OXFORD

REGULAR RESEARCH ARTICLE

Disturbed Resting-State Whole-Brain Functional Connectivity of Striatal Subregions in Bulimia Nervosa

Li Wang, Kun Bi, Zhou Song, Zhe Zhang, Ke Li, Qing-Mei Kong, Xue-Ni Li, Qing Lu, Tian-Mei Si

Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China (Dr Wang); Peking University the Sixth Hospital (Institute of Mental Health); National Clinical Research Center for Mental Health Disorders & Key Laboratory of Mental Health, Ministry of Health (Peking University), Beijing, China (Drs Wang, Kong, Li, and Si); Key Laboratory of Child Development and Learning Science, School of Biological Sciences & Medical Engineering, Southeast University, Nanjing, China (Drs Bi and Lu); Taiyuan Psychiatric Hospital, Taiyuan, Shanxi, China (Drs Song and Zhang); Department of Radiology, 306 Hospital of People's Liberation Army, Beijing, China (Dr Li).

Correspondence: Tian-Mei Si, PhD, Clinical Psychopharmacology Division, Institute of Mental Health, Peking University, No. 51 Hua Yuan Bei Road, Hai Dian District 100191, Beijing, China (si.tian-mei@163.com).

L.W. and K.B. contributed equally to this work.

Abstract

Background: Disturbed self-regulation, taste reward, as well as somatosensory and visuospatial processes were thought to drive binge eating and purging behaviors that characterize bulimia nervosa. Although studies have implicated a central role of the striatum in these dysfunctions, there have been no direct investigations on striatal functional connectivity in bulimia nervosa from a network perspective.
Methods: We calculated the functional connectivity of striatal subregions based on the resting-state functional Magnetic Resonance Imaging data of 51 bulimia nervosa patients and 53 healthy women.
Results: Compared with the healthy women, bulimia nervosa patients showed increased positive functional connectivity in bilateral striatal nuclei and thalamus for nearly all of the striatal subregions, and increased negative functional connectivity in bilateral primary sensorimotor cortex and occipital areas for both ventral striatum and putamen subregions. Only for the putamen subregions, we observed reduced negative functional connectivity in the prefrontal (bilateral superior and middle frontal gyri) and parietal (right inferior parietal lobe and precuneus) areas. Several striatal connectivities with occipital and primary sensorimotor cortex significantly correlated with the severity of bulimia.
Conclusions: The findings indicate bulimia nervosa-related alterations in striatal functional connectivity with the dorsolateral prefrontal cortex supporting self-regulation, the subcortical striatum and thalamus involved in taste reward, as well as the visual occipital and sensorimotor regions mediating body image, which contribute to our understanding of neural circuitry of bulimia nervosa and encourage future therapeutic developments for bulimia nervosa by modulating striatal pathway.

Key Words: Bulimia nervosa, fMRI, striatum, resting-state functional connectivity

Significance Statement

Although studies have implicated a central role of the striatum in the pathological mechanism of BN, there have been no direct investigations on the striatal functional network in BN. This study is, to our knowledge, the first to investigate resting-state functional connectivity of striatal subregions in BN. The findings indicate BN-related alterations in striatal FC with the dorsolateral prefrontal cortex that supports self-regulatory control, the subcortical striatum and thalamus involved in taste rewarding, and the visuospatial and somatosensory networks mediating body image. Several striatal connectivities to primary sensorimotor and occipital areas exhibited a predictive value for the severity of bulimia. Our study provides new evidence for understanding the neural circuitry of BN and encourages further investigations of therapeutic development for BN by normalizing connectivity disturbances of striatum.

Introduction

Bulimia nervosa (BN) is a severe psychiatric disease characterized by episodic binge eating and purging behaviors. Existing treatments, both cognitive behavior therapy and pharmacotherapy, have a 30–40% remission rate for BN at most (Treasure, 2010). The unclear neural mechanism has largely hindered therapeutic development of this disorder.

Difficulties in several psychopathological dimensions, including self-regulation, taste reward, and body image perception, were considered core factors that drive binge eating and purging behaviors (Treasure, 2010; Miyake et al., 2015). The striatum acts in conjunction with the cortical and other subcortical regions to perform reward, affect, and sensorimotor function (Parent and Hazrati, 1995; Buot and Yelnik, 2012), which makes it a critical node to explore the neural circuitry of BN. While direct investigations of striatal functional connectivity (FC) are limited, BN-related changes have been detected in the striatum and its projection regions (Wagner et al., 2009; Frank et al., 2011, 2013; Radeloff et al., 2014).

Difficulty in self-regulation in BN has been associated with functional deficits of the fronto-striatal circuitry. Deficient activation in fronto-striatal circuitry (lateral prefrontal cortex [PFC], inferior frontal gyrus, and lenticular and caudate nuclei) has been observed when BN patients perform an impulsive inhibition task (Marsh et al., 2009, 2011; Cyr et al., 2018). Another functional Magnetic Resonance Imaging (fMRI) study revealed differential engagement of fronto-striatal regions in a binge-eating group during response inhibition tasks as lower activation of the right middle frontal gyrus (MFG) and putamen was found during the go/no-go task, while higher activation of the left MFG was found during the stop signal task (Oliva et al., 2019). The brain imaging changes elicited by reward stimuli are also less consistently reported in BN patients. Whereas studies reported reduced activation in the fronto-striatal circuitry during reward learning (Cyr et al., 2016) and in the mesocorticolimbic circuitry during taste reward tests (Frank et al., 2011), others reported increased dorsolateral PFC and striatal activation during the receipt of food images (Brooks et al., 2011; Simon et al., 2016; Lee et al., 2017) and the learning of probabilistic categories (Brooks et al., 2011; Simon et al., 2016; Lee et al., 2017; Celone et al., 2011). As another central feature of both BN and anorexia nervosa (AN), body image distortion has been associated with functional disturbances of the somatosensory and parietal networks, as indicated by reduced occipitotemporal response during the presentations of body images of abnormal weight (Uher et al., 2005), resting-state FC (RSFC) within the somatosensory and occipital cortex (Lavagnino et al., 2014), and posterior default mode network (DMN) in AN (Via et al., 2018).

Differences in task designs may be a critical reason for the inconsistency of results. Resting-state fMRI (R-fMRI), a neuroimaging technique that measures intrinsic neural activity, avoids the confounds presented by task designs. An R-fMRI study in BN adolescents showed increased positive RSFC between the right ventral supramarginal gyrus and all DMN regions and between the right ventrolateral PFC and left lateral parietal cortex (Domakonda et al., 2019). The binge-eating disorder patients exhibited aberrant RSFC in the dorsal anterior cingulate cortex and medial PFC (Stopyra et al., 2019). Our previous study showed BN-related hyperconnectivity involving sensorimotor and visual association regions, but hypoconnectivity involving subcortical striatum and limbic regions (Wang et al., 2017). However, to our knowledge, there have been no direct investigations on the functional network of striatal subregions of BN. Of note, among the different divisions, the ventral striatum (VS) receives projections from the medial PFC and limbic structures and supports affective function, the dorsal caudate (DC) receives projections from the lateral PFC and supports cognitive function, and the putamen receives inputs from the ACC and somatosensory cortex and supports cognitive and motor function (Cyr et al., 2016). This unique characteristic makes the striatum an important node for investigating reward-related network connectivity. Given that eating behaviors involve a complex psychological process, the analysis of striatal RSFC from a subregion level would be very helpful for demonstrating the neural circuitry characteristics of BN in a broader context.

Therefore, we collected the R-fMRI data from 51 BN women and 53 healthy controls (HCs). We aimed to clarify the RSFC changes between striatal subregions and other eating-related brain regions within the whole brain range. A seed-based approach was used to interrogate the RSFC patterns of 6 striatal subregions (Di Martino et al., 2008). Based on the psychological characteristics of BN and neural correlates revealed by neuroimaging studies depicted above, we hypothesized that the RSFC abnormalities would emerge in the PFC and subcortical areas that support self-regulation and taste reward, the somatosensory and visuospatial areas involved in body image perception. Given the high heterogeneity of the striatum, we expected to find both overlapping and distinct changes across different striatal subregions.

MATERIALS AND METHODS

Patients

One hundred and ten patients (57 BN women and 53 HCs) aged 16–30 years were consecutively admitted. Those with BN were recruited from outpatient and inpatient services of the Eating Disorder Department of Peking University Sixth Hospital. The HCs were recruited via local advertisements. The diagnosis

of BN was made by a psychiatrist specializing in eating disorder using the Mini International Neuropsychiatric Interview (Sheehan et al., 1998), a short structured interview developed according to the DSM-IV criteria. Participants with a current diagnosis of other Axis I psychiatric disorders were excluded. Among the 57 patients, 20 have a history of antidepressant medication, but all of them have no use of any psychotropic drugs for at least 1 month. To ensure that the body is free from malnutrition and other dangerous conditions, we gave patients a physical examination, including general condition, skin, head, eyes, ears, nose, mouth, neck, lymph nodes, breasts, lungs, heart, gastrointestinal, urogenital, and nervous system. In addition, patients were given blood tests, blood biochemistry, and an electrocardiogram.

Control patients were required if they had normal body weight and menstrual cycle and no lifetime history of any psychiatric disorders. We provided economical compensation of 200 RMB for each healthy patient. All patients were required to be female and right-handed and have no history of neurological diseases, mental retardation, unstable medical conditions, or substance use disorders within the last year. The authors asserted that all procedures of this work comply with the ethical standards of the Institutional Review Board of Peking University Sixth Hospital on human experimentation and with the Helsinki Declaration. Written informed consent was obtained from all patients.

Clinical Assessment

Patients completed the Eating Disorder Inventory-1 (EDI-1), 17-item Hamilton Rating Scale for Depression (HAMD), and Hamilton Anxiety Rating Scale (HAMA) on the day of scans. The EDI-1 is a 64-item self-report questionnaire of psychological traits related to eating disorders (Lee et al., 1997). Participants respond on a 6-point Likert scale ("always" through to "never"). This study reported the subscales of drive for thinner, bulimia, body dissatisfaction, and interoceptive deficit. The latest edition of the EDI is EDI-3, but since the reliability and validity research of EDI-3 have not been completed in the Chinese population, the EDI-1 was used in this study. The reliability and effectiveness of EDI-1 have been verified in ED in China (Lee et al., 1997). The Cronbach's coefficient of the "mature fear" subscale of EDI was relatively low (i.e., 0.5), but the Cronbach's coefficients of the other 7 subscales were above 0.8 (Zhang and Kong, 2004). The 1 and 3 editions of EDI have the same content with respect to the subscales selected in this study.

MRI Scan

Images were acquired with a Siemens 3.0 Tesla scanner. The resting-state functional images were obtained using an echo-planar imaging sequence: repetition time/echo time, 2000 ms/30 ms; 90° flip angle; matrix, 64×64; thickness/gap, 4.0 mm/0.8 mm; 30 slices; 7 minutes. For a registration propose, T1-weighted structural images were obtained using a magnetization-prepared rapidly acquired gradient-echo sequence: repetition time/echo time, 2300 ms/3.01 ms; thickness/gap, 1.0/0 mm; matrix, 256×256; voxel size, 1×1×1 mm3; 9° flip angle. Before the resting-state scans, patients were instructed to keep their eyes closed, remain still without head movement, not think of anything in particular, and not fall asleep during the scan. All patients reported good adherence to these instructions confirmed immediately after the scans. No patients showed obvious structural damage based on their structural scans.

Data Preprocessing

The R-fMRI images were preprocessed with Data Processing Assistant for R-fMRI (http://rfmri.org/DPARSF) based on Statistical Parametric Mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm). After removing the first 10 volumes, the remaining 200 volumes were corrected for different signal acquisition times. The functional volumes were motion corrected using a 6-parameter rigid-body transformation. Then, the nuisance signals (including the Friston 24-parameter model [Friston et al., 1996] of head-motion parameters, linear trend, signals of cerebrospinal fluid, white matter, and whole brain) were regressed out. Derived images were normalized to Montreal Neurological Institute (MNI) space and resampled with a $2 \times 2 \times 2$ mm^3 resolution. The transformed images were then band-pass filtered (0.01–0.1 Hz).

Given a possible confounding effect of micro-movements on RSFC (Power et al., 2012), we computed the framewise displacement (FD) value for each patient using the Jenkinson formula (Jenkinson et al., 2002), which reflects the temporal derivative of movement parameters. Data from 6 patients who had a mean FD > 0.2 mm were excluded, with 51 patients and 53 HCs finally used for analysis.

Striatal RSFC

We used a seed-based approach to compute striatal RSFC according to the procedure developed by a previous study (Di Martino et al., 2008). Specifically, the seeds were defined (MNI152 space) bilaterally in the DC ($x = \pm13$, $y = 15$, $z = 9$), superior VS (VSs) ($x = \pm10$, $y = 15$, $z = 0$), inferior VS (VSi) ($x = \pm9$, $y = 9$, $z = -8$), dorsal rostral putamen (DRP) ($x = \pm25$, $y = 8$, $z = 6$), dorsal caudal putamen (DCP) ($x = \pm28$, $y = 1$, $z = 3$), and the ventral rostral putamen (VRP) ($x = \pm20$, $y = 12$, $z = -3$), with each covering 27 voxels in a 2-mm^3 space (radius = 3.5 mm). We extracted the mean time courses of each striatal seed and computed their correlations with the rest of the whole brain. This procedure generated 12 striatal RSFC maps (6 per hemisphere) for each patient. The correlation maps were converted by a Fisher r-to-z transformation and smoothed with a 6-mm Gaussian kernel.

Statistical Analysis

We used the DPABI toolbox (Yan et al., 2016) for statistical analysis, which included the following procedures.

Within-Group Striatal RSFC

One-sample t tests were performed to obtain within-group RSFC patterns of each striatal subregion. The results were corrected for multiple comparison with a 2-tailed voxel $P < .001$ and cluster $P < .05$ according to Gaussian Random Field theory.

Between-Group Difference in Striatal RSFC

To determine between-group differences, independent-sample t tests were performed on striatal RSFC images between BN patients and HCs, controlling for age, educational level, and mean FD values. A Gaussian Random Field correction was performed with 2-tailed voxel $P < .001$ and cluster $P < .05$, which controlled the family-wise error rate <5% (Eklund et al., 2016). We also compared the striatal RSFC between BN and HC groups by adding the HAMD and HAMA scores to covariates given a significant difference in these scales between the 2 groups.

Reproducible Analysis of Head Motion

Although no significant differences were found in maximum movements at each direction between BN patients and HCs, we conservatively evaluated the effects of head motion on the imaging results using the "scrubbing" approach (Power et al., 2012). Briefly, for each patient, we scrubbed the volumes with a FD value >0.5 mm and their adjacent volumes. This step reduced the confounding effect of head motion on the R-fMRI signals. We recalculated the striatal RSFC images using the resultant scrubbed data and performed statistical analysis.

Relationships Between Striatal RSFC and Clinical Variables

The partial correlation analysis was performed between the RSFC values of clusters showing between-group differences and the severity of psychological dimensions evaluated by EDI (including body dissatisfaction, bulimia, drive for thinness, and interoceptive awareness) within the BN patients controlling for age, educational level, and mean FD values. The correlation analysis was also performed within the HC group. Although we excluded the comorbidity of depression, the HAMD and HAMA scores of BN patients were still higher than those of HCs. So, we also analyzed the correlations between striatal RSFC values and scores of HAMD and HAMA to detect some possible effects of depressive and anxiety symptoms on striatal RSFC.

RESULTS

Demographic and Clinical Characteristics

As shown in Table 1, there were no significant differences in age, years of education, or BMI between BN patients and HCs. Patients had higher scores on the EDI-1, HAMD, and HAMA than HCs ($P < .001$).

Within-Group Striatal RSFC

As shown in supplementary Figure 1, the BN and HC groups showed similar patterns of striatal RSFC. All striatal subregions displayed significant positive RSFC with their adjacent subcortical areas. Distinctively, we observed positive RSFC with a gradient change from the dorsolateral to ventromedial divisions of the PFC and anterior cingulate cortex going from the DC to VSs and then to VSi, but negative RSFC was observed in the PFC primarily for the putamen. The DC and VS exhibited larger negative RSFC with the primary sensorimotor cortex, while the putamen exhibited larger negative RSFC with the parietal and occipital areas.

Between-Group Difference in Striatal RSFC

We observed higher positive RSFC in several other striatal nuclei and thalamus and higher negative RSFC in primary sensorimotor areas and occipital cortex in BN patients than the HCs (Figures 1–2; Table 2) in nearly all of the striatal subregions, while lower negative RSFC was observed in the PFC and parietal areas for the putamen subregions (Figure 2; Table 2). Details for each subregion were introduced below.

DC
The right DC exhibited higher positive RSFC with a cluster extending across the right lentiform nucleus, putamen, and thalamus in BN patients than the HCs, while the left DC did not show any differences between groups (Figure 1; Table 2).

VSs, VSi
Both the VSs and VSi exhibited higher positive RSFC in several other striatal nuclei (including bilateral lentiform nucleus, putamen, pallidum, and caudate) and thalamus and higher negative RSFC in primary sensorimotor cortex, including left precentral and postcentral gyri, in BN patients than HCs, while higher negative RSFC was also observed in bilateral occipital gyrus for bilateral VSi subregions (Figure 1; Table 2).

Table 1. Sample Characteristics

Variables	Bulimia nervosa (n=51)	Healthy control (n=53)	Statistics	
			t	P
Age (years)			−0.846	0.4
Education (years)	13.9±2.2	14.2±1.7	−0.831	.408
FD	0.1±0.0	0.1±0.04	1.279	.204
Frequency of binge eating weekly	4.6±1.5			
Current BMI (kg/m²)	20.8±2.2	20.4±1.7	1.076	.285
Lowest previous BMI (kg/m²)	17.8±2.1	20.3±1.6	6.696	<.001
Highest previous BMI (kg/m²)	24.6±4.3	20.6±1.7	−6.244	<.001
Duration of illness (years)	1.9±1.3			
Total score (EDI-1)	265.5±34.5			
Drive for thinness (EDI-1)	34.4±7.1			
Bulimia (EDI-1)	33.9±5.5			
Body dissatisfaction (EDI-1)	41.5±8.8			
Interoceptive awareness (EDI-1)	38.8±7.6	20.1±6.5	8.045	<.001
HAMD	6.2±3.4	0.9±1.1	10.616	<.001
HAMA	4.6±3.4	0.4±0.7	8.735	<.001

Abbreviations: BMI, body mass index; EDI, Eating Disorder Inventory; FD, framewise displacement; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Rating Scale for Depression.
Data are presented as mean±SD.

Table 2. Regions Showing Group Differences (BN vs HC) in Striatal Connectivity

Seed	Region with altered FC	Voxels	Peak MNI coordinate	Peak intensity	z BN	HC
R-DC	LN, putamen, thalamus	228	14, 6, −12	4.702	+*	+*
L-VSs	PreCG, PoCG	161	−32, −24, 42	−4.380	−*	−
R-VSs	PreCG, PoCG	726	−34, −22, 42	−5.145	−*	−
	LN, thalamus	125	16, 2, 4	4.379	+*	+*
L-VSi	PreCG, PoCG	964	−34, −24, 42	−6.005	−*	−
	MOG	758/251	46, −74, 16/−26, −86, 28	−5.078/−5.216	−*	−*
	LN, putamen, pallidum	774	18, 2, 2	4.685	+*	+*
R-VSi	PreCG, PoCG	877	−32, −24, 42	−5.852	−*	−
	MOG, SOG	381/280	48, −76, 16/−28, −84, 28	−4.489/−5.055	−*	−*
	LN, pallidum, putamen	149	−14, 8, 4	4.233	+*	+*
	LN, caudate, putamen, thalamus	756	16, 6, 4	5.237	+*	+*
L-DRP	MFG	322	30, 16, 38	4.552	−	−*
	PreCG, PoCG, IPL	849	26, −30, 54	−4.533	−	+*
	PoCG, IPL	587	−34, −42, 56	−4.481	−	+*
	MOG	1475/417	−26, −94, 2/34, −78, 14	−5.027/−4.108	−*	+/−
	MOG, IOG	804	38, −62, −26	−4.905	−*	−
R-DRP	MFG, SFG	245/203	30, 16, 52/−22, 20, 36	4.704/4.386	−	−*
	PreCG, PoCG, IPL	458/240	16, −30, 68/−36, −36, 56	−4.186/−4.189	−/−*	+
	MOG	2242/1405	−30, −76, 14/32, −76, 14	−5.709/−5.191	−*	+
	LN, putamen, caudate, thalamus	265/389	−12, 2, −8/16, 6, −8	5.848/5.071	+*	+*
L-DCP	MFG	568	48, 16, 44	4.706	−	−*
	PoCG, PoCG, IPL	950/260	42, −34, 50/−36, −36, 54	−4.704/−4.184	−	+
	IPL	214	52, −66, 42	4.339	−	−*
	MOG, IOG	3775	−26, −94, 2/40, −85, −15	−5.517/−4.512	−*	+
R-DCP	MFG, SFG	1050	30, 18, 34	4.69	−	−*
	PoCG, PCL	414	4, −36, 70	−4.288	−*	+
	PCu	173	12, −52, 32	4.326	−	−*
	IPL	722	48, −68, 40	4.658	−	−*
	MOG, IOG	1443/565	−30, −76, 14/36, −86, −16	−5.874/−4.776	−/−*	+/−
	LN, putamen	191	16, 10, −8	4.129	+*	+*
	PoCG, IPL	385	−28 −58, 52	−4.371	−*	−
L-VRP	PoCG	771	−32, −34, 58	−4.822	−*	+
	PCL	391	10, −40, 64	−4.281	−*	+
	LN, putamen, thalamus	321	12, −2, 0	4.488	+*	+*
	MOG, IOG	1091/1578	40, −82, −12, −34 −92 20	−4.816, −6.068	−*	+
R-VRP	MFG, SFG	371	28, 12, 56	4.617	+	−
	PreCG	358	−40, −14, 60	−4.374	−	+
	PreCG, PoCG	495/991	−34, −34, 56/28, −32, 54	−4.717/−4.621	−*	+
	MOG, IOG	2801/2438	32, −78, 12/−26, −92, 12	−5.113, −5.424	−*	+
	LN, putamen, thalamus, pallidum	890	18, 10, −6	5.565	+*	+*

Abbreviations: BN, bulimia nervosa; DC, dorsal caudate; DCP, dorsal caudal putamen; DRP, dorsal rostral putamen; FC, functional connectivity; HC, healthy control; IOG, inferior occipital gyrus; IPL, inferior parietal lobe; L, left; LN, lentiform nucleus; MFG, middle frontal gyrus; MOG, middle occipital gyrus; PCL, paracentral louble; PCu, precuneus; PoCG, postcentral gyrus; PreCG, precentral gyrus; R, right; SFG, superior frontal gyrus; t, t score of peak of connectivity or local maxima; VRP, ventral rostral putamen; VSi, ventral striatum inferior; VSs, ventral striatum superior. * indicate that the correlation between the peak voxel and striatal seeds was statistically significant within groups; + indicate positive FC, while − indicate negative FC.

DCP, DRP, VRP

In nearly all of the putamen subregions, we observed higher positive RSFC in other striatal nuclei and thalamus in a bilateral fashion in BN patients than HCs, while higher negative RSFC was observed in bilateral primary sensorimotor and occipital areas. Conversely, we observed lower negative RSFC in the right superior and middle frontal gyri for nearly all of the putamen subregions and in the parietal areas (including bilateral inferior parietal lobe [IPL] and right precuneus [PCu]) for bilateral DCP in BN patients than HCs (Figure 2; Table 2).

These results were largely preserved after accounting for the effects of head motion (supplementary Figures 2,3) and after including the HAMD and HAMA scores as covariates (supplementary Figures 4,5).

Relationships Between Striatal RSFC and Clinical Variables

The RSFC between the striatal subregions (including bilateral VSi and right DRP) and the right occipital gyrus as well as between bilateral DRP and primary sensorimotor areas showed significant negative correlations with the bulimia scores of EDI (Figure 3). We did not observe any significant correlations between the striatal RSFC and behavioral variables within the HC group. We also have not observed significant correlations between the striatal RSFC and scores of HAMD and HAMA within the BN group, suggesting that the effects of depressive and anxiety symptoms could be largely excluded.

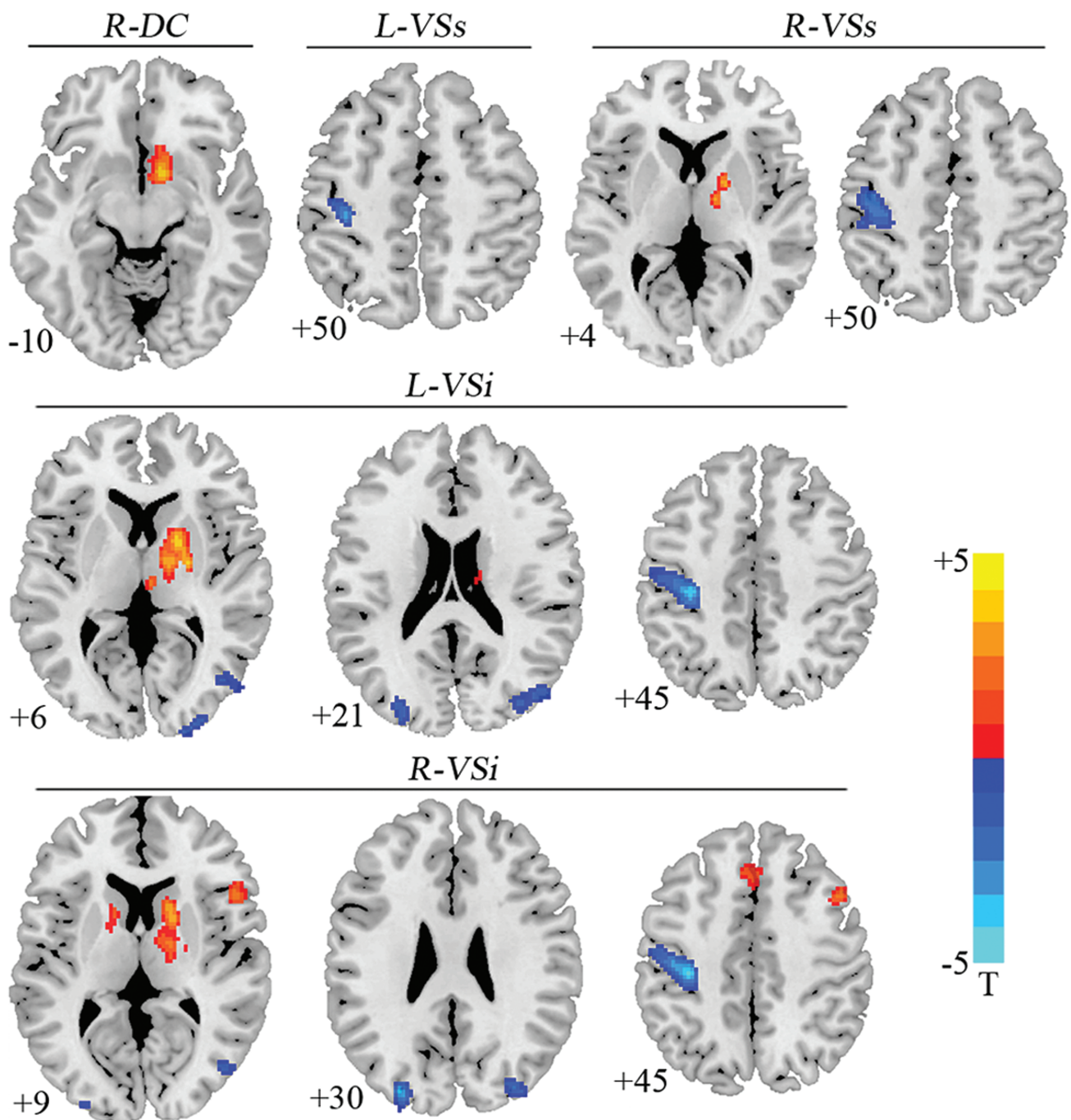## RSFC of caudate and VS (BN vs. HC)

Figure 1. Between-group differences in resting-state functional connectivity (RSFC) of dorsal caudate (DC) and ventral striatum (VS). Between-group differences in RSFC of DC, superior VS (VSs), and inferior VS (VSi). The red colors indicate higher RSFC in bulimia nervosa (BN) patients than healthy controls (HCs), while the blue colors indicate the opposite changes. L, left; R, right. T, t score of the voxel with peak intensity. The numbers at the left lower corner of the axial images refer to the Montreal Neurological Institute z-coordinates.

Discussion

This study is to our knowledge the first to investigate the RSFC of striatal subregions in BN. The RSFC patterns for each striatal subregion were largely consistent with those observed in other normal (Di Martino et al., 2008) and pathological (Di Martino et al., 2011; Gabbay et al., 2013) populations. The between-group comparisons indicate both hyper- and hypo-connectivity in the striatum in BN, with overlapping and distinct changes across different subregions. Overall, for nearly all of the striatal subregions, we observed higher positive RSFC with the thalamus and within the striatum and higher negative RSFC with primary sensorimotor and occipital cortex in BN patients. Conversely, reduced negative RSFC was observed in the PFC and parietal areas for only the putamen subregions.
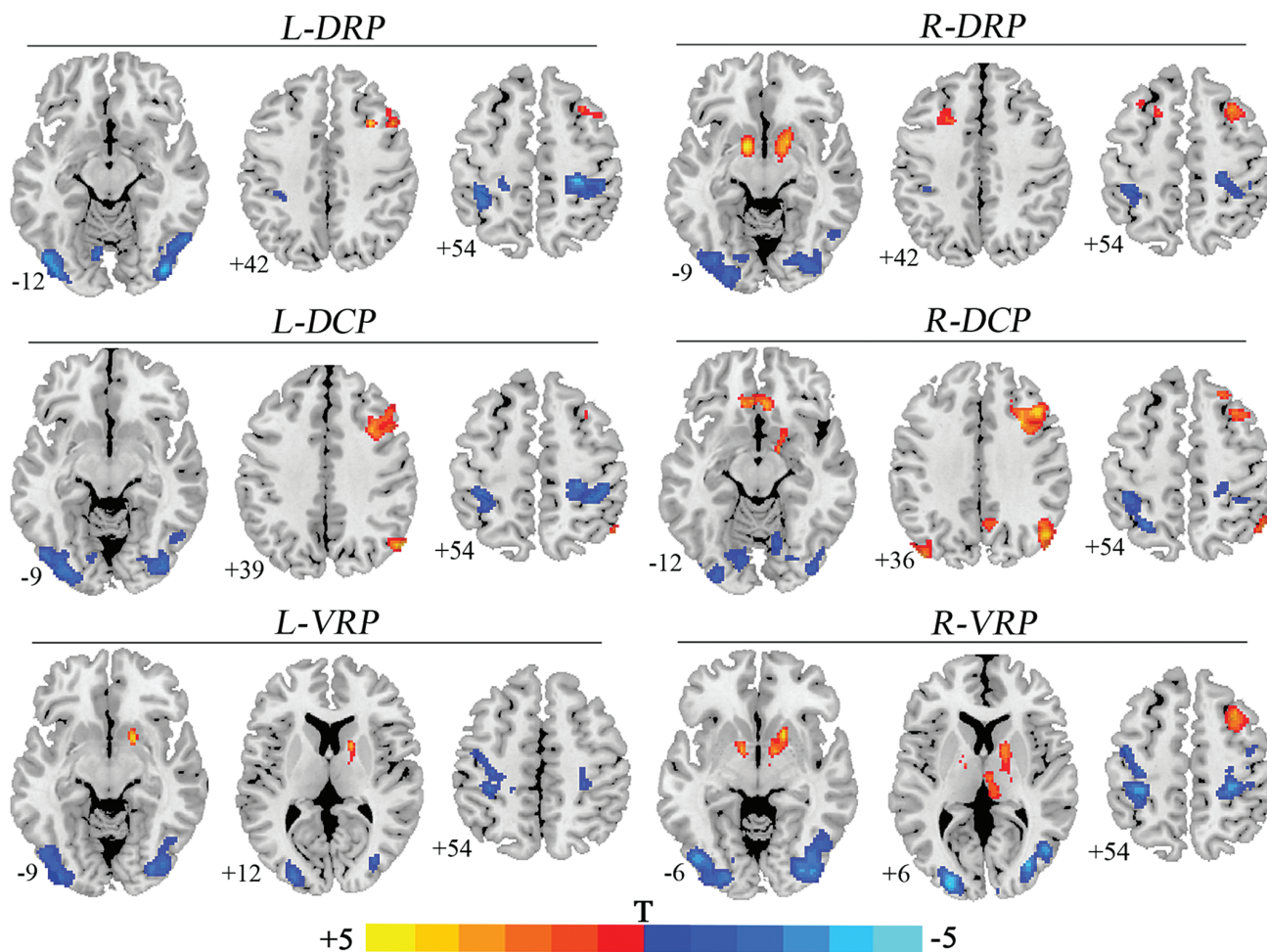
RSFC of putamen (BN vs. HC)

Figure 2. Between-group differences in resting-state functional connectivity (RSFC) of putamen. Between-group differences in the RSFC of putamen subregions, including the dorsal rostral putamen (DRP), dorsal caudal putamen (DCP), and ventral rostral putamen (VRP). The red colors indicate higher RSFC in bulimia nervosa (BN) patients than healthy controls (HCs), while the blue colors indicate the opposite changes. L, left; R, right. T, t score of the voxel with peak intensity. The numbers at the left lower corner of the axial images refer to the Montreal Neurological Institute z-coordinates.
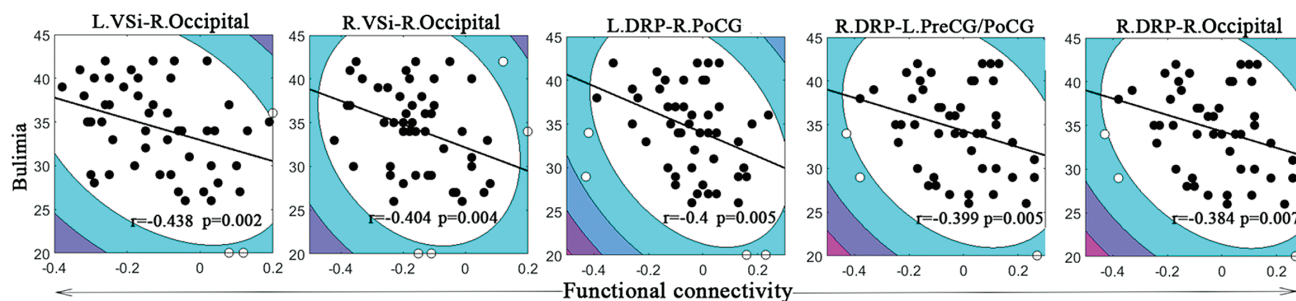

Figure 3. Relationships between striatal resting-state functional connectivity (RSFC) and bulimia scores. Significant correlations between the striatal RSFC values and the Eating Disorder Inventory (EDI) subscale of bulimia within the bulimia nervosa (BN) patients. DRP, dorsal rostral putamen; L, left; PoCG, postcentral gyrus; PreCG, precentral gyrus; R, right; VSi, inferior ventral striatum.

The first important finding is increased positive RSFC within and between all of the striatal nuclei and thalamus as well as reduced positive RSFC between the putamen and dorsolateral PFC in BN patients. As the most important sensory relay station, the thalamus receives input from various sensory pathways

and then projects to the cerebral cortex (Sherman, 2016). We found positive RSFC between the thalamus and all of the striatal subregions. The putamen predicted activity in areas linked to executive control, such as dorsolateral PFC (Di Martino et al., 2008). Our result is of great importance given a critical role of

the PFC and striatum in self-regulation (Wagner et al., 2009). The deficits in self-regulatory control, manifested as response disinhibition to eating, discriminated BN from AN patients who have excessive self-control (Lock et al., 2011). Congruent with the behavioral characteristics, a failure to engage dorsolateral PFC was observed in BN patients when performing tasks requiring effortful cognitive control (Marsh et al., 2009, 2011) and when their clinical symptoms were less severe (Cyr et al., 2018). An impaired control of PFC over the interference by food images was also observed among the binge eating patients (Lee et al., 2017). Moreover, BN has been associated with a loss of interhemispheric RSFC in the dorsolateral PFC (Canna et al., 2017).

The functional disturbance in the fronto-striatal circuitry has been shown in BN patients during the performance of reward tasks. For instance, researchers reported reduced mesocorticolimbic activation during taste reward tests (Frank et al., 2011) but increased dorsolateral PFC and caudate activation during the probabilistic category learning (Marsh et al., 2011) and the receipt of food images (Radeloff et al., 2014; Simon et al., 2016). Despite the inconsistency of abnormal direction, all of these studies indicate an inefficiency of the fronto-striatal circuitry in BN. More specific implication of these results could be interpreted in the context of top-down causal model (Somerville et al., 2011), which assumed that the striatum feedbacks affective and reward information to the dorsolateral PFC through the thalamus, while the PFC in turn exerts cognitive control to the striatum. An appropriate interaction between the up and down information flows within the fronto-striatal circuitry maintains normal output of goal-directed behaviors (Somerville et al., 2011). Reduced negative RSFC between the putamen and PFC but increased positive RSFC within the striatum and thalamus observed in our study reflects disturbed coupling of the fronto-striatal and thalamus-striatal circuitry in BN. More specific association between these RSFC changes and eating behaviors needs to be clarified in combination with task fMRI designs.

Another important finding is higher negative RSFC in primary sensorimotor and occipital areas for nearly all of the striatal subregions. And also, the RSFC between the striatal subregions (including bilateral VSi and right DRP) and right occipital gyrus as well as between bilateral DRP and primary sensorimotor areas showed significant negative correlations with the bulimia scores of EDI. The somatosensory and occipitotemporal system has been associated with body image perception (Downing et al., 2001; Somerville et al., 2011; Fontan et al., 2017). A distorted representation of one's own body is a diagnostic criterion of both AN and BN. A meta-analysis of 42 articles concluded that individuals with AN and BN overestimate their body size compared with controls (Mölbert et al., 2017). After reviewing the literature in AN using fMRI, researchers concluded that the FC changes in AN were mainly located in the corticolimbic circuitry, which is involved in cognitive control and visual and homeostatic integration (Gaudio et al., 2016). In BN, reduced occipitotemporal response has been observed when the patients view abnormal weight bodies (Uher et al., 2005). BN patients also showed reduced RSFC across the somatosensory network and occipital cortex (Lavagnino et al., 2014). The RSFC between the left paracentral lobule and right middle occipital gyrus correlated with psychopathology measures, including bulimia and interoceptive awareness (Lavagnino et al., 2014). Our study links the RSFC changes of the sensorimotor and visual regions to striatum; such a connectivity abnormality reflects an unbalanced relationship between the sensorimotor cortex and striatal reward network, which might reinforce the inclination of inappropriate body check and subsequent purging behaviors to compensate for weight gain. This proposal is further suggested by significant

correlation observed in RSFC between striatum and somatosensory/occipital areas with the severity of bulimia.

We also observed disturbed RSFC in the parietal areas (including bilateral IPL and right PCu) for the putamen subregions. The posterior DMN showed negative correlation with the putamen subregions within the BN and HC groups, which is consistent with the previous study (Di Martino et al., 2008). According to the body schema (Fontan et al., 2017), the parietal cortex integrates sensorimotor and visual information of one's own body and to construct body image. Studies have suggested structural and functional disturbances in the parietal cortex of BN patients (Delvenne et al., 1997; Vocks et al., 2010; He et al., 2016). The IPL is implicated in body image disturbance in ED patients. Among widespread brain regions displaying common responses to body images in AN patients and healthy persons, only the right IPL was more highly activated in AN patients (Wagner et al., 2009). It is also meaningful to interpret our results from another context that both the PCu and IPL are central nodes within the default mode network, which is highly active at rest and supports self-related cognitive activity (Raichle, 2015). Related to the function of DMN, the "undue influence of body shape and weight on self-evaluation" has been considered as a common feature of AN and BN (American Psychiatric Association, 2000). It is therefore possible that altered striatal and parietal RSFCs contribute to inappropriate integration of body image and self-worth overestimation dependent on body appearances. This association needs to be confirmed in conjunction with task-based designs.

Several factors distinguish our study from past investigations. This is the largest sample study of BN using R-fMRI so far. The recruitment of acute and unmedicated BN patients with short illness duration has largely disentangled the effects of medication and chronic course. To minimize the effects of depressive and anxiety symptoms on striatal RSFC, we excluded the patients with moderate-to-severe depression and anxiety. The correlation analysis between depressive and anxiety scores and striatal RSFC did not show statistical significance. Also, the results were largely reserved when we compared the striatal RSFC between groups by adding HAMD and HAMA scores to covariates. We therefore thought the confounding effects of depression and anxiety could be largely excluded.

However, several issues need to be further addressed. First, although BN-related reductions have been reported in striatal dopamine receptor binding (Broft et al., 2012) and serotonergic neurotransmission in the PFC (Bailer et al., 2007), the molecular basis of the striatal RSFC changes observed in our study is unclear. Second, the disorder specificity of our results to BN remains to be clarified given that aberrant striatal RSFC has also been observed in several other psychiatric disorders (Sakai et al., 2011; Stoddard et al., 2016; Huang et al., 2018). Further comparison with AN patients would help to identify the specific changes for AN and BN. Third, though we found several clinical correlations for striatal RSFC, we speculated the behavioral relevance of striatal RSFC changes combining with task-based studies. Future research integrating the resting and task paradigms and psychological tests will help to clarify how the striatal RSFC affects behaviors of BN patients.

CONCLUSION

In conclusion, we found disturbed RSFC within the fronto-striatal circuitry that supports self-regulation and taste rewarding functions as well as the visuospatial and somatosensory networks mediating body image perception. The common and distinct RSFC changes were found across different striatal subregions.

The primary contribution of this study is to provide direct evidence of BN-related changes in the striatal connectivity at the subregion level. By showing disturbed coupling between the reward central area and the visuospatial and somatosensory network, as well as the prefrontal control system, our study provides new evidence for understanding the neural circuitry of BN. We hope this work will encourage further investigations of therapeutic development for BN by normalizing disturbances of the striatal networks.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

Acknowledgments

Statement of Interest

All authors reported no potential conflicts of interest.

References

American Psychiatric Association (2000) Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR. Washington, DC: APA Press.

Bailer UF, Frank GK, Henry SE, Price JC, Meltzer CC, Becker C, Ziolko SK, Mathis CA, Wagner A, Barbarich-Marsteller NC, Putnam K, Kaye WH (2007) Serotonin transporter binding after recovery from eating disorders. Psychopharmacology (Berl) 195:315–324.

Broft A, Shingleton R, Kaufman J, Liu F, Kumar D, Slifstein M, Abi-Dargham A, Schebendach J, Van Heertum R, Attia E, Martinez D, Walsh BT (2012) Striatal dopamine in bulimia nervosa: a PET imaging study. Int J Eat Disord 45:648–656.

Brooks SJ, O'Daly OG, Uher R, Friederich HC, Giampietro V, Brammer M, Williams SC, Schiöth HB, Treasure J, Campbell IC (2011) Differential neural responses to food images in women with bulimia versus anorexia nervosa. PLoS One 6:e22259.

Buot A, Yelnik J (2012) Functional anatomy of the basal ganglia: limbic aspects. Rev Neurol (Paris) 168:569–575.

Canna A, Prinster A, Monteleone AM (2017) Interhemispheric functional connectivity in anorexia and bulimia nervosa. Eur Psychiatry S551.

Celone KA, Thompson-Brenner H, Ross RS, Pratt EM, Stern CE (2011) An fMRI investigation of the fronto-striatal learning system in women who exhibit eating disorder behaviors. Neuroimage 56:1749–1757.

Cyr M, Wang Z, Tau GZ, Zhao G, Friedl E, Stefan M, Terranova K, Marsh R (2016) Reward-based spatial learning in teens with bulimia nervosa. J Am Acad Child Adolesc Psychiatry 55:962–971.e3.

Cyr M, Yang X, Horga G, Marsh R (2018) Abnormal fronto-striatal activation as a marker of threshold and subthreshold bulimia nervosa. Hum Brain Mapp 39:1796–1804.

Delvenne V, Goldman S, Simon Y, De Maertelaer V, Lotstra F (1997) Brain hypometabolism of glucose in bulimia nervosa. Int J Eat Disord 21:313–320.

Di Martino A, Scheres A, Margulies DS, Kelly AM, Uddin LQ, Shehzad Z, Biswal B, Walters JR, Castellanos FX, Milham MP (2008) Functional connectivity of human striatum: a resting state FMRI study. Cereb Cortex 18:2735–2747.

Di Martino A, Kelly C, Grzadzinski R, Zuo XN, Mennes M, Mairena MA, Lord C, Castellanos FX, Milham MP (2011) Aberrant striatal functional connectivity in children with autism. Biol Psychiatry 69:847–856.

Domakonda MJ, Xiaofu H, Seonjoo L, Marilyn C, Rachel M (2019) Increased functional connectivity between ventral attention and default mode networks in adolescents with bulimia nervosa. J Am Acad Child Adolesc Psychiatry 58:232–241.

Downing PE, Jiang Y, Shuman M, Kanwisher N (2001) A cortical area selective for visual processing of the human body. Science 293:2470–2473.

Eklund A, Nichols TE, Knutsson H (2016) Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. Proc Natl Acad Sci U S A 113:7900–7905.

Frank GK, Reynolds JR, Shott ME, O'Reilly RC (2011) Altered temporal difference learning in bulimia nervosa. Biol Psychiatry 70:728–735.

Frank GK, Shott ME, Hagman JO, Mittal VA (2013) Alterations in brain structures related to taste reward circuitry in ill and recovered anorexia nervosa and in bulimia nervosa. Am J Psychiatry 170:1152–1160.

Fontan A, Cignetti F, Nazarian B, Anton JL, Vaugoyeau M, Assaiante C (2017) How does the body representation system develop in the human brain? Dev Cogn Neurosci 24:118–128.

Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R (1996) Movement-related effects in fMRI time-series. Magn Reson Med 35:346–355.

Gabbay V, Ely BA, Li Q, Bangaru SD, Panzer AM, Alonso CM, Castellanos FX, Milham MP (2013) Striatum-based circuitry of adolescent depression and anhedonia. J Am Acad Child Adolesc Psychiatry 52:628–41.e13.

Gaudio S, Wiemerslage L, Brooks SJ, Schiöth HB (2016) A systematic review of resting-state functional-MRI studies in anorexia nervosa: Evidence for functional connectivity impairment in cognitive control and visuospatial and body-signal integration. Neurosci Biobehav Rev 71:578–589.

He X, Stefan M, Terranova K, Steinglass J, Marsh R (2016) Altered white matter microstructure in adolescents and adults with bulimia nervosa. Neuropsychopharmacology 41:1841–1848.

Huang H, Shu C, Chen J, Zou J, Chen C, Wu S, Xiao L, Liu Z, Wang H, Zhou Y, Wang G, Jiang T (2018) Altered corticostriatal pathway in first-episode paranoid schizophrenia: resting-state functional and causal connectivity analyses. Psychiatry Res Neuroimaging 272:38–45.

Jenkinson M, Bannister P, Brady M, Smith S (2002) Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17:825–841.

Lavagnino L, Amianto F, D'Agata F, Huang Z, Mortara P, Abbate-Daga G, Marzola E, Spalatro A, Fassino S, Northoff G (2014) Reduced resting-state functional connectivity of the somatosensory cortex predicts psychopathological symptoms in women with bulimia nervosa. Front Behav Neurosci 8:270.

Lee JE, Namkoong K, Jung YC (2017) Impaired prefrontal cognitive control over interference by food images in binge-eating disorder and bulimia nervosa. Neurosci Lett 651:95–101.

Lee S, Lee AM, Leung T, Yu H (1997) Psychometric properties of the Eating Disorders Inventory (EDI-1) in a nonclinical Chinese population in Hong Kong. Int J Eat Disord 21:187–194.

Lock J, Garrett A, Beenhakker J, Reiss AL (2011) Aberrant brain activation during a response inhibition task in adolescent eating disorder subtypes. Am J Psychiatry 168:55–64.

Marsh R, Steinglass JE, Gerber AJ, Graziano O'Leary K, Wang Z, Murphy D, Walsh BT, Peterson BS (2009) Deficient activity in the neural systems that mediate self-regulatory control in bulimia nervosa. Arch Gen Psychiatry 66:51–63.

Marsh R, Horga G, Wang Z, Wang P, Klahr KW, Berner LA, Walsh BT, Peterson BS (2011) An FMRI study of self-regulatory control and conflict resolution in adolescents with bulimia nervosa. Am J Psychiatry 168:1210–1220.

Miyake Y, Okamoto Y, Jinnin R, Shishida K, Okamoto Y (2015) Eating disorders. Brain Nerve 67:183–192.

Mölbert SC, Klein L, Thaler A, Mohler BJ, Brozzo C, Martus P, Karnath HO, Zipfel S, Giel KE (2017) Depictive and metric body size estimation in anorexia nervosa and bulimia nervosa: a systematic review and meta-analysis. Clin Psychol Rev 57:21–31.

Oliva R, Morys F, Horstmann A, Castiello U, Begliomini C (2019) The impulsive brain: neural underpinnings of binge eating behavior in normal-weight adults. Appetite, 136:33–49.

Parent A, Hazrati LN (1995) Functional anatomy of the basal ganglia. I. The Cortico-basal ganglia-thalamo-cortical loop. Brain Res Brain Res Rev 20:91–127.

Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE (2012) Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage 59:2142–2154.

Radeloff D, Willmann K, Otto L, Lindner M, Putnam K, Leeuwen SV, Kaye WH, Poustka F, Wagner A (2014) High-fat taste challenge reveals altered striatal response in women recovered from bulimia nervosa: a pilot study. World J Biol Psychiatry 15:307–316.

Raichle ME (2015) The brain's default mode network. Annu Rev Neurosci 38:433–447.

Sakai Y, Narumoto J, Nishida S, Nakamae T, Yamada K, Nishimura T, Fukui K (2011) Corticostriatal functional connectivity in non-medicated patients with obsessive-compulsive disorder. Eur Psychiatry 26:463–469.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC (1998) The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 20:22–33.

Sherman SM (2016) Thalamus plays a central role in ongoing cortical functioning. Nat Neurosci 19:533–541.

Simon JJ, Skunde M, Walther S, Bendszus M, Herzog W, Friederich HC (2016) Neural signature of food reward processing in bulimic-type eating disorders. Soc Cogn Affect Neurosci 11:1393–1401.

Somerville LH, Hare T, Casey BJ (2011) Frontostriatal maturation predicts cognitive control failure to appetitive cues in adolescents. J Cogn Neurosci 23:2123–2134.

Stoddard J, Gotts SJ, Brotman MA, Lever S, Hsu D, Zarate C, Ernst M, Pine DS, Leibenluft E (2016) Aberrant intrinsic functional connectivity within and between corticostriatal and temporal-parietal networks in adults and youth with bipolar disorder. Psychol Med 46:1509–1522.

Stopyra MA, Simon JJ, Skunde M, Walther S, Bendszus M, Herzog W, Friederich HC (2019) Altered functional connectivity in binge eating disorder and bulimia nervosa: a resting-state fMRI study. Brain Behav 9:e01207.

Treasure J, Claudino AM, Zucker N (2010) Eating disorders. Lancet 375:583–593.

Uher R, Murphy T, Friederich HC, Dalgleish T, Brammer MJ, Giampietro V, Phillips ML, Andrew CM, Ng VW, Williams SC, Campbell IC, Treasure J (2005) Functional neuroanatomy of body shape perception in healthy and eating-disordered women. Biol Psychiatry 58:990–997.

Via E, Goldberg X, Sánchez I, Forcano L, Harrison BJ, Davey CG, Pujol J, Martínez-Zalacaín I, Fernández-Aranda F, Soriano-Mas C, Cardoner N, Menchón JM (2018) Self and other body perception in anorexia nervosa: the role of posterior DMN nodes. World J Biol Psychiatry 19:210–224.

Vocks S, Busch M, Grönemeyer D, Schulte D, Herpertz S, Suchan B (2010) Neural correlates of viewing photographs of one's own body and another woman's body in anorexia and bulimia nervosa: an fMRI study. J Psychiatry Neurosci 35:163–176.

Wagner A, Aizenstein H, Venkatraman VK, Bischoff-Grethe A, Fudge J, May JC, Frank GK, Bailer UF, Fischer L, Putnam K, Kaye WH (2009) Altered striatal response to reward in bulimia nervosa after recovery. Int J Eat Disord 43:289–294.

Wang L, Kong QM, Li K, Li XN, Zeng YW, Chen C, Qian Y, Feng SJ, Li JT, Su Y, Correll CU, Mitchell PB, Yan CG, Zhang DR, Si TM (2017) Altered intrinsic functional brain architecture in female patients with bulimia nervosa. J Psychiatry Neurosci 42:414–423.

Yan CG, Wang XD, Zuo XN, Zang YF (2016) DPABI: data processing & analysis for (Resting-State) brain imaging. Neuroinformatics 14:339–351.

Zhang D, Kong Q (2004) Applicability of EDI-1 in Beijing. Chin J Ment Health 18: 48–50.