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# Association between the frontoparietal network, clinical symptoms and treatment response in individuals with untreated anorexia nervosa

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## ABSTRACT

**Background** Anorexia nervosa (AN) has been characterised as a psychiatric disorder associated with increased control. Currently, it remains difficult to predict treatment response in patients with AN. Their cognitive abilities are known to be resistant to treatment. It has been established that the frontoparietal control network (FPCN) is the direct counterpart of the executive control network. Therefore, the resting-state brain activity of the FPCN may serve as a biomarker to predict treatment response in AN.

**Aims** The study aimed to investigate the association between resting-state functional connectivity (RSFC) of the FPCN, clinical symptoms and treatment response in patients with AN.

**Methods** In this case-control study, 79 female patients with AN and no prior treatment from the Shanghai Mental Health Center and 40 matched healthy controls (HCs) were recruited from January 2015 to March 2022. All participants completed the Questionnaire Version of the Eating Disorder Examination (version 6.0) to assess the severity of their eating disorder symptoms. Additionally, RSFC data were obtained from all participants at baseline by functional magnetic resonance imaging. Patients with AN underwent routine outpatient treatment at the 4th and 12th week, during which time their clinical symptoms were evaluated using the same measures as at baseline.

**Results** Among the 79 patients, 40 completed the 4-week follow-up and 35 completed the 12-week follow-up. The RSFC from the right posterior parietal cortex (PPC) and dorsolateral prefrontal cortex (dlPFC) increased in 79 patients with AN vs 40 HCs after controlling for depression and anxiety symptoms. By multiple linear regression, the RSFC of the PPC to the inferior frontal gyrus was found to be a significant factor for self-reported eating disorder symptoms at baseline and the treatment response to cognitive preoccupations about eating and body image, after controlling for age, age of onset and body mass index. The RSFC in the dlPFC to the middle temporal gyrus and the superior frontal gyrus may be significant factors in the treatment response to binge eating and loss of control/overeating in patients with AN.

**Conclusions** Alterations in RSFC in the FPCN appear to affect self-reported eating disorder symptoms and treatment response in patients with AN. Our findings offer new insight into the pathogenesis of AN and could promote early prevention and treatment.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Anorexia nervosa (AN) has been considered a disorder of overcontrol and is associated with elevated resting-state functional connectivity (RSFC) in the frontoparietal control network (FPCN).

### WHAT THIS STUDY ADDS

⇒ Alterations in the RSFC of the posterior parietal cortex play an important role in self-reported eating disorder symptoms and the treatment response to cognitive preoccupations about eating and body image.

⇒ Alterations in the RSFC of the dorsolateral prefrontal cortex seem to influence the treatment response to binge eating behaviours and loss of control/overeating behaviours in patients with AN.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study shows the importance of the FPCN in self-reported eating disorder symptoms and treatment response in patients with AN.

⇒ Our findings may formulate new ideas for the pathogenesis of AN and potential strategies for early prevention and treatment of the disorder.

## INTRODUCTION

Anorexia nervosa (AN) is an eating disorder characterised by severe dietary restriction, misperceptions of body shape and weight, and fear of weight gain, combined with some emotional problems.[1] It has the highest and ever-increasing mortality rates (5%–6%) among psychiatric illnesses, and it especially threatens the physical and psychological health of female adolescents.[2] AN is divided into two subtypes with diverse symptoms: the restricting type (AN-R) and the binge/purging type (AN-BP). One study has found

that the ability to control impulses and respond to emotional stimuli is closely associated with risk of binge eating and purging episodes in patients with AN-BP,[3] and enhanced cognitive control function is closely related to distorted body image and excessive focus on food intake and body shape in patients with AN-R.[4] The frontoparietal control network (FPCN) has been reported to be involved in humans' cognitive and impulsive control processes.[5] Alterations in the resting-state functional connectivity (RSFC) of the FPCN, which have been studied widely and implicated in psychiatric disorders,[6] are also associated with the aetiology of AN.[7] Moreover, AN is prone to relapse, and no predictive markers for treatment efficacy have been found. Therefore, further investigation of its pathogenesis and potential predictive markers is necessary.[8]

AN has been described as a disorder with excessive cognitive control functions associated with its related altered brain network, which may contribute to its onset and persistence.[4] The FPCN has been linked to humans' cognitive function and impulsive control processes.[5] As one of its functions, the FPCN regulates eating behaviours; altered brain activation in the FPCN is associated with abnormal eating behaviours.[9] Patients with AN exhibit widespread alterations in executive function and impaired cognitive flexibility, which are seemingly linked to an aberrant FPCN function.[10] Another study suggested that patients with AN had enhanced executive function and greater inhibitory control.[11]

The FPCN is generally known as the central executive network or cognitive control network. It encompasses the brain regions of the bilateral posterior parietal cortex (PPC) and the bilateral dorsolateral prefrontal cortex (dlPFC). It is a flexible hub with a high degree of connectivity across the brain.[12] Alterations in brain-wide connectivity in the FPCN have been linked to a wide range of mental illnesses and are known to play a crucial role in the onset and persistence of mental disorders, including AN.[13] A previous study suggested that neural activities in the frontal and parietal brain were associated with enhanced inhibition and cognitive control abilities.[9] Another study indicated that increased RSFC within the FPCN may be linked to excessive cognitive control in AN.[7] Therefore, dysfunction of the FPCN may be an important neuropathological factor in AN. In addition, previous studies investigated the relationship between antidepressant treatments, psychiatric symptoms and functional connectivity between brain regions. One study showed that altered RSFC related to the FPCN could predict antidepressant medication and psychological treatment outcomes in patients with major depressive disorder.[14] In another study, disease remission was achieved by normalising abnormal regional brain connections through treatment, including the regions in the FPCN.[15] However, the predictive role of RSFC within the FPCN indetermining treatment response in AN has not been studied.

Given the above, the FPCN is robustly related to cognitive control, executive function and disordered eating symptoms in AN. However, few previous studies have predicted the neurological markers of clinical outcomes in patients with AN. The present study addresses the urgent need to explore the neural mechanisms of AN pathogenesis and clinical treatment. It holds the following hypotheses: AN is associated with altered RSFC in the FPCN compared with healthy controls (HCs), and the RSFC in the FPCN may be a neural marker that can predict clinical symptoms and treatment response in AN.

## METHODS

### Participants

Seventy-nine females with treatment-naive AN were recruited from January 2015 to March 2022 at the Eating Disorder Treatment Center, Shanghai Mental Health Center (SMHC), of whom 47 were of AN-R subtype and 32 were of AN-BP subtype. Two or more senior psychiatrists evaluated the patients according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-V*) criteria. Inclusion criteria for patients with AN were as follows: (1) an initial diagnosis of AN according to the *DSM-V* criteria, (2) aged 13–25 years, (3) Han Chinese ethnicity, (4) right-handed and (5) a body mass index (BMI) of 13.0–18.5 kg/m$^2$. Exclusion criteria for this group were as follows: (1) a past diagnosis of or treatment for eating disorders, (2) evidence of a serious or chronic somatic disease and a history of other psychiatric disorders, (3) any psychiatric or psychological therapy for at least 12 weeks prior to the study, (4) currently pregnant or breast feeding and (5) metal implants in their body that would prevent them from undergoing magnetic resonance imaging (MRI) examination. Forty HCs were recruited among the students and health workers at the SMHC by advertisements and were matched to the patients in terms of age and educational level. The same criteria were applied to HCs, except they had no history of eating disorders and no restrictions on BMI parameters. All participants signed informed consent.

### Study design

In this case-control study, all participants were administered a physical examination, a clinical questionnaire and a resting-state functional MRI (fMRI) examination at baseline. Subsequently, patients with AN received routine outpatient treatment, mainly including psychological counselling, nutritional evaluation and pharmacological therapies based on their situations. The pharmacological treatments mainly included selective serotonin reuptake inhibitors (n=32), atypical antipsychotics (n=14) and benzodiazepines (including alprazolam, lorazepam and estazolam; n=6) and zolpidem (n=4). Physical examination and clinical symptoms were evaluated at 4-week and 12-week follow-up.

### Outcome assessments

Demographic and clinical characteristics, including age, educational level and BMI (calculated by current

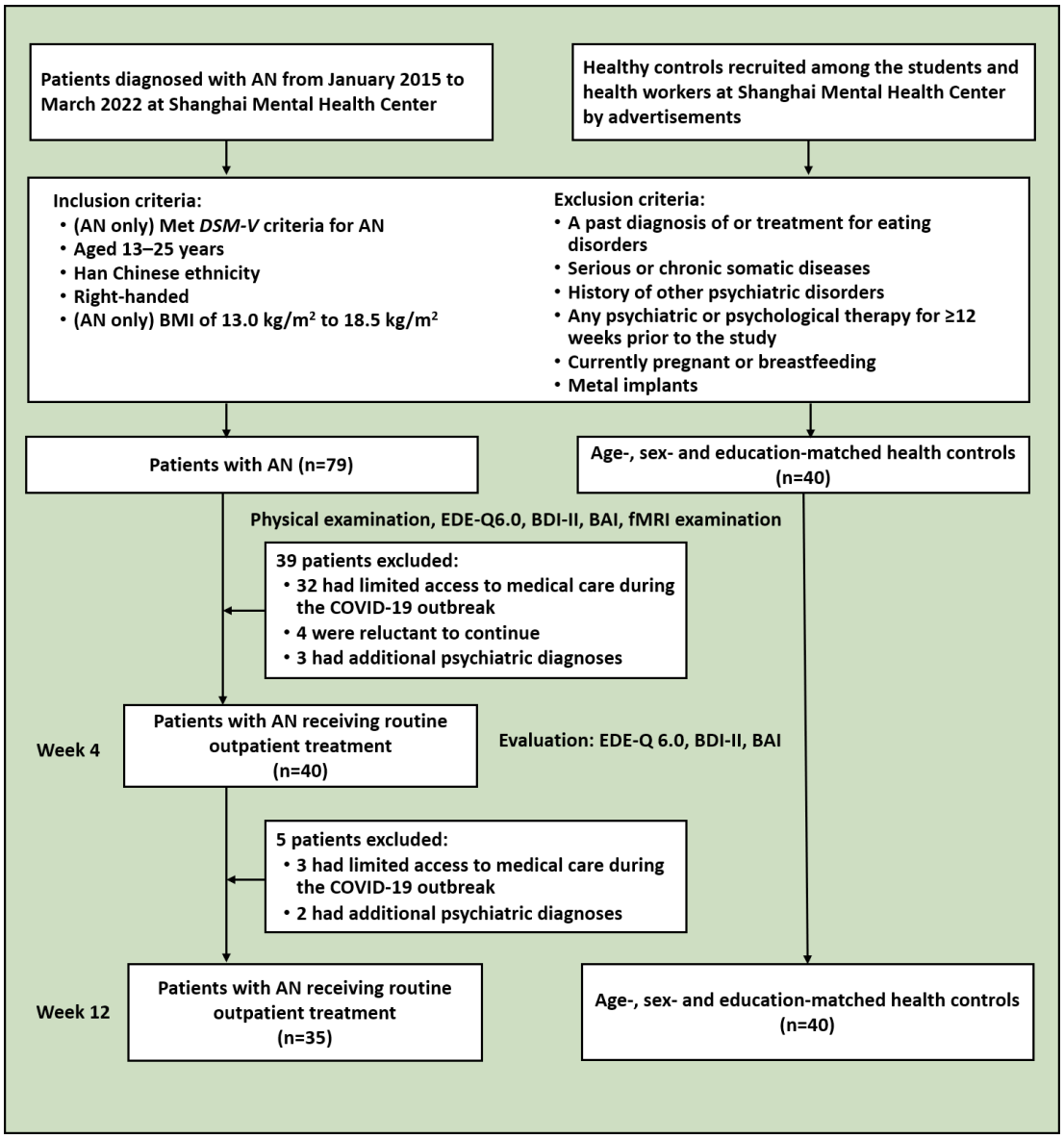


**Figure 1** Flowchart of the study design. AN, anorexia nervosa; BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory; BMI, body mass index; *DSM-V*, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; EDE-Q 6.0, Questionnaire Version of the Eating Disorder Examination (version 6.0); fMRI, functional MRI; HC, healthy control.

weight and height), were collected from all subjects. The severity of eating disorder was measured with the Eating Disorder Examination Questionnaire (EDE-Q 6.0). This widely used scale has 28 items that assess eating disorder symptoms, including thoughts, feelings and behaviours related to eating and body image, over the past 28 days. The scale includes 6 open-ended items—the frequency of overeating, loss of control, binge eating, self-induced vomiting, laxative abuse and compulsive exercise—and 22 attitudinal items, which are combined to create four subscales: restraint, eating, body shape and weight concerns. Purging behaviours are the sum of self-induced vomiting, laxative abuse and compulsive exercise. Higher scores on the four subscales and the total scale indicate more severe symptoms. Our previous study has confirmed good reliability and validity of the scale in mainland China, with Cronbach's alpha coefficients of 0.95 and test-retest reliability of 0.73.[16]

## Additional questionnaires

The Beck Depression Inventory-II (BDI-II) and the Beck Anxiety Inventory (BAI) were adopted to evaluate the depressive and anxiety symptoms of all subjects. The Chinese version of BDI-II has demonstrated excellent internal consistency, with a Cronbach's alpha of 0.94,[17] and the reliability and validity of the Chinese version of BAI were satisfactory.[18]

## MRI acquisition and preprocessing

All fMRIs were acquired on a 3.0T Siemens Verio MRI scanner (Erlangen, Germany) with a 12-channel head coil at the SMHC. The resting-state scans were acquired

Table 1 Demographic and clinical characteristics

| Characteristics | Mean (SD) | | | |
|---|---|---|---|---|
| | AN | HC | Test | P value |
| n | 79 | 40 | | |
| Age (years) | 18.92 (3.88) | 20.08 (2.41) | t=−1.75 | 0.083 |
| Age of onset | 16.63 (3.55) | – | – | – |
| BMI | 15.19 (2.10) | 19.87 (2.64) | t=−10.49 | <0.001 |
| BDI-II total score | 21.22 (16.69) | 6.15 (11.68) | t′=5.88 | <0.001 |
| BAI total score | 16.75 (15.97) | 3.21 (5.19) | t′=6.78 | <0.001 |
| EDE-Q 6.0 total score (baseline) | 2.46 (1.60) | 0.77 (0.66) | t′= 8.07 | <0.001 |
| Restraint | 2.28 (1.92) | 0.72 (1.07) | t′=5.69 | <0.001 |
| Eating concern | 2.43 (1.81) | 0.27 (0.33) | t′=10.30 | <0.001 |
| Shape concern | 2.73 (1.74) | 1.14 (0.85) | t′=6.71 | <0.001 |
| Weight concern | 2.38 (1.74) | 0.96 (0.88) | t′=5.94 | <0.001 |
| Overeating | 8.06 (15.90) | 0.97 (1.36) | t′=3.91 | <0.001 |
| Loss of control | 8.45 (14.49) | 0.11 (0.39) | t′=5.08 | <0.001 |
| Binge eating | 6.94 (10.84) | 0.16 (0.59) | t′=5.51 | <0.001 |
| Purge behaviours | 11.64 (19.60) | 0.47 (1.56) | t′=5.00 | <0.001 |

For continuous variable comparisons, t denotes homogeneity variance was achieved, while t' denotes homogeneity variance was not achieved.
AN, anorexia nervosa; BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory; BMI, body mass index; EDE-Q 6.0, Questionnaire Version of the Eating Disorders Examination (version 6.0); HC, healthy control.

using a gradient echo-planar imaging sequence (number of slices =45 170 scans, repetition time (TR) =3000 ms, echo time (TE) =30 ms, flip angle =85, field of view (FOV) =216 mm, matrix =64×64, voxel size =3×3×3 $mm^3$, slice thickness =3.0 mm). High-resolution anatomical scans were acquired with a T1-weighted three-dimension magnetization-prepared rapid gradient echo sequence (192 sagittal slices, TR=2300 ms, TE=2.96 ms, flip angle=85, FOV=256 mm, matrix =256×256, slice thickness =1 mm). Before scanning, participants were instructed to stay still and remain awake with their eyes closed. Foam padding and earplugs were provided to control head motion and reduce scanner noise.

Image preprocessing and analysis were conducted using SPM V.12 (http://www.fil.ion.ucl.ac.uk/spm) and CONN toolbox V.20.b (http://www.nitrc.org/projects/conn) on MATLAB V.R2021b (Mathworks). The fMRI preprocessing steps were as follows: discarding the first 10 volumes, motion correction, realignment, slice-timing correction and outlier scans for scrubbing. Then, functional and structural images were segmented by grey/white/cerebrospinal fluid and normalised into the Montreal Neurological Institute space. Functional images were spatially smoothed with a Gaussian kernel of 6 mm full width at half maxima, and the bandpass filtering was 0.008–0.09 Hertz. Potential confounders such as white matter, cerebrospinal fluid, realignment, scrubbing and effect of rest were regressed out.

### Region of interest selection and quality check

FPCN seeds were identified using the Harvard-Oxford cortical and structural atlas, and brain regions were defined using the Brodmann area (BA) atlas, including four brain regions of the bilateral PPC and dlPFC. The PPC seed was explored in one brain region located at BA 48, and the dlPFC seed was explored in three brain regions located at BA 8, BA 25 and BA 48. Seed-based correlation analysis was used to investigate time series connectivity between the seeds in the FPCN and all other voxels in the whole brain, and the connection strength was extracted from all participants. The quality of brain image values for each participant was checked based on the registration quality and head motion. Head motion was assessed using mean framewise displacement, with the maximal value set to 0.5 mm. Those with poor image quality were excluded from further analysis. Images from all participants passed the quality check, leading to a sample size of 79 patients and 40 HCs who passed quality checks of both clinical questionnaires and brain images.

### Statistical analyses

The demographic and clinical characteristics were analysed using SPSS V.25.0. Continuous data are presented as mean (SD), and categorical data are presented as numbers or percentages. Group comparisons were conducted using independent-sample t-tests or Mann-Whitney U tests for continuous variables and the $\chi^2$ test for categorical variables. Pearson's correlation was used to assess the correlation between the EDE-Q 6.0 total score and the score on items 13–18, treatment response and the RSFC in seeds of the FPCN. Treatment response was expressed as the rate of decrease or reduction in the EDE-Q 6.0 total score and the score on EDE-Q 6.0 items 13–18 in the sensitive analysis. Multiple linear regression

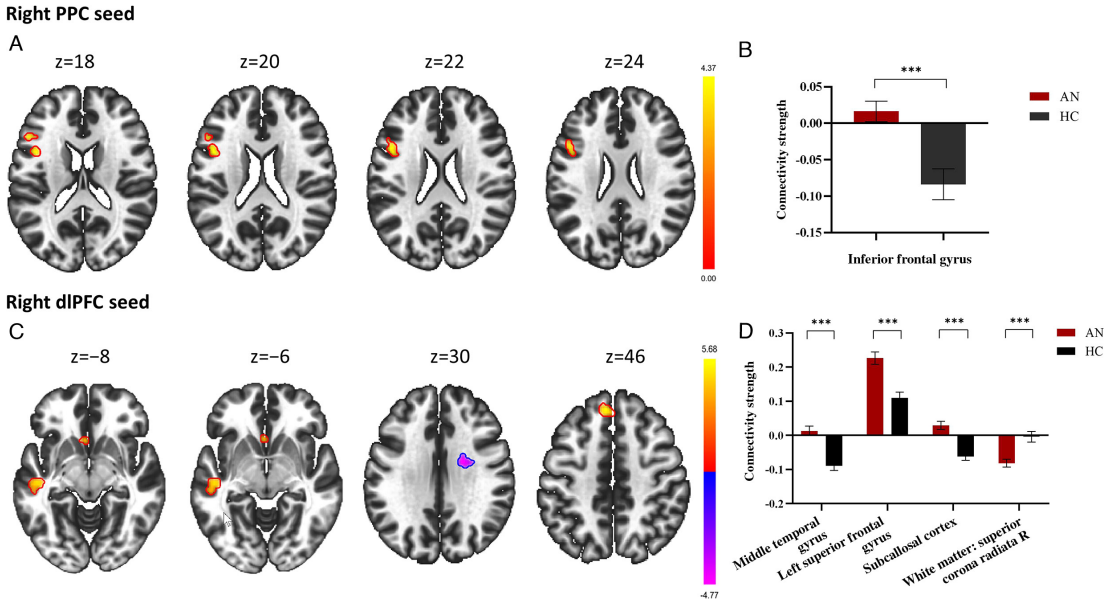


**Figure 2** (A) Voxels showing significant connectivity for the seeds in PPC. (B) Graphs showing significant clusters from PPC seeds between the AN and the HC groups. (C) Voxels showing significant connectivity for the seeds in dlPFC. (D) Graphs showing significant clusters from dlPFC seeds between the AN and the HC groups. Error bars represent SEM. Connectivity strength corresponds to Fisher-transformed correlation coefficient values; ***p<0.001. AN, anorexia nervosa; dlPFC, dorsolateral prefrontal cortex; HC, healthy control; PPC, posterior parietal cortex.

was adopted in the prediction model, with the EDE-Q 6.0 total score, the scores on items 13–18 at baseline and the treatment response as the dependent variables, respectively. The RSFC in the PPC and dlPFC seeds of the FPCN were the independent variables, and age, age of onset and BMI were the covariates. A mixed linear model was used to analyse the clinical response at follow-up time points. All tests were two-tailed, and p<0.05 was considered statistically significant.

A seed-to-voxel analysis was adopted using the CONN toolbox to explore the RSFC between the AN and the HC groups. Fisher-transformed correlation coefficients were generated between blood oxygen level-dependent time series in seeds within the FPCN and all other voxels in the whole brain to create functional connectivity maps. A general linear model was used to explore the differences in functional connectivity between the AN and the HC groups. The BDI-II and BAI total scores were included as covariates to exclude their influence on the results. Connectivity differences were considered significant between the two groups when a voxel height threshold was p<0.001 and a cluster size threshold was corrected at a p<0.05 false discovery rate.

We employed support vector regression (SVR) to construct the prediction model, given the modest size of our data set. SVR is chosen for its documented stability in handling small sample sizes. Five specific brain activities were used as predictive features for each type of variation. Our data set was divided into three subsets: a training set, a validation set and an independent test set comprising 20% of the total data. Data fitting is predominantly assessed through $R^2$ values and scatter plots. A higher $R^2$ value indicates better alignment between the data and the model, although an excessively higher $R^2$ value (~1) indicates overfitting. Scatter plots serve as visual aids to evaluate prediction accuracy, with closer proximity to the diagonal line of equality (where the x-axis is the observed values and the y-axis is the predicted values) indicating the predictive performance is better. Given the limited number of follow-up data points, the risk of overfitting is heightened.

## RESULTS

### Demographic and clinical characteristics

A total of 79 patients with AN and 40 HC participants took part in the study, of whom 40 patients completed the 4-week follow-up and 35 completed the 12-week follow-up. The other 39 patients did not attend the follow-up, mainly due to difficulty accessing medical care during the COVID-19 outbreak, reluctance to continue outpatient visits after improvement or additional comorbid mental disorders during the study. A flowchart of the study is shown in figure 1.

There were no significant differences in age (t=−1.75, p=0.083) and educational level (t=−1.49, p=0.130) between the patients and HCs. The BDI-II scale (t'=5.88, p<0.001), BAI scale (t'=6.78, p<0.001) and EDE-Q 6.0 total score (t'=8.07, p<0.001) were higher for patients with AN than for HCs. As expected, patients with AN had a significantly lower BMI (t=−10.49, p<0.001) than HCs (table 1). There were no significant differences in age, age of onset, BMI, BDI-II and BAI scores, and EDE-Q 6.0 total score between patients who attended the follow-up at the 4th and 12th weeks and those who did not (see online supplemental table 1).

### Resting-state functional connectivity

According to seed-to-voxel analyses, RSFC maps in the FPCN seeds showed significant differences between the AN and the HC groups. A significantly increased RSFC (p<0.05, false discovery rate-corrected) was observed in patients with AN compared with HCs between the right PPC seed and the left inferior frontal gyrus (IFG) (x=−42, y=6, z=20, t=5.48, k=117, size p=0.029), the right dlPFC seed and the middle temporal gyrus (MTG) (x=−48, y=−20, z=−6, t=5.16, k=111, size p=0.032), the posterior division left (x=−6, y=38, z=48, t=5.56, k=102, size p=0.032) and the subcallosal cortex (x=−2, y=18, z=−6, t=5.62, k=96, size p=0.032). For the significant clusters in conn, we extracted their specific values and used SPSS to perform an independent samples t-test statistic. The result shows significantly increased RSFC in the FPCN in patients with AN than HCs, and their statistical values are (t=4.04, p<0.001), (t=5.17, p<0.001), (t=4.75, p<0.001), (t=4.82, p<0.001) respectively in the same order as above. was observed in patients with AN compared with HCs (t(degrees of freedom)=, p=, chon'd=). (figure 2 and online supplemental table 2). No significant differences were found in the RSFC maps generated from the seeds of the left PPC and the left dlPFC. Significant results for the dlPFC seed are presented in figure 2. Furthermore, no significant differences in the RSFC maps of the FPCN seeds were found between the AN-R and AN-BP subtypes.

### Correlations between the RSFC in different brain regions and clinical variables

Pearson's correlation analysis was conducted to explore the associations between the Z scores of clusters that showed significant differences in the RSFC of the FPCN seeds and relevant self-reported eating disorder symptoms at baseline in the AN and HC groups. Significant correlations were found between the PPC to IFG connectivity strength and the EDE-Q 6.0 total score (r=−0.335, p=0.003), frequency of overeating behaviours (r=−0.238, p=0.036) and frequency of loss of control (r=−0.270, p=0.017) at baseline in patients with AN. No significant correlations were found between the RSFC in the FPCN and self-reported eating disorder symptoms in the HCs (figure 3A–C).

Treatment response was expressed as the decrease in the EDE-Q 6.0 total score between baseline and the corresponding treatment node and the decrease rate of the scores on items 13–18 of the EDE-Q 6.0. A mixed linear model was used to analyse the treatment response at the follow-up time points. It showed that the time main effect of the EDE-Q 6.0 total score was not significant over time, and the loss of control and overeating in the model failed to fit due to

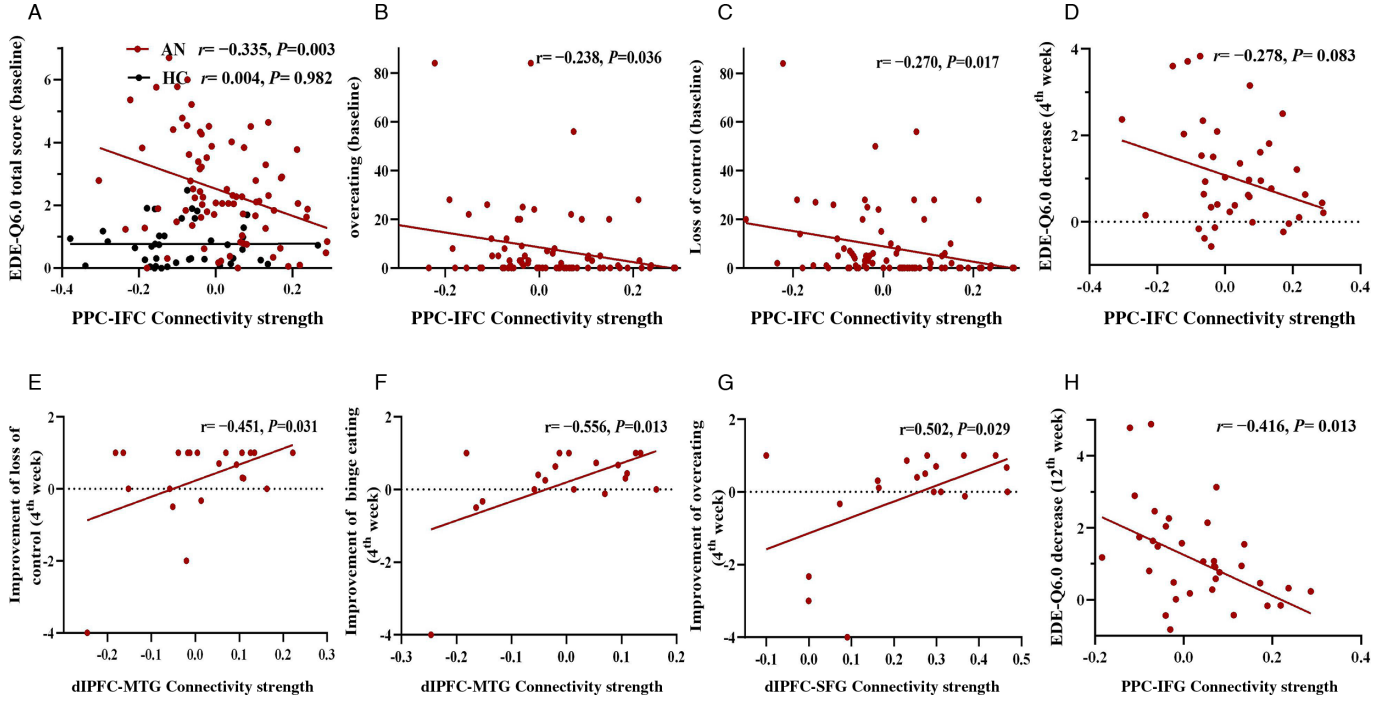


**Figure 3** (A) Correlation between the RSFC in PPC–IFG and the EDE-Q 6.0 total score between AN and HC groups at baseline. (B) Correlation between the RSFC in PPC–IFG and overeating behaviours at baseline in AN. (C) Correlation between the RSFC in PPC–IFG and loss of control at baseline in AN. (D) Correlation between the RSFC in PPC–IFG and the decrease of EDE-Q 6.0 total score in the fourth week. (E) Correlation between the RSFC in dlPFC–MTG and the improvement of loss of control. (F) Correlation between the RSFC in dlPFC–MTG and the improvement of binge eating. (G) Correlation between the RSFC in dlPFC–SFG and the improvement of overeating behaviours. (H) Correlation between the RSFC in PPC–IFG and the decrease of EDE-Q 6.0 total score at the 12th week. AN, anorexia nervosa; dlPFC, dorsolateral prefrontal cortex; EDE-Q 6.0, Questionnaire Version of the Eating Disorder Examination (version 6.0); HC, healthy control; IFG, inferior frontal gyrus; MTG, middle temporal gyrus; PPC, posterior parietal cortex; RSFC, resting-state functional connectivity.

missing data. The results are shown in online supplemental materials (tables 3–7 and figure 1).

Correlation analysis was performed between treatment response and five different brain regions. It showed that the RSFC of the PPC–IFG had an approximately significant or significant correlation with treatment response both in the 4th week (r=−0.278, p=0.083) and 12th week (r=−0.416, p=0.013) (figure 3D,H), and the RSFC of the right dlPFC–MTG had a significant correlation with improvement in the frequency of loss of control (r=0.451, p=0.031) and binge eating (r=0.556, p=0.013) (figure 3E,F). Also, the RSFC of the right dlPFC–left superior frontal gyrus (SFG) had a significant correlation with improvement in the frequency of overeating behaviours (r=0.502, p=0.029) (figure 3G).

Furthermore, multiple linear regression was conducted with the EDE-Q 6.0 total score ($F$=5.16, p=0.008, $R^2$=0.12), frequency of overeating ($F$=2.21, p=0.076, $R^2$=0.11) and loss of control ($F$=2.91, p=0.027, $R^2$=0.14) at baseline as dependent variables, respectively, with the RSFC in seeds of the FPCN as independent variables, and age, age of onset and BMI as covariates. Multiple linear regression was conducted with the decrease in the EDE-Q 6.0 total score in the 4th week ($F$=3.74, p=0.061, $R^2$=0.38) and 12th week ($F$=3.098, p=0.039, $R^2$=0.38), and with the improvement in loss of control ($F$=4.08, p=0.032, $R^2$=0.29) and binge eating ($F$=3.85, p=0.050, $R^2$=0.66) as the dependent variables, respectively. The RSFC in seeds of the FPCN were the independent variables, and age, age of onset and BMI were the covariates. As shown in table 2, the RSFC in the PPC–IFG was a significant factor for both the clinical symptoms at baseline and the treatment response in the 4th and 12th weeks for patients with AN.

We also explored the machine learning prediction model using SVR. Five brain activities were used as predictive features for each type of variation. These results are shown in the support vector machine regression parts of online supplemental tables 8–39 and figures 2–17.

## DISCUSSION

### Main findings

To our knowledge, the present study is the first to investigate the role of significant seeds in the FPCN in self-reported eating disorder symptoms and treatment response in patients with AN. First, after controlling for depression and anxiety symptoms, the RSFC from the PPC and dlPFC of the FPCN increased in patients with AN versus HCs. Second, the RSFC of the PPC to IFG was a significant neural marker of self-reported eating disorder symptoms after controlling for age, and it was a significant neural marker of treatment response to cognitive preoccupations about eating/body image after controlling for age, age of onset and BMI. Likewise, the RSFC of the dlPFC to MTG/SFG may be a significant neural marker of the treatment response to binge eating and loss of control/overeating behaviours in patients with AN. Because no significant differences in the RSFC of the FPCN were found between patients with AN-R or AN-BP, the RSFC of the FPCN may not be a neural marker to differentiate the two subtypes of AN. Thus, these results provide evidence for the important role of the FPCN in patients with AN.

Moreover, the RSFC in the PPC to IFG and the dlPFC to MTG/SMG increased in AN versus HCs in the study, further supporting that AN is a disorder of excessive cognitive control, a finding that agrees with previous studies that found the function in the FPCN increased in patients with AN.[7 19] The FPCN engages in various executive functions by allocating top-down attentional resources to arrange cognitive control processes.[20] The impaired cognitive control ability has been associated with decreased cognitive flexibility and hyperdetailed information processing in patients with AN.[10] One study confirmed that the FPCN functional connectivity contributed to the loss of control in patients with binge drinking, possibly by impairing cognitive function and response inhibition.[21] In addition, the right IFG is involved in inhibiting control and stopping the upcoming impulsive responses, and the impairment of the right IFG is closely related to impaired inhibitory control.[22] One study pointed out that age was an important moderator of overall cognitive performance in AN, including executive function, with younger participants had better performance than the older participants.[19] Considering the increased function in the FPCN at a young onset age, we put forward a viewpoint that the neural circuitry of the FPCN in patients with AN is premature.

Furthermore, our study showed that the aberrant RSFC in the FPCN was related to the abnormal eating disorder symptoms in patients with AN but not in the HCs, supporting the hypothesis that the RSFC in the FPCN may contribute to the regulation of pathological symptoms in patients with AN. The alteration of the FPCN neural function may be an important factor in causing pathological symptoms and psychological characteristics in patients with eating disorders, which is consistent with our findings.[23] The FPCN system is responsible for various cognitive functions and regulates eating behaviours. A lower function connectivity in the FPCN was associated with worse self-control in eating, further contributing to disturbed eating disorders.[24] Additionally, the PPC and dlPFC of the FPCN are involved in regulating eating behaviours through cognitive control when confronted with tempting food.[25] It has been suggested that the food consumption of individuals with AN is closely related to the dlPFC and dorsal striatal connectivity.[23] The above studies have provided the theoretical basis for our results.

The current study also showed that the aberrant RSFC in the PPC to IFG was negatively associated with self-reported eating disorder symptoms, loss of control and overeating, and that the treatment response was negatively associated with cognitive preoccupations about eating/body image. Interestingly, the aberrant RSFC in the dlPFC to MTG/SMG was positively associated with the treatment response to binge eating and loss of control/overeating behaviours of AN. On the other hand, we

**Table 2** Results of linear regression with self-reported eating disorder symptoms or treatment response as the dependent variables and PPC–IFG connectivity strength as the independent variable

| | Unstandardised coefficients | | Standardised coefficients | t | P value | 95% CI (lower to upper) |
|---|---|---|---|---|---|---|
| | B | SE | | | | |
| Dependent variable: EDE-Q 6.0 total score at baseline | | | | | | |
| Constant | 2.952 | 0.756 | | 3.90 | <0.001 | (1.445 to 4.459) |
| PPC-IFG | −4.650 | 1.447 | −0.356 | −3.21 | **0.002** | (−7.534 to −1.766) |
| Age | −0.024 | 0.039 | −0.066 | −0.60 | 0.551 | (−0.102 to 0.055) |
| Dependent variable: overeating at baseline | | | | | | |
| Constant | −22.621 | 17.081 | | −1.32 | 0.190 | (−56.663 to 11.421) |
| PPC-IFG | −29.682 | 14.822 | −0.232 | −2.00 | **0.049** | (−59.223 to −0.142) |
| Age | −0.299 | 0.788 | −0.074 | −0.38 | 0.706 | (−1.870 to 1.272) |
| Age of onset | 0.572 | 0.958 | 0.116 | 0.60 | 0.552 | (−1.337 to 2.481) |
| BMI | 1.799 | 0.882 | 0.237 | 2.04 | **0.045** | (0.041 to 3.558) |
| Dependent variable: loss of control at baseline | | | | | | |
| Constant | −23.028 | 15.309 | | −1.50 | 0.137 | (−53.539 to 7.484) |
| PPC-IFG | −31.714 | 13.285 | −0.272 | −2.39 | **0.020** | (−58.191 to −5.237) |
| Age | −0.484 | 0.706 | −0.132 | −0.69 | 0.496 | (−1.892 to 0.924) |
| Age of onset | 0.808 | 0.859 | 0.179 | 0.94 | 0.350 | (−0.903 to 2.519) |
| BMI | 1.826 | 0.791 | 0.264 | 2.31 | **0.024** | (0.250 to 3.403) |
| Dependent variable: decrease in EDE-Q 6.0 total score at 4-week follow-up | | | | | | |
| Constant | 5.047 | 3.140 | | 1.61 | 0.125 | (−1.551 to 11.644) |
| PPC-IFG | −4.435 | 1.970 | −0.472 | −2.25 | **0.037** | (−8.574 to −0.297) |
| Age | 0.214 | 0.176 | 0.617 | 1.22 | 0.240 | (−0.156 to 0.585) |
| Age of onset | −0.490 | 0.245 | −1.042 | −2.01 | 0.060 | (−1.004 to 0.023) |
| BMI | 0.008 | 0.141 | 0.011 | 0.06 | 0.957 | (−0.288 to 0.304) |
| Dependent variable: decrease in EDE-Q 6.0 total score at 12-week follow-up | | | | | | |
| Constant | 6.241 | 2.810 | | 2.22 | 0.038 | (0.381 to 12.102) |
| PPC-IFG | −6.835 | 2.782 | −0.467 | −2.46 | **0.023** | (−12.639 to −1.032) |
| Age | 0.007 | 0.079 | 0.024 | 0.09 | 0.928 | (−0.158 to 0.172) |
| Age of onset | −0.285 | 0.147 | −0.497 | −1.95 | 0.066 | (−0.591 to 0.021) |
| BMI | −0.040 | 0.135 | −0.058 | −0.30 | 0.770 | (−0.323 to 0.243) |
| Dependent variable: improvement of loss of control | | | | | | |
| Constant | 1.384 | 0.771 | | 1.80 | 0.088 | (−0.224 to 2.993) |
| dlPFC-MTG | 5.028 | 1.899 | 0.508 | 2.65 | **0.015** | (1.067 to 8.989) |
| Age | −0.066 | 0.042 | −0.300 | −1.57 | 0.133 | (−0.154 to 0.022) |
| Dependent variable: improvement of binge eating | | | | | | |
| Constant | 3.012 | 1.278 | 0.615 | 2.36 | 0.046 | (0.064 to 5.959) |
| dlPFC-MTG | −0.063 | 0.032 | −0.859 | −1.96 | 0.086 | (−0.137 to 0.011) |
| Age | 0.069 | 0.079 | 0.427 | 0.88 | 0.405 | (−0.113 to 0.251) |
| Age of onset | −0.102 | 0.084 | −0.400 | −1.21 | 0.262 | (−0.296 to 0.093) |
| BMI | 3.012 | 1.278 | 0.615 | 2.36 | **0.046** | (0.064 to 5.959) |
| Dependent variable: improvement of overeating | | | | | | |
| Constant | −0.082 | 1.045 | | −0.08 | 0.938 | (−2.297 to 2.132) |
| dlPFC-SFG | 4.274 | 1.812 | 0.490 | 2.36 | **0.031** | (0.432 to 8.115) |
| Age | −0.059 | 0.051 | −0.241 | −1.16 | 0.264 | (−0.167 to 0.049) |

Note: P values in bold indicate P<0.05
B, beta; BMI, body mass index; dlPFC, dorsolateral prefrontal cortex; EDE-Q 6.0, Questionnaire Version of the Eating Disorder Examination (version 6.0); IFG, inferior frontal gyrus; MTG, middle temporal gyrus; PPC, posterior parietal cortex; SFG, superior frontal gyrus.

found a stronger RSFC in the PPC predicted poorer clinical outcomes regarding cognitive preoccupations about eating and body concerns. It may be that a stronger RSFC in the PPC implies more attention to eating, body shape and body weight, which leads to potential excessive attention to eating, body shape and body weight, as well as excessive control over diet. However, the increased RSFC in the dlPFC predicted an improvement in loss of control and binge eating or overeating behaviours, analogous to previous results that showed increased dlPFC activity of the cognitive control circuit predicted dietary improvements.[26]

A recent study indicated that the FPCN, as a crucial cognitive control network, and the functions of its different parts were associated with the selection and maintenance of various stimuli and features. Its functional connectivity can also combine external information with internal representations to guide decision-making.[27] It has been argued that treatment response in patients with depressive disorder was associated with altered connectivity within and between networks, including the FPCN.[14] In addition, increased functional connectivity between the frontal cortex and the FPCN may be one of the neurological mechanisms involved in successfully resolving response conflicts.[27] Patients with AN may develop an adaptive neural mechanism to maintain their extreme eating behaviours due to prolonged malnutrition. The above theory may provide the rationale for the seemingly opposing results derived from the study. Further validation of the effect of the PPC and the dlPFC on patients with AN and the clinical outcomes is still needed. It is currently difficult to predict treatment response in patients with AN; however, the resting-state brain activity of the FPCN may serve as a biomarker to predict treatment response in AN. As noted in this study, the dlPFC is an important target for understanding the pathogenesis of AN,[28] and the symptoms of binge eating and loss of control/overeating behaviours. The study also found that the PPC may be a significant target for cognitive preoccupations about eating/body image in patients with AN, suggesting that it may serve as an important target for interventions addressing cognitive preoccupations that could be considered in future treatment protocols. This study did not track the FPCN function after treatment to determine long-term effectiveness, which needs further investigation.

No significant differences in the RSFC of the FPCN between the AN-R and AN-BP subtypes were found in this study. A long-term follow-up study on patients with different subtypes of AN showed that most patients with AN-R have an early age of onset, and most patients with AN started with the AN-R subtype. Approximately 88% of those with AN-R develop bulimic behaviours, and 62% of patients with AN-R eventually develop into the AN-BP subtype.[29] Based on our results, we conjecture that the RSFC of the FPCN is altered in the early onset of AN. Moreover, most patients are adolescents and not yet adults, a stage when the neural activity of the brain is still at a premature stage of development, and the brain is more plastic in structure and function compared to adults,[30] which may explain the short-term improvement of clinical symptoms.

## Limitations

There are several limitations to the present study. First, the study was based on a cross-sectional analysis, which could not determine the causation, and it was not clear how the RSFC of the FPCN changed after treatment. Second, the study did not consider the effect of undernutrition on brain networks. Third, more participants than expected were lost to follow-up due to COVID-19 outbreak; thus, their BMI was not tracked. Fourth, treatment response in AN was expressed as a reduction rather than a reduction rate in the EDE-Q 6.0 total score, which may increase the power to predict the outcome. As the study was exploratory, we did not perform multiple tests for corrections to increase the likelihood of obtaining significant results. Since this study is the first to explore the neurobiological mechanisms of treatment response in AN, future research with larger samples and a longitudinal design is needed to validate our findings.

## Implications

The current study provides evidence that the RSFC in the FPCN is increased in patients with AN versus HCs after controlling for emotional symptoms, and it yields an initial indication that the RSFC in the PPC to IFG may be a significant neural marker of self-reported eating disorder symptoms and treatment response to cognitive preoccupations about eating/body image. Also, the RSFC of the dlPFC to MTG/SMG may be a significant neural marker for treatment response to binge eating behaviours and loss of control/overeating behaviours of AN. These findings are helpful in further understanding the pathogenesis of AN, as well as opening up potential avenues for relevant target strategies for the prevention and treatment of this pervasive mental disorder.

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