

Mechanisms of Cognitive Behavioral Therapy for Bulimia Nervosa: Correlated Factors of Treatment Effect and Predictors of Treatment Response Based on Resting-State Functional Connectivity

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Abstract

Background

Bulimia nervosa (BN) has substantial mortality risk, and cognitive behavioral therapy (CBT) is the first-line treatment; however, remission rates remain modest, and the neurobiological mechanisms of CBT response are unclear. Resting-state functional connectivity (rsFC) may clarify CBT-related brain changes and pretreatment predictors of response, yet longitudinal whole-brain rsFC studies in BN are lacking.

Methods

Thirty Japanese female with BN received multi-site structured CBT (CBT-E: $n = 24$; videoconference CBT: $n = 4$; guided internet-based CBT: $n = 2$). Resting-state fMRI and symptom measures, including the Eating Disorder Examination Questionnaire (EDE-Q), were obtained pre- and post-treatment. Whole-brain region of interest (ROI)-to-ROI rsFC (142×142) was computed in CONN and harmonized across sites using neuroHarmonize/ComBat. Multiple regression analyses controlling for age and psychotropic medication examined (1) rsFC changes associated with symptom improvement and (2) pretreatment rsFC predictors of response. Significance was assessed using seed-level FDR correction ($q < 0.05$), applied across all connections from each seed ROI to all target ROIs. A sensitivity analysis was conducted on the CBT-E subgroup ($n = 24$) using both $q < 0.05$ and $q < 0.1$ thresholds.

Results

Across both the primary analysis including all CBT modalities and the CBT-E–restricted analysis, two findings were consistent ($q < 0.05$): (i) greater EDE-Q improvement was associated with decreased rsFC between the right orbitofrontal cortex (OFC) and right posterior supramarginal gyrus (SMG), and (ii) stronger pretreatment rsFC between the left postcentral gyrus and the temporo-occipital inferior temporal gyrus predicted greater symptom improvement. At the network level, both analyses linked symptom improvement to increased cerebellum–temporal visual connectivity, and better response to stronger pretreatment connectivity between parietal (SMG/superior parietal lobule) and frontal association regions. Although some edge-level results differed between analyses at $q < 0.05$, sensitivity analyses using a more lenient threshold ($q < 0.1$) yielded patterns that largely encompassed the primary findings.

Conclusions

This is the first whole-brain longitudinal analysis to demonstrate that CBT-related BN improvement may involve rsFC modulation regarding reward-control and perceptual-affective food-cue processing. Pretreatment connectivity related to body perception and cognitive control may also be relevant to

responsiveness. These findings provide rsFC markers of CBT-related change and preliminary prognostic features in BN.

Trial registration:

UMIN000039841. Registered 18 March 2020.

Plain English Summary

Bulimia nervosa is a serious eating disorder involving binge eating, purging, and intense concerns about body shape. While Cognitive Behavioral Therapy (CBT) is the leading treatment, only about half of patients achieve full recovery. We conducted this study to understand how therapy changes the brain's "wiring" and why it works better for some people than others. We used brain scans to monitor 30 women before and after they completed therapy. Our results showed that as patients improved, the communication between the brain's "reward center" (which evaluates food) and its "control center" (which manages impulses) changed. It appears that CBT helps the brain better regulate its response to food rewards. We also found that certain brain patterns present before treatment could predict which patients would improve the most. These patterns were in areas responsible for how we perceive our bodies and how we exercise learning and self-control. These findings provide the first evidence of how CBT reshapes brain communication in bulimia nervosa. In the future, this could help develop new treatments that more effectively target these specific brain regions or help doctors predict who will benefit most from therapy.

Introduction

To improve treatment outcomes for bulimia nervosa (BN), a prevalent and severe disorder, it is important to clarify the mechanisms of cognitive behavioral therapy (CBT). BN, marked by recurrent binge eating, compensatory behaviors, and shape/weight overvaluation[1], is particularly common among women (0.6–2.4%) and increases mortality risk by approximately 50% [2–4]. Network meta-analyses indicate that individual CBT and CBT-based guided self-help are among the most effective treatments [5]. However, even enhanced CBT (CBT-E) achieves remission in only 30–50% of cases, and 15–20% develop a chronic course [4, 6]. Improving outcomes requires a better understanding of therapeutic change processes and the active ingredients of psychotherapy, yet research remains limited [6, 7]. Consequently, progress in CBT for BN has plateaued. The remission rate of the broad form of CBT-E, which incorporates four additional modules, remains around 49%, comparable to rates of the standard “focused” form [6].

Longitudinal studies investigating resting-state brain function in BN patients before and after CBT are crucial for elucidating treatment mechanisms. Connectomes based on resting-state functional connectivity (rsFC), an indicator of resting-state brain function measured using functional magnetic resonance imaging (fMRI), are sufficiently stable to serve as a “fingerprint” that can distinguish individuals within large groups and are powerful predictors of cognitive behavior [8]. Therefore,

investigating how rsFC changes with psychotherapy may help us understand therapeutic changes in patients and develop more effective interventions by elucidating the neural mechanisms underlying psychotherapy [9, 10]. For instance, in depression, normalization of prefrontal–limbic dysregulation during psychotherapy has been linked to recovery, and strategies engaging lateral prefrontal cortex appear promising [9, 11].

Despite this rationale, longitudinal rsFC studies in BN are lacking. Even cross-sectional rsFC research in BN remains limited and underpowered [12, 13], with reported alterations in orbitofrontal cortex (OFC) within reward circuitry [14–17], insula/thalamus/anterior cingulate regions implicated in interoceptive–exteroceptive integration [18–21], and motor–somatosensory cortices involved in motor control [16, 20, 22]. To our knowledge, no study has examined pre–post treatment rsFC changes in BN.

Therefore, we measured rsFC before and after CBT in 30 patients with BN and conducted a longitudinal region of interest (ROI)-to-ROI analysis, using all brain regions as both seed ROIs and target ROIs. We aimed to identify (1) changes in resting-state brain function related to the therapeutic effects of CBT and (2) pretreatment resting-state brain function characteristics that predict treatment response.

Methods

Study Design

This study was conducted within the nationwide, multi-center, longitudinal Eating Disorder Neuroimaging Initiative (EDNI; UMIN000039841), which acquires neuroimaging, gene expression, and other measures before and after CBT in patients with eating disorders, enabling longitudinal and transdiagnostic analyses [23]. Here, we analyzed patients with BN. Participants receiving structured CBT at seven sites in Japan underwent brain MRI, resting-state fMRI (rsfMRI), and psychometric assessments before and after the CBT course. At enrollment, a study psychiatrist (or psychosomatic physician) confirmed the clinical appropriateness of CBT and evaluated eligibility. After written informed consent, the first CBT session was scheduled. Baseline MRI/fMRI and psychological testing were performed within 4 weeks before treatment initiation; post-treatment assessments were also completed within 4 weeks after the final session.

Participants

Participants were recruited through posters, websites, and physician referrals at seven Japanese hospitals (details are provided in Table S1). Recruitment began in January 2020 and is ongoing; this report includes 30 Japanese female participants whose pre- and post-treatment assessments were completed by the end of October 2023 and who provided usable longitudinal MRI data. Inclusion criteria were: (1) meet the diagnostic criteria for BN in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); (2) age ≥ 18 years; (3) Body Mass Index (BMI) < 40.0 kg/m²; (4) residence in Japan with native-level Japanese literacy; and (5) ability to provide written informed

consent. Exclusion criteria were: (1) serious medical conditions requiring advanced treatment; (2) pre-BN history of schizophrenia, bipolar disorder, alcohol abuse/dependence, or autism spectrum disorder; (3) intellectual disability; (4) imminent suicide risk; (5) MRI contraindications (e.g., metal, possible pregnancy, claustrophobia) or other conditions posing MRI risk; and (6) inability to complete scheduled visits. Criteria were assessed by the responsible psychiatrist/psychosomatic physician; clinical interviews according to DSM-5 guidelines were used to confirm BN and relevant exclusion criteria. Comorbidities not meeting exclusion criteria were recorded at enrollment. All 30 participants included in the analysis were Japanese females, reflecting the low number of male or non-Japanese BN patients in Japan.

Physical and psychological assessment

At baseline and post-treatment, weight and height were measured, and psychological scales were administered: Beck Depression Inventory-II (BDI-II), State-Trait Anxiety Inventory (STAI), Eating Disorder Examination Questionnaire (EDE-Q), and the Japanese version of the National Adult Reading Test (JART, administered at baseline only). These measures monitored the effects of CBT and served as variables for rsFC regression analyses.

Intervention

Twenty-four participants received CBT-E (20×50-min sessions; UMIN000031625) [24], four received videoconference CBT (vCBT; 16×50-min sessions; UMIN000036825), and two received guided internet-based CBT (ICBT; 12×15-min sessions; UMIN000048732)[25]. Site-by-modality distribution is shown in Table S1. Across modalities, therapists (psychiatrists, psychosomatic physicians, or licensed clinical psychologists) completed dedicated training and delivered manualized, structurally standardized interventions.

MRI acquisition and preprocessing

Scans were performed using 3.0 Tesla scanners (Siemens, GE, or Philips) across sites. Sites utilized either the Harmonized Protocol (HARP; 5-min rsfMRI) [26] or the Strategic Research Program for Brain Science (SRPB) protocol (10-min rsfMRI) [27], depending on multiband imaging capability. Detailed imaging parameters are provided in Table S2.

Preprocessing and quality control were performed using SPM12 and NITRC Functional Connectivity Toolbox (CONN) version 18b. We discarded the first 5 volumes (Repetition time [TR] = 3000 ms) or 6 volumes (TR = 2500 ms). Data were processed with the CONN default pipeline: realignment/unwarp; centering to [0,0,0]; slice-timing correction (SPM default reference); Artifact Detection Tools (ART)-based outlier detection; direct segmentation/normalization to Montreal Neurological Institute (MNI) space (2×2×2 mm); and 8-mm Full width at half maximum Gaussian smoothing. ART flagged outliers based on

motion and global signal (framewise displacement > 0.9 mm or global Blood oxygen level dependent [BOLD] change > 5 standard deviation); flagged volumes were modeled as nuisance regressors (“scrubbing”).

Functional network construction and denoising

ROI-to-ROI rsFC was estimated in CONN/MATLAB R2022a. Denoising used the anatomical component-based noise correction method (aCompCor) to remove signals from white matter (5 components), cerebrospinal fluid (5 components), realignment parameters (6 components and their first-order temporal derivatives), and identified outliers [28]. Data were band-pass filtered (0.008–0.09 Hz). Participants were excluded if > 25% of volumes were flagged by ART as outliers or motion exceeded 3 mm/3° (none met these criteria).

We defined 142 ROIs: 104 cortical/subcortical (Harvard-Oxford Atlas) and 26 cerebellar (AAL Atlas). Critically, the insular cortex was defined using the Brainnetome Atlas (12 subregions) instead of the Harvard-Oxford Atlas. Given the insula’s complex functional topography and its central role in eating disorders [18, 19], subdivision is necessary to detect fine-grained connectivity changes that a single-ROI approach might miss, as demonstrated in our previous studies [29–31]. For each ROI pair, bivariate correlations between BOLD time series were computed and Fisher Z-transformed, yielding a 142×142 rsFC matrix per participant.

Statistical analysis

Demographic and clinical characteristics

Demographic and clinical characteristics were analyzed using SPSS version 25.0. Pre- and post-CBT scores (BMI, BDI-II, STAI, and EDE-Q) were compared using paired t-tests or Wilcoxon signed-rank tests (for non-normal BMI data). Tests were two-tailed with $p < 0.05$.

ComBat harmonization

To minimize site effects, we applied the ComBat algorithm via the neuroHarmonize Python package [32, 33], which supports longitudinal data. Batches were defined by scanner manufacturer/protocol: Batch 1 (Siemens/HARP), Batch 2 (GE/SRPB), and Batch 3 (Philips/SRPB), because site effects in multi-site neuroimaging databases are considered to stem primarily from differences in phase-encoding direction and variability among MRI scanner manufacturers [34]. Age and total intracranial volume measured using Brain Anatomical Analysis using Diffeomorphic deformation (BAAD) version 4.3.2 (Shiga University of Medical Science, Otsu, Japan) were included as covariates. Harmonization parameters estimated from baseline data were applied to post-treatment data. We also conducted sensitivity analyses restricted to CBT-E participants. In the CBT-E-only dataset, manufacturer-based batching yielded only one participant in Batch 2, precluding reliable estimation of ComBat parameters; therefore,

this single participant was excluded from CBT-E-only harmonization and subsequent CBT-E-only analyses.

Group analysis

Second-level group analyses in CONN tested ROI-to-ROI rsFC correlates of CBT response and predictors of treatment outcome. To identify rsFC changes associated with therapeutic effects, we performed multiple regression with change in EDE-Q global score as the dependent variable, rsFC change (post–pre) as independent variables, and age and psychotropic medication status (yes/no) as covariates. This is equivalent to a partial correlation between changes in rsFC and EDE-Q controlling for these covariates. To identify pretreatment characteristics associated with better response, we ran a second regression using EDE-Q change as the dependent variable, pretreatment rsFC values as independent variables, and the same covariates; this identifying baseline rsFC features predicting improvement.

ROI-to-ROI analyses spanned the full set of 142 ROIs, testing all pairwise connections (the full connectome; 10,011 connections). Statistical significance was assessed in CONN using two-sided tests with seed-level FDR correction at $q < 0.05$. Specifically, for each seed ROI, p-values for its connections to all target ROIs were FDR-corrected separately, and connections were considered significant if they survived this within-seed FDR criterion (reported as p-FDR). Thus, seed-level p-FDR refers to correction across all connections from a given seed ROI (seed-to-all-targets), rather than across all ROI-to-ROI connections simultaneously.

CBT modality was not included as a covariate in the primary models because the non–CBT-E subgroups were small (vCBT: $n = 4$; ICBT: $n = 2$), risking overparameterization and unstable estimates. These modalities share core CBT principles, and an RCT comparing face-to-face and Internet-based CBT for BN demonstrated noninferiority of the latter on EDE-Q scores at 12 months [35]. However, to address potential heterogeneity in delivery, we also conducted a sensitivity analysis restricted to the CBT-E subgroup using the same covariates and multiple-comparison control (seed-level p-FDR < 0.05).

For interpretability, effect sizes were reported as partial correlations (partial r) derived from the corresponding t-statistics and residual degrees of freedom ($r = t / \sqrt{t^2 + df}$), and 95% confidence intervals for partial r were computed using Fisher's z transformation.

Results

Demographic and clinical characteristics

Table 1 summarizes demographic characteristics and psychological scale scores before and after CBT. Mean age was 33.6 ± 9.9 years and illness duration 10.3 ± 9.2 years. Mean BMI was 22.9 ± 4.9 kg/m² and did not change significantly after CBT. Regarding medication, 20% received selective serotonin reuptake inhibitors (SSRIs) only, 20% non-SSRI psychotropics only, and 20% both; the remaining 40% were not taking psychotropic medications. Estimated IQ (JART) was 104.2 ± 1.8 , indicating average intellectual

functioning with minimal variability. Before CBT, mean scores were 24.1 ± 12.5 (BDI-II), 48.6 ± 11.7 (STAI-State), and 54.6 ± 11.7 (STAI-Trait), all exceeded clinical cut-offs. After CBT, scores improved significantly; notably, mean BDI-II decreased to 14.9 ± 12.4 , below the clinical threshold. The pretreatment EDE-Q global score was 3.9 ± 1.2 , and all subscales exceeded the commonly used cut-off of 2.8 [36]. Following CBT, EDE-Q global and subscale means fell below this threshold. Comorbid psychiatric disorders are listed in Table S4. The prevalence of depressive disorders, bipolar and related disorders, and alcohol use disorder developing after BN onset was consistent with prior BN samples [37], whereas anxiety disorders, obsessive-compulsive and related disorders, and Attention-deficit/hyperactivity disorder (ADHD) were less prevalent [37].

Table 1
Study demographics and clinical behavioral measures

		Pre-CBT (N = 30)		Post-CBT (N = 30)		Pre-post comparisons		
		Mean (SD)	N	Mean (SD)	N	Statistics (df)	p-Value	r
Age		33.6 (9.9)	30	N/A	N/A	N/A	N/A	N/A
Duration of illness, years		10.3 (9.2)	29	N/A	N/A	N/A	N/A	N/A
Body mass index, kg/m ²		22.9 (4.9)	29	23.1 (5.1)	29	0.8* (28)	.442	.15
PM	SSRI	N/A	6	N/A	N/A	N/A	N/A	N/A
	Non-SSRI drugs	N/A	6	N/A	N/A	N/A	N/A	N/A
	SSRI and non-SSRI drugs	N/A	6	N/A	N/A	N/A	N/A	N/A
Total intracranial volume, ml		1481.1 (84.5)	30	N/A	30	N/A	N/A	N/A
Japanese Adult Reading Test		104.2 (1.8)	27	N/A	N/A	N/A	N/A	N/A
Beck Depression Inventory-II		24.1 (12.5)	30	14.9 (12.4)	30	4.2 (29)	< .001	.61
STAI	State	48.6 (12.4)	30	44.5 (13.4)	30	2.5 (29)	.017	.42
	Trait	54.6 (11.7)	30	48.7 (12.1)	30	5.2 (29)	< .001	.69
EDE-Q	Global	3.9 (1.2)	30	2.0 (1.2)	29	6.8 (28)	< .001	.79
	Restraint	3.3 (1.4)	30	1.6 (1.3)	29	5.1 (28)	< .001	.69
	Eating	3.6 (1.5)	30	1.5 (1.3)	29	6.4 (28)	< .001	.77
	Weight	4.2 (1.4)	30	2.3 (1.4)	29	6.0 (28)	< .001	.75
	Shape	4.4 (1.4)	30	2.4 (1.5)	29	6.5(28)	< .001	.78

	Pre-CBT (N = 30)		Post-CBT (N = 30)		Pre-post comparisons		
	Mean (SD)	N	Mean (SD)	N	Statistics (df)	p-Value	r
* z values, Statistics without a symbol are t values, N, number of participants; SD, standard deviation; df, degrees of freedom; PM, psychotropic medication;							
CBT, cognitive behavioral therapy; SSRI, selective serotonin reuptake inhibitor; STAI, State-Trait Anxiety Inventory; EDE-Q, Eating Disorder Examination Questionnaire.							

rsFC changes associated with the therapeutic effects of CBT

Table 2 (a) and Fig. 1 (a) present the results of a multiple regression analysis in which changes in EDE-Q global scores were the dependent variable, changes in rsFC following CBT (all modalities) were the independent variables, and age and psychotropic medication use (yes/no) were included as covariates. All results reported below survived seed-level p-FDR < 0.05. Greater improvement in EDE-Q global score was significantly associated with increased rsFCs between right anterior temporal fusiform cortex and two cerebellar regions: cerebellar vermis III and right cerebellar hemisphere (Cb) VI and between right caudate nucleus and right Cb IX. Greater improvement in EDE-Q global score was also significantly associated with decreased rsFC between right OFC and right posterior supramarginal gyrus (SMG).

Table 2
rsFC changes associated with the improvement of EDE-Q global score by CBT

(A) All modalities					
Seed	Region	t-Value	partial r	95% CI	p-FDR
Increased rsFCs after CBT (seed-level p-FDR < 0.05)					
Right anterior temporal fusiform cortex	Cerebellar vermis III	4.47	0.67	0.38–0.84	0.0205
	Right cerebellar hemisphere VI	3.88	0.61	0.30–0.81	0.0471
Right caudate nucleus	Right cerebellar hemisphere IX	4.55	0.67	0.39–0.84	0.0167
Decreased rsFC after CBT (seed-level p-FDR < 0.05)					
Right orbitofrontal cortex	Right posterior supramarginal gyrus	4.35	0.66	0.37–0.83	0.0286
(B) CBT-E only					
Seed	Region	t-Value	partial r	95% CI	p-FDR
Increased rsFCs after CBT (seed-level p-FDR < 0.05)					
Left cerebellar hemisphere III	Right temporooccipital part of inferior temporal gyrus	5.38	0.79	0.53–0.91	0.0058
	Left posterior inferior temporal gyrus	4.68	0.74	0.44–0.89	0.0131
	Right posterior temporal fusiform gyrus	4.47	0.73	0.42–0.88	0.0413
Decreased rsFC after CBT (seed-level p-FDR < 0.05)					
Left anterior temporal fusiform gyrus	Right superior parietal lobule	5.32	0.78	0.52–0.91	0.0066
Right orbitofrontal cortex	Right posterior supramarginal gyrus	4.70	0.74	0.45–0.89	0.0254
	Left cerebellar hemisphere X	4.29	0.71	0.39–0.88	0.0313
rsFC, resting-state functional connectivity; EDE-Q, Eating Disorder Examination Questionnaire; CBT, cognitive behavioral therapy; CI, confidence interval;					
p-FDR, two-sided false discovery rate corrected p-value; CBT-E, enhanced cognitive behavioral therapy.					

As a sensitivity analysis, we conducted the same regression analysis restricted to the CBT-E group (Table 2 (b) and Fig. 1 (b)). All results reported below survived seed-level $p\text{-FDR} < 0.05$. Greater improvement in EDE-Q global score was associated with increased rsFCs between left Cb III and three temporal regions: right temporooccipital part of inferior temporal gyrus (toITG), left posterior inferior temporal gyrus (ITG), and right posterior temporal fusiform gyrus. Greater improvement was also associated with decreased rsFCs between left anterior temporal fusiform gyrus and right superior parietal lobule (SPL), between right OFC and right posterior SMG, and between right OFC and the left Cb X. Moreover, because peak significance can fluctuate near threshold boundaries, we examined the CBT-E group results using a more lenient threshold (seed-level $p\text{-FDR} < 0.1$; Figure S1). This analysis revealed a rsFC pattern highly consistent with the primary all-modality analysis, encompassing all significant findings except for the increased connectivity between the right caudate nucleus and right cerebellar hemisphere IX. This indicates that the core rsFC changes associated with CBT are largely consistent across treatment modalities, although individual edges near the stricter threshold may vary.

Pretreatment rsFC characteristics associated with a better response to CBT

Table 3 (a) and Fig. 2 (a) present the results of a multiple regression analysis in which change in EDE-Q global score was the dependent variable, pretreatment rsFC values were the independent variables, and age and psychotropic medication use (yes/no) were included as covariates. All results reported below survived seed-level $p\text{-FDR} < 0.05$. Greater improvement in EDE-Q global score was predicted by stronger pretreatment rsFCs between right SPL and three target regions: left opercular part of inferior frontal gyrus (operIFG), right operIFG, and right temporooccipital part of middle temporal gyrus. Greater improvement was also predicted by stronger pretreatment rsFCs between left postcentral gyrus (PoCG) and right toITG and left toITG.

Table 3
Pretreatment rsFCs which predicted improvement of EDE-Q global score by CBT

(A) All modalities					
Seed	Region	t-Value	partial r	95% CI	p-FDR
Stronger pretreatment rsFCs (seed-level p-FDR < 0.05)					
Right superior parietal lobule	Left opercular part of inferior frontal gyrus	4.66	0.68	0.41–0.84	0.0127
	Right opercular part of inferior frontal gyrus	3.73	0.60	0.28–0.80	0.0495
	Right temporooccipital part of middle temporal gyrus	3.70	0.60	0.28–0.80	0.0495
Left postcentral gyrus	Right temporooccipital part of inferior temporal gyrus	5.13	0.72	0.46–0.86	0.0038
	Left temporooccipital part of inferior temporal gyrus	4.51	0.67	0.39–0.83	0.0093
(B) CBT-E only					
Seed	Region	t-Value	partial r	95% CI	p-FDR
Stronger pretreatment rsFCs (seed-level p-FDR < 0.05)					
Left anterior supramarginal gyrus	Left cerebellar hemisphere crus II	5.38	0.79	0.53–0.91	0.0057
Right posterior supramarginal gyrus	Right middle frontal gyrus	4.12	0.70	0.37–0.87	0.0453
Left postcentral gyrus	Right temporooccipital part of inferior temporal gyrus	4.51	0.73	0.42–0.89	0.0382
Left angular gyrus	Right occipital pole	4.45	0.72	0.41–0.88	0.0434
Weaker pretreatment rsFCs (seed-level p-FDR < 0.05)					
Right posterior supramarginal gyrus	Left inferior lateral occipital cortex	5.14	0.77	0.50–0.91	0.0098
Right planum temporale	Right intracalcarine cortex	4.87	0.75	0.47–0.90	0.0175
	Right lingual gyrus	4.84	0.75	0.46–0.90	0.0185
rsFC, resting-state functional connectivity; EDE-Q, Eating Disorder Examination Questionnaire; CBT, cognitive behavioral therapy; CI, confidence interval;					

(A) All modalities					
Seed	Region	t-Value	partial r	95% CI	p-FDR
Stronger pretreatment rsFCs (seed-level p-FDR < 0.05)					
p-FDR, two-sided false discovery rate corrected p-value; CBT-E, enhanced cognitive behavioral therapy.					

As a sensitivity analysis, we conducted the same regression analysis restricted to the CBT-E group (Table 3 (b) and Fig. 2 (b)). All results reported below survived seed-level p-FDR < 0.05. Greater improvement in EDE-Q global score was predicted by stronger pretreatment rsFCs between left anterior SMG and left Cb crus II, between right posterior SMG and right middle frontal gyrus, between left PoCG and right tolTG, and between left angular gyrus and right occipital pole. Greater improvement was also predicted by weaker pretreatment rsFCs between right posterior SMG and left inferior lateral occipital cortex, and between right planum temporale and two occipital regions: right intracalcarine cortex and right lingual gyrus. To further evaluate the robustness of these findings, we further examined the CBT-E subgroup at a more lenient threshold (seed-level p-FDR < 0.1; Figure S2). At this threshold, the CBT-E analysis encompassed all pretreatment predictor connections identified in the primary all-modality analysis. This suggests that the overall pattern of pretreatment rsFC predictors is broadly preserved in the CBT-E subset, although individual edges near the stricter threshold may vary.

Discussion

In this study, we conducted a longitudinal ROI-to-ROI rsFC analysis in 30 patients with BN who received CBT (CBT-E: n = 24; vCBT: n = 4; ICBT: n = 2), treating all brain regions as both seeds and targets. We tested associations between pre-to-post changes in EDE-Q global score and concomitant rsFC changes using multiple regression (equivalent to partial correlations), adjusting for age and psychotropic medication use, and examined pretreatment rsFC predictors of outcome using the same covariates. To address heterogeneity in CBT delivery, we also performed a CBT-E–restricted sensitivity analysis. Whole-brain longitudinal ROI-to-ROI rsFC studies of CBT in BN remain rare, and this work provides early evidence in this area.

Two findings were entirely consistent across both the primary (all modalities) and CBT-E-restricted analyses: (i) decreased rsFC between right OFC and right posterior SMG was associated with greater symptom improvement (larger reduction in EDE-Q global score), and (ii) stronger pretreatment rsFC between left PoCG and right tolTG predicted greater improvement. Because the CBT-E sample is nested within the full cohort, these analyses are not independent replications; rather, the preserved direction suggests relative insensitivity to CBT delivery format. Prior cross-sectional BN studies have more consistently reported rsFC abnormalities involving OFC, implicated in reward valuation and decision-making [14–17], and altered rsFC involving PoCG, related to somatosensory and motor processing [16,

20, 22, 38]. Thus, our findings align with cross-sectional evidence while extending it by linking OFC–SMG changes to clinical improvement and PoCG-related connectivity to treatment responsiveness.

At the same time, several results did not overlap completely between the primary and CBT-E–restricted sensitivity analyses at the seed-level threshold ($p\text{-FDR} < 0.05$). These discrepancies should not be interpreted as modality-specific effects; instead, they are consistent with statistically expected influences of sample-size differences (and thus power) and edge-level instability near multiple-comparison thresholds. Indeed, when we examined the CBT-E subgroup using a more lenient seed-level threshold ($p\text{-FDR} < 0.1$), the broader rsFC patterns became more closely aligned with those observed in the primary all-modality analysis, suggesting that the apparent “non-overlap” at $p\text{-FDR} < 0.05$ may partly reflect thresholding of effects close to the significance boundary. Importantly, even when individual edges varied, interpretations at the circuit or network level converged across analyses, including cerebellar–temporal visual connectivity changes (e.g., involving fusiform/ITG regions) associated with treatment effects and parietal associative (SPL/SMG)–frontal associations related to treatment responsiveness. In the following sections, we first discuss ROI-level findings that showed consistent directions across analyses, then consider these network-level commonalities that support integrative interpretations, and finally address the clinical implications and limitations of the present study.

Implications of ROI-level convergence across analyses

The association between decreased rsFC of OFC and right posterior SMG and therapeutic effects suggests that reducing abnormally strong coupling between reward-related and inhibitory control networks may contribute to CBT efficacy. OFC plays a central role in emotional evaluation of reinforcers (e.g., food) and serves as a hub for learning, prediction, and decision-making in reward-driven behavior [39]. OFC dysfunction has been linked to impaired impulse control in substance abuse and dependence [40]. Furthermore, OFC is considered a key region for reward processing and food-related evaluation, playing a central role in eating-disorder pathophysiology [41]. Several BN studies have reported OFC-related rsFC and volumetric alterations [14–17]. In contrast, the inferior parietal lobule (IPL; supramarginal and angular gyri) contributes to inhibitory control during executive functioning [42], and a meta-analysis of Wisconsin Card Sorting Test studies found reliable IPL engagement in inhibitory function [43]. OFC and IPL are anatomically and functionally connected [44, 45]. In restrained eaters, stronger rsFC between left medial OFC and IPL was associated with greater eating restraint and predicted binge-eating severity, suggesting that dysregulation within reward-control circuitry may impair eating regulation and contribute to binge episodes [46]. Together, these findings raise the possibility that CBT may partly exert effects by normalizing exaggerated reward-control coupling—particularly between OFC and IPL—thereby supporting adaptive reward evaluation of food and regulation of eating behavior.

Stronger pretreatment rsFC between left PoCG and right toITG predicting better CBT response may indicate that patients with fewer distortions in self- and other-related body perceptions are more likely to benefit. In BN, PoCG shows accelerated age-related volumetric loss and its volume inversely correlates with binge-eating and vomiting frequency; ITG also shows significant volumetric loss [47]. Both regions

contribute to body perception: PoCG hyperactivation has been reported when BN patients view others' bodies, whereas ITG hypoactivation has been observed when viewing one's own body [48]. Thus, stronger PoCG–ITG connectivity may reflect relatively preserved body-related processing that facilitates CBT responsiveness.

Implications of network-level convergence across analyses

At the network level, increased rsFC between cerebellum and temporal visual areas (fusiform gyrus and ITG) associated with symptom improvement suggests that CBT may engage processes modulating coupling between perceptual and affective processing of food-related cues. The cerebellum is thought to receive diverse inputs (interoceptive signals, blood glucose, gustatory/olfactory information) via the hypothalamus and to contribute to the motivation and regulation of eating behavior [49]; the vermis may be especially important for regulating emotional responses to appetite-related cues [50]. Although not directly BN-related, right cerebellar hemisphere volume predicts inpatient outcomes in anorexia nervosa [51], and obesity studies report heightened vermal reactivity to chocolate odor [52]. Fusiform gyrus and ITG support visual processing of food stimuli [53], and altered fusiform responsivity during food-related tasks has been reported in BN [54]. Accordingly, increased cerebellum–temporal visual connectivity may reflect CBT-related modulation of pathways involved in evaluating and responding to visually presented food, contributing to symptom improvement via more adaptive responses to food cues.

Stronger pretreatment rsFC between parietal associative regions (including SPL/SMG) and frontal regions (including IFG/MFG) predicting responsiveness suggests that relatively preserved frontoparietal network (FPN) function—supporting acquisition, maintenance, and everyday application of CBT skills—may facilitate benefit from CBT. The FPN comprises prefrontal regions (IFG/MFG) and posterior parietal associative regions (SPL/SMG), contributes to broad task performance by initiating and regulating cognitive control, and supports learning novel tasks via rapid knowledge transfer through compositional coding [55]. In obsessive–compulsive disorder, pretreatment frontoparietal indices relate to CBT response in structural MRI (cortical thickness) and working-memory task fMRI (load-dependent BOLD modulation in SPL/IPL) [56, 57]. In depression, evidence-accumulation signatures in prefrontal and parieto-occipital regions have also been associated with CBT outcomes [58]. Although conceptually distinct from rsFC, these findings are consistent with the idea that frontoparietal integrity supports learning and implementing therapeutic skills. Moreover, frontal gyri and SPL/SMG cooperate in visuospatial working memory for object recognition [59]. Given that BN is associated with visuospatial and working-memory impairments [60], preserved frontoparietal control functions may support understanding, repetition, and generalization of CBT procedures (e.g., cognitive restructuring and behavioral experiments), thereby contributing to better treatment responsiveness.

Clinical implications

The present findings suggest that CBT—at least in a subset of patients—may engage neural processes involved in regulating responses to food-related cues (e.g., interactions between reward valuation and control systems, and perceptual–affective coupling). Accordingly, future studies could evaluate whether

augmenting CBT with components that more explicitly support inhibitory control in response to food cues yields additional clinical benefit. In addition, the observation that better outcomes were predicted by stronger pretreatment connectivity related to body perception (PoCG–toITG) raises a testable hypothesis: patients with more pronounced disturbances in these functions may benefit from adjunctive strategies that more directly target body-image–related perceptual/cognitive processing and strengthen learning or cognitive control demands within therapy. Such adjunctive approaches could include intensified behavioral modules and, where appropriate, mechanistically informed interventions designed to enhance plasticity within relevant circuits (e.g., neuromodulation), which should be evaluated in controlled trials. Finally, pretreatment rsFC features may be better framed as prognostic markers that could support future stratification—ideally combined with clinical variables in externally validated multivariable prediction models—rather than as stand-alone clinical tests. These implications remain provisional given the modest sample size and single-arm design, and require replication before clinical translation.

Limitations

This study has several limitations. First, the analytic sample was modest relative to the high dimensionality of whole-brain ROI-to-ROI connectome analyses, increasing uncertainty and overfitting risk despite multiple-comparison control. Moreover, seed-level FDR controls false discoveries within each seed (across connections to all targets) rather than across all edges simultaneously; while interpretable, this may allow false positives at the connectome-wide level, and effect-size estimates from selected edges should be interpreted cautiously. Second, the single-arm pre–post design without a control condition limits causal attribution to CBT-specific mechanisms; test–retest effects, spontaneous symptom fluctuation, or nonspecific factors cannot be excluded. Third, although multi-site variability was addressed using ComBat harmonization (batches by manufacturer) and the same model was applied to pre- and post-treatment data, residual site/protocol effects may remain. Fourth, CBT modality heterogeneity was present in the full cohort. Although we conducted a CBT-E–restricted sensitivity analysis, the CBT-E sample is nested within the full cohort and does not provide independent replication; modality-specific effects, therefore, cannot be determined. Fifth, generalizability is limited because all analyzed participants were Japanese women, requiring replication in more diverse samples (including men, gender-diverse populations, and other cultural contexts). Sixth, although age and psychotropic medication status (yes/no) were covariates, residual confounding may persist because medication effects vary by class, dose, and duration, which were not modeled. Differences in cohort clinical profiles (e.g., relatively low rates of anxiety disorders and ADHD compared with some prior BN samples) may also limit comparability and influence observed associations.

Conclusion

This multi-site longitudinal study provides initial evidence that CBT for bulimia nervosa is accompanied by specific changes in whole-brain functional architecture and that pretreatment neural signatures can predict clinical response. Our findings suggest that the therapeutic process of CBT involves a complex

modulation of brain circuits: specifically, a reduction in the coupling between reward-valuation (OFC) and inhibitory control (SMG) regions, alongside an enhancement of connectivity between the cerebellum and temporal visual areas involved in processing food-related cues. These changes may reflect the normalization of maladaptive responses to appetitive stimuli and improved regulatory control. Furthermore, the identification of preserved connectivity within somatosensory-temporal and frontoparietal networks as predictors of improvement may highlight the importance of preserved perceptual processing and cognitive control for successful engagement with CBT. These results require replication in larger, controlled cohorts, but they may serve as a foundation for improving CBT for BN and objective prognostic tools.

Abbreviations

aCompCor

Anatomical component-based noise correction

ADHD

Attention-deficit/hyperactivity disorder

ART

Artifact Detection Tools

BAAD

Brain Anatomical Analysis using Diffeomorphic deformation

BDI-II

Beck Depression Inventory-II

BMI

Body Mass Index

BN

Bulimia Nervosa

BOLD

Blood oxygen level dependent

Cb

Cerebellar hemisphere

CBT

Cognitive behavioral therapy

CBT-E

Enhanced cognitive behavioral therapy

DSM-5

Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

EDE-Q

Eating Disorder Examination Questionnaire

EDNI

Eating Disorder Neuroimaging Initiative

FDR
False discovery rate
fMRI
Functional magnetic resonance imaging
FPN
Frontoparietal network
HARP
Harmonized Protocol
ICBT
Guided internet-based cognitive behavioral therapy
IFG
Inferior frontal gyrus
IPL
Inferior parietal lobule
ITG
Inferior temporal gyrus
JART
Japanese Adult Reading Test
MFG
Middle frontal gyrus
MNI
Montreal Neurological Institute
OFC
Orbitofrontal cortex
operIFG
Opercular part of inferior frontal gyrus
PoCG
Postcentral gyrus
ROI
Region of interest
rsFC
Resting-state functional connectivity
rsfMRI
Resting-state functional magnetic resonance imaging
SMG
Supramarginal gyrus
SPL
Superior parietal lobule
SRPB
Strategic Research Program for Brain Science

SSRI
Selective serotonin reuptake inhibitor
STAI
State-Trait Anxiety Inventory
toITG
Temporo-occipital part of inferior temporal gyrus
TR
Repetition time
vCBT
Videoconference cognitive behavioral therapy

Declarations

Ethics approval and consent to participate

This study protocol was reviewed and approved by the Ethical Committee of the National Center of Neurology and Psychiatry, approval number A2019-072. Written informed consent was obtained from participants after they were fully informed about the study protocol.

Consent for publication

Not applicable.

Availability of data and materials

The datasets of T1-weighted structural MRI images, resting-state fMRI data, and demographic information analyzed during the current study have been deposited in the Brain/MINDS Beyond human brain MRI project and are currently being prepared for public release (<https://hbm.brainminds-beyond.jp/ja/data.html>). The self-report psychological scale data will only be partially available through the same repository. Additional information not included in the public repository can be obtained from the corresponding author upon reasonable request.

Competing Interests

Y.Mo is the representative of Psycho Innovation Co., Ltd. All other authors have no conflicts of interest to declare.

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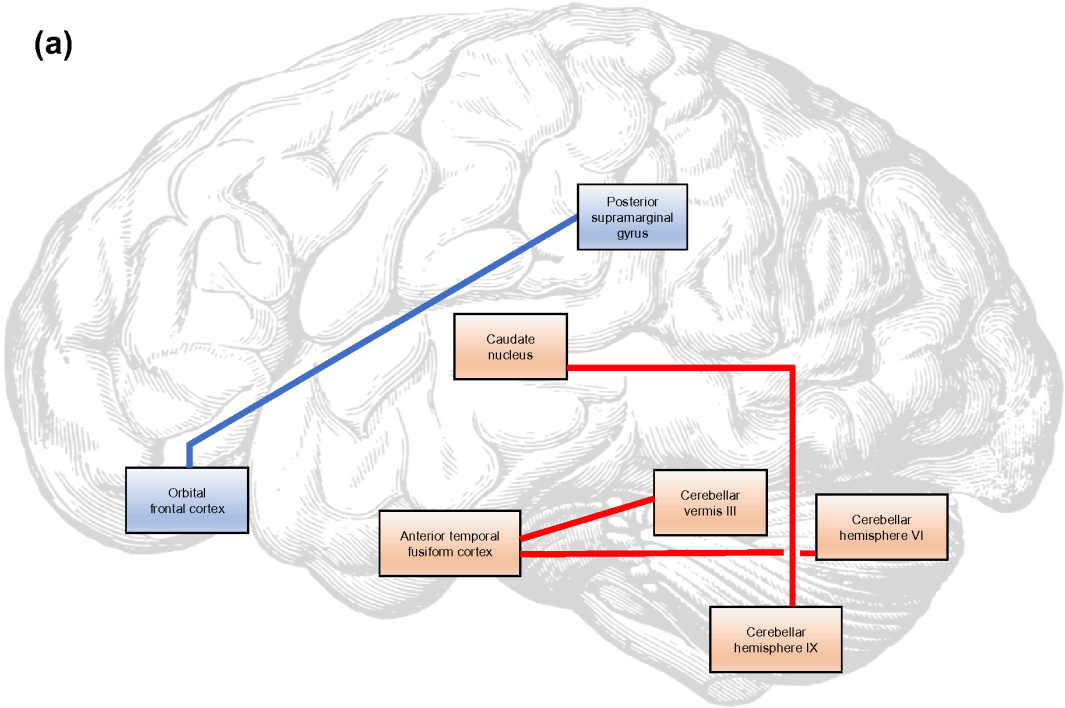
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Figures

Figure 1

(a)



(b)

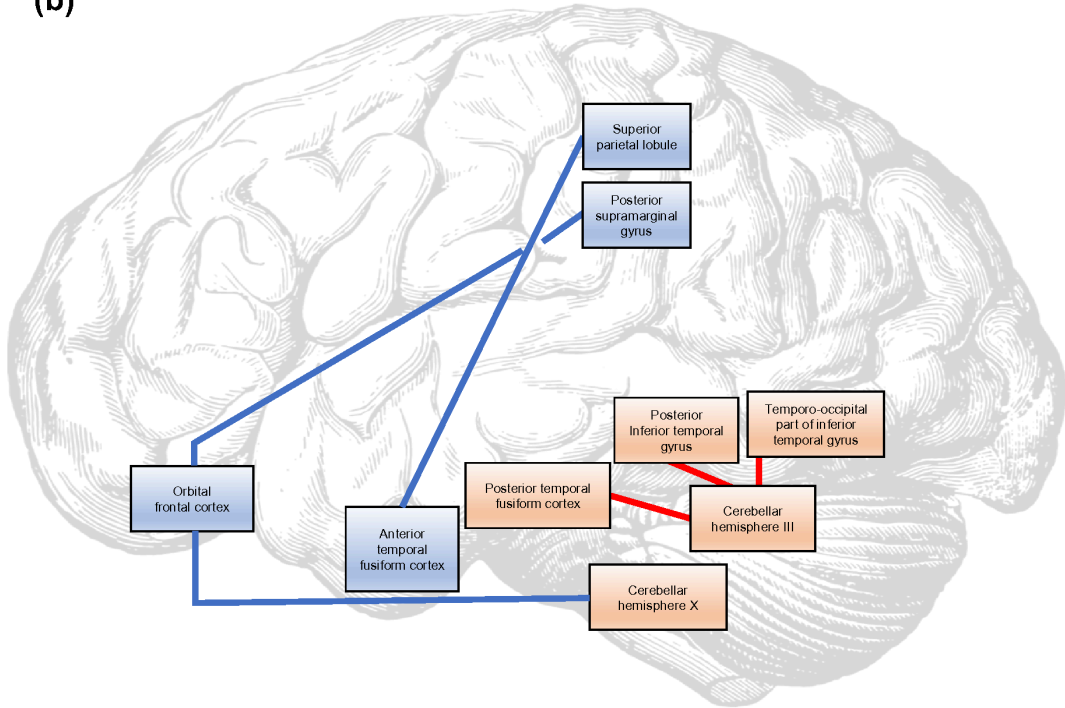


Figure 1

Title: Schematic diagram showing rsFC changes correlated with improvement in EDE-Q global score.

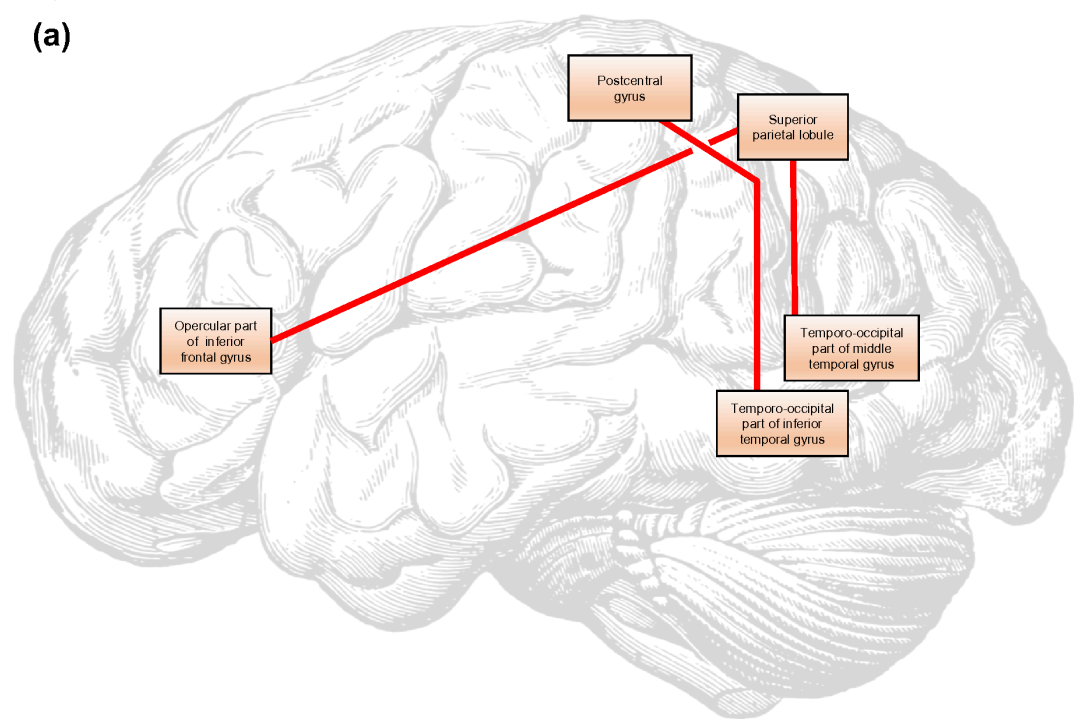
(a) All CBT modalities (primary analysis). Schematic diagram illustrating rsFC changes associated with improvement in EDE-Q global score identified by the multiple regression analysis (change in EDE-Q global score as the dependent variable; rsFC change [post–pre] as the independent variable; covariates:

age and psychotropic medication use [yes/no]). Red lines indicate increased rsFC and blue lines indicate decreased rsFC associated with greater symptom improvement. The left side of the figure corresponds to frontal regions; hemispheric laterality (left vs right) is not explicitly distinguished in this schematic. All connections shown survived seed-level FDR correction ($p\text{-FDR} < 0.05$), where FDR correction was applied separately for each seed ROI across its connections to all target ROIs.

(b) CBT-E only (sensitivity analysis). Schematic diagram illustrating rsFC changes associated with improvement in EDE-Q global score identified by the same regression framework restricted to participants who received CBT-E (covariates: age and psychotropic medication use [yes/no]). Red lines indicate increased rsFC and blue lines indicate decreased rsFC associated with greater symptom improvement. The left side of the figure corresponds to frontal regions; hemispheric laterality is not explicitly distinguished. All connections shown survived seed-level FDR correction ($p\text{-FDR} < 0.05$), applied separately to each seed ROI across its connections to all target ROIs.

Figure 2

(a)



(b)

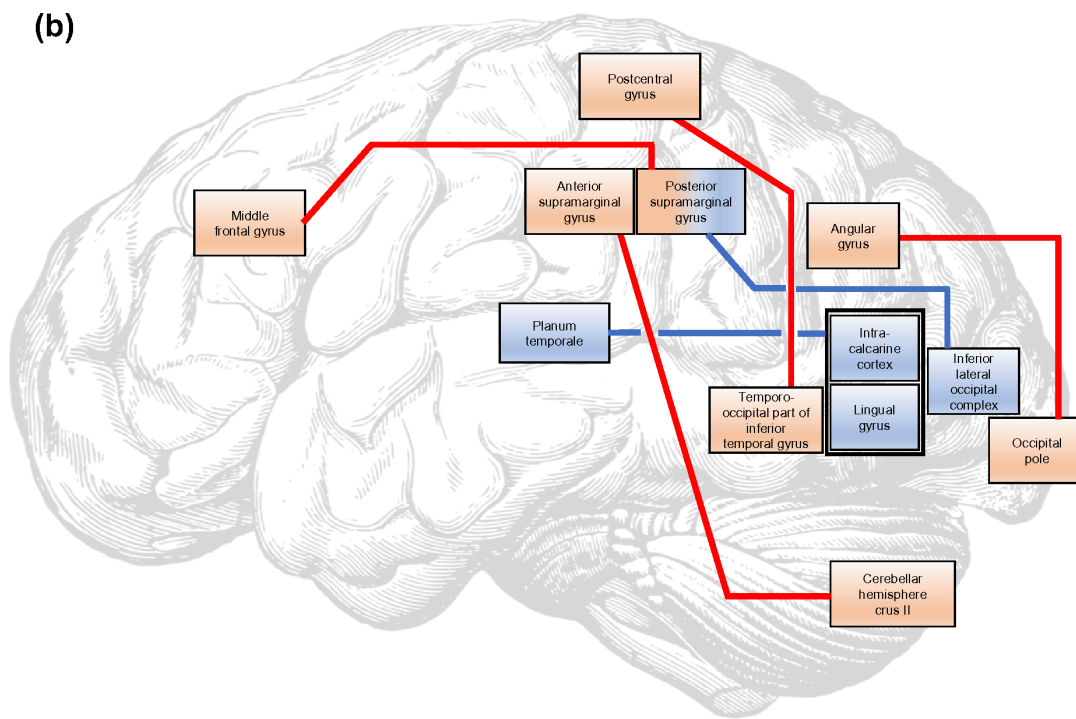


Figure 2

Title: Schematic diagrams of pretreatment rsFC features predicting improvement in EDE-Q global score.

(a) All CBT modalities (primary analysis). Schematic diagram illustrating pretreatment rsFC features that predicted improvement in EDE-Q global score, identified by the multiple regression analysis (change in EDE-Q global score as the dependent variable; pretreatment rsFC as the independent variable;

covariates: age and psychotropic medication use [yes/no]). Red lines indicate stronger pretreatment rsFC predicted greater symptom improvement, while blue lines indicate weaker pretreatment rsFC predicted greater symptom improvement. The left side of the figure corresponds to frontal regions; hemispheric laterality (left vs right) is not explicitly distinguished in this schematic. All connections shown survived seed-level FDR correction ($p\text{-FDR} < 0.05$), where FDR correction was applied separately for each seed ROI across its connections to all target ROIs.

(b) CBT-E only (sensitivity analysis). Schematic diagram illustrating pretreatment rsFC features that predicted improvement in EDE-Q global score, identified using the same regression framework restricted to participants who received CBT-E (covariates: age and psychotropic medication use [yes/no]). Red lines indicate stronger pretreatment rsFC predicted greater symptom improvement, while blue lines indicate weaker pretreatment rsFC predicted greater symptom improvement. The left side of the figure corresponds to frontal regions; hemispheric laterality is not explicitly distinguished. All connections shown survived seed-level FDR correction ($p\text{-FDR} < 0.05$), applied separately to each seed ROI across its connections to all target ROIs.

Supplementary Files

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- [Supplementarymaterials.docx](#)