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Resting-state functional brain connectivity in female adolescents with first-onset anorexia nervosa

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ABSTRACT

Objective: Women with anorexia nervosa (AN) have been shown to demonstrate differences in functional connectivity in brain regions associated with cognitive control, somatosensory processing, and emotion regulation. However, previous studies have been conducted on small samples and have inconsistent findings. Therefore, this study aimed to identify aberrant brain networks related to the core clinical symptoms of AN and to explore the longitudinal association with clinical outcome in a large population of adolescents experiencing their first episode of AN.

Methods: Functional MRI (fMRI) of brain resting-state functional connectivity (RS-FC) of female adolescents with first-onset AN (n = 56) were compared to age- and education-matched typically developing (TD) adolescents (n = 64). To account for the severity of underweight, separate analyses were performed to investigate differences in RS-FC between underweight AN participants and TD adolescents, as well as between underweight (n = 30) and weight-restored AN (n = 26) participants. Clinical outcomes, i.e. body mass index and eating disorder (ED) symptoms, were assessed at baseline and one-year follow-up. Independent component analyses (ICA) were used to extract the brain networks of interest: the default mode (DMN), left and right frontoparietal (FPN), and the insular (IN) networks. Linear regression analyses were conducted to assess differences in RS-FC between AN and TD participants, as well as to assess whether RS-FC was associated with clinical symptoms at baseline and at one-year of follow-up. Two statistical models were used: model 1 adjusted for age and socioeconomic status (SES), and model 2 additionally adjusted for baseline anxiety and depressive symptoms.

Results: Underweight AN participants had lower RS-FC between the DMN-IN, as well as between the FPN-IN compared to the TD adolescents. After correction for multiple testing, no significant differences in RS-FC were found between underweight AN participants and weight-restored AN participants, as well as between the whole AN group and the TD group. RS-FC was not associated with the severity of clinical symptoms at baseline nor at one-year of follow-up.

Conclusion: AN is associated with changes in RS-FC between the FPN-IN and DMN-IN during the underweight state. These changes in RS-FC were no longer observed in weight-restored AN participants, emphasizing the impact of underweight on RS-FC in AN. Changes in these brain networks may partly explain the impaired cognitive control and difficulties with emotion and behavioral regulation in individuals with AN during the underweight state.

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1. Introduction

Anorexia nervosa (AN) is the third most common chronic disorder amongst adolescents with one of the highest morbidity and mortality rates of all psychiatric disorders (Papadopoulos et al., 2009; Schmidt et al., 2016). The eating disorder (ED) typically develops during adolescence, predominantly affecting females (van Eeden et al., 2021). AN is often challenging to treat with few psychological and pharmacological interventions, with limited effectivity (Monteleone et al., 2022; Solmi et al., 2021; Treasure et al., 2020; Zipfel et al., 2014). In recent decades, the development of in-vivo brain imaging in humans have improved our understanding of the underlying neurobiology of AN (Bulik et al., 2022; Frank et al., 2019); although many questions remain. From both a neurobiological and clinical perspective, a deeper understanding of the neurobiological underpinnings of AN may be a key element in early detection, development of interventions, and personalized care (Hill et al., 2016; Kaye et al., 2013).

AN is associated with both structural and functional brain alterations, including volume reductions in the prefrontal and insular cortex, and in the temporal and parietal lobes (Castro-Fornieles et al., 2009; Fujisawa et al., 2015; Kappou et al., 2021). These brain alterations appear largely dependent on the disease-stage, with the most significant reductions in brain volume observed in individuals with the lowest body mass index (BMI) (Walton et al., 2022). The reductions in brain volume often resolve completely with weight recovery in adults, whereas there is limited data for adolescents (Kappou et al., 2021; Seitz et al., 2016; Seitz et al., 2018). Brain volume decreases during the acute phase of AN appear primarily driven by the effects of malnutrition, although baseline imaging studies collected prior to AN development are lacking.

Functional magnetic resonance imaging (fMRI) studies of the brain have primarily utilized task-based approaches focusing on food-, body-, and reward-related tasks. These fMRI studies target key clinical symptoms of AN aiming to identify underlying neurocircuits associated with these symptoms (Garcia-Garcia et al., 2013; Zhu et al., 2012). Altered brain activity has been reported in several different brain regions, including the prefrontal (Steding et al., 2019; Schulte-Ruther et al., 2012), cingulate (Horndasch et al., 2018; Halls et al., 2021) and the insular (Horndasch et al., 2018; Kim et al., 2012) cortices, linked to cognitive control, interoceptive awareness, emotion-regulation, and reward (Hathaway et al., 2023; Rolls, 2019; Kortz and Insular, 2023). However, the diversity of paradigms and stimuli used in task-based fMRI studies limit generalization and replication of findings (Zhong et al., 2023).

To address these issues, resting-state functional magnetic resonance imaging (RS-fMRI), has gained interest over the past decade as a non-invasive method to assess resting-state functional connectivity (RS-FC) by measuring task-independent fluctuations in the blood-oxygenation level dependent (BOLD) signal. Higher RS-FC indicates similarities in the BOLD time series between two brain regions (Rees et al., 1997). While the BOLD signal does not directly measure neuronal activity, it is highly correlated with underlying neural activity (Logothetis and Wandell, 2004; Shmuel et al., 2002). Various approaches have been used in the literature to quantify the functional connectivity patterns between different brain regions, with one common approach being Independent Component Analyses (ICA). ICA separates multivariate signals into independent components in order to identify consistent brain network patterns (Hyvarinen, 1984; Muetzel et al., 2016).

Previous RS-fMRI studies performed in adolescents have shown mixed results, primarily focusing on brain networks related to key features of AN, such as self-referential processing (Gu et al., 2024), emotion regulation (Rowsell et al., 2016), executive functioning (Diaz-Marsa et al., 2023) and body image concerns (Ciwoniuk et al., 2022; Gaudio et al., 2016). The default mode network (DMN) is typically included in analyses exploring RS-FC alteration in AN due to its role in self-referential processing (Boehm et al., 2014). Studies investigating the DMN in individuals with AN have reported both greater RS-FC between the DMN and other regions (Boehm et al., 2014), as well as no significant differences between AN and controls (Phillipou et al., 2016; Boehm et al., 2016). The frontoparietal network (FPN) has been heavily investigated in AN and is associated with executive function and cognitive control (Boehm et al., 2014). Both greater (Boehm et al., 2014) and lower RS-FC (Lotter et al., 2021) have been reported in the FPN in AN. The insular network (IN), considered a gatekeeper of executive function driving the activity of major networks including the medial frontoparietal DMN and lateral frontoparietal 'central executive network' (Molnar-Szakacs and Uddin, 2022), was shown to display reduced RS-FC within the right insula in individuals with current and recovered AN in compared to controls (Scaife et al., 2017).

The IN has been described as both overconnected (Boehm et al., 2014; Amianto et al., 2013) and underconnected with not only the DMN, but also with other regions related to the corticolimbic circuit and the cerebellum (Lotter et al., 2021; Ehrlich et al., 2015; Gaudio et al., 2018; Geisler et al., 2016) in AN. Regarding inter-network RS-FC, Boehm et al. (2014) (Boehm et al., 2014) found greater RS-FC between the DMN and left IN in AN compared to controls. However, no associations between RS-FC and severity of clinical symptoms in AN were found previously (Lotter et al., 2021; Kaufmann et al., 2023). In healthy adolescents with a varying number of ED symptoms, higher levels of ED symptoms were associated with reduced RS-FC within the FPN and between the FPN and DMN (Chen et al., 2021).

To our knowledge, only one study assessed the association between baseline RS-FC and clinical outcome. Dunlop et al. (2015) (Dunlop et al., 2015) found that lower baseline RS-FC between the prefrontal cortex-orbitofrontal cortex, prefrontal cortex-insula and anterior-cingulate cortex-insula was associated with a more favorable treatment response. Despite much effort to understand the functional organization of the brain and the specific involvement of certain brain networks in AN (Kappou et al., 2021; Gaudio et al., 2016), the underlying disease mechanisms are not fully understood (Seidel et al., 2020). A number of factors may contribute to the inconsistencies of findings. First, there is considerable variability in demographic and clinical features of studied populations (i.e. age, severity of ED, duration of illness). Most studies focused on individuals with a prolonged course of AN, limiting the disentanglement of specific underlying disease mechanisms. Second, most studies were relatively underpowered ($n < 30$) (Kappou et al., 2021; Gaudio et al., 2016; Muratore et al., 2024). Third, different analytical approaches have been used in different studies, making direct comparisons difficult (Kappou et al., 2021; Gaudio et al., 2016). Furthermore, AN can be quite heterogeneous with differing levels of comorbid conditions (Calvo-Rivera et al., 2022; Swinbourne et al., 2012) and most studies did not correct for depressive and anxiety symptoms which could confound results. Finally, there is a lack of studies that assess the relationship between baseline RS-FC and longitudinal clinical outcomes in individuals with AN.

The aim of the current study was to examine RS-FC in a large and more homogeneous sample of female adolescents with first-onset AN, and its association with clinical symptoms. We compared these adolescents with age- and education-matched typically developing (TD) adolescents, and took into account the impact of underweight on RS-FC with the goal of providing unique insights into early pathophysiology of AN. In addition, we included depressive and anxiety symptoms as additional covariates in our analyses, allowing a more distinct exploration of these aspects of AN. We hypothesized that adolescents with AN show alterations in RS-FC between the FPN-IN and DMN-IN compared to TD adolescents, which would be more pronounced in AN participants with underweight. In addition, considering the finding of Scaife et al. (2017) (Scaife et al., 2017) that reduced FC was found within the insula, we hypothesized that the AN group shows decreased FC within the IN compared to the TD group. Since we do not expect differences in within-network RS-FC of the DMN and FPN in this early disease-stage, we included these as exploratory analyses. As a secondary aim, we investigated whether there is an association between RS-FC and clinical

outcome at one-year follow-up.

2. Methods

2.1. Participants

The current study was embedded in the BRAVE study. An overview of the study design of the BRAVE study is published elsewhere (Steegers et al., 2024). The sample consisted of a total of 120 female adolescents: 56 participants with first-onset AN (median age = 16.3 years) and 64 age- and education matched TD participants (median age = 17.3 years). One-year clinical follow-up data was available for 40 participants from the AN group. Inclusion criteria for AN included: female sex, aged 12–22 years, diagnosed with first-onset AN or atypical AN according to DSM-5 criteria. The onset of the DSM-5 diagnosis of AN is within 12 months of the date of inclusion. TD adolescents were recruited through advertisements on social media, sport clubs, or through suggestions from the AN participants (e.g. classmates, friends). To be included, TD adolescents had to have a healthy body weight, defined as a 'body mass index – standard deviation score' (BMI-SDS) between −1.3 and + 1.3. Exclusion criteria for both the AN and TD group were presence of a psychotic, neurological, or a substance abuse disorder, severe motor and sensory impairments, IQ < 70 as measured by an intelligence test, and insufficient Dutch language skills to complete the questionnaires, interviews, cognitive tasks, and instructions for the neuroimaging study. The BRAVE study was approved by the Medical Ethical Committee of the Erasmus Medical Center − Sophia Children's hospital (Erasmus MC-Sophia) (MEC 2016–194/NL55175.078.16) and was conducted in agreement with the Declaration of Helsinki.

2.2. Procedure

In short, adolescents with first-onset AN were introduced to the BRAVE study by their health care provider. A physician referred adolescents who had received a diagnosis of AN according to the DSM-5 criteria. The adolescent was contacted and invited to visit the university research clinic. If the eligibility criteria were met, written informed consent was obtained. In cases where the participant was younger than 16 years-of-age, informed consent was obtained from both parents. Participants underwent a physical health assessment, completed psychological questionnaires, and a neuroimaging session. These assessments were performed at baseline and after one year of follow-up. Between baseline and follow-up, participants with AN received care-as-usual for AN.

The neuroimaging session, physical health measures and psychological questionnaires took place in the Erasmus MC-Sophia. ED symptoms, were assessed through an interview with a qualified researcher.

2.3. Clinical measures

ED symptoms and BMI-SDS were defined as the main clinical outcomes. BMI was corrected for age and sex to obtain an adjusted BMI (BMI-SDS), using a growth calculator tool (https://groeiweb.pgdata.nl/calculator.asp).

The *Eating Disorder Examination version 12.0 (EDE)* is considered the gold standard for assessing ED psychopathology and provides a measure of ED symptom severity. A trained researcher conducted the interview with the adolescent at both time points. The EDE assessed the extent to which the participant worried about diet, food, body weight and body shape (rated on a 7-point Likert scale). The internal consistency of the global score is high (α = 0.92).

The *Beck Depression Inventory – Second Edition (BDI-II)* was used to measure the severity of depressive symptoms using statements reflecting mood symptoms within the past week, consisting of 21 items rated on a 4-point Likert scale. The internal consistency for the BDI-II is high (α = 0.9) (Wang and Gorenstein, 2013).

The *Screening for Child Anxiety Related Emotional Disorders (SCARED)* assessed anxiety symptoms using DSM-IV-TR criteria (Boehm et al., 2016). The SCARED consists of 69 items scored on a 3-point Likert scale. Internal consistency of the SCARED is moderate-high (α = 0.74–0.93) (Birmaher et al., 1997).

The Full-Scale Intelligence Quotient (FSIQ) of the *Wechsler Abbreviated scale of Intelligence Quotient – Second Edition (WASI-II)* (McCrimmon, 2013) was used to provide a reliable estimate of the intelligence (Irby et al., 2013). The internal consistency of the WASI-II is high (α = 0.87–0.91) (McCrimmon, 2013).

Diagnoses of depression and anxiety were established using the *Mini International Neuropsychiatric Interview (MINI-KID* (<17 years) / *MINI-PLUS* (>18 years)*)*. This structured interview was administered to evaluate general psychopathology according to DSM-IV criteria. The MINI-KID/MINI-PLUS based on DSM-5 criteria was not yet available at the start of our study.

2.4. RS-fMRI image acquisition

Neuroimaging data were acquired on a single 3 Tesla GE Discovery MR750w MRI system (General Electric, Milwaukee, WI, USA) with an 8-channel head coil. The detailed MRI protocol of the BRAVE study has been published previously (Steegers et al., 2024). Structural T_1-weighted images were acquired using a fast spoiled gradient-recalled echo (FSPGR) sequence [TR = 8.77 ms, TE = 3.4 ms, TI = 600 ms, flip angle = 10°, matrix = 220 × 220, field of view (FOV) = 220 mm, slice thickness = 1.0/230]. A six minute two second RS-fMRI sequence was obtained using the following sequence parameters: TR = 1760 ms TE = 30 ms, flip angle = 85°, field of view (FOV) = 230 x 230, matrix = 64 x 64, slice thickness = 4 mm, in-plane resolution = 3.4 mm^2, volume = 200. During the RS-fMRI scan, participants were placed in the scanner in a supine position and asked to close their eyes and not to think about anything in particular. Of the total BRAVE sample (N = 154), 121 participants (57 AN; 64 TD) underwent the MRI scan. The total number of included RS-fMRI scans is 120 (56 AN; 64 TD). A detailed flowchart of the inclusion of the RS-fMRI scans of the BRAVE sample is shown in Fig. 1.

2.5. Preprocessing RS-fMRI images

Image preprocessing was performed using the Functional MRI of the Brain (FMRIB) software library v6.0.0 (http://www.fmrib.ox.ac.uk/fsl) and Python 3.6. Cleaning of each individual's RS-fMRI dataset was performed using FSL's Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) ICA with FSL's fMRI Expert Analysis Tool (FEAT). The first four volumes of the RS-fMRI sequence were excluded to allow the sequence to reach equilibrium, reducing the scans to 196 volumes each. Individual ICA were used to account for artifact removal. For each individual, independent components were manually labelled as either "signal" or "noise" (e.g. motion). Following this procedure, components classified as noise from individual sessions were removed by regressing out these time series. Subsequently, brain extraction, slice timing correction, motion correction, and image registration were performed. Image registration was performed in a two-step procedure to fit the data to an age-appropriate, standard space (2 mm MNI152 space), T_1-weighted template. First, the RS-fMRI data were registered to the T_1-weighted image, using 12 degrees of freedom (DOF) and a normalized correlation cost function. The anatomical T_1-weighted image was then registered to the age-appropriate, 2 mm, standard space T_1-weighted template using a linear registration. The matrix resulting from this two-step procedure was applied to the de-noised RS-fMRI data resulting in a 4-D image for each individual in standard space.

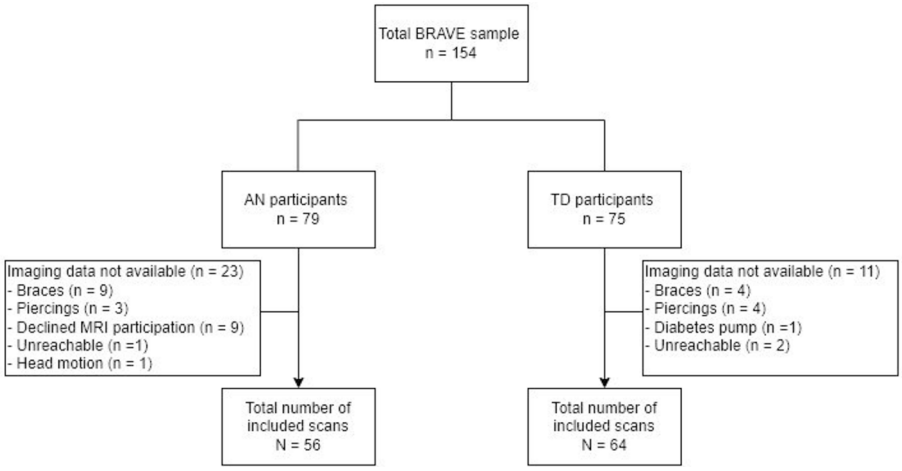

Fig. 1. Flowchart of the inclusion of RS-fMRI scans of the BRAVE sample. *Note:* AN: anorexia nervosa; *RS-fMRI: resting-state functional magnetic resonance imaging;* TD: typically developing.

2.6. Data quality

MRI quality assurance was established by a combination of two steps. First, as described above, single-subject ICA was used to de-noise the data by regressing out components of non-interest. Second, the output matrices of the motion correction step consisting of rotation and translation coordinates were used to exclude data of poor quality. Data were defined as poor quality and excluded if the maximum translation was greater than 1 mm and the mean TR-to-TR translation was greater than 0.2 mm (for further information see the study design paper (Geisler et al., 2016).

2.7. Independent component analyses

FSL's MELODIC tool was used to generate spatial component maps and perform spatial and temporal filtering with the dimensionality set to 25 components (Muetzel et al., 2016). A high-pass temporal filter with a cutoff of 100 s and spatial smoothing with a Gaussian filter (FWHM = 5-mm) were applied (White et al., 2001). The labeling of the components was based on Muetzel et al. (2016) (Muetzel et al., 2016) and the networks of interest (DMN, FPN, IN) were selected based on these labels. Each individual region underwent thresholding, determined by a z-score greater than seven. Subsequently, the masks of the components of interest were created and labeled using the Harvard-Oxford structural atlas and the Cerebellar atlas in MNI152 space. If a region had less than two voxels, it was excluded. Subsequently, the times series of all regions of interest were extracted and Pearson correlations were calculated between the 26 nodes that made up the networks of interest. Between the 26 nodes, 215 correlations were made. Finally, the values of the correlations were transformed into z-scores, which were used for data analysis. The descriptive information of the derived regions are shown in Table 1.

2.8. Covariates

To adjust for potential confounders, age, socioeconomic status (SES), depressive- and anxiety symptoms were included as covariates. SES was based on maternal education and divided into three categories: high (higher vocational secondary education and higher academic education), medium (higher general secondary education), and low (primary education and lower general secondary education). Depressive- and anxiety symptom scores were entered as covariates in the second model.

Table 1
Descriptive information of derived regions.

Region	Network	Anatomical labels	Size (mm^3)
1	DMN-I	R. Frontal Orbital Cortex/Frontal Pole/ Temporal pole	31.88
2	DMN-I	Frontal Pole/Paracingulate Gyrus/Superior Frontal Gyrus	1182.25
3	DMN-I	Precuneus/Cingulate Gyrus-PD	86.00
4	DMN-I	Cingulate Gyrus-PD	35.13
5	DMN-I	L. Frontal Orbital Cortex/Frontal Pole/ Temporal pole	65.38
6	DMN-I	L. Lateral Occipital Cortex-SD/Agular Gyrus	15.00
7	DMN-I	L. Middle Temporal Gyrus-PD/ Middle Temporal Gyrus-AD.	6.13
8	DMN-II	Precuneus Cortex/Cingulate Gyrus-PD/L. and R. Lateral Occipital Cortex-SD/Occipital Cortex-SD	1257.38
9	DMN-II	R. Thalamus	2.25
10	DMN-II	Cingulate Gyrus-AD/Paracingulate Gyrus	74.25
11	Left FPN	R. Crus II	35.63
12	Left FPN	Cingulate Gyrus-PD	5.25
13	Left FPN	Mid. Frontal Gyrus/Sup. Frontal Gyrus	794.50
14	Left FPN	L. Caudate	2.88
15	Left FPN	L. Lateral Occipital Cortex-SD/Supramarginal Gyrus-PD	423.25
16	Left FPN	Mid. Temporal Gyrus-PD/Inf. Temporal Gyrus-PD	108.13
17	Right FPN	R. Mid. Temporal Gyrus-PD/Inf. Temporal Gyrus-PD	30.63
18	Right FPN	R. Lat. Occipital Cortex-SD/Angular Gyrus	396.25
19	Right FPN	R. Mid. Frontal Gyrus/Sup. Frontal Gyrus	809.75
20	Right FPN	Cingulate Gyrus-PD	4.00
21	Right FPN	L. Crus II	18.88
22	IN	R. Insular Cortex/Central Opercular Cortex	603.50
23	IN	R. VI	14.25
24	IN	Juxtapositional Lobule Cortex (formerly Supplementary Motor Cortex)	24.75
25	IN	L. VI	22.00
26	IN	L. Insular Cortex/Central Opercular Cortex	549.00

Note. The DMN consisted of two components: DMN-I: frontal; DMN-II: posterior cingulate cortex, precuneus.
Abbreviations; AD: anterior division; DMN: default mode network; FPN: frontoparietal network; IN: insular network; Inf: inferior; Mid.: middle, L.: left; Lat: lateral; PD: posterior division, R.: right, SD: superior division, Sup.: superior.

2.9. Statistical analyses

Data analyses were performed using SPSS Statistics (version 28.0, IBM Corporation, Armonk, NY, USA). Effect sizes were reported as R^2 change, with values between 1.0 % and 5.9 % considered as small, between 5.9 % and 13.8 % as medium, and above 13.8 % as large (Cohen, 1988).

Our primary analyses used separate linear regression analyses to assess the differences between participants with AN and TD participants in intra-network connectivity in the IN; and inter-network connectivity between the FPN-IN and the DMN-IN.

Two statistical models were used. In model 1, RS-FC was entered as dependent variable and group (AN/TD), age, and SES were entered as independent variables. Model 2 was similar to model 1, with the additional correction for anxiety and depressive symptoms. There were a total of 115 tests performed. The analyses were corrected for multiple testing using the False Discovery Rate (FDR) at a q-value of 0.05. We conducted the following sensitivity analyses to rule out the effect of possible confounders: (Papadopoulos et al., 2009) we repeated our analyses with an additional correction for total brain volume, and (Schmidt et al., 2016) we performed analyses excluding participants who were taking medication.

As a proportion of the AN participants had already regained weight (BMI-SDS ≥ -1.3) at inclusion, we conducted separate analyses to examine differences in RS-FC between underweight AN and TD participants within the same brain networks. Additional analyses were performed between underweight AN participants (BMI-SDS < -1.3) and those who were partially weight-restored (BMI-SDS ≥ -1.3), as well as between weight-restored participants and TD participants. The analyses were corrected for multiple testing by controlling the FDR at a q-value of 0.05.

As exploratory analyses, we assessed differences in RS-FC within the FPN and DMN between AN and TD participants. We conducted linear regression analyses correcting for age at scanner and SES in model 1, and additionally corrected for anxiety and depressive symptoms in model 2. There were a total of 100 tests performed. The analyses were corrected for multiple testing by controlling the FDR at a q-value of 0.05.

Second, we examined whether RS-FC was associated with ED severity (i.e. ED symptoms and BMI-SDS) in the AN group. We conducted separate linear regression analyses, correcting for age at scanning and SES in model 1, and additionally for depression and anxiety symptoms in model 2. The analyses were corrected for multiple testing by controlling the FDR at a q-value of 0.05.

Finally, to investigate whether RS-FC was associated with recovery at the one-year follow-up visit, a total of 26 additional analyses were performed on regions that showed statistically significant differences between participants with AN and TD participants. We assessed whether between-network and within-network correlations were associated with one-year clinical outcome in the AN group using separate logistic regression analyses. In model 1 recovery was entered as the dependent variable. Subsequently, RS-FC, age at the time of imaging, SES and weight status (underweight/weight-recovered) at baseline were entered as independent variables. In model 2, there was additional correction for depressive and anxiety symptoms. Recovery was defined by a combination of reaching 90 % of their ideal body weight and an EDE restraint subscale score within one SD of the mean score in a healthy population (Couturier and Lock, 2006). We used our TD group to determine the reference value for the EDE restraint subscale. First, we calculated the mean score of the EDE restraint subscale of the TD group (mean(SD) = 0.2(0.3)). Subsequently, a z-score was derived from the TD group and applied to the AN group. In cases where the z-score was less than one, the participant was considered as having recovered from ED symptoms. Data on recovery was available for 40 participants with AN, of which 8 were considered recovered. At follow-up, 71 % of AN participants were weight restored. We performed sensitivity analyses to assess the association between RS-FC and both BMI-SDS and EDE score at follow-up separately. Linear regression analyses were performed correcting for age at scanner, SES and baseline BMI-SDS or EDE score in model 1, and additionally corrected for anxiety and depressive symptoms in model 2. These analyses were corrected for multiple testing by controlling the FDR at a q-value of 0.05.

3. Results

3.1. Sample characteristics

Sociodemographic and clinical characteristics of participants with AN and TD participants are shown in Table 2. Of the 121 participants who underwent a MRI scan, the data from one participant was excluded due to head motion. This resulted in a final sample of 120 participants, consisting of 56 participants with AN and 64 TD participants. The majority of the participants were of Dutch national origin (AN: 92.6 %, TD: 84.4 %) and had mothers with high educational levels (AN: 50.0 %, TD: 62.7 %). Participants with AN and TD participants included in the neuroimaging analyses were matched on IQ (AN mean ± SD = 109.8 (12.9), TD mean ± SD = 111.8 (12.0); $t(113) = 0.09$, $p = 0.39$). TD participants were slightly older than participants with AN (TD median age (interquartile range (IQR)): 17.3 (16.1, 18.3) years; AN median age (IQR): 16.3 (15.5, 18.3) years, $p = 0.05$). As expected, participants with AN had significantly higher levels of ED symptoms ($p < 0.001$), anxiety ($p < 0.001$), and depressive symptoms ($p < 0.001$).

3.2. Differences in RS-FC between AN and TD participants

The significant results for the primary analyses, are shown in Table 3. These analyses assessed differences in intra-network connectivity within the IN and inter-network connectivity between the FPN-IN and between the DMN-IN between participants with AN and TD participants. We found that participants with AN showed lower RS-FC between the left FPN and IN compared to TD participants in model 1. This finding was close to statistical significance after multiple-testing correction, suggesting a potential trend that warrants further investigation. There were no significant between-group differences in RS-FC after additionally correcting for depressive and anxiety symptoms. The overall effect sizes of the results were small and varied between $0.00 - 0.11$. Full results are shown in Supplementary Table 1. The sensitivity analyses, including those with additional correction for total brain volume and those excluding participants taking medication, did not have an effect on the results. These findings suggest that the observed results are not driven by these factors.

We performed separate analyses to explore differences in RS-FC between AN participants with underweight and TD participants. The analyses revealed reduced RS-FC between the FPN-IN and DMN-IN in underweight AN participants compared to TD participants. The overall effect sizes varied between 0.00 and 0.13 (see Table 4 and Supplementary Table 2). There were no differences in RS-FC between weight-restored AN participants and TD participants (Supplementary Table 3).

3.3. Differences in RS-FC between underweight and weight-restored AN participants

Within the AN group, we performed additional analyses to examine potential differences in RS-FC between underweight AN participants (BMI-SDS < -1.3) and partially weight-restored AN participants (BMI-SDS ≥ -1.3). Before applying multiple testing correction, we observed that individuals with underweight AN had lower RS-FC in 7 out of the 30 analyses between the IN and the left FPN, and in 3 out of 50 analyses between the IN and DMN (see Supplementary Table 4), compared to the partially weight-restored participants with AN in statistical model 1. In statistical model 2, a slightly higher number of analyses were significant before correction for multiple testing: 6 out of 30 between the IN and left FPN, 7 out of 50 between the IN and DMN, and 1 out of 10 within the IN.

Table 2
Sociodemographic and clinical characteristics of the AN and TD participants.

			AN participants (n = 56)		TD participants (n = 64)	
	N	Statistic	Baseline	One-year follow-up		*p* value #
Age at MRI measurement (years)	120	Median (IQR)	16.3 (15.5, 18.4)		17.3 (16.1, 18.3)	0.171
Ethnicity	117	Percentage				0.419
Dutch			92.6		84.4	
Western			5.6		9.4	
Non-western			1.9		6.3	
SES	113	Percentage				0.142
Low			13.0		6.8	
Middle			37.0		30.5	
High			50.0		62.7	
FSIQ score	120	Mean (SD)	109.8 (12.9)		111.8 (12.0)	0.389
BMI-SDS	119	Mean (SD)	−1.3 (1.3)	−0.8 (1.1)	0.5 (1.0)	<0.001***
BMI-SDS < −1.3	30	Percentage	53.6	29.3	–	
BMI-SDS ≥ −1.3	26	Percentage	46.4	70.7	–	
EDE total score	120	Median (IQR)	3.8 (2.6, 4.6)	2.5 (1.3, 3.3)	0.2 (0.1, 0.5)	<0.001***
Psychotropic medication (% using)	120	Percentage				
Antidepressant			5.4		1.6	0.338
Anxiolytic			3.6		1.6	0.598
Antipsychotic			12.5		0.0	0.004**
Stimulant			0		6.3	0.122
Duration of illness (months)	49	Median (IQR)	3.8 (1.7, 7.4)		–	–
BDI total score	109	Median (IQR)	29.0 (20.0, 42.5)[a]		4.0 (1.0, 7.8)[b]	<0.001***
Any mood disorder	118	Percentage	58.2		14.3	<0.001***
SCARED total score	110	Median (IQR)	44.5 (28.0, 68.5)[c]		21.5 (13.3, 32.3)[d]	<0.001***
Any anxiety disorder	118	Percentage	45.5		12.7	<0.001***

Note. Ethnicity is based on birth country of mother; SES: Socioeconomic status based on maternal education; categorized into: Low: primary education and lower general secondary education; Middle: higher general secondary education; High: higher vocational secondary education and higher academic education;
Abbreviations.
AN: anorexia nervosa; BDI-II: Beck Depression Inventory – Second edition; BMI-SDS: body mass index – standard deviation score; EDE: Eating Disorder Examination; FSIQ: Full Scale Intelligence Quotient; MRI: Magnetic Resonance Imaging; SCARED: Screening for Child Anxiety Related Emotional Disorders; TD: typically developing.
*$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
 # AN participants at baseline versus TD participants at baseline.
[a] A median BDI total score of 29.0 corresponds to 'severe depression'.
[b] A median BDI total score of 4.0 corresponds to 'minimal depression'.
[c] A median SCARED score of 44.5 'may indicate the presence of an Anxiety Disorder'.
[d] A median SCARED score of 21.5 indicates that an Anxiety Disorder may not be present.

The effect sizes of the significant results were medium and varied between 0.07 and 0.13. However, none of the between-network correlations were significant after correction for multiple testing.

Second, we explored whether there were differences in within-network connectivity of the DMN and FPN. Overall, participants with AN showed a lower within-network connectivity in some regions of the DMN (mainly between the anterior and posterior component) and the FPN compared to TD participants, although the findings did not survive multiple-testing correction (Supplementary Table 5). In most analyses, the statistical model led to decreased effect sizes following additional correction for comorbid depression and anxiety. Effect sizes were small and varied between 0.00 and 0.07. Full results are shown in Supplementary Table 6.

3.4. Association of RS-FC with baseline clinical symptoms and one-year clinical outcome in the AN group

The results of the analyses assessing the association between RS-FC at baseline with one-year clinical outcome are shown in Table 5. In the AN group, 6 out of 26 associations were linked to the one-year clinical outcome in statistical model 1, which was adjusted for age at the time of scanning, SES, and weight status (underweight/weight-restored) at the time of scanning. When additionally correcting for anxiety and depressive symptoms, 5 out of 26 associations were linked to one-year clinical outcome. Reduced RS-FC between the IN and DMN, as well as between the IN and FPN at baseline was associated with clinical recovery at one-year follow-up. However, these associations did not remain significant after correction for multiple testing. In accordance with our previous results, our analyses with continuous outcomes instead of dichotomous outcome did not yield any significant findings after correction for multiple testing (Supplementary Table 7 and 8).

There were no statistically significant associations between RS-FC and clinical symptoms (i.e. BMI-SDS and ED symptoms) at baseline in the AN group.

4. Discussion

4.1. Principal findings

The primary goal of our study was to examine RS-FC in a large female adolescent AN cohort with a short illness duration compared to a group of matched TD adolescents. Separate analyses were conducted to compare the underweight AN group with the TD participants, as well as the underweight AN group versus the weight-restored AN group. Additionally, the relationship between RS-FC and the severity of clinical symptoms was studied, and whether baseline RS-FC was related to recovery at one-year of follow-up. We found that underweight adolescents with AN showed reduced RS-FC between the FPN-IN and DMN-IN compared to TD adolescents. Another interesting finding is that reduced RS-FC between the IN and DMN, as well as between the IN and FPN at baseline, was significantly associated with clinical recovery at one-year follow-up, although significance was lost after multiple-testing correction.

4.2. Differences in RS-FC between participants with AN and TD participants

We found that differences in RS-FC were present between

Table 3
Primary analyses – Differences in RS-FC between AN and TD participants – Significant results before FDR.

Region 1	Region 2	Model 1	β	R^2 change	95 % CI		p value	Model 2	β	R^2 change	95 % CI		p value
Between the IN and DMN					Lower limit	Upper limit					Lower limit	Upper limit	
2	24		-0.196	0.037	-0.237	-0.005	0.041		-0.010	0.004	-0.270	0.133	0.500
2	26		−0.193	0.036	−0.234	−0.002	0.047		−0.193	0.013	−0.324	0.083	0.242
6	22		−0.196	0.037	−0.201	−0.005	0.041		−0.396	0.055	−0.368	−0.043	0.014
6	26		−0.199	0.038	−0.218	−0.007	0.037		−0.388	0.053	−0.391	−0.043	0.015
7	26		−0.226	0.049	−0.239	−0.023	0.018		−0.288	0.029	−0.348	0.015	0.072
8	22		−0.234	0.052	−0.251	−0.027	0.016		−0.268	0.025	−0.353	0.031	0.100
8	24		−0.194	0.036	−0.224	−0.003	0.044		−0.229	0.018	−0.318	0.053	0.160
9	22		−0.228	0.050	−0.242	−0.024	0.017		−0.157	0.009	−0.280	0.096	0.333
Between the IN and left FPN													
12	26		−0.225	0.049	−0.210	−0.019	0.019		−0.278	0.027	−0.312	0.022	0.089
13	22		−0.248	0.059	−0.255	−0.036	0.010		−0.186	0.012	−0.301	0.080	0.253
13	26		−0.321	0.099	−0.288	−0.079	<0.001		−0.304	0.032	−0.359	0.005	0.056
14	22		−0.235	0.053	−0.215	−0.025	0.014		−0.173	0.010	−0.254	0.078	0.294
14	26		−0.225	0.049	−0.217	−0.020	0.019		−0.187	0.012	−0.270	0.073	0.258
15	22		−0.229	0.050	−0.228	−0.022	0.018		−0.236	0.019	−0.308	0.047	0.149
15	26		−0.244	0.057	−0.230	−0.030	0.011		−0.282	0.028	−0.322	0.020	0.083
16	22		−0.129	0.044	−0.241	−0.017	0.025		−0.123	0.005	−0.261	0.114	0.440
16	26		−0.222	0.048	−0.254	−0.024	0.018		−0.221	0.017	−0.334	0.058	0.166
Between the IN and right FPN													
17	22		−0.190	0.035	−0.204	−0.001	0.049		−0.056	0.001	−0.204	0.143	0.143
18	22		−0.222	0.047	−0.216	−0.018	0.021		−0.282	0.028	−0.326	0.022	0.086
18	24		−0.228	0.050	−0.220	−0.021	0.018		−0.298	0.031	−0.332	0.013	0.069
19	22		−0.256	0.063	−0.263	−0.041	0.008		−0.224	0.018	−0.334	0.059	0.168
19	24		−0.205	0.090	−0.284	−0.070	0.001		−0.280	0.027	−0.346	0.020	0.080
19	26		−0.239	0.055	−0.241	−0.029	0.013		−0.256	0.023	−0.331	0.037	0.117
20	22		−0.312	0.094	−0.275	−0.071	0.001		−0.329	0.038	−0.364	−0.010	0.039
20	24		−0.272	0.071	−0.260	−0.048	0.005		−0.211	0.016	−0.297	0.059	0.188
20	26		−0.284	0.077	−0.255	−0.053	0.003		−0.295	0.030	−0.337	0.011	0.066
Within the IN													
–													

Note. β's are standardized betas of statistical model I and II; R^2 change = R^2 for adding group (anorexia nervosa/typically developing participant) to the model represents the explained variance; Model 1 adjusted for age and socioeconomic status, model 2 additionally adjusted for baseline anxiety and depressive symptoms; *Abbreviations*.
AN: anorexia nervosa; CI: Confidence Interval; DMN: default mode network; FPN: frontoparietal network; IN: insular network; TD: typically developing; RS-FC: resting-state functional connectivity.
Bold: significant *p* value after correction for multiple testing using FDR with a cut-off point of 0.05.

underweight participants with AN and TD participants, but no significant differences were found when comparing the entire AN group with the TD group. This suggests that alterations in RS-FC may be more specifically linked to the underweight status, aligning with findings from structural neuroimaging studies that showed more pronounced brain volume reductions while being underweight (Walton et al., 2022). In line with previous studies, we replicated reduced inter-network connectivity between the FPN and IN in underweight AN participants (Lotter et al., 2021; Scaife et al., 2017; Gaudio et al., 2018) and we found reduced inter-network connectivity between the DMN and IN. Based on the commonly used phrase in RS-fMRI: "what is wired together, fires together" (Eickhoff and Functional, 2015; White and Calhoun, 2019), this suggests disrupted neuronal signaling between these two regions. The IN plays a role in emotion regulation, risk-reward behavior, decision making, and interoception, and those with AN have distortions in interpreting sensory input about their body (Kortz and Insular, 2024). In addition, the DMN is linked to self-referential processing (Boehm et al., 2014) which may contribute to the perseverative internal focus on weight and body issues, reflected in connectivity differences between the IN and DMN. Finally, the FPN is implicated in cognitive processes and executive function (Marek and Dosenbach, 2018). Thus, a disrupted connectivity between the FPN and the IN may disrupt the cognitive elements in the interpretation of sensory input about their body and may therefore partly explain the challenges that individuals with AN experience (Haynos et al., 2015; Giannunzio et al., 2018).

In line with our hypothesis, we did not observe significant differences in the DMN between participants with AN and TD participants after multiple-testing correction, in accordance with previous findings (Phillipou et al., 2016; Boehm et al., 2016). Lastly, no significant differences in RS-FC in the IN were found between AN and TD participants, in contrast to previous studies that report either greater connectivity (Boehm et al., 2014; Amianto et al., 2013) or lower connectivity (Ehrlich et al., 2015; Gaudio et al., 2018; Geisler et al., 2016) in AN. Possible explanations for these discrepancies include differences in sample characteristics (i.e. sample size, illness severity, and duration of illness), as well as differences in statistical approach. It is possible that adolescents earlier in the course of their illness may have greater heterogeneity, with only those with more chronic AN showing more homogeneous patterns in RS-FC. Furthermore, RS-FC also appears to be related to disease progression. In the early stages, networks associated with emotional regulation and cognitive control are more affected, whereas in later stages, networks associated with self-referential processing are more frequently affected (Gaudio et al., 2016). Thus, alterations in RS-FC may change over time or manifest at a later stage of the disease.

Overall, our effect sizes regarding the comparison of RS-FC between participants with AN and TD participants were small, as in most other RS-FC studies in AN. The median sample size in most neuroimaging studies tends to be around 25 participants (Marek et al., 2022), whereas our study involved a considerably larger sample (n = 121). Despite our unique sample size, a major challenge in the field of neuroimaging is that thousands of individuals are often required for replication (Marek et al., 2022). Therefore RS-FC measures alone may not be sufficient to identify behavioral predictors. To enhance the reliability and predictive power of neuroimaging findings, future studies could benefit from developing multimodal algorithms that integrate biopsychosocial

Table 4
Differences in RS-FC between underweight AN and TD participants – Significant results before FDR.

Region 1	Region 2	Model 1	β	R^2 change	95 % CI		p value	Model 2	β	R^2 change	95 % CI		p value
Between the IN and DMN					Lower limit	Upper limit					Lower limit	Upper limit	
2	23		−0.214	0.045	−0.288	−0.004	**0.045**		−0.019	0.000	−0.306	0.279	0.929
2	24		−0.314	0.097	−0.346	−0.075	**0.003**		−0.380	0.037	−0.543	0.019	0.067
2	26		−0.241	0.057	−0.302	−0.021	0.025		−0.372	0.035	−0.542	0.034	0.084
3	22		−0.241	0.057	−0.275	−0.020	0.024		−0.470	0.056	−0.539	−0.035	0.026
3	24		−0.245	0.059	−0.282	−0.023	0.021		−0.454	0.053	−0.547	−0.025	0.032
6	22		−0.228	0.051	−0.246	−0.011	0.032		−0.439	0.049	−0.484	−0.018	0.035
6	24		−0.249	0.061	−0.282	−0.032	0.014		−0.400	0.041	−0.512	−0.005	0.045
6	26		−0.230	0.052	−0.264	−0.014	0.029		−0.441	0.050	−0.518	−0.023	0.032
7	26		−0.262	0.068	−0.300	−0.034	0.014		−0.307	0.024	−0.463	0.067	0.142
8	22		−0.300	0.088	−0.331	−0.060	**0.005**		−0.536	0.073	−0.615	−0.084	0.010
8	24		−0.273	0.073	−0.307	−0.041	0.011		−0.575	0.085	−0.625	−0.106	0.006
8	26		−0.242	0.057	−0.289	−0.020	0.025		−0.395	0.040	−0.526	0.017	0.066
9	22		−0.300	0.089	−0.313	−0.059	**0.005**		−0.413	0.044	−0.511	−0.003	0.048
9	26		−0.227	0.051	−0.270	−0.011	0.033		−0.302	0.023	−0.449	0.075	0.160
Between the IN and left FPN													
11	22		−0.219	0.047	−0.268	−0.007	0.039		0.009	0.000	−0.263	0.275	0.965
11	25		−0.223	0.049	−0.304	−0.008	0.039		−0.043	0.000	−0.334	0.273	0.842
12	22		−0.260	0.066	−0.264	−0.029	**0.015**		−0.384	0.038	−0.463	0.022	0.074
12	24		−0.255	0.064	−0.276	−0.029	0.016		−0.353	0.032	−0.466	0.041	0.099
12	26		−0.289	0.082	−0.273	−0.045	0.007		−0.422	0.046	−0.471	−0.003	0.048
13	22		−0.302	0.089	−0.323	−0.060	0.005		−0.330	0.028	−0.48	0.053	0.115
13	23		−0.256	0.064	−0.302	−0.032	0.016		−0.203	0.011	−0.404	0.135	0.324
13	24		−0.244	0.059	−0.289	−0.024	0.022		−0.216	0.012	−0.406	0.127	0.301
13	26		−0.368	0.133	−0.351	−0.103	**<0.001**		−0.430	0.047	−0.522	−0.019	0.035
14	22		−0.349	0.120	−0.289	−0.076	**<0.001**		−0.497	0.063	−0.484	−0.047	0.018
14	24		−0.241	0.057	−0.259	−0.018	0.024		−0.500	0.064	−0.521	−0.045	0.021
14	26		−0.331	0.107	−0.291	−0.068	**0.002**		−0.482	0.059	−0.497	−0.038	0.023
15	22		−0.298	0.087	−0.296	−0.053	**0.005**		−0.455	0.053	−0.512	−0.026	0.031
15	24		−0.217	0.046	−0.252	−0.006	0.039		−0.412	0.043	−0.498	−0.001	0.049
15	26		−0.310	0.094	−0.294	−0.060	**0.004**		−0.490	0.062	−0.514	−0.047	0.019
16	22		−0.275	0.074	−0.314	−0.046	0.009		−0.351	0.031	−0.488	0.034	0.087
16	23		−0.213	0.045	−0.263	−0.006	0.040		−0.189	0.009	−0.381	0.139	0.355
16	26		−0.280	0.077	−0.329	−0.054	0.007		−0.415	0.044	−0.561	−0.007	0.044
Between the IN and right FPN													
17	22		−0.278	0.076	−0.268	−0.039	0.009		−0.427	0.047	−0.461	−0.010	0.041
17	24		−0.243	0.058	−0.258	−0.020	0.022		−0.439	0.049	−0.481	−0.015	0.037
17	26		−0.233	0.053	−0.244	−0.012	0.031		−0.346	0.031	−0.418	0.037	0.100
18	22		−0.277	0.075	−0.261	−0.037	0.010		−0.557	0.079	−0.530	−0.079	0.009
18	24		−0.267	0.070	−0.274	−0.035	0.012		−0.624	0.100	−0.598	−0.127	0.003
18	26		−0.242	0.058	–232	−0.232	0.016		−0.488	0.061	−0.466	−0.036	0.023
19	22		−0.311	0.095	−0.321	−0.065	**0.004**		−0.429	0.047	−0.535	−0.010	0.042
19	24		−0.359	0.126	−0.351	−0.099	**<0.001**		−0.536	0.073	−0.588	−0.087	0.009
19	26		−0.297	0.086	−0.287	−0.052	**0.005**		−0.436	0.049	−0.489	−0.015	0.038
20	22		−0.321	0.101	−0.314	−0.068	**0.003**		−0.439	0.049	−0.513	−0.019	0.035
20	24		−0.295	0.085	−0.312	−0.054	**0.006**		−0.502	0.065	−0.561	−0.057	0.017
20	26		−0.274	0.074	−0.284	−0.038	0.011		−0.324	0.027	−0.439	0.054	0.123
Within the IN													
–													

Note. β's are standardized betas of statistical model I and II; R^2 change = R^2 for adding group (anorexia nervosa/typically developing participant) to the model represents the explained variance; Model 1 adjusted for age and socioeconomic status, model 2 additionally adjusted for baseline anxiety and depressive symptoms; *Abbreviations*.

AN: anorexia nervosa; CI: Confidence Interval; DMN: default mode network; FPN: frontoparietal network; IN: insular network; TD: typically developing; RS-FC: resting-state functional connectivity.

Bold: significant *p* value after correction for multiple testing using FDR with a cut-off point of 0.05.

factors, such as clinical symptoms, genetics, and other relevant variables in order to enhance the reliability and predictive power of the findings (White, 2022). Future studies could also benefit from using multivariate approaches to examine differences in RS-FC between AN and TD participants, as well as predictors of clinical outcome. Larger sample sizes and collaborations with other AN samples are essential to increase statistical power.

4.3. Association of RS-FC with clinical outcome in the AN group

To our knowledge, our study is the first to investigate the relationship between RS-FC and clinical recovery in AN. We observed that a reduced RS-FC between the IN and DMN, as well as between the IN and FPN at baseline was associated with clinical recovery at one-year follow-up in adolescents with AN. However, this finding did not survive multiple-testing correction, possibly due to insufficient power given the relatively small sample size at follow-up (n = 40 AN participants). Longitudinal studies could further investigate the neural connectivity patterns between the IN and the DMN and FPN respectively, as they may be involved in the early stages of AN. In addition, future studies should use larger sample sizes and longer follow-up periods to further investigate the relationship between connectivity patterns and clinical outcome, especially considering the heterogeneity of the AN phenotype. In line with prior studies we found no association between RS-FC and clinical symptoms.

Table 5
Associations of RS-FC at baseline with one-year clinical outcome in AN participants.

Region 1	Region 2	Model 1	Odds ratio	95 % CI for OR		p value	Model 2	Odds ratio	95 % CI for OR		p value
				Lower limit	Upper limit				Lower limit	Upper limit	
Between the IN and the DMN											
2	24		0.071	0.003	1.826	0.110		0.055	0.001	2.439	0.134
2	26		0.010	0.000	1.281	0.063		0.011	0.000	3.305	0.121
6	22		0.010	0.000	1.486	0.071		0.016	0.000	3.703	0.136
6	26		0.037	0.001	2.354	0.120		0.075	0.001	8.000	0.277
7	26		0.008	0.000	2.212	0.092		0.011	0.000	5.526	0.154
8	22		0.006	0.000	0.630	0.031*		0.007	0.000	0.885	0.044*
8	24		0.033	0.001	1.509	0.080		0.031	0.000	2.475	0.120
9	22		0.112	0.004	0.3538	0.214		0.095	0.002	4.190	0.223
Between the IN and left FPN											
12	26		0.010	0.000	2.367	0.098		0.023	0.000	4.726	0.023*
13	22		0.036	0.001	1.235	0.065		0.026	0.000	1.675	0.026*
13	26		0.043	0.001	1.786	0.098		0.044	0.001	3.011	0.148
14	22		0.210	0.008	5.621	0.352		0.145	0.003	7.526	0.338
14	26		0.449	0.018	10.916	0.623		0.456	0.008	25.550	0.702
15	22		0.018	0.000	0.928	0.046*		0.021	0.000	1.341	0.021*
15	26		0.018	0.000	1.314	0.067		0.018	0.000	2.165	0.100
16	22		0.001	0.000	0.344	0.021*		0.000	0.000	1.182	0.053
16	26		0.000	0.000	0.424	0.027*		0.000	0.000	0.641	0.040*
Between the IN and right FPN											
17	22		0.137	0.000	0.867	0.044*		0.000	0.000	5.411	0.094
18	22		0.055	0.001	2.210	0.124		0.036	0.001	2.176	0.112
18	24		0.123	0.003	5.490	0.280		0.104	0.002	6.607	0.104
19	22		0.095	0.003	2.634	0.165		0.067	0.001	3.152	0.328
19	24		0.131	0.004	3.905	0.241		0.093	0.002	5.136	0.246
19	26		0.085	0.002	3.144	0.181		0.070	0.001	4.678	0.214
20	22		0.011	0.000	2.310	0.098		0.012	0.000	2.540	0.106
20	24		0.006	0.000	0.669	0.034*		0.003	0.000	1.029	0.051
20	26		0.051	0.000	5.220	0.207		0.064	0.001	7.435	0.258

Note. Model 1 adjusted for age and socioeconomic status, model 2 additionally adjusted for baseline anxiety and depressive symptoms;
Abbreviations.
AN: anorexia nervosa; CI: Confidence Interval; DMN: default mode network; FPN: frontoparietal network; IN: insular network; OR: Odds ratio; RS-FC: resting-state functional connectivity.
*: significant *p* value before correction for multiple testing using FDR with a cut-off point of 0.05. **Bold**: significant *p* value after correction for multiple testing using FDR with a cut-off point of 0.05.

4.4. Clinical implications

Our study shows that there is reduced RS-FC in an early phase of AN in the underweight state. These reductions are notably less pronounced in weight-restored AN participants. This highlights the importance of therapeutic intervention in an early stage of the disease. In the clinical setting it may also be important to take into account other relevant factors (e.g. ED duration and severity). Our exploratory analyses showed that RS-FC at an early stage of the illness may have predictive value for the clinical outcome of AN, although our findings did not survive multiple-testing correction. Perhaps, this study may have been underpowered to detect statistically significant differences. Larger sample sizes may help identify homogeneous groups that may provide greater predictions of the course of the illness. As it is still very difficult for clinicians to predict the course of AN, identifying predictors is one of the highest priorities in ED research (van Furth et al., 2016; Zipfel et al., 2015). Our findings underscore the importance of improving our knowledge of the neural underpinnings of AN and its association with clinical symptoms, serving as a pathway towards the development of more targeted interventions. Thus, future studies could further investigate the relationship between connectivity patterns and clinical outcomes.

4.5. Strengths and limitations

Strengths of our study include the relatively large sample of adolescents with first-onset AN, matched on age-, gender-, and education to TD adolescents. Another strength is that we adjusted our analyses for frequently occurring comorbid symptoms, which offers the opportunity to investigate the specific neurobiology related to AN. In addition, we performed sensitivity analyses to correct for total brain volume, and to rule out the potential effects of medication, as the use of serotonergic antidepressants and/or antipsychotic medication could have had an effect on RS-FC patterns (McCabe and Mishor, 2011; van de Ven et al., 2013; Lui et al., 2010). The limitations of the study were that the number of statistical analyses performed increased the probability of Type I errors, which was addressed by a thorough correction for multiple testing. We also used a hypothesis-driven rather than a data-driven approach assessing whole-brain connectivity in order to limit the large number of tests. We did not take into account environmental factors, such as childhood maltreatment, which may influence RS-FC measures (Amiri and Sabzehparvar, 2024; Guo et al., 2024), although we included a wide range of neurobiological measures. By presenting all the results, our findings can be used for future hypothesis-driven studies focusing on specific brain regions and *meta*-analytic purposes. To address the abovementioned limitations, we advise future research to employ a longitudinal study design with a larger sample size, longer follow-up period and to take into account the underweight status, illness severity, and illness duration to disentangle state and trait effects of AN.

5. Conclusion

In conclusion, we found that underweight adolescent females with AN have reduced RS-FC between the FPN-IN, as well as between the DMN-IN compared to TD adolescent females. The absence of alterations in RS-FC in weight-restored AN participants underscores the significant influence of being underweight while having AN on RS-FC. Alterations in these specific RS-FC networks may partly explain the impaired cognitive control and difficulties with emotion and behavioral regulation in individuals with AN.

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CRediT authorship contribution statement

Katrien F.M. Bracké: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Laura Monteiro Rente Dias:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Marisha N. Meijer:** Writing – review & editing, Formal analysis. **Cathelijne P.M. Steegers:** Writing – review & editing, Data curation. **Laurinde F. den Heijer:** Writing – review & editing, Data curation. **Tess van der Harst:** Writing – review & editing, Data curation. **Marjolein H. G. Dremmen:** Writing – review & editing, Funding acquisition, Conceptualization. **Meike W. Vernooij:** Writing – review & editing, Funding acquisition, Conceptualization. **Gwen C. Dieleman:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Tonya White:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2025.103745.

Data availability

Data will be made available on request.

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