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ORIGINAL CONTRIBUTIONS

Sleeve Gastrectomy Rescuing the Altered Functional Connectivity of Lateral but Not Medial Hypothalamus in Subjects with Obesity

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Abstract

Background Lateral and medial hypothalamus (LH and MH) play important roles in energy balance. Changed hypothalamic function has been found in subjects with obesity. However, the effect of bariatric surgery on the function of the two sub-regions has been poorly investigated.

Methods Thirty-eight subjects with obesity and 34 age- and sex-matched normal-weight controls were included. Seventeen of the 38 subjects underwent laparoscopic sleeve gastrectomy. Functional magnetic resonance imaging data and metabolic parameters were collected to investigate functional connectivity networks of the two hypothalamic sub-regions as well as the influence of sleeve gastrectomy on the two networks in subjects with obesity.

Results Compared to normal-weight controls, pre-surgical subjects had increased functional connectivity (FC) in the reward region (putamen) within the LH network, and increased FC in somatosensory cortical area (insula), as well as decreased FC in the cognitive control regions (prefrontal regions) within the MH network. After the surgery, post-surgical FC of the putamen within the LH network changed towards the patterns found in the control group. Furthermore, the changes in fasting glucose before and after the surgery were associated with the changes in FC of the putamen within the LH network.

Conclusions The FC within the LH and MH networks were changed in subjects with obesity. Part of these altered FC was rescued after the surgery.

Keywords Functional MRI · Obesity · Bariatric surgery · Hypothalamus · Metabolism

Introduction

Obesity has been a worldwide problem due to its prevalence and complications, such as diabetes, hypertension, cardiovascular disease, cerebrovascular disease, and several cancers [1, 2]. Unfortunately, there is no effective treatment to bring it under control [3]. Up to now, what is known by researchers is that obesity is a complex neurobehavioral disorder and results from

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excessive energy intake and insufficient energy expenditure [4], yet underlying mechanisms are far from understood.

The hypothalamus plays a linchpin role in food intake regulation and energy balance, as well as reward and motivated behavior [4, 5], whose dysfunction has been emerged as a cause of obesity [6]. The regulatory function of hypothalamus in food intake or feeding behavior was first found by lesion studies in rats [7]. In recent years, distinct neuron types and circuits have been found in lateral hypothalamus (LH) and medial hypothalamus (MH), which play a key role in regulating energy intake and feeding behavior [4, 8]. Especially, stimulating GABA and orexin/hypocretin neurons in LH can promote food intake, whereas stimulating glutamate neurons in LH can reduce food intake [9, 10]; stimulating neuropeptide Y and agouti-related protein (NPY-AgRP) neurons in MH provides orexigenic signals [11, 12], whereas stimulating proopiomelanocortin and cocaine and amphetamine-related transcript (POMC-CART) neurons in MH can suppress appetite [13, 14].

Beyond rodent studies, several human brain imaging studies have shown that hypothalamic dysfunction plays an important role in the development of obesity. Most of these studies have found profoundly decreased activity in the hypothalamus after glucose ingestion or food-related stimulation in subjects with obesity [15–17]. Furthermore, hypothalamus damage can result in obesity [18, 19]. The cooperation with other regions, such as communication with the striatum and higher-order cortical areas, constitutes the energy regulator [4, 20]. Altered functional connectivity (FC) between the hypothalamus and the somatosensory cortex, the insula, the dorsal anterior cingulate cortex, the putamen, and the prefrontal cortex has been found in subjects with obesity [21–24]. Furthermore, the lateral hypothalamus is a potential neural target for deep brain stimulation (DBS) in the treatment of obesity [25, 26]. In recent years, the reversion of regional brain dysfunction and metabolic parameters after bariatric surgery has been reported [27–30]. Furthermore, a recent longitudinal study has reported that the body mass reduction caused by bariatric surgery can reverse the hypothalamic dysfunction in subjects with obesity [22]. Relative to behavioral interventions and pharmacological interventions, surgical interventions are most effective for weight loss in both a short and long term. Surgical interventions may provide excellent models to help understand the neuromechanism of obesity, as weight loss is a novel mechanism of change. However, precise physiological mechanisms underlying post-surgical weight loss are poorly comprehended.

Hence, in this study, we investigated the altered FC networks of the medial hypothalamus and lateral hypothalamus in subjects with obesity using "resting-state" functional magnetic resonance imaging. Furthermore, body mass reduction model was used to insight the effect of weight loss after the surgery on networks of the two hypothalamic sub-regions.

Materials and Methods

Participants

Forty-four subjects with obesity who met the including conditions were recruited from the inpatients of two hospitals. Thirty-six age- and sex-matched normal-weight participants were recruited from the local community. The including conditions for the two groups were as follows: (1) age range from 18 to 40; (2) not having neurological and psychiatric disorder, substance addiction such as drugs, cigarette, and alcohol; (3) BMI range from 18 to 25 for the controls as well as from 30 to 56 for the pre-surgical group. As major participants seeking bariatric surgery for weight loss in the recruited BMI range had a history of diabetes, subjects with obesity who had well-controlled diabetes without taking insulin were included in this research. Two subjects with obesity were excluded from the study due to thyroid cancer and congenital cerebrovascular malformations as revealed by pre-surgical medical examination. Furthermore, one subject with obesity was excluded from the study due to too much body fat that unable to comfortably lie in the MRI scanner. In addition, three subjects with obesity and two normal-weight controls were excluded from the study due to poor scanning compliance. In the final, 38 participants with obesity and 34 age- and sex-matched normal-weight subjects were included in this study. Seventeen of the 38 obese participants underwent laparoscopic sleeve gastrectomy (LSG), and three of the 38 obese participants underwent Roux-en-Y gastric bypass surgery (RYGB), in two sites. The other 18 obese participants dropped out from the study due to not having the surgery or not having the post-surgical scan. To exclude the effect of different surgical procedures, we only included the 17 post-surgical patients who underwent LSG. The study protocol was approved by the ethics committee in the hospital. All participants were fully informed of the study procedures and signed the informed consent. The demographic information was given out in Table 1.

Metabolic Variables Evaluation

Before blood sampling, participants were asked to avoid strenuous physical activity and fast for 12 h. Venous blood was sampled from the antecubital vein and collected into Vacutainer tubes and immediately transferred to 4 °C. Blood samples were analyzed for fast glucose (FG), HbA1c, total cholesterol (TC), triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL), serum uric acid (SUA), creatinine, and carbamide with an automatic analyzer (Roche modular 7600 automatic biochemistry analyzer).

Table 1 Demographic information of participants

	The normal-weight $N = 34$, 15 females Mean ± SD	The pre-surgical $N = 38$, 16 females Mean ± SD	The pre-surgical $N = 17$, 6 females Mean ± SD	The post-surgical $N = 17$, 6 females Mean ± SD	P1	P2	P3	Power
BMI (kg/m^2)	21.8 ± 1.8	40.0 ± 6.5	41.6 ± 7.3	34.4 ± 5.9	***	***	***	99%
Age (years)	26.7 ± 6.8	27.8 ± 6.9	27.1 ± 7.1	–	Ns	Ns	–	–
Sex	–	–	–	–	0.86#	0.66#	–	–
SBP (mmHg)	123.7 ± 7.8	142.9 ± 15.5	139.0 ± 16.8	127.1 ± 14.2	***	Ns	**	29%
DBP (mmHg)	73.9 ± 8.0	87.5 ± 7.9	86.3 ± 8.5	78.9 ± 5.8	***	Ns	**	73%
FG (mmol/L)	4.5 ± 0.6	6.0 ± 1.8	5.6 ± 1.8	5.1 ± 1.5	**	Ns	*	63.3%
HbA1c (%)	5.0 ± 0.3	6.6 ± 1.6	6.7 ± 1.8	5.7 ± 0.9	***	**	*	99%
TC (mmol/L)	4.0 ± 0.3	5.1 ± 1.1	5.0 ± 1.0	4.9 ± 0.9	**	**	Ns	98%
Triglyceride (mmol/L)	1.0 ± 0.3	2.2 ± 1.2	2.6 ± 1.5	1.3 ± 0.6	**	Ns	*	76%
HDL (mmol/L)	1.3 ± 0.2	1.0 ± 0.2	1.1 ± 0.3	1.1 ± 0.3	***	**	Ns	87%
LDL (mmol/L)	2.3 ± 0.5	3.3 ± 0.6	3.1 ± 0.8	2.7 ± 0.7	***	**	*	91%
SUA (μmol/L)	312.4 ± 67.8	420.9 ± 132.5	488.3 ± 166.6	416.6 ± 113.8	***	***	*	91%
Creatinine (mmol/L)	74.5 ± 10.9	65.1 ± 12.2	65.2 ± 13.0	69.1 ± 12.1	**	Ns	*	48%
Carbamide (μmol/L)	4.6 ± 0.9	4.7 ± 1.0	5.0 ± 1.0	4.5 ± 0.8	Ns	Ns	Ns	10%

P1 *P* values of the comparisons between the 38 pre-surgery and normal-weight participants revealing by two-sample *t* test unless stated; P2 *P* values of the comparisons between the 17 post-surgery and normal-weight participants revealing by two-sample *t* test unless stated; P3 *P* values the comparisons between the 17 pre-surgery and 17 post-surgery participants revealing by paired *t* test; power represents the statistical power in the comparisons between the post-surgery and the normal-weight participants; # Chi-square test; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, NS no significance, SBP systolic blood pressure, DBP diastolic blood pressure, FG fating glucose, TC total cholesterol, HDL high-density lipoprotein, LDL low-density lipoprotein, SUA serum uric acid

MRI Data Acquisition

All MRI data were obtained on a 3.0T MRI scanner (Discovery 750, GE Healthcare, Milwaukee, WI) with a 32-channel head coil at the General Hospital of Chinese People's Liberation Army. Vacuum cushions were applied to reduce the noise and movement artifact. The resting-state sequence lasted 6 min, and participants were instructed to relax but not to fall asleep. During scanning, their eyes were kept closed, and their ears were fitted with soft earplugs. After the scanning, each participant was confirmed not having fallen asleep. One hundred and eighty resting-state whole-brain fMRI blood oxygen-level dependent scans for each participants were obtained by a multi-slice gradient-echo EPI sequence [repetition time (TR)/echo time (TE) = 2000/30 ms; flip angle = 90°; slice thickness = 4 mm, 36 slices, no slice gap; field of view (FOV) = 240 mm × 240 mm; matrix = 64 × 64, 3.75 × 3.75 × 4 mm^3]. The post-surgical scanning was performed with the same sequence about 4 months after the surgery.

fMRI Data Preprocessing

The resting-state fMRI data preprocessing was conducted using DPARSF (Data Processing Assistant for Resting-State fMRI; http://www.restfmri.net): A MATLAB toolbox for "pipeline" data analysis of resting-state fMRI [31]. Data were preprocessed starting with removing the first 10 volumes (fMRI images) of functional scans for ameliorating possible effects of scanner instability and subjects' adaptation to the environment. Then, volumes were slice time corrected for within-scan acquisition time differences between slices. To correct the effect of head motions, the functional images were realigned and registered to the mean image. Thereafter, normalization into Montreal Neurological Institute (MNI) space (2 mm isotropic voxel size) and Gaussian spatial smoothing (full-width at half-maximum 8 mm) were performed. Following spatial normalization, the linear detrend was performed to remove noise due to long-term physiological shifts, movement-related noise remaining after realignment, and instrumental instability. Data were filtered by a temporal band-pass filter (0.01–0.08 Hz) to reduce the very low-frequency drift and high-frequency respiratory and cardiac noise. Finally, the six head motion parameters, global mean signal, whiter matter signal, and cerebrospinal fluid signal were regressed out as nuisance covariates to remove these unwanted signals.

Resting-State Functional Connectivity Analysis

Functional connectivity (FC) maps were obtained by computing correlation coefficients between the time courses (fMRI signals) in the region of interest (ROI) and each other brain voxel. A voxel represents the smallest unit in the fMRI images. Baroncini et al. create the MRI atlas of human hypothalamus which can identify sub-regions of hypothalamus from

MRI images [32]. We defined two ROIs according to the hypothalamic MRI atlas by Baroncini [32] and the method in a recent research [5]: the bilateral LH ($x \pm 6$, $y -9$, $z -10$ plus 2 mm sphere) and MH ($x \pm 4$, $y -2$, $z -12$ plus 2 mm sphere) (Fig. 1). The coordinates of LH and MH are in the standard space (MNI space). The LH included part of lateral hypothalamic area. The MH included the arcuate nucleus, medial preoptic nucleus, ventromedial, and part of the dorsomedial nucleus of the hypothalamus. We chose the time courses in the peak voxel of each ROI representing the time courses of the ROI to minimize overlap between the two ROIs. The FC maps were transferred to Z-maps by using Fisher's Z transformation [33].

Statistical Analysis

Two-sample *t* test and paired *t* test were performed to evaluate the difference in metabolic parameters between the normal-control participants, pre-surgical participants, and post-surgical participants. As the reduced post-surgical sample size may increase the probability of type II error, the statistical power was calculated referenced to H. Wang et al. [34].

The Fisher's Z-maps were analyzed by SPM8 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm). Two-sample *t* test model including one covariate to adjust for age was used to calculate differences in FC maps between the pre-surgical group with obesity and normal-weight group. And paired *t* test model was used to evaluate the change in the two networks caused by the body mass reduction. The statistical threshold was set as $p < 0.001$ and cluster size > 400 mm^3 (50 voxels) after multiple comparison correction. The multiple comparison correction was determined by Monte Carlo simulation (1000 iterations) using the REST Alphasim program [33].

Pearson correlation coefficients between the changes in FC and changes in metabolic variables before and after the surgery were calculated to explore possible relationships between the altered FC and abnormal metabolic parameters. Significant association was threshold as $p < 0.05$.

Results

Clinical and Demographic Characteristics

There was no difference in age and sex between the three groups (Table 1). Pre-surgical subjects with obesity had increased systolic blood pressure (SBP), diastolic blood pressure (DBP), FG, HbA1c, TC, Tri, LDL, and SUA, as well as decreased HDL and creatinine when compared to the normal-

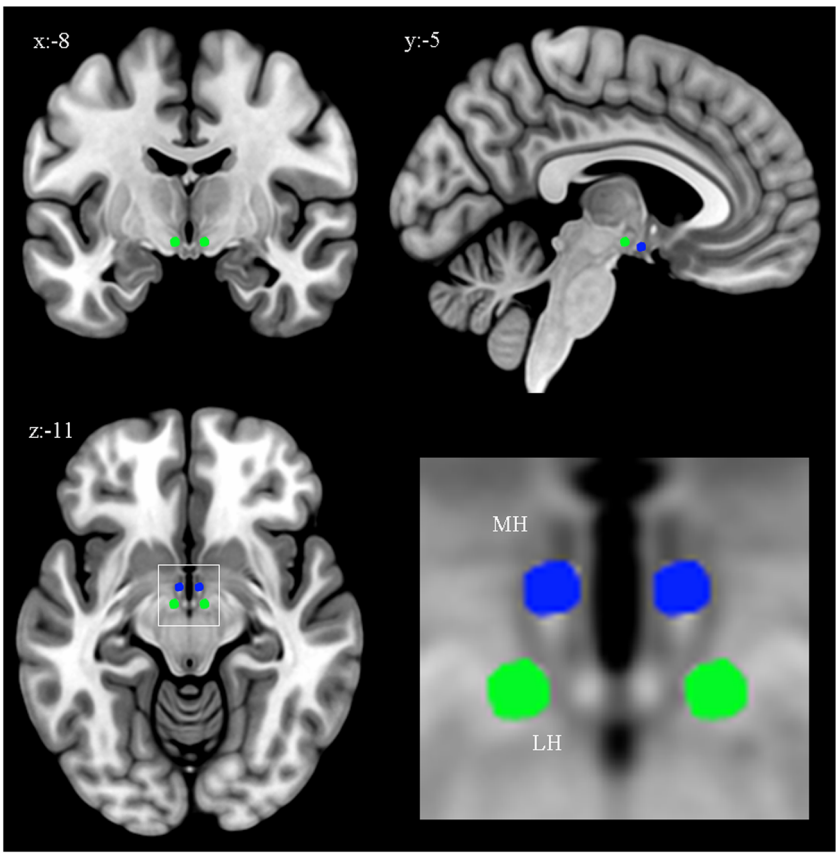

Fig. 1 Two sub-regions of hypothalamus used as seeds for FC analyses. Green represents the LH and blue represents the MH displayed on an anatomical template in the MNI space. Abbreviations: LH, lateral hypothalamus; MH, medial hypothalamus

weight controls (Table 1). The 17 post-surgical participants had recovered SBP, DBP, FG, triglyceride, and creatinine (Table 1).

Alterations of LH and MH Networks

In this study, the pre-surgical subjects had increased FC in the putamen, and decreased FC in the postcentral gyrus within the LH network compared to normal-weight subjects (Fig. 2a). Within the MH network, the pre-surgical subjects had disordered FC, revealing increased FC in the cerebellum and insula, as well as decreased FC in the prefrontal regions including inferior orbitofrontal cortex, middle frontal cortex, and superior medial frontal cortex (Fig. 3a).

No significant difference between the post-surgical FC and the normal-control FC was found within the LH network by two-sample *t* test (Fig. 2b). The post-surgical FC in the putamen within the LH network had significant decreased compared to the pre-surgery FC by paired *t* test, but not in the postcentral gyrus within the LH network (Fig. 2b). Compared to the pre-surgery FC in the putamen within the LH network, most of the post-surgical FC was decreased, only one post-surgical FC increased (Fig. 2b). Thus, the post-surgical subjects with obesity had recovered FC in the putamen within the LH network (Fig. 2). Within the MH network, no significant difference was found between subjects before and after the surgery (Fig. 3b). Most of the post-surgical FC had significant differences when compared to the normal-

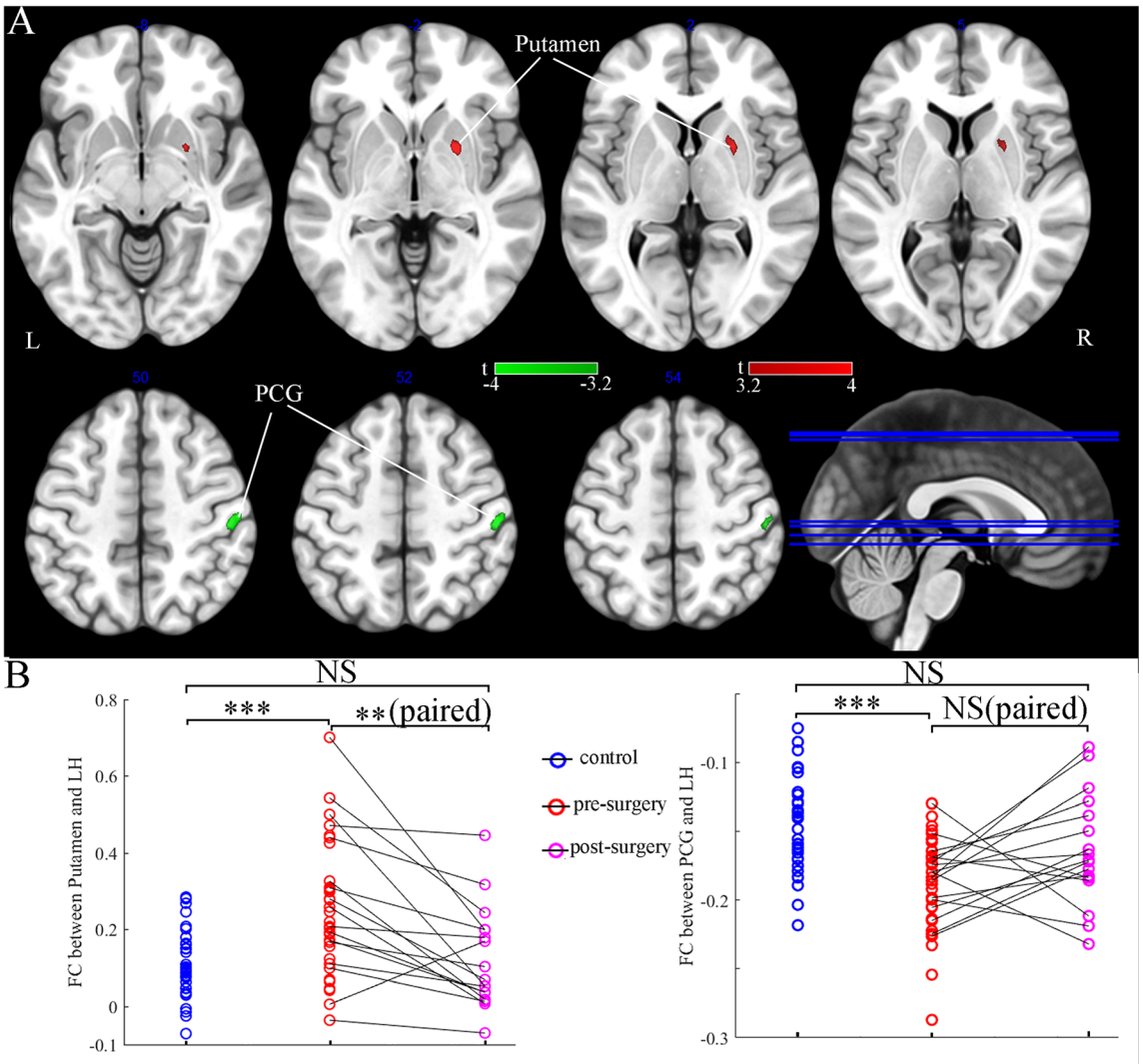

Fig. 2 Group differences in the LH network. **a** Voxel-wise difference between the pre-surgical subjects and the normal-weight controls. Color bar represents *t* value ($p < 0.001$ after Alphasim correction, cluster size bigger than 50 for display). Pre-surgical participants with obesity showed increased FC in the putamen and decreased FC in the postcentral gyrus. **b** Line graphs represent the mean FC across voxels within those clusters as presented in **a**. The difference between the pre-surgical subjects and post-surgical subjects was performed by paired *t* test, and the others were performed by two-sample *t* test. The recovery of the FC within the LH network can be reflected by the FC in the putamen within the LH network in each group. Abbreviation: FC, functional connectivity; LH, lateral hypothalamus; PCG, postcentral gyrus; L, left; R, right; NS, no significance. **: $P < 0.005$, ***: $P < 0.0001$

control FC (Fig. 3b). Furthermore, the FC changes before and after the surgery were close to random distribution. Therefore, the FC within the MH network was not recovered.

Associations Between Changes in FC and Metabolic Variables

Only the changes in FC of putamen within the LH network had significant association with changes in fasting glucose before and after the surgery (Fig. 4). The changes of the FC within the MH network did not show significant correlation with changes in metabolic parameters.

Discussion

For the first time, we assessed the effect of sleeve gastrectomy on the functional networks of two hypothalamic sub-regions in humans by resting-state fMRI. In this research, pre-surgical subjects with obesity showed altered FC within the LH network and the MH network. After the surgery, the FC of the putamen within the LH network was reversed, while not in the MH network. Meanwhile, the changes in FC of the putamen within the LH network were associated with changes in fasting glucose before and after the surgery. Taken together, our data suggests that alterations in the circuit of the LH associated with obesity may be reversed after the surgery.

Significance of the Found Alterations in FC

Some of the altered circuits within the networks of LH and MH were first found in subjects with obesity. The detected circuits in this research have been reported in the normal-weight group; however, only altered FC within the MH network was reported in a recent research [5]. In this research, we expanded the sample size and found group differences in the FC within the LH and

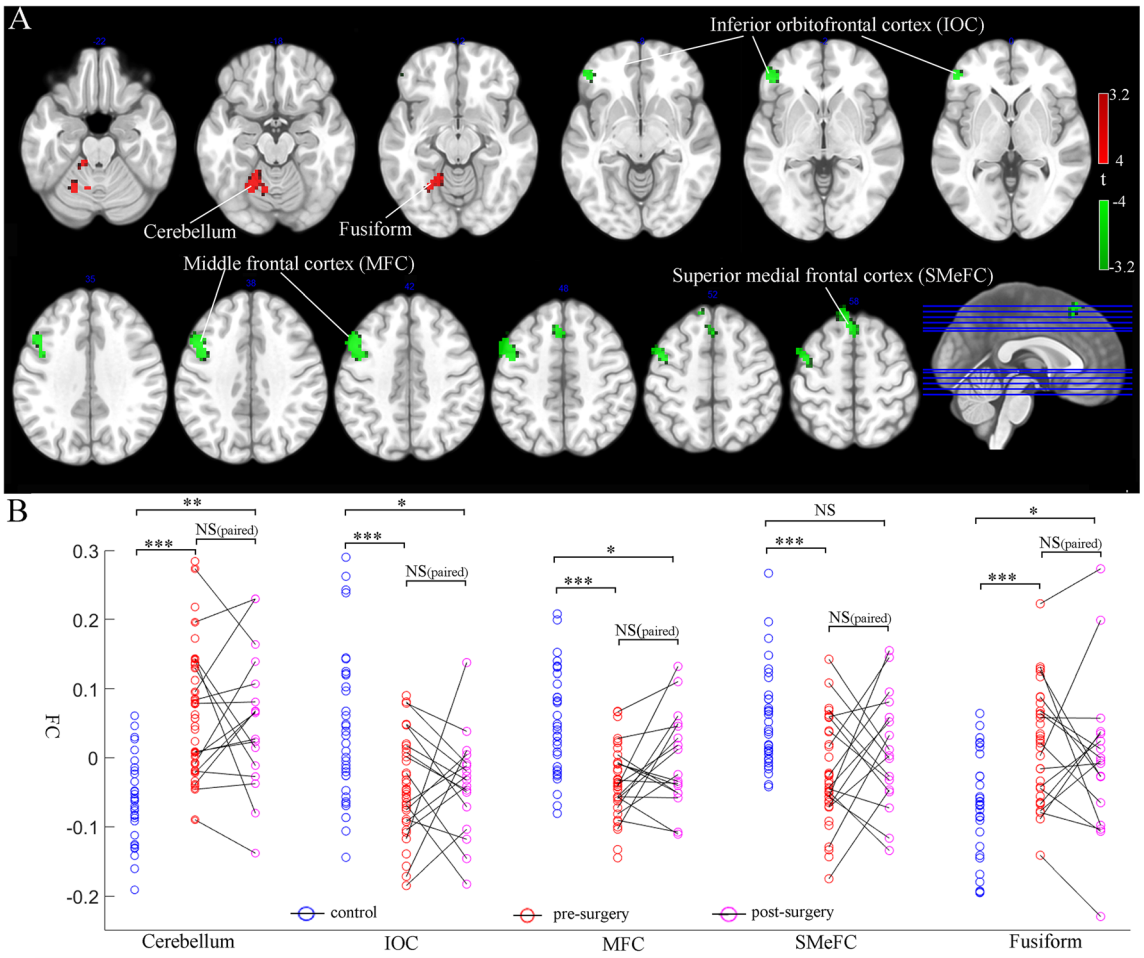

Fig. 3 Group differences in the MH network. **a** Voxel-wise difference between the pre-surgical subjects and the normal-weight controls. Pre-surgical participants showed increased FC in cerebellum and fusiform, as well as decreased FC in the inferior orbitofrontal cortex (IOC), middle frontal cortex (MFC), and superior medial frontal cortex (SMeFC). Color bar represents *t* value ($p < 0.001$ after Alphasim correction, cluster size bigger than 50 for display). **b** Line graphs represent the mean FC across voxels within those clusters as presented in **a**. The difference between the pre-surgical subjects and post-surgical subjects was performed by paired *t* test, and the others were performed by two sample *t* test. Abbreviation: FC, functional connectivity; MH, medial hypothalamus; NS, no significance. $^{*}P < 0.05$, $^{**}P < 0.005$, $^{***}P < 0.0001$

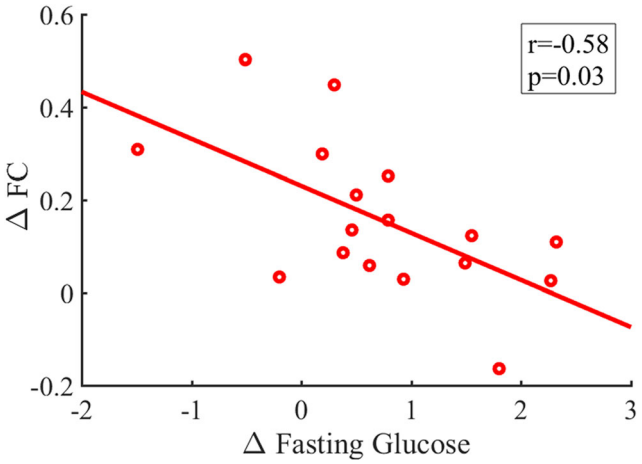

Fig. 4 Relationships between changes in FC and changes in metabolic parameters before and after the surgery. The Δ represents the changes before and after the surgery. The FC in this figure represents the functional connectivity between the putamen and lateral hypothalamus. The r and p represent the Pearson correlation coefficient and significance of the trend, respectively. The changes in FC of other regions did not show significant correlation ($p < 0.05$) with changes in metabolic parameters

MH networks. Brain regions within the LH network, the putamen is a part of striatum which is a main input structure of the basal ganglia and receives afferent projections from the orbitofrontal cortex [35, 36]. In function, the putamen is an important reward region whose dysfunction has been reported in subjects with obesity [37, 38]. The neuronal circuit between the LH and striatum has been found in rodent animals whose dysfunction is thought to involve in hedonic feeding [39, 40]. In addition, stimulating LH increases motivation and induces potent rewarding effects in food reward tasks [41]. The lateral hypothalamus is also a neural target for deep brain stimulation (DBS) in treatment of obesity [25, 26]. Furthermore, the activity of melanin-concentrating neurons in LH has been implicated in rewarding effects of sugar consumption by modulating striatal dopamine release [42]. Thus, it is possible that the increased FC between putamen and LH may relate to the disordered food reward regulation in subjects with obesity.

Brain regions within the MH network, the insula is a somatosensory cortical area [43, 44], and the prefrontal cortex is a cognitive control region [45]. Functional connectivity of them has been thought to involve in circuits motivating feeding, preventing overeating, and terminating feeding upon satiation [46], and functional disorder has been reported in these regions in subjects with obesity [47, 48]. These brain regions occurred frequently in previous obesity studies may indicate that they are related to obesity. More attention is needed to reveal the role of these altered FC in subjects with obesity.

Reversed FC After the Surgery

About 4 months after the surgery, the increased FC of the putamen within the LH network was reversed to the control category. Though each post-surgical participant had changed FC between the detected circuits when compared to themselves before the surgery, only significant difference was found in the FC between the putamen and LH before and after the surgery. This indicates that the reversion of the functional circuits between the putamen and LH is a meaningful physiological phenomenon not due to some useless noise interference. Furthermore, we gave out the change line of the FC for each participant before and after the surgery to exclude that the reversion of FC between the putamen and LH was caused by random error. Meanwhile, the metabolic parameters such as BMI, blood pressure, fasting glucose, triglyceride, and serum uric acid were also changed greatly though some of them were still in the obesity category. It seems that the reversion of brain function is independent of surgical procedures as the reversion has been reported by different surgical procedures [22, 27, 49, 50]. However, only Sande-Lee et al. examined the effect of bariatric surgery on the function of hypothalamus [22]. Our study extents these previous findings by suggesting that part of the altered LH network in subjects with obesity can be rescued by the surgery.

Although the reversion of brain function after the surgery appears to be likely, the acknowledgement about it is superficial as a lot of factors add up [51]. A possible viewpoint is that weight loss after the surgery reduces the neuroinflammation to rescue some aspects of defects in cognition and behavior [22, 50, 52, 53]. In addition, the reversion of some metabolic parameters including serum uric acid, SBP, DBP, triglyceride, and creatinine serum uric acid following the weight loss after the surgery may also affect the fMRI signal [51]. Furthermore, based on the result in correlation analysis, the post-surgical energy restriction could also affect central nervous processes, as post-surgical evaluation was performed at a time of major caloric restriction [28]. Except for these factors, gastrointestinal hormones especially ghrelin which is well known modulated by SLG [54, 55] can affect neural activities in hypothalamus [56, 57]. On the other hand, it may be argued that the reversed FC after the surgery can facilitate weight loss as the changed FC occurred in the homeostatic and reward circuitry [49, 58, 59]. Thus, it is possible that changed FC after the surgery is a complex neurological processing intertwined such as energy restriction, as well as changes in neuroinflammation, hormone, and metabolism after the surgery [28]. Perhaps in the future, more sophisticated studies will provide key insight into understanding the relationships between these changes.

Limitations

A limitation of the current study is that we only have one-time post-surgical scanning and small post-surgical sample size. Reduced post-surgical sample size may reduce the statistical power and increase type II error. Another limitation is the high inter-individual variability of FC as in most previous neuroimaging researches. This inter-individual variability may come from biological diversity as high inter-individual variability is also existent in the metabolic parameters. No matter how, high inter-individual variability may increase type II error. Therefore, we calculated the statistical power of the comparisons between the controls and post-surgical group. Luckily, paired *t* test reveals significant difference before and after the surgery, which suggests that the no significant difference between the control and the post-surgical participants is really due to the reversion of these variables, not by the type II error. However, bigger sample size will increase the power if we cannot control the inter-individual variability.

Conclusions

In summary, our data highlights that the FC within the LH and MH networks related to cognitive performance were altered in subjects with obesity. The altered FC of the putamen within the LH network could be rescued after the surgery.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Statement and Consent Statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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