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• RESEARCH PAPER •
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Bariatric surgery induces alterations in effective connectivity between the orbitofrontal cortex and limbic regions in obese patients

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Abstract Obese subjects show enhanced brain responses in motivation and reward neurocircuitry encompassing sensory and somatic integration-interception, motivation-reward (striatal), emotion, and memory processes, which attenuate frontal region activation during food cues. Bariatric surgery (BS) is the only reliable treatment for morbid obesity. Unfortunately, it is unknown how BS affects neurocircuitry after weight loss. We aimed to examine effects of BS on the basal activity of brain areas involved in reward and motivation processing, emotion, memory, and gut-brain interaction. We combined resting-state fMRI with amplitude of low-frequency fluctuation (ALFF) and Granger causality analysis (GCA) to assess interactions between regions within the frontal-mesolimbic circuitry in 16 obese subjects (OB) and 22 normal-weight (NW) subjects. The OB group was studied at baseline and 1 month post BS. Comparisons between OB and NW, and pre- and post BS showed significant differences in ALFF in areas involved in drive (caudate, orbitofrontal cortex (OFC)), arousal (thalamus), and conditioning/memory (amygdala, hippocampus) ($P < 0.05$, FDR correction). GCA revealed that in the OB group, the OFC had greater connectivity to limbic regions (amygdala, hippocampus, and medial thalamus) and the caudate. Post BS, the connectivity of the OFC to limbic regions decreased, whereas the connectivity from the amygdala and hippocampus to the caudate and thalamus was enhanced, particularly in subjects with lower body mass index (BMI). OFC activation in the OB group was associated with BMI prior to surgery, and changes in OFC post surgery were associated with alterations in BMI. Overall, the functional connectivity of the OFC was significantly decreased. As it is important for salience attribution and connected to limbic brain regions involved with emotional reactivity and conditioning after BS, its significant association with BMI changes indicates the contribution of OFC changes to the improved control of eating behavior after surgery.

Keywords fMRI, Granger causality analysis, obesity, bariatric surgery, frontal-mesolimbic

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1 Introduction

Obesity is caused by overeating due, in part, to dysfunctional food ingestion regulation and reward-related circuitry [1–3]. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET)

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indicate that certain brain regions/circuits are related to food ingestion [1–3], reward [4,5], motivation [6], mood [7], and inhibitory control [8]. These non-homeostatic factors are mainly in cortico-limbic structures including the prefrontal cortex (PFC), amygdala (AMY), hippocampal gyrus (HIPP), insula, and striatum [9]. Impaired function in such brain areas/circuits in obesity [10] is related to food cravings [11] and abnormal eating patterns [12].

Mesolimbic reward pathways provide value to rewards [2], thus influencing behavioral responses to food cues on the basis of their perceived reward value [13]. In humans, dopamine D2 receptor (D2R) levels are negatively correlated with emotional eating in the dorsal-striatum [5] and decreased striatal D2R receptors have been reported in morbidly obese subjects [14], implicating impaired self-control with reduced reward sensitivity [4]. Obese subjects also have decreased brain responses to food consumption [4], consistent with hypoactivation of reward circuitry. Regions within the mesolimbic/mesocortical pathways that determine the reward value of food cues and for regulating food intake include the ventral striatum, ventral tegmental area (VTA), HIPP, AMY [2,13], posterior insula, and orbitofrontal cortex (OFC) [15]. The thalamus has also been implicated in emotional eating scores [7] and the somatosensory cortex in increased sensitivity to palatability in obese individuals [16]. All aforementioned brain regions within the mesolimbic circuitry fall under the executive control of the PFC [13,17]. Reward-related information from corticolimbic regions and thalamic sensory input is all integrated by the PFC [2,17], and is responsible for initiating behavior in response to food cues [2,13,17]. Modulation of responses to high-calorie foods by the PFC is strongly linked to executive attention [18], inhibitory control [19], and emotional regulation [20]. Besides reports of brain responses to food-cue stimulation, a number of resting-state fMRI studies have been performed to examine abnormal functional connectivity (FC) in brain regions within resting-state networks (RSNs), including the default-mode network (DMN), salience network (SN), and frontoparietal network (FPN), which are involved in self-referential, food reward, and executive control processing [21–23]. Obese subjects have increased FC strength in the precuneus and decreased FC strength in the right anterior cingulate cortex [23]. A seed-based correlation analysis revealed increased FC between the posterior cingulate cortex (PCC) and precuneus and between the PCC and PFC [24]. In addition, one newly published paper from our group investigated differences in FC in the DMN, SN, and FPN, as well as alterations in internetwork connectivity, and reported increased FC between the SN and FPN in obesity [25].

Among multiple anti-obesity interventions, currently the most reliable procedure for treating obesity is bariatric surgery (BS) [26]. BS includes laparoscopic sleeve gastrectomy (LSG) [27], which was utilized here, and it promotes significant alterations in gut microbiota and neuroendocrinology [28]. fMRI revealed alterations in both homeostatic and hedonic neural pathways after BS. Following BS, molecular and functional alterations occur in obese subjects, which include increased D2R levels in mesolimbic/mesostriatal pathways [29], partial reversal of hypothalamic dysfunction, and altered neural function following body mass index (BMI) decrease [30]. Another surgery, the Roux-en-Y gastric bypass (RYGB), decreases activity in mesolimbic reward regions [31], such that decreased post surgery cravings for high-calorie (HC) foods were associated with decreased activation of mesolimbic regions and the dorsolateral-PFC post RYGB [32].

In general, obese people have heightened brain activation in motivation and reward pathways, encompassing sensory and somatic integration, and emotional processes when exposed to favorite foods or stress [33], and such people also have lower activation of frontal regions involved with pathways of self-control to food stimulation [19]. It is unknown (i) how various brain areas are involved in reward/motivation processing, emotion and memory, and gut-brain interaction during baseline in obese subjects and (ii) how these interactions are affected by BS. We combined resting-state fMRI (RS-fMRI) with Granger causality analysis (GCA) [34] to examine the interactions between neural regions within the frontal-mesolimbic circuitry in 16 obese patients before LSG surgery and 1 month post surgery, and in 22 normal-weight (NW) subjects. We predicted that BS would result in increased signaling from areas implicated in sensory, emotional, and memory processing (AMY, HIPP, and thalamus) and reward/motivation (caudate), but in decreased signaling from regions involved with impulsivity and/or motivation (OFC).

Table 1 Demographic and clinical information of obese and normal-weight subjects[a)]

	OB ($N = 16$)		NW ($N = 22$) (Mean ± SE)	F value	P value	
	PreBS (Mean ± SE)	PostBS (Mean ± SE)			a	b
Age (yrs)	25.44 ± 1.82	25.44 ± 1.82	26.77 ± 1.56	0.458	0.580	1
Gender	6M/10F	6M/10F	8M/14F	0.041	0.945	1
Duration of obesity (yrs)	12.75 ± 2.19	12.75 ± 2.19	–	19.051	–	1
Weight (kg)	109.45 ± 4.28	96.91 ± 4.36	59.52 ± 2.22	48.796	0.000	0.023
BMI (kg/m^2)	38.17 ± 1.45	33.72 ± 1.48	21.48 ± 0.58	50.075	0.000	0.012
WC (cm)	117.19 ± 3.72	104.91 ± 4.38	80.98 ± 2.33	25.897	0.000	0.031
Food intake (kg/meal)	0.80 ± 0.13	0.21 ± 0.03	0.39 ± 0.03	14.825	0.000	0.019
YFAS	4.50 ± 0.56	2.94 ± 0.49	1.68 ± 0.27	9.659	0.000	0.017
HAMD	11.94 ± 2.89	12.31 ± 2.01	6.27 ± 0.86	6.894	0.037	0.896
HAMA	9.94 ± 2.37	8.38 ± 1.72	4.55 ± 0.67	2.313	0.017	0.510

a) OB: obese candidates for bariatric surgery; PreBS: obese subjects who were image-scanned before surgery; PostBS: obese subjects who received bariatric surgery and were image-scanned again at 1 month post surgery; NW: normal weight; SE: standard error; BMI: body mass index; WC: waist circumference; YFAS: Yale food addiction scale; HAMD: Hamilton depression rating scale; and HAMA: Hamilton anxiety rating scale. a: cross-group comparison between obese individuals and normal weight controls (OB vs. NW) to examine the effect of obesity. b: within group comparison between obese subjects pre- and post surgery (PreBS vs. PostBS) to investigate the effect of bariatric surgery.

2 Materials/methods

2.1 Participants

We recruited 29 obese (OB) subjects to receive LSG at Xijing Hospital of Digestive Diseases affiliated with the Fourth Military Medical University. Those with former intestinal surgeries, organ dysfunction, psychiatric/neurological diseases, IBD, or taking any current drugs that may affect the central nervous system were not included. Patients that were >150 kg were not included [31, 32, 35–39]. In this case, 6 OB patients did not qualify for the MRI scans. The rest of the OB patients ($n = 23$) underwent BS [27] and underwent all presurgery MRI scanning. Exact MRI scanning was done 1 month post BS. Seven obese patients had significant weight reduction post BS. Unfortunately, they were not able to complete their follow-up scanning because of traveling distance. Thus, the OB group consisted of 16 total subjects (Table 1). Controls were 22 NW subjects that were gender-, age-, and education-matched with the OB group ($P > 0.05$).

2.2 Experimental protocol

All participants underwent 12-hour fasting overnight. MRI scanning was conducted between 9 and 10 AM for consistency and minimization of circadian influence.

Severity of the subjects' anxiety and depression status was evaluated by one psychiatrist using the Hamilton Anxiety Rating Scale [40] and the Hamilton Depression Rating Scale [41]. All subjects completed the Yale Food Addiction Scale (YFAS) evaluation [42] (Table 1), which was validated in a group that received BS [43]. All measurements were conducted in an identical manner pre- and 1 month post surgery. All LSG surgeries were done by one surgeon.

2.3 Peripheral hormone measurements

Blood was collected before and 1 month post BS and stored at −80°C. Serum insulin, ghrelin, C-peptide, leptin, GIP, GLP-1, and glucagon concentrations were assayed using the Bio-Plex 200TM suspension array system.

2.4 MRI scanning

MRI scans were conducted using a 3.0 T GE scanner. High-resolution 3D images were acquired with magnetization-prepared rapid acquisition gradient-echo sequences (with voxels measuring 1 mm × 1 mm × 1 mm) and with an axial fast spoiled gradient echo sequence (TR = 7.8 ms, TE = 3.0 ms, matrix = 256 × 256, FOV = 256 mm × 256 mm, 166 slices). A T2*-weighted EPI sequence acquired RS-fMRI images (TR = 2000 ms, TE = 30 ms, matrix = 64 × 64, FOV = 256 mm × 256 mm, angle = 90°, resolution = 4 mm × 4 mm, 32 axial slices). The RS-fMRI scan lasted 360 s and contained 180 echo-planar volumes.

2.5 Imaging data processing

All data preprocessing was done with SPM 12, which included slice-timing, correction for head-movement using a frame-wise method, normalization, and a band-pass filter approach (0.01–0.08 Hz), followed by global normalization [43] (Appendix A). Head-motion parameters, white-matter signals, and CSF signals were regressed out.

2.6 ROI definition

The amplitude of low-frequency fluctuation (ALFF) method was performed to localize ROIs [44, 45] (Appendix A). Briefly, ALFF was designed to quantify fluctuations in fMRI signal amplitude, as it has been employed in a number of neurological diseases as a reliable biomarker [44, 45]. Two-sample t-tests were utilized to evaluate ALFF differences between OB/NW groups (OB > NW), and a post-hoc paired t-test was used for presurgery (PreBS) and postsurgery (PostBS) comparisons (PreBS > PostBS). Brain areas with significant ALFF changes related to frontal-mesolimbic circuits were chosen as ROIs ($P < 0.05$, cluster size > 100 voxels, FDR).

2.7 GCA method

GCA [46] was used to define ROIs as in our previous studies [44, 45] (see Appendix A). This method uses effective connectivity (EC) analysis to depict regional interactions [47]. EC changes were obtained by both calculating differences between OB and NW, and between PreBS and PostBS in the OB group.

2.8 Correlation analysis

A partial correlation analysis was carried out using age, anxiety, gender, and HAMD as confounding factors to evaluate the relationship between alterations in neural activity/EC and clinical evaluations [48]. Such measurements included BMI, ALFF, YFAS, and normalized ratios Rx'y of pair-wise ROIs. Then, Bonferroni correction was employed to assess multiple comparisons with $P < 0.001$ (0.05/50).

3 Results

3.1 Demographics

As controls were matched, the OB and NW groups had no differences in age or gender (Table 1). Baseline measurements included weight, BMI, WC, food intake, YFAS, HAMD, and HAMA; all were increased in OB compared to NW ($P < 0.05$). The OB group had decreased weight, BMI, WC, food intake, and YFAS PostBS than PreBS ($P < 0.05$, Table 1). No significant differences in HAMD or HAMA were found between PreBS and PostBS ($P > 0.05$, Table 1).

3.2 Peripheral hormone concentrations

Peripheral hormones including insulin, ghrelin, and leptin were decreased PostBS compared to PreBS ($P < 0.01$, Figure 1). Other peripheral hormones including GLP-1, C-peptide, glucagon, and GIP were unchanged.

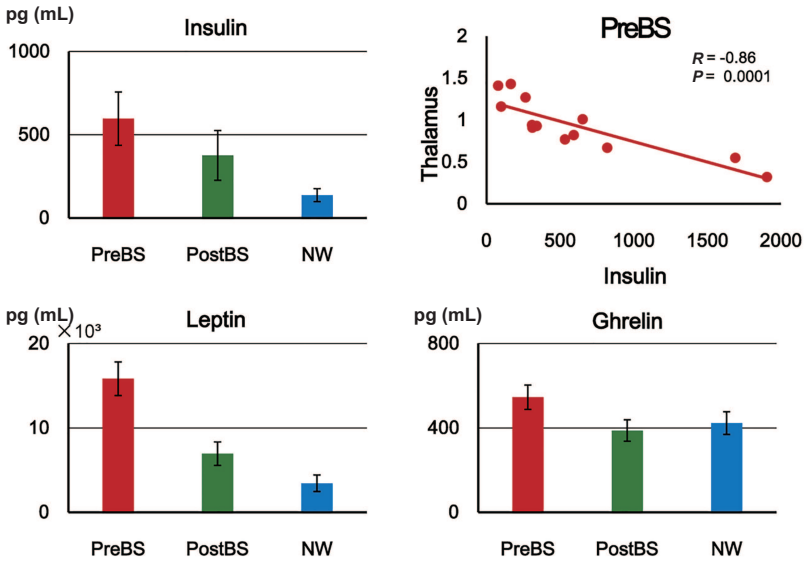

Figure 1 (Color online) Correlations between baseline plasma gut peptide measures and regional ALFF.

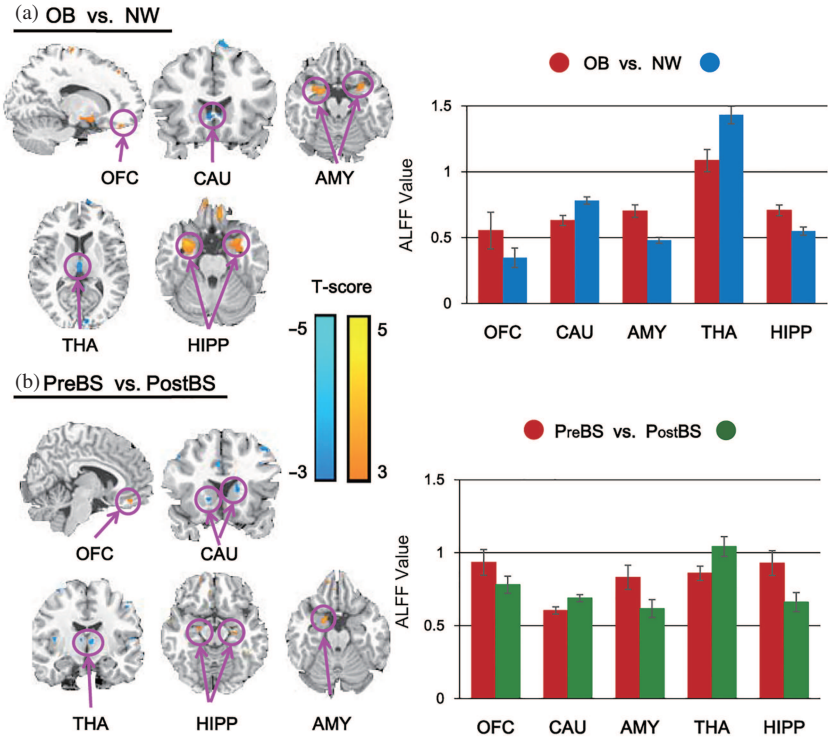

Figure 2 (Color online) Functional mapping of brain areas demonstrates significant ALFF alterations between OB and NW groups and in the OB group between before and after surgery (PreBS > PostBS) during the resting state ($P < 0.05$, FDR corrected). (a) Compared to the NW group, the OB group had increased ALFF in the OFC, AMY, and HIPP, and decreased ALFF in the caudate and thalamus. (b) After surgery, the OB group had increased ALFF in the caudate and thalamus, and decreased ALFF in the OFC, AMY, and HIPP.

3.3 ROIs definition

The OB group had increased ALFF in the OFC, AMY, and HIPP and decreased ALFF in the caudate and thalamus ($P_{\mathrm{FDR}} < 0.05$; Figure 2(a) and Table S1). Paired t-test indicated that after BS, OB had enhanced ALFF in the caudate and thalamus, and decreased ALFF in the OFC, AMY, and HIPP ($P_{\mathrm{FDR}} < 0.05$; Figure 2(b) and Table S1). These regions were selected as ROIs because they are part of the

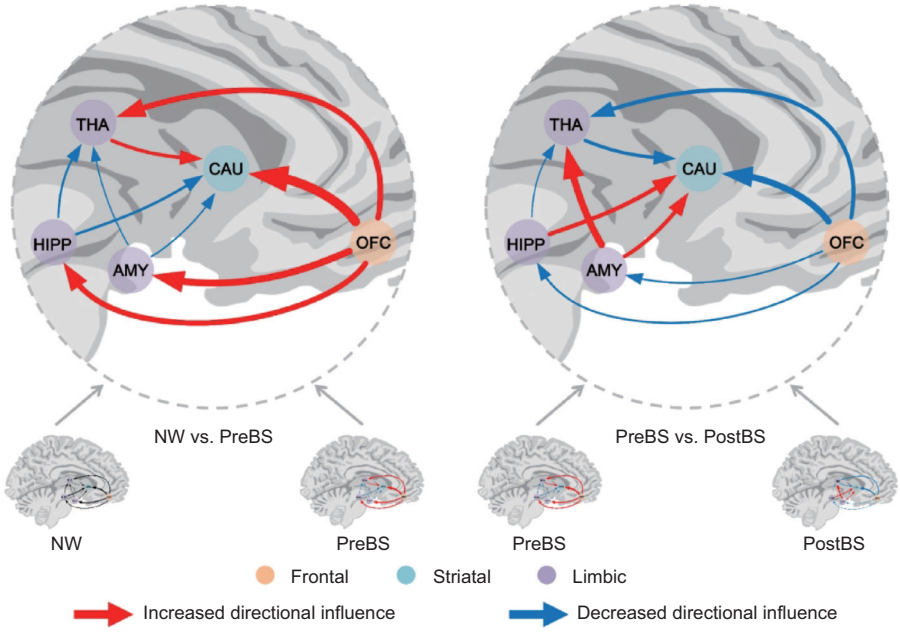

Figure 3 (Color online) Alterations of frontal-mesolimbic interactive causal influence in obese subjects before and after BS. GCA results showed that in OB the OFC propels the limbic regions (amygdala, hippocampus, and medial thalamus); the OFC and the medial thalamus propel the caudate. After surgery, the amygdala and hippocampus propel the caudate. In addition, there was enhanced connectivity between the amygdala and medial thalamus, and connectivity between the OFC and reward/limbic region decreased.

frontal-mesolimbic neurocircuit involved in control and regulation of eating behaviors [10].

3.4 Altered frontal-mesolimbic interactions

Compared to NW, OB showed stronger EC from the OFC to mesolimbic regions (caudate, AMY, and HIPP) and to the thalamus, and from the thalamus to the caudate. OB showed weaker EC from the AMY and HIPP to the caudate, and from the HIPP and AMY to the thalamus. The OB PostBS group had stronger EC from the AMY and HIPP to the caudate, and from the AMY to the thalamus. The OB group also exhibited weaker EC from the OFC to mesolimbic regions (caudate, AMY, HIPP) and the thalamus (Figure 3 and Table S2).

3.5 Clinical assessment

In the PreBS OB group, insulin concentrations were negatively correlated with ALFF in the thalamus ($R = -0.86$, $P = 0.0001$; Figure 1). There were no significant correlations between peripheral hormones (ghrelin, leptin) and ALFF in other brain regions.

In the PreBS OB group, BMI was significantly correlated with ALFF in the OFC ($R = 0.67$, $P = 0.0006$). PostBS had positive associations between ALFF in the HIPP and BMI ($R = 0.67$, $P = 0.001$). Changes in ALFF in the OFC (PreBS-PostBS) were positively correlated with changes in BMI ($R = 0.73$, $P = 0.001$; Figure 4(a)).

BMI in OB was positively correlated with the ratio of OFC and THA ($R = 0.68$, $P = 0.0003$), and YFAS was negatively associated with the ratio of AMY and THA ($R = -0.69$, $P = 0.0002$). In PostBS, BMI was negatively correlated with the ratio of HIPP and THA ($R = -0.79$, $P = 0.0002$; Figure 4(b)).

4 Discussion

We utilized RS-fMRI and GCA to evaluate changes in frontal-mesolimbic interactions in OB subjects pre- and post LSG surgery. Significant differences in resting-state activities were found in brain areas

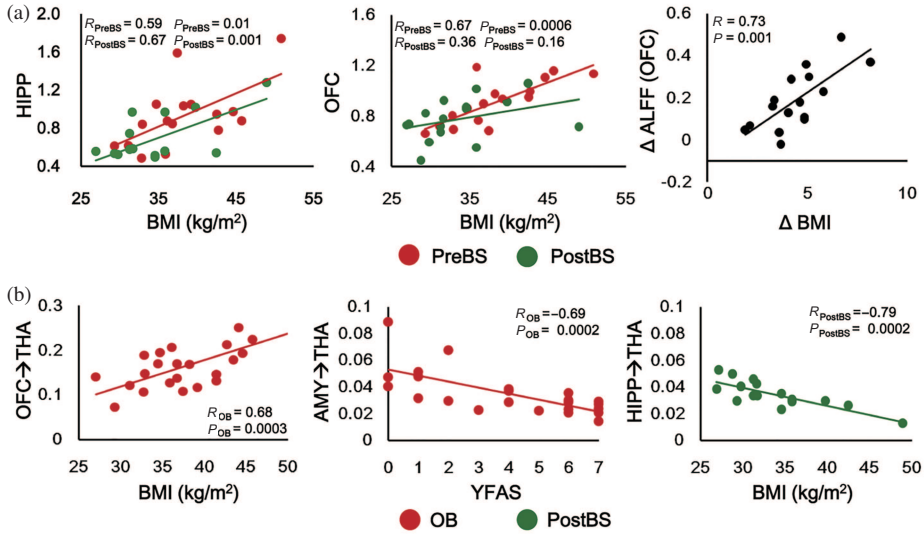

Figure 4 (Color online) Correlation analysis between baseline brain activity/interactions and BMI changes, and between changes in brain activity and changes in BMI before and after surgery. (a) In the OB group before surgery (PreBS), BMI was significantly correlated with ALFF in the OFC ($R = 0.67$, $P = 0.0006$). After surgery, the OB group (PostBS) showed positive correlations between BMI and ALFF in the HIPP ($R = 0.67$, $P = 0.001$). Changes in ALFF in the OFC (PreBS-PostBS) was positively correlated with changes in BMI ($R = 0.73$, $P = 0.001$). (b) In the OB group, BMI was positively correlated with the ratio of OFC to THA ($R = 0.68$, $P = 0.0003$), and YFAS was negatively associated with the ratio of the AMY to THA ($R = -0.69$, $P = 0.0002$). In the OB group after surgery, BMI was negatively correlated with the ratio of HIPP to THA ($R = -0.79$, $P = 0.0002$).

implicated in motivation, drive, and emotional processing. GCA results revealed that the OFC, which is related to salience attribution, had greater connectivity to limbic regions (AMY, HIPP, and medial thalamus) and to the caudate in the OB group. After surgery, AMY and HIPP had enhanced connectivity to the caudate and medial thalamus. This enhanced connectivity may provide better integration for controlling excessive salience of food reward and sensory and emotional processing. Attenuated connectivity between the OFC and reward and limbic regions could contribute to decreased impulsivity and regulatory control of eating behavior.

4.1 Altered motivational effects

The OFC is associated with motivation and compulsive behavior [49], as it tracks subjective pleasantness of stimuli [50] and is involved in decision-making and reward [51]. Higher YFAS scores are correlated with greater activation within the OFC [52], and this area is activated by food cues [53]. Greater responsiveness of the OFC to HC food stimuli may indicate hypersensitivity to food reward [52], thus increasing the risk of gaining weight. Our results revealed increased ALFF in the OFC in OB compared to NW subjects, and decreased ALFF in the OFC post BS. A positive correlation between baseline ALFF in the OFC and BMI revealed OFC hyperactivity in obesity. The linear association between surgery-related alterations in BMI and ALFF in the OFC suggests that there are benefits of BS for OFC hyperactivity normalization. GCA revealed that the OB group had stronger effective OFC connectivity with the caudate, AMY, HIPP, and THA. Significant correlations between BMI and ratio of OFC and THA might reflect larger responses to the motivational network in obese subjects initiated by OFC hyperactivation [9]. After surgery, the OB group showed reduced connectivity from the OFC to mesolimbic areas (AMY, HIPP, thalamus). The OFC receives visceral sensory information that could be affected by BS. Alterations in the interactions between the OFC and mesolimbic areas PostBS may allow for input from areas implicated in emotional processing to regulate the drive from the OFC to control enhanced appetite.

4.2 Altered emotion-memory effects

Neuroimaging studies showed activation of the AMY with food-related stimuli [54]; the AMY is involved in food motivation [55], learning [56], and emotional eating [57]. The AMY evaluates cues that represent these reinforcers, presenting stable responses to food cues [9, 15]. It is also related to emotional food intake; ingestion of HC food can dampen stress-induced activation [58]. In addition, our prior study using gastric distention showed activation of the AMY, providing evidence that it processes interceptive signals of fullness important for controlling food intake [59, 60].

Activation of the HIPP, which stores and retrieves food memories, was associated with specific food cravings. Using implantable gastric stimulation in our previous study, we determined that HIPP activity was a result of downstream activation of the vagus nerve and solitary nucleus [61], implicating there was an association between the stomach and HIPP [61].

The thalamus plays an important role in integrating and relaying numerous bottom-up data [62], and the VL of the thalamus receives information from the basal ganglia and projects it to the premotor areas [63]. HC food cues may act as highly arousing stimuli, which could confound sensory processing through the thalamus to the reward pathways away from the executive circuitry [64]. During a food-cue paradigm, OB subjects demonstrated increased activation in the thalamus, putamen, insula, and hypothalamus [33]. The medical thalamus, AMY, and ventral striatum are preferentially activated by food cues and anticipation [65]. One study reported a negative association between insulin concentrations and thalamic activity in the PreBS OB group, which is consistent with findings reported in OB subjects when they were exposed to HC food cues [66]. Decreases in relative neural responsivity in the thalamus (homeostasis) and other brain regions significantly predicted reductions in appetite for HC foods pre- and post surgery [32].

Our data revealed increased ALFF in the AMY and HIPP in the OB group; ALFF in these regions was normalized after surgery. Gastric stimulation reduced stomach curvature and enhanced glucose metabolism in the HIPP in association with suppressed emotional eating [60]. Thus, greater EC from the HIPP and AMY to the caudate as well as a negative association between BMI and the ratio of HIPP to THA connectivity might contribute to decreased food intake after BS.

4.3 Altered reward effects

The caudate is associated with reward processing [7]. OB subjects have enhanced activity in the corticolimbic-striatal circuitry when exposed to food cues [33]. Enhanced DA activity in the caudate was reported in binge eating [67]. An impairment of the ability of DA to decrease the impact of leptin on the NAc along with decreased D2R in the striatum may cause hyperactivity in the mesolimbic circuitry, contributing to reward cues in OB patients. Dopamine responses may also be associated with food reward leading to weight gain [11]. Therefore, this is a possible explanation for the difficulty of appetite control and establishing eating habits based on actual needs in OB patients.

Peripheral hormone analysis showed altered insulin levels and trends of negative correlations between insulin levels and ALFF in the caudate, suggesting their contribution to altered brain activity in reward areas. In addition, a PET study from Dunn et al. showed negative correlations between ghrelin concentrations and D2R levels in the striatum in OB patients [67], while our current study showed decreased ghrelin levels after BS. Decreased ghrelin levels might result in enhanced DA function in the OB group after surgery. EC from other brain regions to the caudate is consistent with integration of information from limbic regions to the caudate in the OB group after surgery. Caudate predominantly projects to the PFC and is a hub area of convergence for multiple inputs [68] that could further enhance executive function and control overeating behaviors. Activation of the mesolimbic areas was decreased in response to HC foods after BS [31], which was consistent with a reduced reward value of foods [69].

5 Conclusion

The current study investigated which brain regions were implicated in frontal-mesolimbic circuitry prior to BS in obese subjects, and how BS modulated these interactions. We employed RS-fMRI and GCA to examine alterations of frontal-mesolimbic interactions in OB subjects pre- and post BS. Our results showed significant modulation of connectivity in brain areas associated with motivation and sensory, emotion, and memory processing after BS. This study highlighted the importance of the OFC as a main target for therapeutic benefits of BS.

Compliance and ethics All protocols were approved by the Institutional Review Board of Xijing Hospital and were conducted according to the Declaration of Helsinki. All subjects were given an explanation of the purpose of the experiment and signed consent forms.

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Supporting information Appendix A. The supporting information is available online at info.scichina.com and link.springer.com. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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