Brain Imaging and Behavior (2019) 13:830–840
https://doi.org/10.1007/s11682-018-9904-2

ORIGINAL RESEARCH

Structural changes in brain regions involved in executive-control and self-referential processing after sleeve gastrectomy in obese patients

Li Liu[1] · Gang Ji[2] · Guanya Li[1] · Yang Hu[1] · Qingchao Jin[1] · Chunxin Hu[1] · Jizheng Zhao[3] · Qianqian Meng[1] · Karen M. von Deneen[1] · Antao Chen[4] · Guangbin Cui[5] · Huaning Wang[6] · Qingchuan Zhao[2] · Kaichun Wu[2] · Jie Tian[1,7] · Ehsan Shokri-Kojori[8] · Dardo Tomasi[8] · Nora D. Volkow[8] · Yongzhan Nie[2] · Yi Zhang[1] · Gene-Jack Wang[8]

Published online: 14 June 2018

Abstract

Obesity-related brain gray (GM) and white matter (WM) abnormalities have been reported in regions associated with food-intake control and cognitive-emotional regulation. Bariatric surgery (BS) is the most effective way to treat obesity and induce structural recovery of GM/WM density and WM integrity. It is unknown whether the surgery can promote structural changes in cortical morphometry along with weight-loss. Structural Magnetic Resonance Imaging and surface-based morphometry analysis were used to investigate BS-induced alterations of cortical morphometry in 22 obese participants who were tested before and one month post-BS, and in 21 obese controls (Ctr) without surgery who were tested twice (Baseline and One-month). Results showed that fasting plasma ghrelin, insulin, and leptin levels were significantly reduced post-BS ($P < 0.001$). Post-BS there were significant decreases in cortical thickness in the precuneus ($P_{FDR} < 0.05$) that were associated with decreases in BMI. There were also significant increases post-BS in cortical thickness in middle (MFG) and superior (SFG) frontal gyri, superior temporal gyrus (STG), insula and ventral anterior cingulate cortex (vACC); and in cortical volume in left postcentral gyrus (PostCen) and vACC ($P_{FDR} < 0.05$). Post-BS changes in SFG were associated with decreases in BMI. These findings suggest that structural changes in brain regions implicated in executive control and self-referential processing are associated with BS-induced weight-loss.

Keywords Obesity · Bariatric surgery · Cortical morphometry · Linear mixed effects

Li Liu and Gang Ji contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11682-018-9904-2) contains supplementary material, which is available to authorized users.

✉ Gang Ji
jigang@fmmu.edu.cn

✉ Yi Zhang
yizhang@xidian.edu.cn

✉ Gene-Jack Wang
gene-jack.wang@nih.gov

[1] Center for Brain Imaging, School of Life Science and Technology, Xidian University, Xi'an 710071, Shaanxi, China

[2] Xijing Gastrointestinal Hospital, The Fourth Military Medical University, No. 127 Changle West Road, Xi'an 710032, Shaanxi, China

[3] College of Mechanical and Electronic Engineering, Northwest A&F University, Yangling 712100, Shaanxi, China

[4] Department of Psychology, Southwest University, Chongqing 400715, China

[5] Department of Radiology, Tangdu Hospital, The Fourth Military Medical University, Xi'an 710038, Shaanxi, China

[6] Depart of Psychiatry, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, Shaanxi, China

[7] Institute of Automation, Chinese Academy of Sciences, Beijing 100190, China

[8] Laboratory of Neuroimaging, National Institute on Alcohol Abuse and Alcoholism, 10 Center Drive, MSC1013, Building 10, Room B2L304, Bethesda, MD 20892-1013, USA

Introduction

Bariatric surgery is currently the most effective treatment for combating morbid obesity and producing sustained long-term weight-loss (Sjostrom et al. 2007). Surgeries, such as laparoscopic sleeve gastrectomy (LSG), can cause profound changes in appetite-regulating peptides and neuroendocrine function (Diamantis et al. 2014). Notably, functional neuroimaging studies revealed alteration occurring in homeostatic and hedonic neurocircuits post-surgery (Frank et al. 2014; Lepping et al. 2015; Ochner et al. 2011, 2012; Steele et al. 2010; van de Sande-Lee et al. 2011; Wiemerslage et al. 2017). Aforementioned brain functional changes in obesity might be related to brain structural alterations (Hao et al. 2013). Only a limited number of structural imaging studies have been performed to examine bariatric surgery-induced alterations in brain anatomy (Tuulari et al. 2016; Zhang et al. 2016). Our recent study using diffusion tensor imaging and 3D-structural imaging revealed LSG surgery generated partial neuroplastic structural recovery (increased GM density and white-matter (WM) integrity) in regions associated with food-intake and cognitive-emotional regulation (Zhang et al. 2016). By using voxel-based morphometry, Tuulari et al. (2016) also reported that bariatric surgery and concomitant weight loss resulted in a global increase in WM density and a local increase in GM density including occipital and inferior temporal region.

However, brain structural imaging studies in obese patients have shown that obesity is also associated with cortical morphometric abnormalities. Several investigations using surface-based morphometry (Fischl and Dale 2000), which decomposes cortical GM volume into its constituent parts, revealed cortical thickness alterations in regions associated with the executive-control network (anterior cingulate cortex-ACC and middle frontal gyrus-MFG) and emotional regulation (superior frontal gyrus-SFG and insula), and in the temporal lobe (inferior temporal gyrus-ITG), somatosensory (precentral gyrus-PreCen, and postcentral gyrus-PostCen), self-referential processing (precuneus) and occipital visual cortices (occipital gyri) (Hassenstab et al. 2012; Kaur et al. 2015; Marques-Iturria et al. 2013; Medic et al. 2016; Sharkey et al. 2015; Veit et al. 2014). Association between body mass index (BMI) and cortical thickness/volume in a variety of brain regions were also reported (Kurth et al. 2013; Medic et al. 2016; Veit et al. 2014).

To help clarify the effects of bariatric surgery in cortical morphometry and its relation to weight loss, we employed structural MRI and surface-based morphometry analysis to quantify cortical thickness and volume in 22 obese patients prior to and at one-month after LSG surgery, and in 21 obese control individuals who did not undergo surgery. We hypothesized that LSG surgery would promote cortical morphometric changes in brain regions involved in executive control, somatosensory and self-referential processing.

Materials and methods

Subjects

Thirty-five morbidly obese patients were recruited for LSG surgery at Xijing Gastrointestinal Hospital affiliated to the Fourth Military Medical University in Xi'an, China. Patients with psychiatric/neurological diseases, previous intestinal surgery/inflammatory intestinal disease/organ dysfunction or taking any current medication that could affect the central nervous system were excluded. Obese individuals who had a waist circumference (WC) greater than the interior diameter of the scanner were excluded (Zhang et al. 2016). Given these criteria, six candidates were disqualified (one had a body weight more than 150 kg, three had metal implants, one decided not to have surgery, and one subject's imaging data were corrupted due to a technical problem). Twenty-nine remaining obese candidates (BS) completed the pre-surgical MRI scan (PreBS) and underwent LSG surgery (Vidal et al. 2013). The same MRI scans were performed one-month post-surgery (PostBS). Seven obese subjects reported having significant weight-loss after surgery via their local clinics. However, these subjects could not return for follow-up MRI assessment. Thus, 22 patients remained in the BS group. Twenty-one obese patients who did not receive LSG surgery were recruited as the control group (Ctr). The BS and Ctr group were matched for BMI, age, and gender ($P > 0.05$, Table 1). The Ctr group completed two identical MRI scans mirroring the BS group, one (CtrT) at baseline, and retest (CtrRT) one month later (1 Month Later). The experimental protocol was approved by the Institutional Review Board of Xijing Hospital and registered in the Chinese Clinical Trial Registry Center as ChiCTR-OOB-15006346 (http://www.chictr.org.cn). The experiments were conducted in accordance with the Declaration of Helsinki. All participants were informed of the nature of the research and provided written informed consent.

Experimental design

All participants underwent 12-h overnight fasting, and fasting blood samples were taken prior to MRI. MRI scans were performed between 9 to 10 AM to ensure consistency across assessment and to minimize circadian influence.

Peripheral hormone measurements

In the BS group, blood samples were collected in EDTA-coated tubes before and one month after surgery and were immediately mixed with protease inhibitors, such as dipeptidylpeptidase IV inhibitor (Millipore) and phenylmethanesulfonyl fluoride (Sigma). After being

Table 1 Demographic and clinical information of obese subjects in both BS and Ctr groups

	PreBS (22) (Mean ± SE)	PostBS (22) (Mean ± SE)	CtrT (21) (Mean ± SE)	CtrRT (21) (Mean ± SE)	PreBS vs. CtrT *P*
Age (yrs)	27.14 ± 1.76	27.14 ± 1.76	29.90 ± 2.09	29.90 ± 2.09	0.326
Gender	10 M/12F	10 M/12F	14 M/7F	14 M/7F	0.161
Duration of Obesity (yrs)	11.59 ± 1.37	11.59 ± 1.37	13.24 ± 1.54	13.24 ± 1.54	0.439
Weight (kg)	110.15 ± 3.78	98.26 ± 3.80	104.28 ± 3.69	103.35 ± 3.59	0.285
BMI (kg/m^2)	38.45 ± 1.12	34.10 ± 1.18	35.85 ± 0.98	35.69 ± 0.96	0.094
WC (cm)	118.55 ± 2.97	110.25 ± 2.89	114.83 ± 2.33	113.62 ± 2.10	0.345
Food Intake (kg/meal)	0.62 ± 0.08	0.19 ± 0.02	0.52 ± 0.05	0.52 ± 0.05	0.326
YFAS	5.18 ± 0.50	2.68 ± 0.42	4.28 ± 0.77	4.05 ± 0.65	0.340
HAMD	12.09 ± 2.16	11.32 ± 1.71	9.93 ± 1.63	8.62 ± 1.81	0.439
HAMA	10.36 ± 1.69	7.91 ± 1.42	8.73 ± 1.63	7.00 ± 1.33	0.501

BMI, body mass index; *WC*, waist circumference; *YFAS*, Yale Food Addiction Scale; *HAMD*, Hamilton Depression Rating Scale; *HAMA*, Hamilton Anxiety Rating Scale; *BS*, obese candidates for bariatric surgery who had image-scan at baseline (PreBS) and again one month after surgery (PostBS); *Ctr*, obese subjects who did not receive bariatric surgery and had image-scan at baseline (CtrT), and one month after the first scan (CtrRT); *SE*, standard error

centrifuged at 1400×g per 10 min at 4 °C, the supernatants were stored at −80 °C until assayed (Vitaglione et al. 2015). Plasma concentrations of total ghrelin, insulin, and leptin were measured using a Bio-Plex 200™ suspension array system (BIO-RAD, Inc., Hercules, California, USA).

Questionnaires

A designated clinician rated the severity of subjects' anxiety using the Hamilton-Anxiety-Rating-Scale (Hamilton 1959), and depression using the Hamilton-Depression-Rating-Scale (Hamilton 1960). Subjects were required to complete the Yale-Food-Addiction-Scale (YFAS) evaluation (Gearhardt et al. 2009) (Table 1), which has been validated in a bariatric surgery population (Clark and Saules 2013). All clinical measurements were identically conducted before /baseline and one month after surgery/baseline in the BS/Ctr groups, and the same surgeon performed all surgical procedures.

MRI acquisition

The experiment was carried out using a 3.0 T GE Signa Excite HD MRI scanner (GE, Milwaukee, WI, USA). The high-resolution structural images for each subject were acquired using a T1-weighted three-dimensional magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequences with the following parameters: TR = 7.8 ms, TE = 3.0 ms, flip angle =20°, matrix size = 256 × 256, field of view = 256 × 256 mm^2, voxel size = 1 × 1 × 1 mm^3, slice thickness = 1 mm and 166 slices. A radiologist examined the imaging data to rule out abnormalities in brain structure.

Image processing

T1-weighted images were processed with the well documented and freely available FreeSurfer image analysis suite (Version 5.3.0, http://surfer.nmr.mgh.harvard.edu/), which is a set of automated programs used for surface-based cortical reconstruction and measurement (Dale et al. 1999; Fischl and Dale 2000; Fischl et al. 1999). First, several steps including non-brain tissue removal, Talairach-like space segmentation of GM/WM tissues transformation, intensity normalization, GM/WM boundaries tessellation, automatic topology correction and surface deformation were done using the toolkit (Fischl et al. 2004; Segonne et al. 2004). Then, deformable procedures such as surface inflation, spherical atlas registration, cerebral cortical parcellation and surface creation were executed following intensity gradients to optimally place the gray/white and gray/CSF borders (Fischl and Dale 2000; Fischl et al. 1999).

In order to reduce the confounding effect of inter-individual morphological variability, we introduced a longitudinal design which used each subject as his or her own control (http://surfer.nmr.mgh.harvard.edu/fswiki/LongitudinalProcessing). The longitudinal stream in FreeSurfer used robust, inverse and consistent registration to create an unbiased within-subject template space and image (Reuter and Fischl 2011; Reuter et al. 2010). Processing steps included skull stripping, Talairach transformation, and atlas registration; spherical surface maps and parcellations were then initialized with basic information from the within-subject template, significantly increasing reliability and statistical power (Reuter et al. 2012). The cortical data were estimated for each cerebral hemisphere at each time point separately and smoothed using a 10-mm full-width-half-maximum Gaussian kernel. All images were processed with the same hardware and version to avoid potential confounds.

Statistical analyses

Demographic and clinical variables were conducted using SPSS Statistics (Version 22, IBM) for the analyses. Two sample *t*-tests were used to examine the difference between BS and Ctr groups at baseline. A two-way ANOVA was implemented to model the effects of group (BS, Ctr) and time (Baseline, 1 Month Later) on behavioral/clinical data. T-tests were utilized as post-hoc tests where ANOVA indicated significant interaction effects.

Baseline comparison analyses

Baseline comparisons of global brain measures were performed using analysis of covariance (ANCOVA) in SPSS software between the BS and Ctr group by controlling for age and gender.

Longitudinal analyses

We employed a linear mixed effects (LME) model, which is a standard analysis approach for longitudinal data that correctly models the mean and covariance structure of repeated measures within participants and across assessments (Bernal-Rusiel et al. 2013), to estimate the LSG effects of group (BS, Ctr) × time (Baseline, 1 Month Later) on cortical morphology using FreeSurfer LME MATLAB tools (http://surfer.nmr.mgh.harvard.edu/fswiki/LinearMixedEffectsModels; Freesurfer Version 5.3.0; MATLAB Version 2013b, The MathWorks, Natick, MA, USA). LME model was fitted in each vertex across the reconstructed cortical thickness or volume as the dependent variable and intercept, group (Ctr = 0, BS = 1), time (Baseline = 0, 1 Month Later = 1), interaction (group × time), and age/gender as covariates; intercept as random factor. Contrast vector was set in order to test for an interaction effect between group and time. To correct for multiple comparisons, the two p-maps both from the left and right hemispheres were combined and thresholded to yield an expected false discovery rate (FDR) of 0.05 (Benjamini et al. 2006). Clusters with significant interaction effects were defined as the regions of interests (ROIs), which were mapped on the Desikan-Killiany atlas including thirty-four regions in each hemisphere (Desikan et al. 2006). The values of the cortical thickness or volume in ROIs were extracted respectively across all subjects and then paired *t*-tests were utilized as post-hoc tests.

Association between behaviors and cortical morphology

A partial correlation analysis with age and gender as covariates was performed to assess the cortical thickness or volume in ROIs with significant interaction effects and clinical measurements with significant interaction effects. We also performed a correlation analysis between changes in cortical morphology in these ROIs and changes in clinical measurements (BMI, ghrelin, insulin, leptin). Bonferroni-correction was applied for multiple-comparisons, and level of significance was set at $P < 0.0021(0.05/24)$.

Results

Demographic characteristics

At baseline, there were no significant differences in age, gender, duration of obesity, weight, BMI, WC, food-intake, YFAS, HAMD and HAMA between the BS and Ctr groups ($P > 0.05$, Table 1). There were significant group × time interaction effects for weight ($F(1, 41) = 123.9$, $P < 0.001$), BMI ($F(1, 41) = 119.0$, $P < 0.001$) and WC ($F(1, 41) = 12.9$, $P < 0.001$) due to significant weight-loss (t (1,21) = −12.3, $P < 0.001$), reduction of BMI (t(1,21) = −12.2, $P < 0.001$) and WC (t (1,21) = −6.1, $P < 0.001$) in the BS group but not in the Ctr group. There were significant interaction effects in food-intake ($F(1, 41) = 17.2$, $P < 0.001$) and YFAS ($F(1, 41) = 9.7$, $P = 0.003$), due to decreased food-intake (t(1,21) = −4.8, $P < 0.001$) and YFAS score (t (1,21) = −4.1, $P < 0.001$) in the BS group post-surgery, but not in the Ctr group (Supplementary Table 1).

Peripheral hormone measurements

In the BS group, fasting plasma total ghrelin levels were negatively correlated with BMI ($r = -0.50$, $P = 0.017$, Fig. 1A) and fasting plasma leptin levels were positively correlated with BMI ($r = 0.45$, $P = 0.034$, Fig. 1B) before LSG. After surgery, plasma total ghrelin, insulin, and leptin levels were lower than before surgery ($P < 0.001$, Fig. 1C-E).

Baseline global brain measures

There were no differences in intracranial volume, total gray matter, cortical gray matter, white matter volume, surface area or mean cortical thickness in the whole brain between the BS and Ctr groups ($P > 0.05$, Table 2).

Alterations of cortical morphology

There were significant interaction effects (group × time) on cortical thickness in the insula, superior temporal gyrus (STG), middle frontal gyrus (MFG) in the left hemisphere and superior frontal gyrus (SFG), ventral anterior cingulate cortex (vACC), precuneus in the right hemisphere ($P_{FDR} < 0.05$, Fig. 2, Table 3). Post-hoc tests showed significant increases in cortical thickness in the insula, MFG, STG, SFG and vACC, and significant decreases in precuneus in the BS

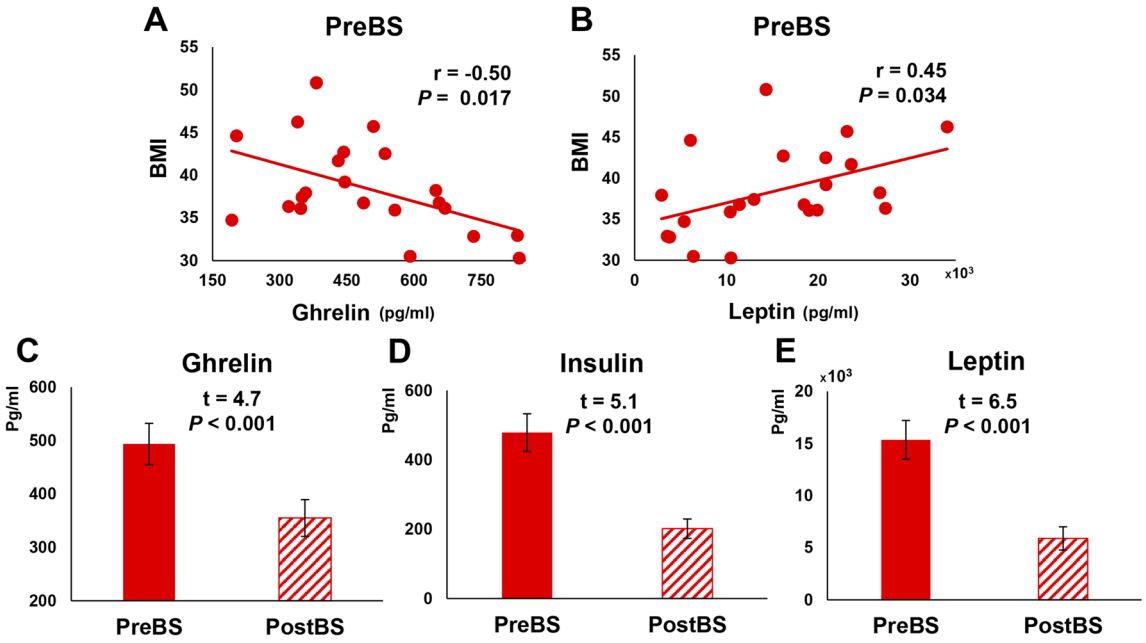

Fig. 1 The alterations of plasma peripheral hormones before and after LSG surgery and the correlation between peripheral hormones and behavioral measurements. **A** In the PreBS group, fasting plasma ghrelin levels were negatively correlated with BMI. **B** In the PreBS group, fasting plasma leptin levels were positively correlated with BMI. **C**-**E** Ghrelin, insulin, and leptin levels were lower than before surgery. Abbreviations: LSG, laparoscopic sleeve gastrectomy; BMI, body mass index; PreBS, obese patients who received MRI scan before surgery; PostBS, obese patients who received MRI scan at one month after surgery

group post-surgery. The Ctr group did not show significant changes in cortical thickness one month after baseline imaging (Fig. 2, Supplementary Table 2).

Similarly, there were significant interaction effects (group × time) on cortical volume in the left postcentral gyrus (PostCen) and right vACC ($P_{FDR} < 0.05$, Fig. 3, Table 3). Post-hoc tests showed significant increases in cortical volume in the two regions post-surgery in the BS but not in the Ctr group one-month post-baseline (Fig. 3, Supplementary Table 2).

Table 2 Global brain measures comparisons between the obese subjects in both BS and Ctr groups

	PreBS (Mean ± SE)	CtrT (Mean ± SE)	*F*	*P*
ICV(cm^3)	1550.41 ± 33.49	1618.19 ± 31.28	0.908	0.346
Total GM(cm^3)	627.33 ± 12.92	652.82 ± 12.54	0.808	0.374
Cortical GM(cm^3)	466.09 ± 10.69	483.78 ± 10.56	0.385	0.539
White matter(cm^3)	429.10 ± 9.92	449.51 ± 11.61	0.626	0.434
Surface area(cm^2)	1599.21 ± 30.05	1642.03 ± 35.95	0.052	0.820
Mean thickness (mm)	2.59 ± 0.03	2.64 ± 0.02	1.727	0.196

BS, obese candidates for bariatric surgery who had image-scan at baseline (PreBS); *Ctr*, obese subjects who did not receive bariatric surgery and had image-scan at baseline (CtrT); *ICV*, intracranial volume; *GM*, gray matter; *SE*, standard error

Clinical measurement correlation at baseline and post-surgery

At baseline, BMI was significantly correlated with cortical thickness in SFG in the BS (PreBS) ($r(21) = -0.64$, $P = 0.001$, uncorrected) and Ctr ($r(20) = -0.65$, $P = 0.001$, uncorrected, Fig. 4A) groups. Baseline BMI was also correlated with cortical volume in left PostCen in the BS (PreBS) ($r(21) = -0.63$, $P = 0.002$, uncorrected) and Ctr ($r(20) = -0.66$, $P = 0.001$, uncorrected, Fig. 4B) groups. Correlation between baseline fasting peripheral hormone levels with cortical morphology in the BS group showed that plasma total ghrelin levels were positively correlated with cortical volume in PostCen (Supplementary Fig. 1A). The correlation did not survive after correction for multiple comparisons.

Correlation analyses between the changes in the clinical measures and those in the brain following BS surgery revealed a positive correlation between cortical thickness in the precuneus in the BS group before and after surgery ($r(21) = 0.64$, $P = 0.001$, uncorrected, Fig. 4C). Changes in BMI were negatively correlated with changes in cortical thickness in SFG ($r(21) = -0.61$, $P = 0.003$, uncorrected, Fig. 4D) such that the greater the increases the larger the BMI losses. In addition, changes in fasting plasma leptin levels were also negatively correlated with changes in cortical thickness in SFG, which did not survive in the correction for multiple comparisons (Supplementary Fig. 1B).

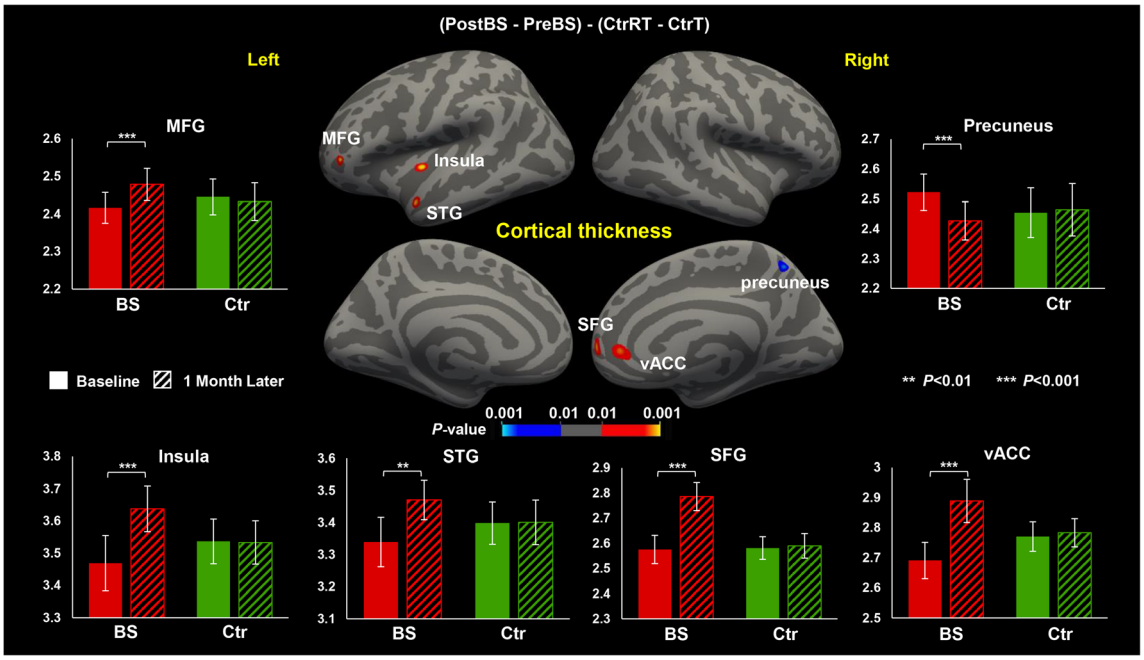

Fig. 2 Interaction effects (Group × Time) for cortical thickness (vertex size-corrected, $P_{FDR} < 0.05$). There were significant interaction effects (Group × Time) on cortical thickness in the insula, STG, MFG and SFG in the left hemisphere and vACC and precuneus in the right hemisphere. BS group after surgery had increased cortical thickness in the insula, STG, MFG, SFG and vACC and decreased in the precuneus. Ctr group did not show significant cortical thickness changes. The error bars are the standard error. Abbreviation: STG, superior temporal gyrus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; vACC, ventromedial anterior cingulate cortex; BS, obese candidates for bariatric surgery who had image-scan at baseline (PreBS) and again one month after surgery (PostBS); Ctr, obese subjects who did not receive bariatric surgery and had image-scan at baseline (CtrT), and one month after the first scan (CtrRT)

Discussion

In the current study, we showed that LSG significantly decreased fasting plasma total ghrelin, insulin and leptin levels, and decreased cortical thickness in the precuneus, which is a brain region involved with self-referential processing. LSG also increased cortical thickness in regions associated with executive-control (MFG, vACC), emotion (SFG), interoception (insula), and visual processing (STG); and increased cortical volume in regions associated with somatosensory processing (left PostCen) and vACC. Additionally, we showed that post-BS decreases in BMI were associated with

Table 3 Interaction effects (Group × Time) for cortical thickness and volume (vertex size-corrected, $P_{FDR} < 0.05$)

ROIs	lh/rh	BA	Size(mm^2)	Nvtxs	Peak talairach coordinates			Peak P-value
					X	Y	Z	
Cortical thickness: (PostBS - PreBS) - (CtrRT - CtrT)								
Insula	lh	48	72.72	155	−34.4	−17.3	−3.1	0.0006
STG	lh	38	92.15	138	−51.6	5.8	−16.0	0.0011
MFG	lh	47	63.79	89	−39.4	37.6	−1.3	0.0011
SFG	rh	10	112.43	144	10.8	52.6	1.7	0.0015
vACC	rh	11	109.41	216	9.9	38.4	−1.1	0.0018
Precuneus	rh	7	75.06	209	7	−53.4	51.1	0.0017
Cortical volume: (PostBS - PreBS) - (CtrRT - CtrT)								
PostCen	lh	3	32.75	79	−26.5	−21.3	48.9	0.0016
vACC	rh	11	85.25	177	13.0	38.6	−2.0	0.0009

ROIs, regions of interest; *lh/rh*, left hemisphere or right hemisphere; *BA*, Brodmann Area; *Nvtxs*, number of vertices; *BS*, obese candidates for bariatric surgery who had image-scan at baseline (PreBS) and again one month after surgery (PostBS); *Ctr*, obese subjects who did not receive bariatric surgery and had image-scan at baseline (CtrT), and one month after the first scan (CtrRT); *STG*, superior temporal gyrus; *MFG*, middle frontal gyrus; *SFG*, superior frontal gyrus; *vACC*, ventromedial anterior cingulate cortex; *PostCen*, postcentral gyrus

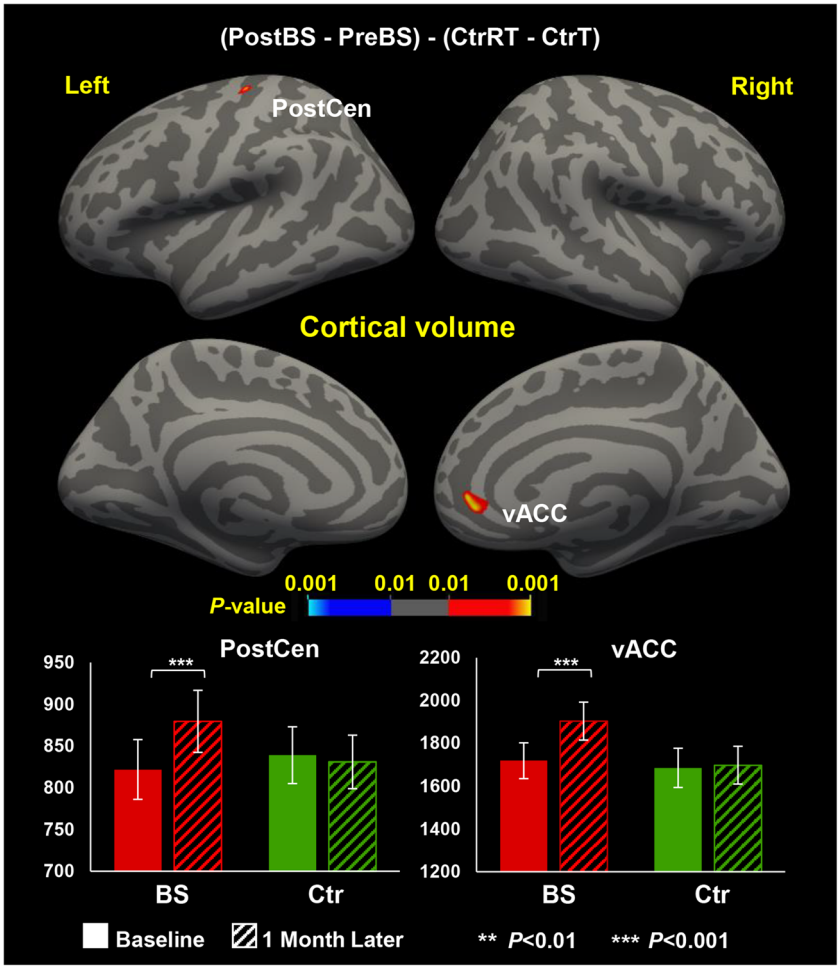

Fig. 3 Interaction effects (Group × Time) for cortical volume (vertex size-corrected, $P_{FDR} < 0.05$). There were significant interaction effects (Group × Time) on cortical volume in the postcentral in the left hemisphere and vACC in the right hemisphere. BS group after surgery had increased cortical volume in postcentral and vACC. Ctr group did not show significant cortical volume changes. The error bars are the standard error. Abbreviations: vACC, ventromedial anterior cingulate cortex; PostCen, postcentral gyrus; BS, obese candidates for bariatric surgery who had image-scan at baseline (PreBS) and again one month after surgery (PostBS); Ctr, obese subjects who did not receive bariatric surgery and had image-scan at baseline (CtrT), and one month after the first scan (CtrRT)

increases in cortical thickness in SFG and with decreases in cortical thickness in precuneus.

Alterations in regions associated with emotional regulation

Results showed LSG increased cortical thickness in the SFG. SFG plays a critical role in emotional/behavioral functions that may affect appetite, and it is a core brain region for value-based decision-making (Killgore et al. 2013; Weilbacher and Gluth 2016) and plays a unique role in cognitive control (Hu et al. 2016). SFG also monitors visceral signals and guides reward-related behaviors (Vogt 2005). At baseline, both BS and Ctr groups exhibited a negative correlation between BMI and cortical thickness in SFG, suggesting that the higher the BMI the thinner the cortical thickness in SFG in the brain of obese individuals. The negative association between surgery-induced changes in BMI and cortical thickness in the SFG suggested that the greater the reduction in BMI post-surgery the greater the increase in cortical thickness in SFG. Dysregulation of leptin has also been associated with reduced cortical thickness in both human and animal models (Pannacciulli et al. 2007) and some studies suggested that leptin might exert its appetite-regulating effect at least in part by interacting with the mesolimbic pathways (Grosshans et al. 2012; Makaronidis and Batterham 2018). Though one could, therefore, posit that leptin decreases post-BS could contribute to the increases in cortical thickness in SFG, the correlation between them was not significant (Supplementary Fig. 1B). The lack of a correlation could reflect additional changes in leptin signaling (i.e. tolerance reversal) post-BS that are not captured by the measurement of plasma leptin levels (Bluher and Mantzoros 2009). Surgery-induced cortical thickness change in the SFG might help to increase its ability in responding to visceral signal and regulating reward-related eating behaviors.

Alterations in regions associated with executive-control

LSG increased cortical thickness in MFG and vACC, consistent with previous studies reporting that obese patients had decreased cortical thickness in these brain regions (Hassenstab et al. 2012; Marques-Iturria et al. 2013). The MFG is involved in motivation/drive, salience attribution, and

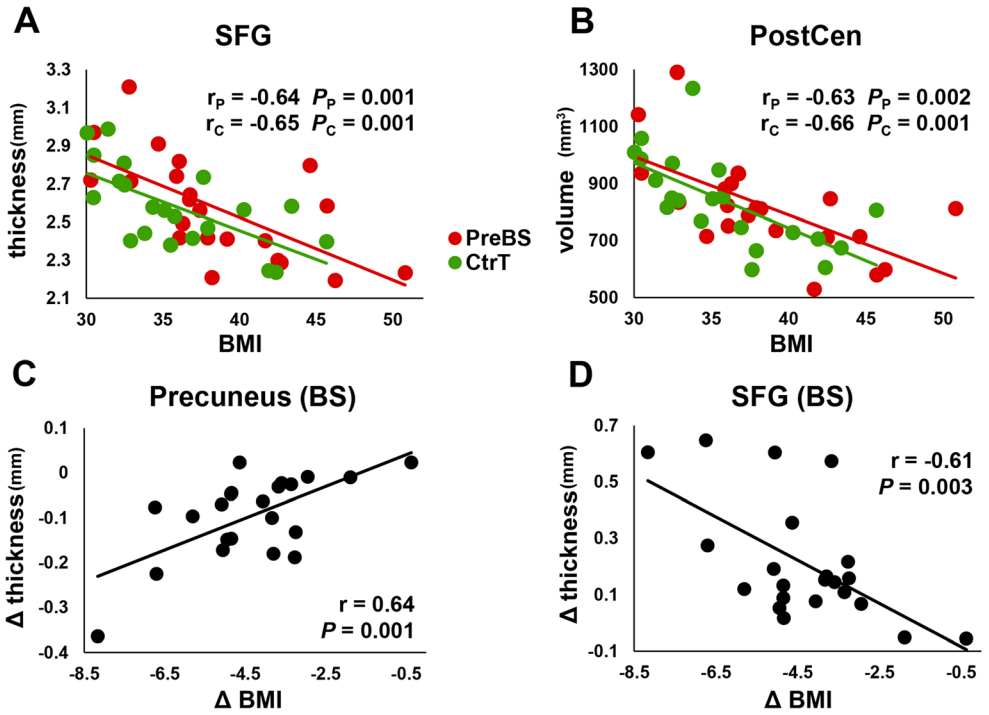

Fig. 4 Correlation analysis between behavioral measurements and cortical morphology. **A** BMI was significantly negatively correlated with cortical thickness in the SFG in the BS group before surgery and at baseline in the Ctr group. **B** BMI was significantly negatively correlated with cortical volume in the PostCen in the BS group before surgery and at baseline in the Ctr group. **C** Changes in BMI were positively correlated with changes in cortical thickness in the precuneus. **D** Changes in BMI were negatively correlated with changes in cortical thickness in the SFG. Abbreviations: SFG, superior frontal gyrus; PostCen, postcentral gyrus; PreBS, obese candidates for surgery who received image-scan before surgery; CtrT, obese subjects who did not receive bariatric surgery at baseline; BMI, body mass index

output of compulsive behaviors (Volkow and Fowler 2000) tracking the subjective pleasantness of stimuli (Grabenhorst and Rolls 2009) and contributing to decision-making processes involving pleasure/reward (Grabenhorst and Rolls 2011). The MFG also receives visceral sensory information and thus the removal of the gastric fundus by LSG might contribute to the MFG structural changes (Fig. 2, Supplementary Table 2). This, in turn, might improve the MFG modulation for better control over stronger urges to eat (Li et al. 2010). ACC is implicated in the executive-control of internal/external stimuli, and context-dependent behaviors involving evaluation of salience of emotional information and modulation of the emotional response (Bush et al. 2000; Cohen et al. 2005; Li et al. 2010). Impaired ACC function may contribute to an imbalance between cognitive/emotional processing and consequentially an increased risk of overeating (Cohen et al. 2005; Kullmann et al. 2012; Li et al. 2010). Significant increases in cortical thickness in vACC might be related to an enhanced ability to govern emotional regulation post-BS (Wallis et al. 2017).

Alterations in regions associated with self-referential processing

LSG decreased cortical thickness in the precuneus, which is a region associated with self-referential processing involving diverse functions linked with eating behaviors and obesity. The precuneus plays a critical role in appetite control such as evaluating benefits of not eating compared to eating high-calorie food (Yokum and Stice 2013). The precuneus is also involved in obesity-inducing/preventing behavior through self-body consciousness as well as body weight control, whose failure can be manifested as obesity (Nakamura and Ikuta 2017). Prior findings of a positive correlation between cortical thickness in the precuneus/posterior cingulate cortex and visceral fat volume (Kaur et al. 2015) were consistent with our findings showing a positive association between BMI and cortical thickness in the precuneus in obese subjects (Fig. 4C). LSG-was associated with reduction in cortical thickness in the precuneus. The positive association between changes in precuneus thickness and changes in BMI indicates that alterations of cortical morphometry within the default-mode network could be related to improvements in consciousness and self-referential processing associated with weight-loss post-LSG.

Alterations in regions associated with interoception

The insular cortex is involved in the interceptive sense of the body and in emotional awareness (Craig 2011). Prior studies used balloon extension to mimic gastric distension during normal food-intake showing activation of the insula while

supporting its role in the awareness of body state (Wang et al. 2008). Evidence indicated that reduced awareness of the bodily state and appetite signaling might cause obese individuals to consume more food to respond to interoceptive cues (Frank et al. 2013), and adiposity might interfere with the normal perception of interoceptive signals (Mata et al. 2015). Although we did not include a normal weight control group that would have allowed us to assess the thickness in the insula, which was decreased in obese patients before surgery, its increase after surgery suggests that increases in cortical thickness in obesity might contribute to weight loss.

Alterations in visual processing regions

STG has been involved in the perception of emotions in facial stimuli and has been linked to many cognitive processes including semantic memory, language, visual perception and sensory integration. STG is also more active during exposure to food-cues (Ojemann et al. 2002). LSG surgery increased cortical thickness in the left STG in the BS group which may reflect the role of surgery to induce structural changes in regions associated with visual processing.

Alterations in somatosensory regions

PostCen is the location of the primary somatosensory cortex (S1) and is the main sensory receptive area for the sense of touch (Freund 2003; Kim et al. 2014). Obesity is linked to alterations in somatosensory processing of reward feedback (Navas et al. 2017; Pleger et al. 2008), and prior studies showed that obese subjects had abnormally increased S1 metabolism at baseline (Wang et al. 2002). Our data showed a negative correlation between BMI and baseline cortical volume in the left PostCen, indicating that the higher the BMI the smaller the cortical volume in the left PostCen, and LSG induced increased cortical volume.

Limitations

Due to strict exclusion criteria and difficulty in retaining patients' post-surgery for follow-up scanning, we did not have a larger cohort for the BS group pre- and post-surgery including the controls. We assessed obese participants at two time points only. However, multiple time-point assessments are warranted for future investigations on the progression of brain structural changes after surgery. It would have also been desirable to include a group of normal weight participants which would have allowed us to assess if there were differences in brain structure between obese and healthy weight individuals and whether LSG normalized those differences. These factors limit the generalizability of our results.

Conclusion

This study investigated the alterations of cortical morphometry after LSG and found decreased cortical thickness in precuneus involving self-referential processing, increased cortical thickness in regions associated with executive control (MFG, vACC), emotion (SFG), interoception (insula), and visual processing (STG); and increased cortical volume in regions associated with somatosensory processing (left PostCen) and vACC. Changes in BMI were negatively correlated with changes in cortical thickness in SFG and positively correlated with changes in cortical thickness in precuneus. These findings suggest that structural changes in brain regions implicated in executive control and self-referential processing are associated with BS-induced weight-loss.

Acknowledgements This work is supported by the National Natural Science Foundation of China under Grant Nos. 61431013, 81470816, 81501543, 81601563, and 81730016; National Clinical Research Center for Digestive Diseases, Xi'an, China under Grant No. 2015BAI13B07; and support in part from the Intramural Research Program of the United States National Institute on Alcoholism and Alcohol Abuse, Z01AA3009 (ESK, DT, NDV, GJW). We thank Mingzhu Xu and Long Qian for their contribution to the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical statements Informed consent was obtained from all patients included in the study.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

References

Benjamini, Y., Krieger, A. M., & Yekutieli, D. (2006). Adaptive linear step-up procedures that control the false discovery rate. *Biometrika, 93*(3), 491–507.

Bernal-Rusiel, J. L., Greve, D. N., Reuter, M., Fischl, B., & Sabuncu, M. R. (2013). Statistical analysis of longitudinal neuroimage data with linear mixed effects models. *Neuroimage, 66*, 249–260.

Bluher, S., & Mantzoros, C. S. (2009). Leptin in humans: Lessons from translational research. *American Journal of Clinical Nutrition, 89*(3), 991S–997S.

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences, 4*(6), 215–222.

Clark, S. M., & Saules, K. K. (2013). Validation of the Yale food addiction scale among a weight-loss surgery population. *Eating Behaviors, 14*(2), 216–219.

Cohen, M. X., Heller, A. S., & Ranganath, C. (2005). Functional connectivity with anterior cingulate and orbitofrontal cortices during decision-making. *Cognitive Brain Research, 23*(1), 61–70.

Craig, A. D. (2011). Significance of the insula for the evolution of human awareness of feelings from the body. *Annals of the New York Academy of Sciences, 1225*, 72–82.

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage, 9*(2), 179–194.

van de Sande-Lee, S., Pereira, F. R., Cintra, D. E., Fernandes, P. T., Cardoso, A. R., Garlipp, C. R., Chaim, E. A., Pareja, J. C., Geloneze, B., Li, L. M., et al. (2011). Partial reversibility of hypothalamic dysfunction and changes in brain activity after body mass reduction in obese subjects. *Diabetes, 60*(6), 1699–1704.

Desikan, R. S., Segonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., et al. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage, 31*(3), 968–980.

Diamantis, T., Apostolou, K. G., Alexandrou, A., Griniatsos, J., Felekouras, E., & Tsigris, C. (2014). Review of long-term weight loss results after laparoscopic sleeve gastrectomy. *Surgery for Obesity and Related Diseases, 10*(1), 177–183.

Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceeding of the National Academy Sciences United States of America, 97*(20), 11050–11055.

Fischl, B., Sereno, M. I., & Dale, A. M. (1999). Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *Neuroimage, 9*(2), 195–207.

Fischl, B., Salat, D. H., van der Kouwe, A. J., Makris, N., Segonne, F., Quinn, B. T., & Dale, A. M. (2004). Sequence-independent segmentation of magnetic resonance images. *Neuroimage, 23*(Suppl 1), S69–S84.

Frank, S., Kullmann, S., & Veit, R. (2013). Food related processes in the insular cortex. *Frontiers in Human Neuroscience, 7*, 499.

Frank, S., Wilms, B., Veit, R., Ernst, B., Thurnheer, M., Kullmann, S., Fritsche, A., Birbaumer, N., Preissl, H., & Schultes, B. (2014). Altered brain activity in severely obese women may recover after roux-en Y gastric bypass surgery. *International Journal of Obesity (London), 38*(3), 341–348.

Freund, H. J. (2003). Somatosensory and motor disturbances in patients with parietal lobe lesions. *Advances in Neurology, 93*, 179–193.

Gearhardt, A. N., Corbin, W. R., & Brownell, K. D. (2009). Preliminary validation of the Yale food addiction scale. *Appetite, 52*(2), 430–436.

Grabenhorst, F., & Rolls, E. T. (2009). Different representations of relative and absolute subjective value in the human brain. *Neuroimage, 48*(1), 258–268.

Grabenhorst, F., & Rolls, E. T. (2011). Value, pleasure and choice in the ventral prefrontal cortex. *Trends in Cognitive Sciences, 15*(2), 56–67.

Grosshans, M., Vollmert, C., Vollstadt-Klein, S., Tost, H., Leber, S., Bach, P., Buhler, M., von der Goltz, C., Mutschler, J., Loeber, S., et al. (2012). Association of leptin with food cue-induced activation in human reward pathways. *Archives of General Psychiatry, 69*(5), 529–537.

Hamilton, M. (1959). The assessment of anxiety states by rating. *British Journal of Medical Psychology, 32*(1), 50–5.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry, 23*(1), 56–62.

Hao, X., Xu, D., Bansal, R., Dong, Z., Liu, J., Wang, Z., Kangarlu, A., Liu, F., Duan, Y., Shova, S., Gerber, A. J., & Peterson, B. S. (2013). Multimodal magnetic resonance imaging: The coordinated use of multiple, mutually informative probes to understand brain structure and function. *Human Brain Mapping, 34*(2), 253–271.

Hassenstab, J. J., Sweet, L. H., Del, P. A., McCaffery, J. M., Haley, A. P., Demos, K. E., Cohen, R. A., & Wing, R. R. (2012). Cortical thickness of the cognitive control network in obesity and successful weight loss maintenance: A preliminary MRI study. *Psychiatry Research, 202*(1), 77–79.

Hu, S., Ide, J. S., Zhang, S., & Li, C. R. (2016). The right superior frontal gyrus and individual variation in proactive control of impulsive response. *Journal of Neuroscience, 36*(50), 12688–12696.

Kaur, S., Gonzales, M. M., Strasser, B., Pasha, E., McNeely, J., Tanaka, H., & Haley, A. P. (2015). Central adiposity and cortical thickness in midlife. *Psychosomatic Medicine, 77*(6), 671–678.

Killgore, W. D., Weber, M., Schwab, Z. J., Kipman, M., DelDonno, S. R., Webb, C. A., & Rauch, S. L. (2013). Cortico-limbic responsiveness to high-calorie food images predicts weight status among women. *International Journal of Obesity (London), 37*(11), 1435–1442.

Kim, J., Muller, K. R., Chung, Y. G., Chung, S. C., Park, J. Y., Bulthoff, H. H., & Kim, S. P. (2014). Distributed functions of detection and discrimination of vibrotactile stimuli in the hierarchical human somatosensory system. *Frontiers in Human Neuroscience, 8*, 1070.

Kullmann, S., Heni, M., Veit, R., Ketterer, C., Schick, F., Haring, H. U., Fritsche, A., & Preissl, H. (2012). The obese brain: Association of body mass index and insulin sensitivity with resting state network functional connectivity. *Human Brain Mapping, 33*(5), 1052–1061.

Kurth, F., Levitt, J. G., Phillips, O. R., Luders, E., Woods, R. P., Mazziotta, J. C., Toga, A. W., & Narr, K. L. (2013). Relationships between gray matter, body mass index, and waist circumference in healthy adults. *Human Brain Mapping, 34*(7), 1737–1746.

Lepping, R. J., Bruce, A. S., Francisco, A., Yeh, H. W., Martin, L. E., Powell, J. N., Hancock, L., Patrician, T. M., Breslin, F. J., Selim, N., Donnelly, J. E., Brooks, W. M., Savage, C. R., Simmons, W. K., & Bruce, J. M. (2015). Resting-state brain connectivity after surgical and behavioral weight loss. *Obesity (Silver Spring), 23*(7), 1422–1428.

Li, C. S., Morgan, P. T., Matuskey, D., Abdelghany, O., Luo, X., Chang, J. L., Rounsaville, B. J., Ding, Y. S., & Malison, R. T. (2010). Biological markers of the effects of intravenous methylphenidate on improving inhibitory control in cocaine-dependent patients. *Proceeding of the National Academy Sciences United States of America, 107*(32), 14455–14459.

Makaronidis, J. M., & Batterham, R. L. (2018). Obesity, body weight regulation and the brain: Insights from fMRI. *British Journal of Radiology*. https://doi.org/10.1259/bjr.20170910.

Marques-Iturria, I., Pueyo, R., Garolera, M., Segura, B., Junque, C., Garcia-Garcia, I., Jose, S. M., Vernet-Vernet, M., Narberhaus, A., Ariza, M., et al. (2013). Frontal cortical thinning and subcortical volume reductions in early adulthood obesity. *Psychiatry Research, 214*(2), 109–115.

Mata, F., Verdejo-Roman, J., Soriano-Mas, C., & Verdejo-Garcia, A. (2015). Insula tuning towards external eating versus interoceptive input in adolescents with overweight and obesity. *Appetite, 93*, 24–30.

Medic, N., Ziauddeen, H., Ersche, K. D., Farooqi, I. S., Bullmore, E. T., Nathan, P. J., Ronan, L., & Fletcher, P. C. (2016). Increased body mass index is associated with specific regional alterations in brain structure. *International Journal of Obesity (London), 40*(7), 1177–1182.

Nakamura, Y., & Ikuta, T. (2017). Caudate-Precuneus functional connectivity is associated with obesity preventive eating tendency. *Brain Connectivity, 7*(3), 211–217.

Navas, J. F., Barros-Loscertales, A., Costumero-Ramos, V., Verdejo-Roman, J., Vilar-Lopez, R., & Verdejo-Garcia, A. (2017). Excessive body fat linked to blunted somatosensory cortex response to general reward in adolescents. *International Journal of Obesity (London), 42*, 88–94.

Ochner, C. N., Kwok, Y., Conceicao, E., Pantazatos, S. P., Puma, L. M., Carnell, S., Teixeira, J., Hirsch, J., & Geliebter, A. (2011). Selective reduction in neural responses to high calorie foods following gastric bypass surgery. *Annals of Surgery, 253*(3), 502–507.

Ochner, C. N., Stice, E., Hutchins, E., Afifi, L., Geliebter, A., Hirsch, J., & Teixeira, J. (2012). Relation between changes in neural responsivity and reductions in desire to eat high-calorie foods following gastric bypass surgery. *Neuroscience, 209*, 128–135.

Ojemann, G. A., Schoenfield-McNeill, J., & Corina, D. P. (2002). Anatomic subdivisions in human temporal cortical neuronal activity related to recent verbal memory. *Nature Neuroscience, 5*(1), 64–71.

Pannacciulli, N., Le, D. S., Chen, K., Reiman, E. M., & Krakoff, J. (2007). Relationships between plasma leptin concentrations and human brain structure: A voxel-based morphometric study. *Neuroscience Letters, 412*(3), 248–253.

Pleger, B., Blankenburg, F., Ruff, C. C., Driver, J., & Dolan, R. J. (2008). Reward facilitates tactile judgments and modulates hemodynamic responses in human primary somatosensory cortex. *Journal of Neuroscience, 28*(33), 8161–8168.

Reuter, M., & Fischl, B. (2011). Avoiding asymmetry-induced bias in longitudinal image processing. *Neuroimage, 57*(1), 19–21.

Reuter, M., Rosas, H. D., & Fischl, B. (2010). Highly accurate inverse consistent registration: A robust approach. *Neuroimage, 53*(4), 1181–1196.

Reuter, M., Schmansky, N. J., Rosas, H. D., & Fischl, B. (2012). Within-subject template estimation for unbiased longitudinal image analysis. *Neuroimage, 61*(4), 1402–1418.

Segonne, F., Dale, A. M., Busa, E., Glessner, M., Salat, D., Hahn, H. K., & Fischl, B. (2004). A hybrid approach to the skull stripping problem in MRI. *Neuroimage, 22*(3), 1060–1075.

Sharkey, R. J., Karama, S., & Dagher, A. (2015). Overweight is not associated with cortical thickness alterations in children. *Frontiers in Neuroscience, 9*, 24.

Sjostrom, L., Narbro, K., Sjostrom, C. D., Karason, K., Larsson, B., Wedel, H., Lystig, T., Sullivan, M., Bouchard, C., Carlsson, B., et al. (2007). Effects of bariatric surgery on mortality in Swedish obese subjects. *New England Journal of Medicine, 357*(8), 741–752.

Steele, K. E., Prokopowicz, G. P., Schweitzer, M. A., Magunsuon, T. H., Lidor, A. O., Kuwabawa, H., Kumar, A., Brasic, J., & Wong, D. F. (2010). Alterations of central dopamine receptors before and after gastric bypass surgery. *Obesity Surgery, 20*(3), 369–374.

Tuulari, J. J., Karlsson, H. K., Antikainen, O., Hirvonen, J., Pham, T., Salminen, P., Helmio, M., Parkkola, R., Nuutila, P., & Nummenmaa, L. (2016). Bariatric surgery induces white and Grey matter density recovery in the morbidly obese: A voxel-based morphometric study. *Human Brain Mapping, 37*(11), 3745–3756.

Veit, R., Kullmann, S., Heni, M., Machann, J., Haring, H. U., Fritsche, A., & Preissl, H. (2014). Reduced cortical thickness associated with visceral fat and BMI. *Neuroimage Clinical, 6*, 307–311.

Vidal, P., Ramon, J. M., Goday, A., Benaiges, D., Trillo, L., Parri, A., Gonzalez, S., Pera, M., & Grande, L. (2013). Laparoscopic gastric bypass versus laparoscopic sleeve gastrectomy as a definitive surgical procedure for morbid obesity. Mid-term results. *Obesity Surgery, 23*(3), 292–299.

Vitaglione, P., Mennella, I., Ferracane, R., Rivellese, A. A., Giacco, R., Ercolini, D., Gibbons, S. M., La Storia, A., Gilbert, J. A., Jonnalagadda, S., et al. (2015). Whole-grain wheat consumption reduces inflammation in a randomized controlled trial on overweight and obese subjects with unhealthy dietary and lifestyle behaviors: Role of polyphenols bound to cereal dietary fiber. *American Journal of Clinical Nutrition, 101*(2), 251–261.

Vogt, B. A. (2005). Pain and emotion interactions in subregions of the cingulate gyrus. *Nature Reviews Neuroscience, 6*(7), 533–544.

Volkow, N. D., & Fowler, J. S. (2000). Addiction, a disease of compulsion and drive: Involvement of the orbitofrontal cortex. *Cerebral Cortex, 10*(3), 318–325.

Wallis, C. U., Cardinal, R. N., Alexander, L., Roberts, A. C., & Clarke, H. F. (2017). Opposing roles of primate areas 25 and 32 and their putative rodent homologs in the regulation of negative emotion. *Proceeding of the National Academy Sciences United States of America, 114*(20), E4075–E4084.

Wang, G. J., Volkow, N. D., Felder, C., Fowler, J. S., Levy, A. V., Pappas, N. R., Wong, C. T., Zhu, W., & Netusil, N. (2002). Enhanced resting activity of the oral somatosensory cortex in obese subjects. *Neuroreport, 13*(9), 1151–1155.

Wang, G. J., Tomasi, D., Backus, W., Wang, R., Telang, F., Geliebter, A., Korner, J., Bauman, A., Fowler, J. S., Thanos, P. K., & Volkow, N. D. (2008). Gastric distention activates satiety circuitry in the human brain. *Neuroimage, 39*(4), 1824–1831.

Weilbacher, R. A., & Gluth, S. (2016). The interplay of Hippocampus and ventromedial prefrontal cortex in memory-based decision making. *Brain Sciences, 7*(1), 4.

Wiemerslage, L., Zhou, W., Olivo, G., Stark, J., Hogenkamp, P. S., Larsson, E. M., Sundbom, M., & Schioth, H. B. (2017). A resting-state fMRI study of obese females between pre- and postprandial states before and after bariatric surgery. *European Journal of Neuroscience, 45*(3), 333–341.

Yokum, S., & Stice, E. (2013). Cognitive regulation of food craving: Effects of three cognitive reappraisal strategies on neural response to palatable foods. *International Journal of Obesity (London), 37*(12), 1565–1570.

Zhang, Y., Ji, G., Xu, M., Cai, W., Zhu, Q., Qian, L., Zhang, Y. E., Yuan, K., Liu, J., Li, Q., Cui, G., Wang, H., Zhao, Q., Wu, K., Fan, D., Gold, M. S., Tian, J., Tomasi, D., Liu, Y., Nie, Y., & Wang, G. J. (2016). Recovery of brain structural abnormalities in morbidly obese patients after bariatric surgery. *International Journal of Obesity (London), 40*(10), 1558–1565.