mental disorders (Arcelus, Mitchell, Wales, & Nielsen, 2011; Harris & Barraclough, 1998). The rate of patients fully recovering from AN is only 46%, and the rate of chronicity is ~20%, indicating that the long-term prognosis of AN can be poor (Steinhausen, 2009). Although the etiology of AN is unknown, neurobiological factors for the development of AN are considered because AN patients have common personality traits, such as perfectionism, inflexibility, and obsession (Kaye, Wierenga, Bailer, Simmons, & Bischoff-Grethe, 2013; Zipfel, Giel, Bulik, Hay, & Schmidt, 2015).

Many studies investigating resting-state functional connectivity (rsFC) using functional magnetic resonance imaging (fMRI) have been conducted since the 2010s to elucidate changes in brain function occurring in AN; connectomes based on rsFCs are stable and act as a 'fingerprint' that can accurately identify subjects from a large group. Therefore, rsFCs represent a promising predictor of cognitive behavior (Finn et al., 2015; Horien, Shen, Scheinost, & Constable, 2019). Brain regions and networks identified as having altered rsFCs in two or more previous studies of AN include insula (Amianto et al., 2013; Boehm et al., 2014; Ehrlich et al., 2015; Gaudio, Olivo, Beomonte Zobel, & Schiöth, 2018; Geisler et al., 2016; Kullmann et al., 2014; Lord et al., 2016), anterior cingulate cortex (ACC) (Gaudio et al., 2018; Lee et al., 2014), thalamus (Biezonski, Cha, Steinglass, & Posner, 2016; Ehrlich et al., 2015; Geisler et al., 2016; Lord et al., 2016), inferior frontal gyrus (Collantoni et al., 2016; Cowdrey, Filippini, Park, Smith, & McCabe, 2014; Kullmann et al., 2014), parietal cortex (Amianto et al., 2013; Favaro et al., 2012; Olivo et al., 2018), cerebellum (Amianto et al., 2013; Gaudio et al., 2018; Olivo et al., 2018), precuneus (Cowdrey et al., 2014; Lee et al., 2014), dorsolateral prefrontal cortex (DLPFC) (Biezonski et al., 2016; Cowdrey et al., 2014), visual network (Favaro et al., 2012; Phillipou et al., 2016; Scaife, Godier, Filippini, Harmer, & Park, 2017), and default mode network (DMN) (Boehm et al., 2014; Cowdrey et al., 2014).

However, the sample sizes of previous studies were small, ranging from 12 to 36 participants per group (Alfano, Mele, Cotugno, & Longarzo, 2020; Gaudio, Wiemerslage, Brooks, & Schiöth, 2016). This limited the reliability of the results, leading to a major source of inconsistency in study results among previous studies (Marek et al., 2022). For example, stronger rsFCs were found in the DMN in certain studies (Boehm et al., 2014; Cowdrey et al., 2014), whereas in other studies, no differences were found in the DMN between AN patients and healthy controls (HC) (Phillipou et al., 2016). The lack of sample size also prevents extending the region of interest (ROI) to the whole brain in studies adopting seed-based analysis, which has the advantage of a clarity of meaning when quantifying functional connectivity compared to independent component analysis (ICA) or graph analysis. This is because the greater the number of ROIs used, the greater the number of statistical tests, the stricter the significance level, and the more difficult it is to obtain significant results with small sample size. No meta-analysis exists of studies examining rsFC changes in AN partially due to the insufficient sample size; only meta-analyses of positron emission tomography (PET), single photon emission computed tomography (SPECT), arterial spin labeling (ASL), amplitude of low-frequency fluctuation (ALFF), and fractional ALFF (fALFF) have been reported, showing bilateral anterior to middle cingulate cortex hypofunction and right parahippocampal gyrus hyperfunction (Su et al., 2021). Furthermore, no previous studies have identified differences in rsFCs between AN subtypes (AN restricting type: AN-R and AN binge/purge type: AN-BP), which may also be partly due to the lack of AN participants. Due to these problems stemming from insufficient sample sizes, there is no unified view regarding the brain dysfunctions that may underlie the neurobiology of AN, and many aspects have remained unexplored.

Therefore, in this study, we secured a sample size of more than 100 subjects in each AN and HC group via a multicenter study, and we set whole brain regions as ROIs. The objective of this study was to comprehensively elucidate the resting-state rsFC changes occurring in AN with a high degree of reliability.

Methods

Participants

This study was conducted at five Japanese hospitals: (a) Chiba University Hospital; (b) Hospital of the University of Occupational and Environmental Health (UOEH); (c) Tohoku University Hospital; (d) Kyushu University Hospital; and (e) Kyoto University Hospital. AN patients were recruited from outpatients of these hospitals, as well as from those who applied through the participant recruitment websites and recruitment notices of these hospitals. HC participants were recruited from those who had applied via the participant recruitment websites and recruitment notices in each hospital. Participants for sites (a) through (d) were recruited between July 2015 and March 2021 as part of A Multi-Site Study on the Brain of Eating Disorder Patients, and participants for site (e) were recruited between March 2014 and February 2019. An appropriate sample size for a single group in fMRI studies is reported to be 21 when the type I error rate α is set at 0.002, and twice that number, 42, when multiple comparisons are made (Desmond & Glover, 2002)., Therefore, we tried to secure a minimum of 50 participants in each group, assuming a dropout rate of about 20%. The number of participants per site is shown in online Supplementary Table S1. Information on race was not collected, but almost all participants were Japanese females. Eligibility criteria for the study required that AN participants met the Diagnostic and Statistical Manual, 5th Edition (DSM-5) diagnostic criteria, and HC participants were required to be at least 12 years of age. Diagnosis and AN subtypes were determined by a structured interview based on DSM-5 conducted by psychosomatic physicians or psychiatrists. HC participants had no history of mental disorders and were confirmed to be free of current mental disorders by psychosomatic physicians or psychiatrists. Any subjects with claustrophobia, head trauma, neurological disorders, or substance abuse were excluded from the study. AN participants who had imminent thoughts of death or with a medical history of psychiatric disorders other than depression, bipolar disorder, obsessive-compulsive disorder, anxiety, and personality disorder were also excluded. Due to their rarity, we could recruit only two male AN participants. Therefore, the two male AN patients and 36 male HC were excluded from the study, and only women were included in the analysis. The final number of participants was 114 in the AN group and 135 in the HC group. In the AN group, 61 patients had AN-R and 53 had AN-BP.

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Physical and psychological assessment

Participants' height and weight were measured on the same day as their MRI scans. Participants were also evaluated by Japanese adult reading test: Japanese version of National Adult Reading Test (JART), Stait-Trait Anxiety Inventory (STAI), Beck Depression Inventory-II (BDI-II), and Eating Disorder Examination Questionnaire (EDE-Q) within two weeks before and after MRI. EDE-Q consists of four subscales (restraint, eating concern, shape concern, and weight concern), and global score is the average of the subscales' scores. These self-reported psychological scales were collected to characterize the participants and perform a correlation analysis between these scales and rsFCs that showed group differences.

Dataset

The dataset used for the analysis was the secondary release (pilot version), but studies analyzing the primary release dataset will be published. The secondary release dataset (pilot version) includes the following data not included in the primary release dataset: (1) data on duration of illness, psychotropic medication, JART, BDI-II, and STAI for all participants; and (2) data on MRI, JART, EDE-Q, BDI-II, STAI, age, height and weight of 12 AN patients and 15 HC subjects collected at Chiba University.

MRI acquisition and preprocessing

Brain MRI scans were obtained using 3.0 Tesla scanners at all sites (Chiba and UOEH: GE Discovery MR750; Tohoku and Kyushu: Philips Achieva; Kyoto: Siemens MAGNETOM TrioTim). The parameters including total scan time used to acquire T1-weighed images and resting-state fMRI (rsfMRI) are shown in online Supplementary Table S2. Preprocessing and quality control were performed using Statistical Parametric Mapping-12 (SPM12) and NITRC Functional Connectivity Toolbox (CONN) 18b. To stabilize the magnetic field, we excluded the first five volumes from rsfMRI data taken at repetition time (TR) = 3000 ms and the first six volumes from rsfMRI data taken at TR = 2500 ms. Then, using the default preprocessing pipeline of CONN, the functional realignment and unwarp, functional center to coordinates, functional slice-timing correction, functional outlier detection, functional direct segmentation and normalization, structural center to coordinates, structural segmentation and normalization, and functional smoothing were executed. For functional outlier detection, outlier scans were identified from the observed global BOLD signal and the amount of subject motion in the scanner. Acquisitions with a framewise displacement above 0.9 mm or global BOLD signal changes above five standard deviations were flagged as outliers.

Functional network construction

Calculations of region-to-region rsFCs were computed using CONN and the aCompCor (anatomical component-based noise correction procedure) method in MATLAB R2022a. Confounding factors (white matter, cerebrospinal fluid, six realignment parameters, first-order temporal derivatives of motion, and outlier scans) were removed using the regression of CONN's default denoising pipeline which implements aCompCor (Behzadi, Restom, Liau, & Liu, 2007). Then we applied band pass filtering (0.008–0.09 Hz) to fMRI data to reduce both high- and low-frequency noise. Seed ROIs and target ROIs were defined by CONN atlas consisting of the Harvard–Oxford cortical and subcortical atlas (106 ROIs), AAL cerebellum atlas (26 ROIs), and network parcellation from ICA analysis of the HCP dataset (32 ROIs). In other words, to make the whole brain into seed ROIs and target ROIs, all regions including network parcellation were selected as ROIs rather than artificially selecting only part of the regions registered in CONN. In the ROI-to-ROI connectivity analysis, we calculated a bivariate correlation separately on the individual BOLD time series between each pair of ROIs, and the correlation coefficients were converted to Fisher's Z-scores. The output of ROI-to-ROI rsFCs for each participant was a 164×164 matrix of the Fisher-transformed correlation coefficient.

Statistical analysis

Demographic and clinical characteristics

Demographic variables were analyzed and compared by SPSS (Statistical Package for Social Science version 25.0. IBM Corp., Armonk, New York). Demographical variables (age, body mass index [BMI], psychological test results: JART, EDE-Q, STAI, BDI-II) that were found not to be normally distributed as a result of the Shapiro-Wilk test of normality were compared between groups by the Kruskal–Wallis test followed by multiple comparisons by the Dunn's test. Duration of illness was compared between groups by Mann–Whitney U test. The chi-square test was used to compare groups with and without psychotropic medication. Normally distributed total intracranial volume (TIV) was compared between groups by one-way ANOVA, followed by multiple comparisons by Bonferroni's multiple comparison test. All the above statistical tests were two-tailed, and a p-value <0.05 was considered statistically significant.

Combat harmonization and group comparison of functional network

To correct for the site effects of multi-site databases, we applied Combat (Combining Batches) harmonization, which adjusts for batch effects in datasets by an empirical Bayes framework to the ROI-to-ROI rsFCs of each participant using the neuroCombat Python package (Fortin et al., 2017). The numbers of AN patients in this study at the Hospital of UOEH and Kyushu University Hospital were considerably lower than at other sites. Moreover, the site effects of multi-site databases are mostly derived from differences in the phase encoding direction and differences in fMRI manufacturers (Yamashita et al., 2019). Therefore, we configured the batches in Combat harmonization according to fMRI manufacturer, which governs the phase encoding direction. As shown in online Supplementary Table S2, fMRI was performed while participants kept their eyes closed at Tohoku University Hospital, unlike the other sites. However, the influence of the difference in imaging conditions due to eye-opening and closing on rsFC is considered to be limited (Patriat et al., 2013), so harmonization based on the difference in phase encoding direction was given priority. In this harmonization, the data acquired by GE Discovery MR750 were input as batch 1, the data obtained by a Philips Achieva were input as batch 2, and the data imaged by Siemens MAGNETOM TrioTim were input as batch 3. In addition to age and group (AN-R or AN-BP or HC), the BMI and TIV measured by Brain Anatomical Analysis using Diffeomorphic Deformation version 4.3.2 (BAAD; Shiga University of Medical Science, Otsu, Japan) were also entered as

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covariates. After applying Combat harmonization, the ROI-to-ROI rsFCs of each participant were re-entered into CONN. Then, we performed group-level analysis using the general linear model. Group comparisons of ROI-to-ROI rsFCs were conducted by analysis of covariance (ANCOVA) with age as a covariate. The significance of group comparisons was determined by the two-sided false discovery rate corrected p-value (p-FDR) <0.01, seed-level correction, which applies FDR separately for each seed ROI.

Correlation analysis of psychological scales and rsFCs with significant differences between AN and HC

We performed correlation analysis with self-reported psychological scales (EDE-Q, BDI-II, STAI) to identify significantly different connectivities between HC and AN patients. Specifically, Spearman's rank correlation coefficient was calculated between the ROI-to-ROI rsFCs values of AN patients in these connectivities and their scores on the self-reported psychological scales using SPSS version 25.0. The significance of the correlation was determined by two-sided p-FDR <0.05.

Results

Demographics and clinical characteristics

The demographics and psychological test results of the participants are shown in Table 1. Age was slightly higher in AN-BP, and BMI was higher in HC. Duration of illness was longer in AN-BP than in AN-R. JART score was higher in HC than in AN. EDE-Q scores were higher in AN-BP, AN-R, HC, in that order for both global and subscale scores. STAI and BDI-II scores were all higher in the AN group than in HC.

Comparison of rsFCs between groups (HC v. AN)

The rsFCs that were significantly stronger or weaker in AN compared to HC are listed in Table 2, Figs 1 and 2 (p-FDR <0.01 level). AN showed 12 significantly stronger rsFCs and 33 significantly weaker rsFCs than HC. Significantly stronger rsFCs in AN were observed mainly in rostral prefrontal cortex; stronger rsFCs were observed between this region and hippocampus, amygdala, superior temporal gyrus, anterior middle temporal gyrus, and temporal pole. rsFCs were also stronger between frontal operculum cortex and temporal pole, and between frontal operculum cortex and anterior middle temporal gyrus. Significantly weaker rsFCs in AN were found mainly within temporal lobe, within cerebellum, between ACC and thalamus, temporal occipital fusiform cortex and lateral part of visual network, supramarginal gyrus and vermis, posterior parietal lobe and cerebellar hemisphere, cerebellum and frontal pole. In particular, weaker rsFCs were significant even at the p-FDR <0.001 level between left temporal pole and hippocampus, left temporal pole and anterior parahippocampal gyrus, right temporal occipital fusiform cortex and right lateral part of visual network, hippocampus and right anterior middle temporal gyrus, and vermis VI and the anterior part of cerebellar network.

Comparison of rsFCs between AN subtypes (AN-R v. AN-BP)

The significantly stronger rsFCs in AN-R compared to AN-BP are listed in Table 2 and Fig. 3 (p-FDR <0.01). Stronger rsFCs were found between right lingual gyrus and right supracalcarine cortex, and between left temporal occipital fusiform cortex and medial part of visual network in AN-R compared to AN-BP.

Correlations between rsFCs with group differences and self-reported psychological scales

Correlation coefficients between rsFCs, which showed group differences between HC and AN, and scores on self-reported psychological scales (EDE-Q, BDI-II, STAI) are shown in online Supplementary Tables S3 and S4. There was no significant correlation between rsFCs, which showed group differences between HC and AN, and the scores on each psychological scale at the level of p-FDR <0.05.

Discussion

This study showed that 45 rsFCs were significantly changed in AN compared to HC. The rsFC changes were elucidated in greater detail for regions such as ACC, thalamus, DLPFC, fusiform cortex, posterior parietal lobes, cerebellum, and visual network, where changes in rsFCs had already been noted in previous studies. Temporal pole, superior temporal gyrus, hippocampus, parahippocampal gyrus, amygdala, supramarginal gyrus, and frontal pole were newly identified as important regions involved in multiple rsFC changes in AN. Furthermore, this study revealed the differences in rsFCs among AN subtypes. The following paragraphs discuss the rsFCs that differed between AN and HC, followed by those that differed between AN-R and AN-BP. Finally, the implications of the lack of correlation between rsFCs showing group differences and psychological scales are discussed.

Rostral prefrontal cortex, which showed stronger rsFCs in multiple regions in AN, corresponds to DLPFC, and the stronger rsFCs of the network including DLPFC may be the neurological basis for the suppression of excessive eating behavior in AN. The MNI coordinates of rostral prefrontal cortex in CONN are $X = -32$, $Y = 45$, $Z = 27$ on the left side and $X = 32$, $Y = 46$, $Z = 27$ on the right side, corresponding to DLPFC (Lacadie, Fulbright, Constable, & Papademetris, 2008). The prefrontal cortex is the main locus of biological executive control processes of eating behavior (Dohle, Diel, & Hofmann, 2018; Hall, 2016; Hofmann, Friese, & Strack, 2009). DLPFC is particularly involved in self-regulation (Hofmann, Schmeichel, & Baddeley, 2012; Miller & Cohen, 2001), controlling cravings and consuming food (Lowe, Vincent, & Hall, 2017). In healthy adults, DLPFC activation during dietary self-regulation tasks is negatively correlated with BMI (Han, Boachie, Garcia-Garcia, Michaud, & Dagher, 2018), and people with obesity have lower DLPFC activity in response to diet stimulation than those with leaner bodies (Gautier et al., 2000, 2001; Gluck, Viswanath, & Stinson, 2017; Le et al., 2006). It has also been found that high-frequency repetitive transcranial magnetic stimulation of the right DLPFC in AN patients reduces fat avoidance on a food choice task (Muratore et al., 2021).

Stronger rsFCs between DLPFC and amygdala or hippocampus indicates that AN patients may cope with emotion through excessive cognitive control. DLPFC is activated during rational decision-making (Greene, Nystrom, Engell, Darley, & Cohen, 2004) and inhibits emotional expression (Lévesque et al., 2003). DLPFC is more active in AN patients when they are presented with unpleasant vocabulary (Miyake et al., 2012) or food images (Sanders et al., 2015). These previous studies proposed the hypothesis that AN patients cope with negative emotional reactions through excessive cognitive control by DLPFC (Sato & Fukudo, 2017). The stronger rsFCs between DLPFC and the loci of emotion (i.e. amygdala or hippocampus) are consistent with this hypothesis.

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Table 1. Study demographics and clinical behavioral measures

		AN (total $N = 114$)								Effect sizes d		
		HC ($N = 135$)		AN-R ($n = 61$)		AN-BP ($n = 53$)		Group comparisons				
		Mean (s.d.)	N	Mean (s.d.)	N	Mean (s.d.)	N	Statistics (DF)	p Value	Post-hoc comparisons	HC $v.$ AN-R	HC $v.$ AN-BP	AN-R $v.$ AN-BP
Age		31.0 (11.2)	135	28.9 (11.8)	61	36.7 (10.7)	53	15.1 (2)	0.001	HC < AN-BP ($p = 0.004$)	0.18	0.52	0.69
										AN-R < AN-BP ($p = 0.001$)			
Body mass index, kg/m^2		20.8 (2.4)	135	14.3 (2.2)	61	15.3 (1.9)	53	169.0 (2)	<0.001	AN-R < HC ($p < 0.001$)	2.78	2.42	0.50
										AN-BP < HC ($p < 0.001$)			
TIV, ml		1481.4 (109.8)	135	1461.2 (114.2)	61	1444.6 (101.1)	53	2.3* (2, 246)	0.10	n. s. ($p = 0.098$)	0.18	0.34	0.15
Duration of illness, years				9.3 (8.8)	50	15.1 (8.6)	44	658.5	0.001	AN-R < AN-BP ($p = 0.001$)			0.67
Psychotropic medication					22/61		27/53	2.5† (1)	0.11	n.s. ($p = 0.110$)			0.15
JART	FSIQ	108.8 (7.3)	97	99.2(10.5)	45	103.2 (8.8)	32	30.2 (2)	<0.001	AN-R < HC ($p < 0.001$)	1.14	0.73	0.38
										AN-BP < HC ($p = 0.007$)			
EDE-Q	Global	0.7 (0.7)	119	1.9 (1.4)	53	3.3 (1.6)	41	84.8 (2)	<0.001	HC < AN-BP ($p < 0.001$)	1.24	2.58	0.94
										HC < AN-R ($p < 0.001$)			
										AN-R < AN-BP ($p = 0.007$)			
	Restraint	0.6 (0.9)	119	1.7 (1.6)	53	3.2 (1.8)	41	68.2 (2)	<0.001	HC < AN-BP ($p < 0.001$)	0.95	2.18	0.91
										HC < AN-R ($p < 0.001$)			
										AN-R < AN-BP ($p = 0.001$)			
	Eating	0.2 (0.5)	119	1.7 (1.5)	53	3.2 (2.0)	41	106.1 (2)	<0.001	HC < AN-BP ($p < 0.001$)	1.62	2.74	0.86
										HC < AN-R ($p < 0.001$)			

(*Continued*)

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Table 1. (*Continued.*)

		HC ($N = 135$)		AN (total $N = 114$) AN-R ($n = 61$)		AN-BP ($n = 53$)		Group comparisons			Effect sizes *d*		
		Mean (s.d.)	*N*	Mean (s.d.)	*N*	Mean (s.d.)	*N*	Statistics (DF)	*p* Value	Post-hoc comparisons	HC *v.* AN-R	HC *v.* AN-BP	AN-R *v.* AN-BP
										AN-R < AN-BP ($p = 0.039$)			
	Weight	0.9 (1.0)	119	2.1 (1.6)	53	3.4 (1.9)	41	60.7 (2)	<0.001	HC < AN-BP ($p < 0.001$)	0.99	1.94	0.75
										HC < AN-R ($p < 0.001$)			
										AN-R < AN-BP ($p = 0.010$)			
	Shape	1.2 (1.1)	119	2.3 (1.6)	53	3.6 (1.7)	41	61.8 (2)	<0.001	HC < AN-BP ($p < 0.001$)	0.86	1.88	0.79
										HC < AN-R ($p < 0.001$)			
										AN-R < AN-BP ($p = 0.007$)			
STAI	State	36.3 (9.2)	117	49.5 (13.2)	49	55.0 (12.0)	35	76.9 (2)	<0.001	HC < AN-BP ($p < 0.001$)	1.25	1.89	0.43
										HC < AN-R ($p < 0.001$)			
	Trait	44.2 (13.1)	116	58.9 (18.1)	49	61.7 (10.9)	35	61.0 (2)	<0.001	HC < AN-BP ($p < 0.001$)	1.00	1.39	0.18
										HC < AN-R ($p < 0.001$)			
BDI-II		5.9 (5.8)	122	22.3 (12.3)	53	28.7 (13.5)	40	102.7 (2)	<0.001	HC < AN-BP ($p < 0.001$)	1.97	2.73	0.50
										HC < AN-R ($p < 0.001$)			

N, number of participants; s.d., standard deviation; DF, degrees of freedom; AN, anorexia nervosa; HC, healthy control; AN-R anorexia nervosa restricting type; AN-BP, anorexia nervosa binge/purge type; JART, Japanese adult reading test; EDE-Q, eating disorder examination questionnaire; STAI, state-trait anxiety inventory; BDI-II, beck depression inventory-II.
*F values, $^{\dagger}\chi^2$ values, statistics without a symbol are H values.

Table 2. Difference of resting-state functional connectivity in AN *v.* HC and AN-R *v.* AN-BP

Seed	Region	*t*-value	*p*-FDR
HC < AN (*p*-FDR <0.01)			
SN, right rostral prefrontal cortex	Right anterior superior temporal gyrus	4.25	0.0024
	Right posterior superior temporal gyrus	3.65	0.0087
	Right hippocampus	3.73	0.0077
	Left hippocampus	3.77	0.0077
	Right amygdala	4.08	0.0033
	Left amygdala	4.26	0.0024
Left temporal pole	Right frontal operculum cortex	3.60	0.0063
	SN, right rostral prefrontal cortex	3.52	0.0065
	SN, left rostral prefrontal cortex	3.55	0.0065
Right anterior middle temporal gyrus	SN, left rostral prefrontal cortex	3.78	0.0080
	Left frontal operculum cortex	3.67	0.0096
Right amygdala	SN, left rostral prefrontal cortex	4.45	0.0021
AN < HC (*p*-FDR <0.01)			
Left temporal pole	Left posterior temporal fusiform cortex	3.53	0.0065
	Right hippocampus	4.66	0.0002
	Left hippocampus	5.15	0.0001
	Right amygdala	3.70	0.0063
	Right anterior parahippocampal gyrus	4.84	0.0002
	Left anterior parahippocampal gyrus	4.72	0.0002
	Left posterior parahippocampal gyrus	4.17	0.0014
	Subcallosal cortex	3.62	0.0063
	Vermis I, II	3.65	0.0063
	Left cerebellum IV,V	3.63	0.0063
Anterior right middle temporal gyrus	Right hippocampus	4.12	0.0028
	Left hippocampus	4.53	0.0015
	Subcallosal cortex	4.14	0.0028
Left cerebellar Crus II	Right frontal pole	4.20	0.0020
	Right angular gyrus	4.35	0.0020
	FPN, right posterior parietal cortex	4.20	0.0020
SN, left supramarginal gyrus	Vermis VI	4.01	0.0066
	Vermis VII	4.12	0.0066
Anterior left superior temporal gyrus	Right hippocampus	3.98	0.0074
	Left hippocampus	4.29	0.0041
Posterior left inferior temporal gyrus	Left posterior temporal fusiform cortex	4.34	0.0035
	Right anterior parahippocampal gyrus	4.00	0.0067
Anterior cingulate gyrus	Right thalamus	4.43	0.0011
	Left thalamus	4.61	0.0011
	VN, right lateral	4.72	0.0007
Right cerebellum VI	Left frontal operculum cortex	3.90	0.0099
	LN, left posterior superior temporal gyrus	3.94	0.0099
Vermis VII	Left posterior supramarginal gyrus	4.29	0.0041
	Right cerebellum VIIb	3.96	0.0054

(*Continued*)

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Table 2. (*Continued.*)

Seed	Region	*t*-value	*p*-FDR
Left temporal occipital fusiform cortex	VN, right lateral	4.15	0.0076
Right hippocampus	Left hippocampus	3.92	0.0047
Left hippocampus	Left anterior middle temporal gyrus	3.81	0.0055
Vermis VI	CN, anterior	5.20	0.0001
AN-BP < AN-R (*p*-FDR <0.01)			
Right lingual gyrus	Right supracalcarine cortex	4.21	0.0059
Left temporal occipital fusiform cortex	VN, medial	4.20	0.0060

p-FDR, false discovery rate corrected p; HC, healthy control; AN, anorexia nervosa; AN-R AN, restricting type; AN-BP AN, binge/purge type; SN, salience network; FPN, Frontoparietal network; VN, visual network; LN, language network; CN, cerebellar network.

Stronger rsFCs between DLPFC and superior temporal gyrus or temporal pole suggest that theory of mind (ToM) impairment, as in autism spectrum disorder (ASD), may be occurring in AN. Several studies have provided collateral evidence that ToM, the ability to reason about the mental states of others, is impaired in AN. One meta-analysis found that AN patients have lower cognitive empathy than HC (Kerr-Gaffney, Harrison, & Tchanturia, 2019). Another meta-analysis showed that AN patients have lower results in the Reading the Mind in the Eyes Test than HC (Preti, Siddi, Marzola, & Abbate Daga, 2022). ToM is realized by consistent activation of the posterior superior temporal gyrus, temporal pole, and medial prefrontal cortex (MPFC) (Frith & Frith, 2003). However, in ASD, where ToM is impaired, there is stronger functional connectivity between DLPFC and superior temporal gyrus, but not MPFC, and this change has been found to correlate with ASD severity (Ma et al., 2021).

The weaker rsFC between temporal pole and parahippocampal gyrus may contribute to the alexithymia tendency in AN, and the weaker rsFC between temporal pole and hippocampus may contribute to deficits in cognitive empathy in AN. The tendency toward alexithymia in AN has been well studied, and validated by a systematic review (Tauro, Wearne, Belevski, Filipčíková, & Francis, 2022). Temporal pole is activated when evaluating one's own emotions in response to stimuli (Terasawa, Fukushima, & Umeda, 2011), and it was found that the alexithymia tendency is higher when temporal pole is impaired in response to unpleasant emotional experiences (Aust et al., 2014). Parahippocampal gyrus has also been found to be inversely correlated with alexithymia when subjects are presented with emotional facial stimuli (Reker et al., 2010). Regarding rsFC between temporal pole and hippocampus, it has been reported that the strength of rsFC between right temporal pole and left anterior hippocampus was associated with greater empathic interest in a person based on episodic information (Pehrs, Zaki, Taruffi, Kuchinke, & Koelsch, 2018).

The weaker rsFC between posterior division of temporal fusiform cortex and posterior inferior temporal gyrus suggests that anomalies in visual perception of food are occurring in AN. This is because the temporal fusiform cortex and inferior temporal gyrus are both key regions in the visual processing of food (Chen, Papies, & Barsalou, 2016).

The weaker rsFC between temporal occipital fusiform cortex and lateral part of a visual network may be responsible for body image distortion in AN. Temporal occipital fusiform cortex is known as a spindle gyrus body area that responds strongly to human body shape (Schwarzlose, Baker, & Kanwisher, 2005), and it is considered a region associated with body image distortion because its activity is reduced during body shape task identification in AN (Suda et al., 2013). On the other hand, lateral occipitotemporal lobe, which contains a lateral part of the visual network, is also a region that selectively responds to images of the human body and is known as the extrastriate body area (Downing, Jiang, Shuman, & Kanwisher, 2001).

The weaker rsFC between ACC and thalamus may lead to impaired set-shifting in AN. ACC exerts cognitive control over behavior by monitoring conflicts (Botvinick, Braver, Barch, Carter, & Cohen, 2001) and errors in information processing and is activated during the performance of behavioral set-shifting tasks (Shafritz, Kartheiser, & Belger, 2005). Basal ganglia-thalamocortical circuits, including the thalamus, are also involved in maintaining and switching behavioral sets by their regulation of frontal lobe activity (Alexander, Crutcher, & DeLong, 1991). Furthermore, in AN, rsFCs of the network including ACC and thalamus have been found to be weaker during the performance of behavioral set-shifting tasks (Zastrow et al., 2009).

Weaker rsFCs within the cerebellum and between the cerebellum and multiple regions of the brain may be associated with abnormal eating behavior in AN. The cerebellum is in direct bidirectional communication with the hypothalamus (Haines, Dietrichs, Mihailoff, & McDonald, 1997) and is responsible for motivating and regulating feeding behavior by sensing blood glucose levels, visceral stimulation, gastrointestinal hormones, taste, and smell (Zhu & Wang, 2008). The size of the right cerebellar hemisphere has also been found to be a prognostic factor regarding inpatient treatment of AN (Milos et al., 2021).

The weaker rsFC between cerebellar Crus II and frontal pole may be involved in cognitive dysfunction. The weaker rsFC between cerebellar Crus II and posterior parietal cortex may contribute to visuospatial dysfunction, and weaker rsFCs between vermis and supramarginal gyrus or temporal pole may be involved in emotion regulation disorder in AN. Cerebellum receives higher-order information from the prefrontal cortex, posterior parietal lobe, and temporal lobe regarding motivation, emotion, etc (Schmahmann, 2010). Indeed, damage to Crus I or II of cerebellum has been found to produce cognitive dysfunction, damage to posterior cerebellar lobes including Crus II to produce visuospatial impairment, and damage to vermis to result in emotional dysregulation (Schmahmann, 2010).

For the regions with strengthened rsFCs in AN-R relative to AN-BP, the stronger rsFC between supracalcarine cortex and lingual gyrus may indicate that internally directed attention is more active in AN-R than in AN-BP. This is because the cuneus and lingual gyrus, both of which contain supracalcarine cortex, are

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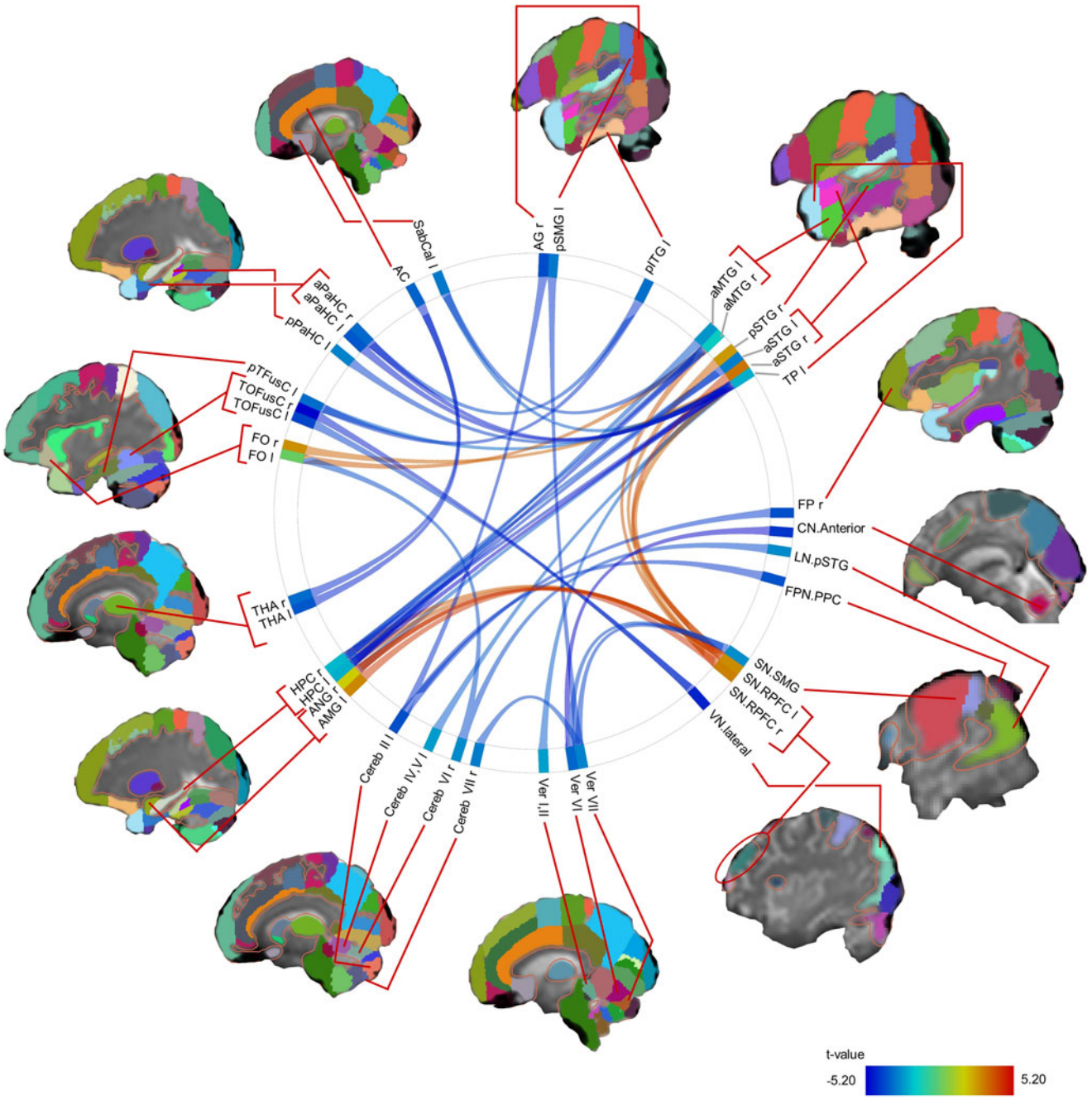

Figure 1. Connectome showing rsFCs altered in AN patients relative to HC. This figure presents the connectome showing rsFCs altered in AN patients relative to HC. The red lines indicate significantly stronger rsFCs and the blue lines indicate significantly weaker rsFCs in AN patients (114 persons) relative to HC (135 persons). Group comparison of ROI-to-ROI rsFCs was done by ANCOVA and using age as covariate. The significance of the group comparison was determined by two-sided *p*-FDR <0.01, seed-level correction, which applies FDR separately for each seed ROI. The 'p' before each region indicates posterior division, and 'a' means anterior division. The 'r' after each region indicates right, and the 'l' shows left. *AG* angular gyrus, *SMG* supramarginal gyrus, *ITG* inferior temporal gyrus, *MTG* middle temporal gyrus, *STG* superior temporal gyrus, *TP* temporal pole, *FP* frontal pole, *CN* cerebellar network, *LN* language network, *FPN* Frontoparietal network, *PPC* posterior parietal cortex, *SN* salience network, *RPFC* rostral prefrontal cortex, *VN* visual network, *Ver* vermis, *Cereb* cerebellar, *AMG* amygdala, *HPC* hippocampus, *THA* thalamus, *FO* frontal operculum cortex, *TOFusC* temporal occipital fusiform cortex, *TFusC* temporal fusiform cortex, *PaHC* parahippocampal gyrus, *PaHC* parahippocampal gyrus, *AC* anterior division of cingulate gyrus, *Subcal* subcallosal cortex.

responsible for the maintenance of internally oriented attention (Benedek et al., 2016), are thought to be sites that are significantly activated during go/no-go tasks in AN, and are involved in the reduction of external attention (Noda et al., 2021). The medial part of the visual network corresponds to the combined cuneus and lingual gyrus. The stronger rsFC between that region and temporal occipital fusiform cortex, known as the spindle gyrus body area may suggest that the internally oriented attention, which is heightened in AN-R, is especially directed to one's own body. In fact, AN-R patients have been found to show significantly more attention to their own unattractive body parts compared to AN-BP (Bauer et al., 2017).

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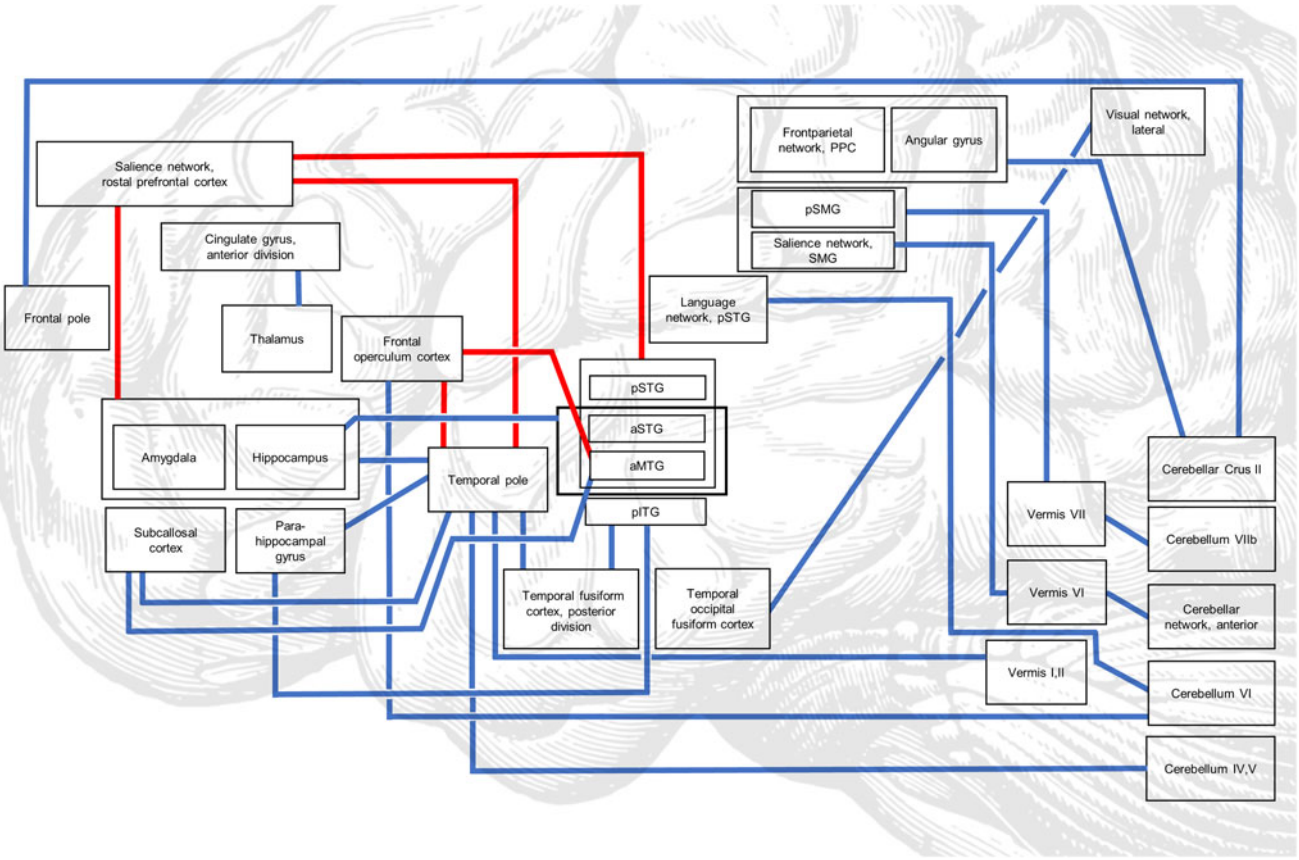

Figure 2. Schematic diagram showing rsFCs with change in AN patients compared to HC. This figure presents a schematic diagram showing the rsFC changes in AN patients (114 persons) relative to HC (135 persons), based on a sagittal section of the brain. The left side of the figure corresponds to the frontal region, and the right side corresponds to the occipital region. The left and right sides of the brain are not clearly shown in this figure. The red lines indicate significantly stronger rsFCs, and the blue lines indicate significantly weaker rsFCs in AN relative to HC. Group comparison of ROI-to-ROI rsFCs was done by ANCOVA and using age as covariate. The significance of the group comparison was determined by two-sided *p*-FDR < 0.01, seed-level correction, which applies FDR separately for each seed ROI. The 'p' before each region indicates posterior division, and 'a' means anterior division. *STG* superior temporal gyrus, *MTG* middle temporal gyrus, *ITG* inferior temporal gyrus, *SMG* supramarginal gyrus, *PPC* posterior parietal cortex.

Finally, the lack of correlation between rsFCs, which differed between AN and HC groups, and psychological scales (EDE-Q, BDI-II, STAI) is discussed. The rsFCs, which showed significant differences between AN patients and HC in this study, include rsFCs that were suggested in previous studies to be associated with depression and anxiety. For example, rsFCs within the executive control network, with DLPFC as the main region, have been reported to be correlated with BDI-II scores in AN patients (Gaudio et al., 2015). Therefore, there is concern that rsFCs affected by depression and anxiety were included in rsFCs that showed differences between groups. However, in the present study, the lack of correlation between the rsFCs showing group differences and BDI-II or STAI suggests that there was no confounding of rsFCs involved in depression and anxiety, which are common but non-specific psychiatric symptoms in AN. Furthermore, no correlation was found with EDE-Q, suggesting that the rsFCs that showed group differences do not vary continuously with AN severity. Given the above, the rsFCs that differed significantly between AN and HC in this study are considered to be categorical diagnostic markers for AN.

A limitation of this cross-sectional study was that it could not determine whether the rsFCs that showed group differences were related to AN development or reflected temporal changes in brain function due to starvation. However, previous studies in participants recovering from AN have shown changes in the frontoparietal network (FPN), which consists of brain regions such as DLPFC and posterior parietal cortex (Boehm et al., 2016), and the present study showed multiple changes in rsFCs in the FPN component regions, suggesting that at least some of the altered rsFCs in this study may be involved in the development of AN. Moreover, because weight loss is essential for diagnosing AN, the inability to distinguish whether the altered rsFCs were the causes or the effects of AN may not undermine the significance of the rsFC changes shown in this study as a categorical diagnostic marker. It should be noted, however, that atypical AN, AN without significant weight loss, exists, and psychiatric symptoms sometimes persist in AN after weight regain. Therefore, to better elucidate the brain dysfunctions involved in the development of AN, we are currently carrying out a cohort study investigating changes in the brain before and after treatment (Hamatani et al., 2021). We are also collecting fMRI data on non-AN healthy, skinny women, taking advantage of the fact that as much as 17% of young Japanese women have a BMI below 18.5 (Yamamoto et al., 2022). As for demographic data, there were two apparent concerns. The first was the lack of data on participants' comorbidities. Concerning depression and anxiety, the most common comorbidities in AN (Swinbourne & Touyz, 2007; Ulfvebrand, Birgegård, Norring, Högdahl, & von

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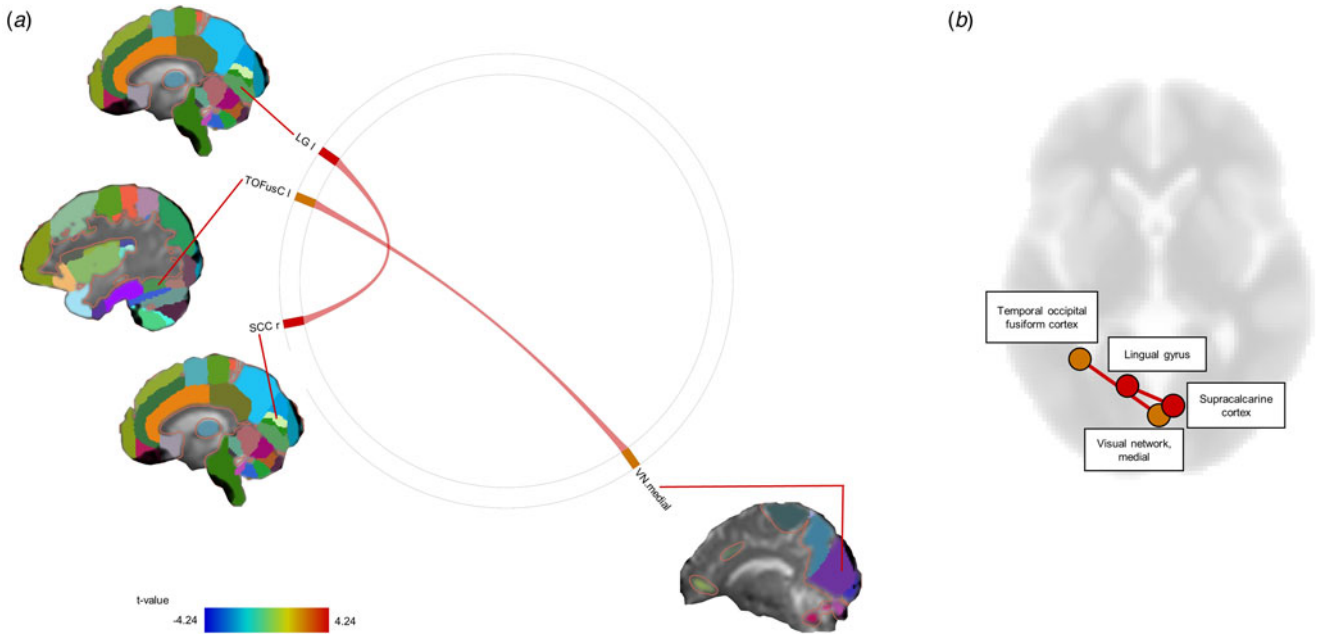

Figure 3. Connectome showing rsFCs altered in AN-R compared to AN-BP. (a) This figure presents the connectome showing rsFCs altered in AN-R compared to AN-BP. The red line indicates significantly stronger rsFCs in AN-R (61 persons) relative to AN-BP (53 persons). A group comparison of ROI-to-ROI rsFCs was done by ANCOVA and using age as covariate. The significance of the group comparison was determined by two-sided *p*-FDR < 0.01, seed-level correction, which applies FDR separately for each seed ROI. The 'r' at the end of *SCC* indicates right, and the 'l' at the end of *LG* and *TOFusC* means left. *LG* lingual gyrus, *TOFusC* temporal occipital fusiform cortex, *SCC* supracalcarine cortex, *VN* visual network. (b) This figure shows rsFCs that were significantly stronger in AN-R relative to AN-BP in a horizontal brain section.

Hausswolff-Juhlin, 2015), particularly the distribution among participants and the impact of comorbidities on study results should have been carefully considered. Although participants were carefully scrutinized in structured interviews based on the DSM-5 for eligibility and exclusion criteria, each participant's comorbidities were not recorded. However, this study found no significant correlation between the changes in rsFCs observed in the AN group and the depression and anxiety scores (i.e. BDI-II and STAI). Therefore, the observed differences in rsFCs were specific to AN, and the impact of comorbid depression and anxiety was likely to be relatively small. The second concern was that the mean EDE-Q global score of the AN-R group was lower than 2.3, which is generally considered the cut-off for eating disorders (Mond, Hay, Rodgers, Owen, & Beumont, 2004). However, because the mean BMI of the AN-R group was sufficiently low (14.3 kg/m^2), it may be inferred that this did not indicate a lower severity of the AN-R group in this study but rather a lack of awareness of the disease. Other limitations of this study were as follows. Because this study included only Japanese women, it is unclear to what extent the findings can be generalized to other races, men, and gender-diverse populations. Because we could not collect self-report psychological scales from all participants, missing values may have affected the results of the correlation analysis between rsFCs and the scales. Although rsFC changes have been noted in many previous studies of the insular region, no significant rsFC changes in insula were observed in the present study. If insula had been divided into multiple regions based on functional localization as in previous studies (Ehrlich et al., 2015; Kullmann et al., 2014; Lord et al., 2016), significant rsFC changes might have been observed in this study. In this study, we used the widely used atlas and network parcellation registered in CONN, but in the future, more detailed parcellation should be used not only for the insular cortex but also for other regions.

Conclusion

This study of setting whole brain regions as ROIs, with a sample size of more than 100 subjects per group, revealed that 12 rsFCs were stronger and 33 rsFCs were weakened in AN. Stronger rsFCs occurred mainly in the regions containing rostral prefrontal cortex (corresponding to DLPFC), and weaker rsFCs were found mainly in regions containing cerebellum, within temporal lobe, between posterior fusiform cortex and lateral part of visual network, and between ACC and thalamus. Furthermore, AN-R showed stronger rsFCs between right lingual gyrus and right supracalcarine cortex and between left temporal occipital fusiform cortex and medial part of visual network compared to AN-BP. These rsFC changes can represent categorical diagnostic markers discriminating AN from HC and AN-R from AN-BP.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291724000485.

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Competing interests. YM is employed by Lundbeck Japan, KK. All other authors have no conflicts of interest to declare.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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