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Supplementary methods

Participants

Participants with anorexia nervosa were recruited from specialized eating disorder programs of a university child and adolescent psychiatry and psychosomatic medicine department within 96 hours of initiating nutritional rehabilitation. Since nutritional rehabilitation has to be carried out with caution at the beginning of the treatment owing to possible complications, such as refeeding syndrome,[1,2] our patients had at that stage of treatment a calorie intake of about 1000–1500 kcal/d. The regular treatment program included a nutritional rehabilitation program with weight goals, regular meals, limitation of exercise and normalization of fluid intake. In addition patients received regular sessions of supportive psychotherapy. The multidisciplinary treatment included several elements: 1) individual and group counselling to restore healthy eating behaviours, 2) individual therapy based on cognitive behavioural principles that targeted dysfunctional thoughts, 3) group therapy to enhance motivation and self-confidence, 4) group psychoeducation for parents of patients. The patients also participated in occupational, art, body-oriented and relaxation sessions. However, within the first 96 hours patients participated only in a very limited subset of the aforementioned interventions. Body mass index (BMI) cut-offs for patients were defined according to Kromeyer-Hauschild and colleagues and Hebebrand and colleagues.[3,4]

Healthy controls were recruited through advertisement among middle school, high school and university students. For case–control age matching an implementation of the Munkres algorithm was used.[5]

Control participants were excluded (before scanning) if they had any history of psychiatric illness, a lifetime BMI below the tenth age percentile (if younger than 18 years)/BMI below 18.5 (if older than 18 years), or were currently obese (BMI not over 97th age percentile if younger than 18 years; BMI not over 30 if older than 18 years).

Participants of all study groups were excluded if they had a lifetime history of any of the following clinical diagnoses: organic brain syndrome, schizophrenia, substance dependence, psychosis not otherwise specified, bipolar disorder, bulimia nervosa or binge-eating disorder (or "regular" binge eating, which was defined as bingeing at least once weekly for 3 or more consecutive months). Further exclusion criteria for all participants were IQ lower than 85; psychotropic medication within 6 weeks prior to the study; current substance abuse; current inflammatory, neurologic or metabolic illness; chronic medical or neurological illness that could affect appetite, eating behaviour, or body weight (e.g. diabetes); clinically relevant anemia; pregnancy; and breastfeeding.

Psychiatric and psychological assessments

Exclusion criteria and possible confounding variables (e.g., the use of psychotropic medications and medical comorbidities), were determined using the expert version of the Structured Interview for Anorexia and Bulimia Nervosa (SIAB-EX) for DSM-IV[6] and our own semistructured interview. The SIAB-EX is a well-validated 87-item semi-standardized interview that assesses the prevalence and severity of specific eating-related psychopathology over the past 3 months. The interview provides diagnoses according to the ICD-10 and DSM-IV and is suitable for adolescents as well as adults. It has been used widely in eating disorder research. [7–9] A good inter-rater reliability (κ = 0.81) for the diagnostic interview has been demonstrated.[6]

For patients with anorexia nervosa, comorbid psychiatric diagnoses other than eating disorders were derived from medical records and confirmed by an expert clinician with more than 10 years of experience after careful chart review (including consideration of medical and psychiatric history, physical examination, routine blood tests, urine analysis and a range of psychiatric screening instruments). All diagnostic information was ascertained at the time of treatment and the principal investigator of this study is also the chief consultant of the eating disorder treatment centre.

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Psychiatric conditions in potential healthy controls were ascertained using the same instruments as in patients (Table S1). All interviews were carried out by trained graduate students (psychology or medicine). If there were any indications of psychiatric symptoms, each case was discussed with a fully board-certified expert clinician and assessments were extended if necessary.

Handedness was assessed using a short version of the Annett Scale of Hand Preference,[10] as previously implemented by Gollub and colleagues.[11] This questionnaire asks for handedness in typical daily life situations, such as writing or brushing teeth. Response categories are 0 (right hand), 1 (both hands) and 2 (left hand). A mean score for handedness was calculated.

Study data were collected and managed using secure, web-based electronic data capture tools, including REDCap (Research Electronic Data Capture[12]).

Table S1: Clinical measures used during the assessment procedure.

Inventory	Abbreviation
Structured Interview for Anorexia and Bulimia Nervosa for DSM-IV[6]	SIAB-EX
Beck Depression Inventory II[13]	BDI-II
Eating Disorder Inventory 2[14]	EDI-2
Revised symptom checklist 90[15]	SCL-90-R
Wechsler Adult Intelligence Scale (short version)[16]	WAIS*
Wechsler Intelligence Scale for Children (short version)[17]	WISC*

*IQ was assessed with WAIS for participants aged ≥16 years or WISC otherwise.

Functional MRI data preprocessing and analysis

The following software tools were also used: DARTEL[18] for generating anatomical group templates, Nipype framework[19] for running imaging processing workflows, DPARSFA toolbox[20] for extraction of timeseries, R toolbox[21] for statistical analysis, and BrainNet Viewer[22] software for visualization of brain networks.

During preprocessing smoothing was not performed, because it would impose new correlations among seed regions, emphasizing those that are adjacent and hence bias the network structure toward a lattice topology and alter graph metrics.[23] Similarly, during preprocessing we did not apply global mean regression, which would bias correlations and complicate the interpretation of negative correlations.[24]

The resulting volumes were parcellated into 160 spherical regions of interest (ROIs), as defined by Dosenbach.[25] This functionally defined parcellation scheme has been derived from meta-analyses of task-related fMRI studies, covers the cerebrum and cerebellum, and consists of nonoverlapping spheres with a diameter of 10 mm.

To assess whether residual motion biases group differences by causing spurious correlation structures throughout the brain, which would be reflected in the derived graph metrics, the data sets were reprocessed with additional application of scrubbing after regression of nuisance covariates to eliminate timepoints with a framewise displacement > 0.5 mm.[26] According to standard procedure, 1 preceding and 2 subsequent timepoints were also excluded.[26] Two-sample t tests were used to test for potential differences of framewise displacement and subsequently for differences in length of time series after scrubbing.

To test whether previously observed group differences persist after the application of scrubbing, between-group comparisons on global as well as local graph metrics were performed and the resulting p values were false discovery rate (FDR)–corrected for the number of tests.

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Structural MRI data preprocessing and analysis

For measuring cortical thickness (CT) and grey matter volumes the structural data were registered, motion-corrected, realigned, averaged and analyzed in an automated manner with the FreeSurfer software suite (http://surfer.nmr.mgh.harvard.edu, version 5.1.0), a well-documented program for volumetric segmentation and cortical surface reconstruction.[27–32]

Using standard FreeSurfer procedures to measure CT, surface reconstruction was first performed for each hemisphere and included tessellation of the grey matter–white matter boundary, automated topology correction and surface deformation following intensity gradients to optimally place the grey–white and grey–cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class. The resulting surfaces were then used to calculate CT at each vertex as the closest distance from the grey–white boundary to the pial surface. For the subcortical volumetric analyses, we used the automated segmentation procedures implemented in the FreeSurfer pipeline to assign an anatomical label to each voxel based on probabilistic information estimated from a manually labelled training set. The quality of the surface reconstruction and segmentation was assured according to FreeSurfer user guidelines by visual inspection of the resulting output and, if necessary, edited with minor manual intervention.

The output of the FreeSurfer standard procedure includes total grey matter volume, intracranial volume, volumes of subcortical labels[28] and thickness values of cortical labels based on the Desikan-Killiany atlas.[27] Furthermore, we calculated the right and left hemispheric thickness by averaging the thickness values of all right and left hemispheric labels, respectively. We also extracted the cortical thickness values and grey matter volume for the cortical subset of the 160 Dosenbach ROIs as follows: (1) for each ROI in volume space we created a surface-based ROI by mapping the volume on the surface of the FreeSurfer standard brain; (2) for every participant and for all surface-based ROIs the mean thickness value and surface area was extracted; and (3) using cortical thickness and area we calculated the grey matter volumes of the cortical ROIs.

Table S2: Extracted cortical thickness values, cortical and subcortical volumes across groups used for correlational analysis

	Region; mean ± SD*								
Group	Total grey matter volume, cm^3	Right hemisphere thickness, mm	Left hemisphere thickness, mm	Left thalamus volume, cm^3	Right thalamus volume, cm^3	Left midinsula volume, mm^3	Left posterior insula volume, mm^3	Left midinsula thickness, mm	Left posterior insula thickness, mm
Anorexia nervosa	654.5 ± 51.30†	2.72 ± 0.13†	2.70 ± 0.13†	6.84 ± 0.54†	6.94 ± 0.55†	112.6 ± 31.1	108.2 ± 25.4	3.82 ± 0.49	2.42 ± 0.29
Control	727.5 ± 60.07†	2.9 ± 0.16†	2.90 ± 0.15†	7.51 ± 0.65†	7.58 ± 0.70†	105.6 ± 32.3	99.5 ± 20.3	3.75 ± 0.24	2.53 ± 0.24

SD = standard deviation.
*The local regions of interest correspond exactly to the seed regions used in our resting state connectivity analysis.
†Group differences were tested using Student *t* tests, $p < 0.001$.

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Additional statistical analyses

Demographic and symptom variables were compared using Student *t* tests. Correlational analyses were performed using Pearson coefficients. In all statistical analyses we used age-adjusted BMI standard deviation scores (BMI-SDS) calculated using the LMS method from Cole and German population reference data from Kromeyer-Hauschild and colleagues (for participants ≤ 18 yr) and Hemmelmann and colleagues (for participants ≥ 19 yr).[4,33,34] The BMI-SDS is a better measure than absolute BMI in pediatric populations because what is considered a healthy BMI changes with age.[4,35]

Supplementary results

Motion and time series

A 2-sample *t* test revealed no significant differences in framewise displacement index (FWD) between groups (control: mean 0.199± 0.145; anorexia nervosa: mean 0.168 ± 0.086; t_{68} =1.08, p = 0.28). The number of remaining timepoints after scrubbing did not significantly differ between groups (control: mean 169.86 ± 30.66; anorexia nervosa: mean 178.23 ± 20.84; t_{68} = –1.32, p = 0.10).

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Group differences in graph metrics

After the application of scrubbing, previously observed group differences revealed in local and global graph metrics remained significant ($p < 0.05$, FDR-corrected).

Table S3: Group differences in local and global graph metrics for scrubbed data (FWD< 0.5mm) including specific *p* values, FDR corrected for the number of tests (part 1 of 2)

Sparsity, %	Metric	ROI	*p* value
Global			
18	CPL	Global	0.044
22	CPL	Global	0.027
24	CPL	Global	0.019
26	CPL	Global	0.015
28	CPL	Global	0.015
30	CPL	Global	0.016
18	Assortativity	Global	0.044
20	Assortativity	Global	0.040
22	Assortativity	Global	0.027
24	Assortativity	Global	0.019
26	Assortativity	Global	0.015
28	Assortativity	Global	0.015
Local			
10	Strength	Midinsula_L_61	0.002
10	Strength	Postinsula_L_76	0.001
10	Degree	Midinsula_L_61	0.003
10	Degree	Postinsula_L_76	0.001
10	CPL	Midinsula_L_61	0.001
10	CPL	Postinsula_L_76	0.002
10	CPL	Thalamus_L_47	0.001
10	CPL	Thalamus_R_58	0.002
12	Strength	Midinsula_L_61	0.002
12	Strength	Postinsula_L_76	0.001
12	Degree	Postinsula_L_76	0.001

CPL = characteristic path length.

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Table S3: Group differences in local and global graph metrics for scrubbed data (FWD< 0.5mm) including specific *p* values, FDR corrected for the number of tests (part 2 of 2)

Sparsity, %	Metric	ROI	*p* value
Local (continued)			
12	CPL_{loc}	Postinsula_L_76	0.002
12	CPL_{loc}	Thalamus_L_47	0.001
12	CPL_{loc}	Thalamus_R_58	0.001
14	Strength	Midinsula_L_61	0.001
14	Strength	Postinsula_L_76	0.001
14	Strength	Thalamus_L_47	0.002
14	Degree	Midinsula_L_61	0.001
14	Degree	Postinsula_L_76	0.001
14	CPL_{loc}	Midinsula_L_61	0.001
14	CPL_{loc}	Postinsula_L_76	0.003
14	CPL_{loc}	Thalamus_L_47	0.002
14	CPL_{loc}	Thalamus_R_58	0.002
14	LEGE	Postoccipital_R_158	0.002
16	Strength	Midinsula_L_61	0.001
16	Strength	Postinsula_L_76	0.002
16	Strength	Thalamus_L_47	0.002
16	Degree	Midinsula_L_61	0.001
16	Degree	Postinsula_L_76	0.002
16	CPL_{loc}	Midinsula_L_61	0.001
16	CPL_{loc}	Postinsula_L_76	0.003
16	CPL_{loc}	Thalamus_L_47	0.003
16	CPL_{loc}	Thalamus_R_58	0.002
16	LEGE	Postoccipital_R_158	0.001
16	E_{loc}	aPFC_R_2	0.001
24	LEGE	Postoccipital_R_158	0.001

CPL_{loc} = characteristic path length; E_{loc} = local efficiency; FDR = false discovery rate; FWD = framewise displacement index; LEGE = normalized local efficiency; ROI = region of interest.

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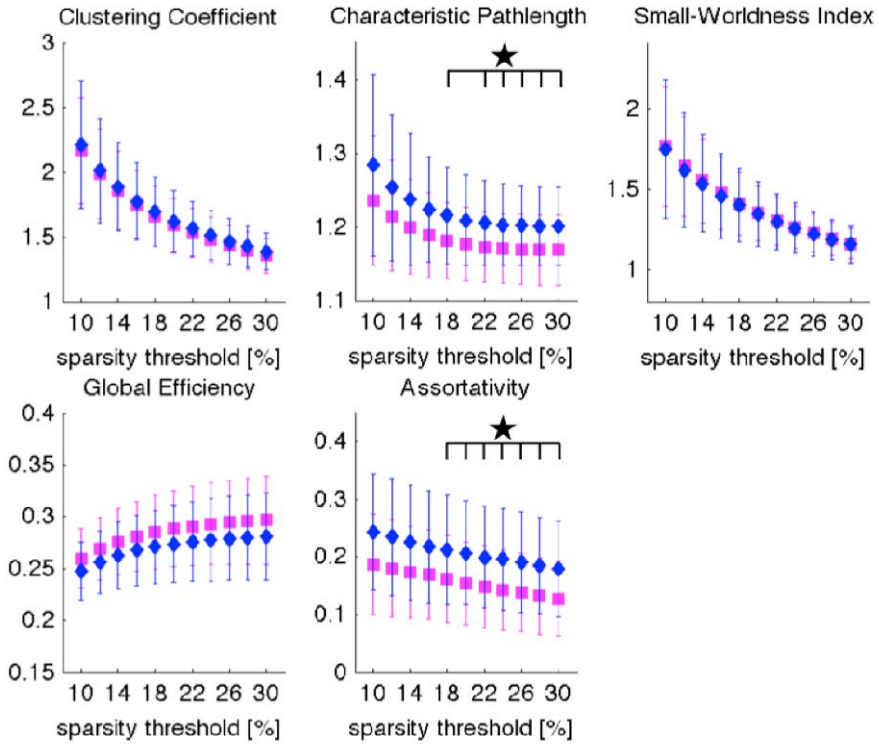

Fig. S1: Topological properties of brain networks of healthy controls (magenta squares) and patients with anorexia nervosa (blue diamonds). Global graph metrics derived from scrubbed data sets are depicted: clustering coefficient (CC), characteristic path length (CPL), small-worldness index (SWI) as well as global efficiency (E_{glob}) and assortativity (α) for sparsity thresholds between 10% and 30%.

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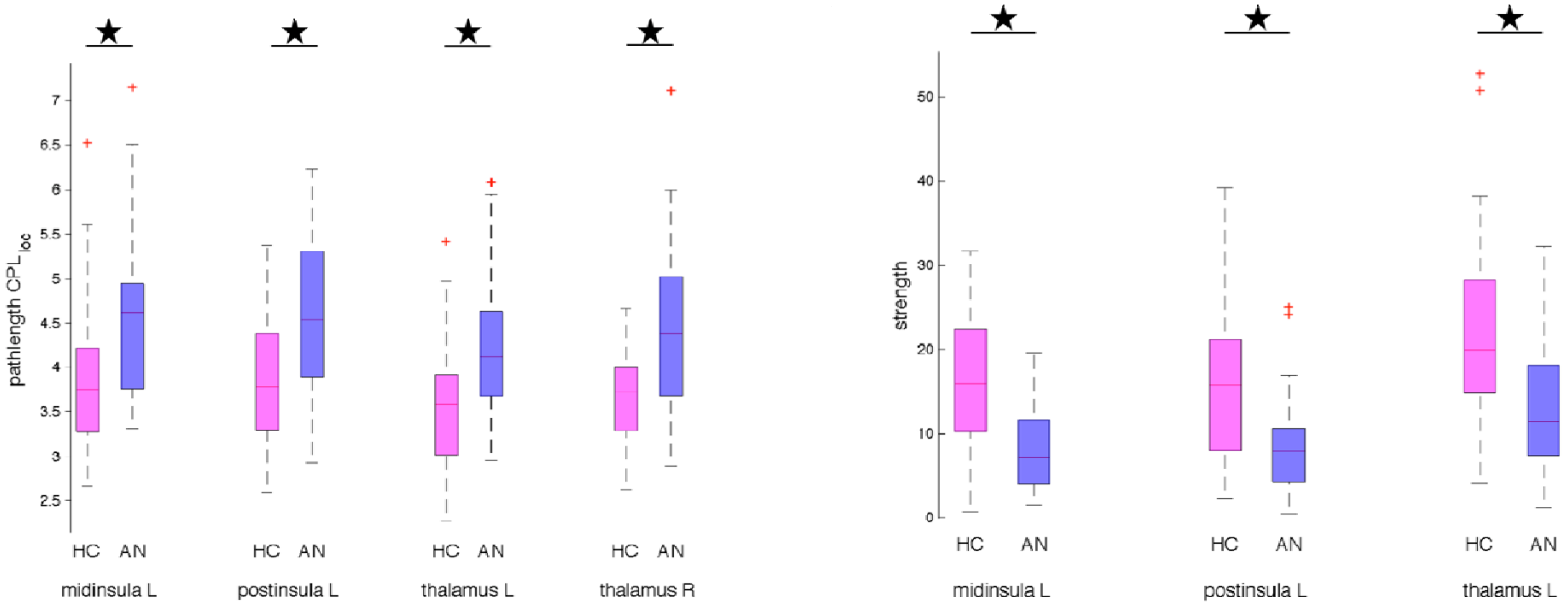

Fig. S2: Significant differences between healthy controls (HC; magenta) and patients with anorexia nervosa (AN; blue) at a sparsity threshold of 16% after scrubbing of the data sets. Group differences in the metric characteristic path length (CPL_{loc}) in the left middle insula, left posterior insula, left thalamus and right thalamus are depicted in the left panel. The right panel depicts group differences in the metric strength in the left middle insula, left posterior insula and left thalamus.

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Topological properties

Table S4: Correlations between selected global graph theoretical metrics and grey matter thickness (with age as a covariate) or grey matter volume (with age and total intracranial volume as covariates) in patients with anorexia nervosa

	Measure; *r*, *p* value					
Metric	Right hemisphere thickness		Left hemisphere thickness		Total grey matter volume	
α	0.121	0.51	0.088	0.63	0.142	0.45
CPL	–0.100	0.59	–0.174	0.34	–0.019	0.92

CPL = characteristic path length.

Table S5: Correlations between age and graph theoretical metrics across groups

	Group; *r*, *p* value			
Metric	Anorexia nervosa		Control	
α	0.153	0.38	0.186	0.29
CPL	0.075	0.67	0.152	0.38

CPL = characteristic path length.

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Nodal characteristics

Table S6: Correlations between local graph theoretical metrics and grey matter volume (with age and total intracranial volume as covariates) and cortical thickness (with age as a covariate) of exactly corresponding customized regions of interest in patients with anorexia nervosa

	Measure; *r*, *p* value											
Region	Left thalamus volume		Right thalamus volume		Left midinsula volume		Left posterior insula volume		Left midinsula thickness		Left posterior insula thickness	
Thalamus_L_47_PathLength	0.024	0.90	—	—	—	—	—	—	—	—	—	—
Thalamus_L_47_Strength	-0.069	0.71	—	—	—	—	—	—	—	—	—	—
Thalamus_R_58_PathLength	—	—	0.098	0.60	—	—	—	—	—	—	—	—
Thalamus_R_58_Strength	—	—	0.064	0.73	—	—	—	—	—	—	—	—
Midinsula_L_61_PathLength	—	—	—	—	–0.024	0.89	—	—	–0.008	0.97	—	—
Midinsula_L_61_Strength	—	—	—	—	–0.114	0.52	—	—	0.017	0.93	—	—
Postinsula_L_76_PathLength	—	—	—	—	—	—	0.060	0.74	—	—	-0.470	0.80
Postinsula_L_76_Strength	—	—	—	—	—	—	–0.067	0.71	—	—	0.009	0.96

Table S7: Correlations between age and graph-theoretical metrics across groups.

	Group; *r*, *p* value			
Region	Anorexia nervosa		Control	
Thalamus_L_47_PathLength	0.009	0.96	0.048	0.78
Thalamus_L_47_Strength	0.063	0.70	–0.089	0.61
Thalamus_R_58_PathLength	0.158	0.36	0.050	0.78
Thalamus_R_58_Strength	–0.199	0.25	–0.050	0.78
Midinsula_L_61_PathLength	0.055	0.76	0.224	0.20
Midinsula_L_61_Strength	–0.072	0.68	–0.305	0.08
Postinsula_L_76_PathLength	–0.151	0.39	–0.003	0.99
Postinsula_L_76_Strength	0.250	0.15	–0.031	0.86

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Table S8: Overview of all known resting-state functional connectivity studies in anorexia nervosa

Study*	Method	*N*	DMN	Cognitive-control network	Salience network	Sensory-motor network	Visual network	Other
Cowdrey et al[36]	ICA	recAN=16, HC=15	recAN>HC: Precuneus, dlPFC/IFG	No difference		No difference	No difference	
Favaro et al [37]	ICA	acAN=29, recAN=16, HC=26				acAN>HC: Superior parietal cortex	acAN<HC, recAN<HC: occipital temporal junction	
McFadden et al[38]	ICA	acAN =20, recAN=24, HC=24	acAN<HC: Precuneus		acAN<HC, recAN<HC: ACC			
Amianto et al[39]	ICA	acAN=12, BN=12, HC=10						AN>HC: Cerebrellum
Boehm et al[40]	ICA	acAN=35, HC=35	acAN>HC: Anterior insula	acAN>HC: Angular gyrus	No difference	No difference	No difference	
Favaro et al[41]	Seed-based	acAN=33, HC=30		No difference with seed in dlPFC, vmPFC and vlPFC				
Favaro et al[42]	Seed-based	acAN=35, recAN=16, HC=35						acAN<HC: dorsal rostral putamen and bilateral putamen
Lee et al[43]	Seed-based	acAN=18, BN=20, HC=20	acAN>HC: dACC and precuneus, retrosplenial cortex acAN<HC: dACC and dlPFC					
Kim et al[44]	Seed-based	acAN=18, BN=20, HC=20			acAN>HC: Left anterior insula and right IFG/insula cluster			

acAN: patients acutely ill with anorexia nervosa; ACC: anterior cingulate cortex; BN = bulimia nervosa; dACC: dorsal anterior cingulate cortex; dlPFC: dorsolateral prefrontal cortex; DMN: default mode network; HC: healthy control; ICA: independent component analyses; IFG: inferior frontal gyrus; recAN: patients recovered from anorexia nervosa; vlPFC: ventrolateral prefrontal cortex; vmPFC: ventromedial prefrontal cortex.
*In the studies by McFadden and colleagues and Kim and colleagues, fMRI data were acquired during a conditioned stimulus task and a picture processing task.

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Table S9: Overview of task-based fMRI studies in anorexia nervosa (by category in alphabetical order, selection), that have (indirectly) targeted insular dysfunction (i.e. by using food, body or pain stimuli) and reported findings related to the insula (part 1 of 2)

Study*	*N*	Paradigm	Results
Food			
Brooks et al [45]	acAN=18, BN=8, HC=24	Passive viewing of food and non-food images	• BN<HC: superior temporal gyrus/insula, visual cortex, • BN<AN: right parietal lobe, left dorsal posterior cingulate cortex; • BN>AN: right superior temporal gyrus and left supplementary motor area
Cowdrey et al[46]	recAN=15, HC=16	Oral application of pleasant and aversive taste stimuli and presentation of food images	• Pleasant taste: recAN>HC: ventral striatum; • Pleasant image: recAN>HC: occipital cortex; • Aversive taste: recAN>HC: insula,putamen, • Aversive image: recAN>HC: ACC, caudate
Frank et al[47]	acAN=21, obese=19, HC=23	Conditioning task associating oral application of sucrose solution, no sucrose solution or artificial saliva with geometric shapes	• Estimated prediction error-associated BOLD response: AN>HC: anteroventral striatum, insula, PFC
Gizewski et al [48]	acAN=12, HC=12,	Passive viewing of food and non-food images before and after eating	• Premeal: food: acAN>HC: midcingulate cortex; HC>acAN: pregenual ACC; • Postmeal: food: acAN>HC: left insula; HC>acAN: right insula, right PFC
Holsen et al[49]	acAN=12, recAN=10, HC=11	Passive viewing of food and non-food images before and after eating	• Premeal: food: acAN, recAN<HC: hypothalamus, amygdala, anterior insula • Postmeal: food: acAN<HC: anterior insula
Lawson et al [50]	acAN=13, recAN=9, HC=13	Passive viewing of food and non-food images before and after eating, association with leptin and oxytocin level	• Premeal: oxytocin was associated with activation differences between AN and HC in the hypothalamus, amygdala, hippocampus , OFC and insula • Postmeal: oxytocin was associated with activation differences in amygdala and insula
Oberndorfer et al [51]	recAN=14, HC=12	Visual anticipatory task of food and non-food images	• Anticipation of food images: recAN>HC: right ventral anterior insula
Wagner et al [52]	recAN=16, HC=16	Oral application of sucrose solution or water	• Sucrose & water: recAN<HC: insula, ventral and dorsal striatum

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Table S9: Overview of task-based fMRI studies in anorexia nervosa (by category in alphabetical order, selection), that have (indirectly) targeted insular dysfunction (i.e. by using food, body or pain stimuli) and reported findings related to the insula (part 2 of 2)

Study*	*N*	Paradigm	Results
Body			
Friederich et al[53]	acAN=17, HC=18	Comparison of themselves with images of slim idealized female bodies	• acAN>HC: insula, premotor cortex, • acAN<HC: rostral ACC
Mohr et al[54]	acAN=16, HC=16	Body satisfaction task that includes selecting an image matching their ideal body size	• Satisfaction: acAN>HC: insula, lateral PFC
Redgrave et al [55]	acAN=6, HC=6	Emotional Stroop task with fat, thin and neutral words	• Thin: acAN>HC: junction of left insula, frontal and temporal lobes, medial frontal gyrus • Fat: acAN<HC: left dlPFC, right parietal areas
Sachdev et al [56]	acAN=10, HC=10	Passive viewing of self- and non-self-images	• Self-image: acAN<HC: middle frontal gyrus, insula, precuneus, occipital region
Pain			
Bär et al[57]	acAN=19, HC=19	Delivery of noxious thermal stimuli	• acAN<HC: left insula, superior temporal gyrus
Strigo et al[58]	recAN=12, HC=10	Pain anticipation task; delivery of noxious thermal stimuli	• Pain anticipation: recAN>HC: right anterior insula, dlPFC • Pain experience: recAN>HC: dlPFC; recAN<HC: posterior insula

acAN: patients acutely ill with anorexia nervosa; ACC: anterior cingulate cortex; BN: patients acutely ill with bulimia nervosa; dlPFC: dorsolateral prefrontal cortex; HC: healthy control; OFC:orbitofrontal cortex; PFC: prefrontal cortex; recAN: patients recovered from anorexia nervosa.
*The 2 studies by Holsen and Lawson are based on the same sample/fMRI data.

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