Recovery of brain structural abnormalities in morbidly obese patients after bariatric surgery

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Short title: Bariatric surgery reversing brain structural abnormalities

Key words: obesity, bariatric surgery, fMRI & diffusion tensor imaging, neuronal repairment, brain plasticity

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Abstract

Background/Objectives: Obesity-related brain structural abnormalities have been reported extensively, and bariatric surgery (BS) is currently the most effective intervention to produce sustained weight reduction in overtly obese people. It is unknown if BS can repair the brain circuitry abnormalities, concomitantly with long-term weight loss.

Subjects/Methods: In order to investigate if BS promotes neuroplastic structural recovery in morbidly obese patients, we quantified fractional anisotropy (FA), mean diffusivity (MD), and gray (GM) and white (WM) matter densities in 15 morbidly obese patients (OB) and in 18 normal weight (NW) individuals. OB patients were studied at baseline and also one month after laparoscopic sleeve gastrectomy (LSG) surgery.

Results: Two sample t-test between OB (baseline) and NW groups showed decreased FA values, GM/WM densities and increased MD value in brain regions associated with food intake control (i.e., caudate, orbitofrontal cortex, body and genu of corpus callosum) and cognitive-emotion regulation (i.e., inferior frontal gyrus, hippocampus, insula, external capsule) ($P < 0.05$, FWE correction). Paired t-test in OB group between before and after surgery showed that the BS generated partial neuroplastic structural recovery in the OB group, but the differences had relative less strength and smaller volume ($P < 0.001$).

Conclusions: This study provides the first anatomical evidence for BS-induced acute
neuroplastic recovery that might in part mediate the long-term benefit of BS in weight reduction. It also highlights the importance of this line of gut-brain axis research employing the combined BS and neuroimaging model for identifying longitudinal changes in brain structure correlates with obesity status.

**Key words:** obesity, bariatric surgery, fMRI & diffusion tensor imaging, neuronal repairment, brain plasticity
Introduction

Neuroimaging studies show that brains of obese individuals display impaired gray (GM) and white (WM) matter integrity. These disruptions are associated with both functional and behavioral changes. Specifically, GM reductions are noted in brain regions of food intake control (e.g. middle frontal cortex—MFC) and executive function (e.g. right inferior frontal gyrus—IFG), in emotional limbic areas (e.g. insula, amygdala—AMY), reward processing centers (e.g. caudate and putamen), anterior cingulate cortex (ACC), hippocampus (HIPP) and thalamus. GM atrophy is also found in the temporal lobe (e.g. inferior temporal gyrus—ITG, right middle temporal gyri—MTG), and the somatosensory (e.g. left postcentral gyrus) and occipital visual (e.g. occipital gyri) cortices. GM volume in many anterior and posterior cortical areas is negatively correlated with waist circumference and body mass index (BMI).

Less is known about changes in WM structure in obesity. Existing fractional anisotropy (FA) data from diffusion tensor imaging (DTI) analysis demonstrate an obesity-related decrease in WM integrity in the genu, splenium, fornix, midbrain and brainstem tracts. It is unknown if these obesity-related structural abnormalities in brain are repairable. We hypothesize that procedures that cause significant long-term loss of weight can repair the brain circuitry abnormalities in morbidly obese patients.

Bariatric surgery (BS) has recently emerged as the most effective clinical treatment for morbid obesity. Various types of BS, such as laparoscopic sleeve gastrectomy
used in this study, can cause profound changes in gastrointestinal microbiota, appetite-regulating peptides and neuroendocrine function. Molecular and functional changes in obese subjects after BS include an increase in dopamine receptors in mesolimbic reward pathways (e.g. in the ventral striatum, caudate and putamen), partial reversal of hypothalamic dysfunction and altered brain activity following BMI reduction. Roux-en-Y gastric bypass (RYGB), also attenuates activation in reward circuits. An association between lessened postoperative craving for high-calorie (HC) foods and diminished activity within mesolimbic areas and dorsolateral prefrontal cortex (DLPFC) has been observed one month after RYGB. Other effects of RYGB include suppressed fusiform gyrus, hypothalamic, hippocampal, and cerebellar activation, as well as attenuated functional connectivity in the default-mode network.

Here we investigate if LSG surgery promotes neuroplastic structural recovery in the obese brain. We hypothesized there would be measurable neuroanatomical changes in brain regions involving food intake and cognitive-emotion regulation after LSG surgery compared to baseline measures. We quantified fractional anisotropy (FA), mean diffusivity (MD), and gray (GM) and white (WM) matter densities in morbidly obese patients before LSG surgery and at the early time point of one month after surgery, in order to capture any acute BS-induced neuroplastic recovery, and in 18 normal weight individuals. We predicted this could be one mechanism explaining
prolonged BS-induced weight loss.

Materials/Subjects and Methods

Subjects

Twenty-eight 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 or neurological diseases, previous intestinal surgery, inflammatory intestinal disease, organ dysfunction, or any current medication that could affect the central nervous system, eating behavior were excluded. Obese individuals who weighed more than 150 kg or had a waist circumference greater than the interior diameter of the scanner were also excluded. Given the criteria, six obese candidates were disqualified for the MRI scan. Twenty-two remaining obese (OB) candidates underwent LSG surgery and completed pre-surgical MRI scans. The same MRI scans were performed one month after surgery. However, seven obese subjects were not willing to come back for this follow-up assessment. As a result, 15 patients remained in the OB group. The control group consisted of 18 normal weight (NW) subjects. The groups (OB and NW) were age-, gender-, and education-matched ($P > 0.05$, Table 1). The experimental protocol was approved by the Institutional Review Board of Xijing Hospital and registered in the Chinese Clinical Trial Registry center under the number: 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.

All participants underwent 12 hours overnight fasting. All MRI scans were performed in the morning between 9 to 10 AM to ensure consistency across assessment and to minimize circadian influence. Food intake was standardized by providing the subjects a liquid meal (200 ml; UHT Milk, Milch-Union Hocheifel eG, Germany) 30 min before the MRI measurements.

A designated clinician (HW) rated the severity of the subject’s anxiety using the Hamilton Anxiety Rating Scale and depression status using the Hamilton Depression Rating Scale. Subjects were required to complete the Yale Food Addiction Scale, a 25-item questionnaire that adopted the 7 symptoms of substance dependence listed in the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV-TR) for assessing addictive eating behaviors (Table 1), which has been validated in a bariatric surgery population. All clinical measurements were identically conducted before and one month after surgery, and the same surgeon (GJ) performed all surgical procedures.

**MRI Acquisition**

The experiment was carried out using a 3.0T GE (SIGNA EXCITE) scanner. First, a
high-resolution structural image for each subject was acquired using three-dimensional magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequence with a voxel size of 1 mm$^3$ and with an axial Fast Spoiled Gradient Echo sequence (TR = 7.8 ms, TE = 3.0 ms, matrix size = 256 x 256, field of view = 256 x 256 mm$^2$ and 166 slices). Then, diffusion-weighted images were acquired using a single-shot echo-planar imaging sequence. The diffusion sensitizing gradients were applied along 60 non-collinear directions (b = 1000 s/mm$^2$) with ten acquisitions without diffusion weighting (b = 0 s/mm$^2$). The imaging parameters were 75 continuous axial slices with a slice thickness of 2 mm and no gap, field of view = 256 x 256 mm$^2$; TR = 9400 ms; TE = 84 ms; matrix size = 128 x 128, resulting in 2 mm isotropic voxels. A radiologist (QL) examined the imaging data and excluded subjects with structural abnormalities.

White matter statistics using tract-based spatial statistics (TBSS) analysis

FA and MD were analyzed using the FMRIB Software Library (FSL, http://www.fmrib.ox.ac.uk/fsl). First, we adopted FDT (part of FSL) to process the DTI data and generate FA maps within a brain mask obtained via BET (also part of FSL) after eddy current correction. Secondly, we used the FA maps as input to investigate group WM differences at baseline between the OB and NW groups in a voxel-wise manner by using Tract-Based Spatial Statistics (TBSS). All FA images were non-linearly registered to an FMRIB58-FA standard space template (FMRIB
Centre University of Oxford, Department of Clinical Neurology, John Radcliffe Hospital Headington, Oxford, United Kingdom; [http://www.fmrib.ox.ac.uk/fsl/data/FMRIB58_FA.html](http://www.fmrib.ox.ac.uk/fsl/data/FMRIB58_FA.html) and aligned to the Montreal Neurological Institute space. The mean image of all aligned FA images was generated and thinned (non-maximum-suppression perpendicular to the local tract structure) to create a skeletonized mean FA image, which had threshold at the FA value of 0.2. Then, the aligned FA image was projected onto this skeleton. These mean FA skeletons represented the center of all tracts common to a particular subject group. Each subject’s FA data was then projected onto the subject’s group skeleton and used to conduct statistical analyses with age, gender, anxiety and depression as covariates. A permutation nonparametric test (5,000 permutations) was employed to assess group-related differences using threshold-free cluster enhancement. Statistical significance was defined at the cluster level ($P_{FWE} < 0.05$) using a cluster forming threshold of $P < 0.05$ and the family-wise error (FWE) correction. Finally, according to the ICBM-DTI-81 white-matter label atlas, each cluster was disassembled into sub-regions (based on overlap between the clusters and atlas) defined as regions of interest (ROIs). The mean FA was then extracted for the ROIs across all the subjects including OB and NW. MD was analyzed similarly. 

**GM/WM densities statistics using voxel-based morphometry (VBM) analysis**

GM and WM densities were analyzed using VBM8 toolbox by default parameter
settings (http://dbm.neuro.uni-jena.de/vbm/). First, T1 image data was normalized to MNI standard space using a set of non-linear functions and segmented into GM, WM, and cerebrospinal fluid (CSF) images according to SPM8’s prior probability templates.\(^3\) The normalized, segmented GM images were then smoothed and the final resultant images used to represent GM density; these density maps were later used in statistical analyses. We did not modulate resulting images and they represented GM density. Secondly, voxel-by-voxel statistical parametric maps of regional differences in GM density between the OB and NW groups at baseline were calculated using age, gender, anxiety, depression and total brain GM volume as covariates (ANCOVA) in SPM8 (Wellcome Department of Imaging Neuroscience, London, UK. http://www.fil.ion.ucl.ac.uk/spm). The statistical significance was set at \(P < 0.05\), corrected for multiple comparisons using FWE correction with the minimum size set at 20 voxels to form clusters \((P < 0.001, \text{uncorrected})\).\(^1\) Finally, each cluster was disassembled into sub-regions (based on overlap between the clusters and atlas) on the AAL Atlas,\(^3\) and all the sub-regions were labeled accordingly and defined as ROIs. The mean GM density was extracted for the ROIs across all the subjects including OB and NW. WM density was similarly analyzed.

Correlation analysis

We conducted the partial correlation analysis\(^3\) with age, gender, anxiety and depression as covariates to assess the association between changes in brain structures
and clinical measurements. These involve clinical statistical data sets such as BMI and YFAS, mean FA/MD values of white matter, and mean GM/WM density values. The Bonferroni correction was applied for multiple comparisons. All tests were 2-tailed, and the level of significance was $P < .025 (.05/2)$.

**Results**

*Clinical and demographic characteristics*

There were no age or gender differences between the OB and NW groups (Table 1). At baseline, the average weight ($P < 0.0001$), BMI ($P < 0.0001$), food intake ($P < 0.001$), YFAS ($P < 0.0001$), HAMD ($P < 0.05$) and HAMA ($P < 0.05$) were higher for OB than for NW. OB had lower mean weight ($P < 0.05$), BMI ($P < 0.05$), food intake ($P < 0.0001$), and YFAS ($P < 0.05$) after surgery (i.e., PostBS) than before surgery (i.e., PreBS) (Table 1). There were no differences in depression and anxiety between pre- and post-surgery sessions ($P > 0.05$; Table 1).

*Alterations of white matter integrity pre- and post-surgery*

Two sample $t$-test between OB and NW (OB > NW) groups showed that the OB group had decreased white matter directionality and integrity in several brain regions, after controlling for age, gender, anxiety and depression ($P_{\text{FWE}} < 0.05$). Relative to the NW group, before surgery the OB group had lower FA values in the left anterior corona radiate (ACR), corpus colosum (body and genu—BCC and GCC), fornix and stria
terminalis (FX_ST), and left sagittal stratum (SS) including inferior longitudinal and
fronto-occipital fasciculus (Fig 1 & Table 2). Paired t-test in the OB group between
before and after surgery (PreBS > PostBS) showed that after surgery the OB group
had higher FA values than before surgery in the identical brain regions ($P < 0.001$; Fig
1 & Table 2).

Compared to the NW group, the before surgery OB group showed increased MD
values in the left anterior (ACR), posterior (PCR) and superior (SCR) corona radiate,
left external capsule (EC), left posterior limb (PLIC) and the retrolenticular part
(PLIC) of internal capsule, left superior longitudinal fasciculus (SLF) and left SS (e.g.
the inferior longitudinal and fronto-occipital fasciculus) ($P_{FWE} < 0.05$; Supplement
Fig 1 and Table 2). Paired t-test in the OB group (n=15) between before and after
surgery (PreBS > PostBS) showed that after surgery the OB group had lower MD
values than before surgery in the identical brain regions ($P < 0.05$; Supplement Fig 1
and Table 2).

**Alterations of GM/WM density pre- and post-surgery**

In comparison to the NW subjects, before surgery the OB patients demonstrated
decreased GM and WM densities in multiple brain regions ($P_{FWE} < 0.05$, cluster size >
20 voxels) according to the VBM analysis (Fig 2 & Supplement Fig 2, Table 3 & 4).
Specifically, GM densities were diminished in the caudate, putamen, insula, thalamus,
HIPP, olfactory, frontal lobe (inferior frontal gyrus—IFG and superior frontal gyrus—SFG), rostral anterior cingulate cortex (rACC), dorsomedial prefrontal cortex (DMPFC), right orbitofrontal cortex (OFC), temporal lobe, left fusiform, lingual gyrus, left inferior occipital gyrus, postcentral gyrus, cuneus and the precuneus in the OB versus in the NW group. Paired $t$-test in the OB group ($n=15$) between before and after surgery ($\text{PreBS} > \text{PostBS}$) showed that after surgery the OB group had increased GM densities in the IFG, SFG, rACC, DMPFC, left ITG, MTG, temporal lobe, left fusiform and postcentral ($P < 0.001$; Fig 2 & Table 3).

Similar to GM density, two sample $t$-test showed that WM densities were also decreased in the caudate, insula, thalamus, HIPP, parahippocampus (PHIPP), frontal lobe (IFG, rACC, OFC), middle cingulate cortex (MCC), parietal lobe, right fusiform, left superior occipital gyrus (SOG), pre- and postcentral gyrus and the precuneus in the OB (before surgery) relative to the NW group ($P_{FWE} < 0.05$, cluster size $> 20$ voxels). Paired $t$-test in the OB group between before and after surgery ($\text{PreBS} > \text{PostBS}$) showed that after surgery the OB group had increased WM densities in the caudate, thalamus, right IFG, rACC, MCC, postcentral gyrus and precuneus ($P < 0.001$; Supplement Fig 2 and Table 4).

Correlations between clinical variables and DTI, VBM measures

In the OB groups before surgery, BMI was negatively correlated with FA values in the
fornix, and YFAS was also exhibited inverse association with FA values in SS (Fig 3A). BMI was negatively correlated with FA values in the SS in the OB group after surgery (Fig 3B). Before surgery the MD values in the left SCR and PLIC were correlated with the BMI of OB subjects (Supplement Fig 3), and MD values in the left SCR, PLIC and EC were associated with their YFAS (Supplement Fig 3). There was no correlation between MD value and BMI and YFAS in the OB group after surgery.

In the OB group before surgery, BMI showed negative correlation with GM in the lingual gyrus, left IOG, postcentral and precuneus (Supplement Fig 4A). YFAS and BMI were associated with GM in the temporal pole and thalamus, and in the temporal pole, respectively (Supplement Fig 4B). There was no correlation between GM density and BMI and YFAS in the OB group after surgery. BMI and YFAS showed negative correlation with WM in caudate, thalamus and postcentral gyrus (Supplement Fig 4C), and in the rACC, MCC, IFG, OFC, HIPP, insula, PHIIPP, IPL, Pre- and postcentral, and thalamus, respectively (Supplement Fig 4C). WM densities in the rACC, IFG and postcentral in OB group after surgery still exhibited negative correlation with BMI (Supplement Fig 4D).

**Discussion**

Our study confirmed that obese patients have reductions in WM integrity and in GM...
and WM densities in brain regions associated with food intake control and
cognitive-emotion regulation. More importantly, we present the first evidence for a
BS-prompted acute recovery of obesity-related brain structural abnormalities in obese
patients in just one month after surgery. Even though the disruption of brain structure
was not fully normalized to the control status, we found after surgery the OB group
showed significant differences of FA values in the left ACR, BCC, GCC, fornix and
left SS, and GM densities in IFG, SFG, rACC, DMPFC, left ITG, MTG, fusiform and
postcentral when compared to the OB group before surgery. These findings suggest
that BS triggers an early neuro-repair mechanism in the brain, which may mediate
weight loss in the long-term. Our findings support previous fMRI studies that altered
brain activation to visual food cues following RYGB and laparoscopic adjustable
gastric banding (LAGB) surgery.21,34

Whether the brain’s structural renewal is dependent upon or independent of the
surgery-induced weight loss is currently unknown. The neural repair mechanism
could provide a structural basis for an attenuated appetite BS that contributes to
obesity reduction following BS procedure. Follow up investigations are needed to
further examine the relationship between this anatomical rejuvenation and brain
functional as well as behavioral changes after the BS procedure.

Structural alterations in regions associated with food intake control and
cognitive-emotion regulation
The obese subjects exhibited decreased GM and WM densities in caudate and putamen, decreased FA values in the BCC and GCC, and increased MD values in the PLIC, RLIC and SCR compared to the NW controls. These brain regions have been linked to reward processing. The GM/WM deficiency in obese patients may underscore an abnormal reward response. The BS procedure partially reverts these changes toward normal, non-obese levels at the early one-month post-surgery time point. BMI and YFAS were negatively associated with FA values and GM/WM densities. At the same time, BMI and YFAS were positively correlated with MD values. In other words, the higher the BMI and YFAS values, the more severe the brains atrophy. Other studies have demonstrated that functional alterations following BS procedures usually oppose those occurring with obesity. For instance, obese subjects display persistent mesolimbic hyperactivation in response to food cue. The RYGB surgery in turn diminishes mesolimbic activation in response to HC versus low-calorie (LC) foods. The LSG procedure has also been shown to induce the remission of food addiction. It is currently unclear if the neural structural changes we report here could underlie altered behavioral adaptations to changing hedonic values of stimuli or reward processing.

OB subjects exhibited reduced GM and WM densities in the HIPP, PHIPP, insula, thalamus and the olfactory bulb, decreased FA values in the fornix and SS, and increased MD values in the EC, PLIC, RLIC and SS compared to the NW group,
these results are consistent with previous study. The LSG surgery generated the trends of increase and decrease in these limbic brain regions, which oppose those exhibited in obesity. Due to the critical importance of these neuronal sites for memory, learning and emotion, the recovery of obesity-induced brain abnormalities following BS might reflect functional and behavioral outcome changes. Our current data are insufficient for drawing this connection. In comparing obese subjects pre- versus post-surgery, we also detected altered WM integrity (i.e. changes in fiber connections) in the EC, a brain region that relates the AMY and HIPP to the PFC and OFC regions. This suggests that the BS procedure may recover parts of the taste reward circuitry disrupted by obesity.

The OB group also had lower GM/WM densities in the IFG, SFG, rACC, DMPFC and OFC, decreased FA values in the BCC and GCC, and increased MD values in the EC, SLF and SS (inferior fronto-occipital fasciculus) relative to the NW group, our findings are consistent with previous studies. BS partially normalized these values to non-obese levels. Both BMI and YFAS were negatively correlated with GM and WM. Our data is consistent with past findings demonstrating decreased activation in the MPFC and IFG (food motivation and reward) and increased activation in the prefrontal cortex (cognitive control and inhibition) in obese patients after adjustable gastric band surgery. Conversely, YFAS showed positive correlations with the MD values in the EC.
The OFC component of brain is important for motivation, drive and salience evaluation, and regulates the output of compulsive food intake behaviors. In the current study, the GM/WM densities in OFC showed negative correlation with BMI and YFAS in obesity, suggesting an augmented motivation or drive for food intake before surgery. The postcentral gyrus, which links to somatosensory signal processing, also displayed lower GM/WM densities that were negatively correlated with BMI and YFAS. This finding suggests that obesity or high BMI may impair somatosensory processing, thus aggravating food intake and weight gain. In an earlier report, RYGB surgery was linked with increased OFC and somatosensory cortex activation.

Collectively, our study reveals structural changes in pivotal neural circuit that could account for aberrant functional outcomes in reward, inhibition and somatosensory processing associated with obesity. The fact that BS triggers neuro-repair in the obese brain in these sites favors the speculation that structural changes may precede or encode neural functions and/or behavioral alterations.

Structural alterations in visual processing pathway

Our current study reveals decreased GM/WM densities in the ITG, MTG, STG and temporal pole of the temporal lobe, and reduced MD values in the inferior longitudinal fasciculus in obese patients compared with NW controls, the findings are consistent with previous studies. We show that BS partially reversed these changes.
The GM/WM densities in the temporal lobe showed significant correlation with BMI and YFAS, and the MD values in left PLIC and SCR showed positive correlation with BMI. Alterations in GM/WM densities and MD values with obesity or BS within these regions indicate possible impairment or recovery of cognitive processing in the temporal lobe.

Obese individuals displayed lower GM/WM densities in visual cortical areas including the fusiform gyrus, lingual gyrus, IOG, cuneus and precuneus, and attenuated FA values in the BCC and GCC compared to NW subjects. Conversely, obese individuals exhibited increased MD values in the SLF, inferior longitudinal fasciculus and inferior fronto-occipital fasciculus. BS again tended to reverse these alterations. While the fusiform, lingual gyri and IOG take part in visual processing, the cuneus and precuneus participate in the recognition of the salience of visual stimuli. Both BMI and YFAS showed negative correlation with GM/WM densities in the lingual gyrus and precuneus. Furthermore, GM density was negatively associated with BMI in only the IOG. In aggregates, higher BMI or obesity was associated with GM/WM damage, and it is possible BS alters the influence of obesity on visual processing.

**Limitations**

Due to the strict exclusion criteria and difficulty in retaining patients after surgery for
follow-up scanning, we did not have a large cohort size for the OB group. We assessed the obese participants only at two particular time point. e.g., before and one month after the surgery. Since our study showed the LSG-BS procedure partially normalized many GM/WM structural abnormalities in obese patients, assessments at more time-points post-surgery will help clarify the course of the neural repair and demonstrate a possible full recovery.

Conclusion

The current study examined the effects of obesity and weight loss bariatric surgery on brain anatomy both longitudinally (before versus after surgery) and cross-sectionally (obsess versus normal weight). The data demonstrated widespread neurocircuitry abnormalities associated with obesity, and revealed remarkable neuroplasticity that allowed the impaired obese brain to recover after BS. Our results highlight the importance of the gut-brain axis for neural network integrity and associated functions. Equipped with the BS model in combination with sensitive neuroimaging technology, we can expect to gain a better understanding of the mechanisms of brain atrophy, as well as how to treat or reverse such damage. This opens doors for development of new innovative strategies to improving neural function not only in patients of obesity, but also in neurodegenerative diseases such as Alzheimer’s (AD) and Parkinson’s disease (PD) and in psychiatric disorders like schizophrenia.
Conflict of interest

The authors declare no conflict of interest.

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Figures and Figure Legends

**Figure 1.** Differences in FA between OB (pre-surgery) and NW (OB vs. NW), and between pre- and post-surgery (PreBS vs. PostBS) in obese subjects. Compared to NW, OB exhibited WM abnormalities in brain areas in left ACR, BCC, GCC, fornix and left SS ($P_{FWE} < 0.05$). While, relative to obese status, obese subjects after surgery demonstrated less WM abnormalities in those above brain regions ($P < 0.001$), which suggested LSG surgery partially repair the brain circuitry abnormalities in obese patients.

Abbreviation: ACR_L, left anterior corona radiata; BCC, body of corpus callosum; GCC, genu of corpus callosum; SS, sagittal stratum.
Figure 2. The brain regions showing altered gray matter (GM) densities between OB and NW (OB vs. NW), and between pre- and post-surgery (PreBS vs. PostBS) in obese subjects. A. Compared to the NW group, the OB group had lower GM densities in caudate, putamen, insula, thalamus, HIPP, olfactory, frontal lobe (i.e., IFG and SFG), rACC, DMPFC, OFC, temporal lobe, left fusiform, lingual gyrus, left inferior occipital gyrus, postcentral gyrus, cuneus and the precuneus ($P_{FWE} < 0.05$, cluster size > 20 voxels). B. Paired $t$-test showed that after surgery the OB group had increased GM densities in IFG, SFG, rACC, DMPFC, left ITG, MTG, temporal lobe, left fusiform and postcentral gyrus ($P < 0.001$).

Fig 2 inserts here

Abbreviation: HIPP_R, right hippocampus; IFG, inferior frontal gyrus; SFG, superior frontal gyrus; rACC, rostral anterior cingulate cortex; DMPFC, dorsal medial prefrontal cortex; OFC, orbitofrontal cortex; IOG_L, left inferior occipital gyrus.
Figure 3. Correlation results between the clinical measurements data and FA value in the OB group before and after surgery. A. BMI was negatively correlated with FA values in the fornix, and YFAS was also exhibited inverse association with FA values in SS (Fig 3A). B. BMI was negatively correlated with FA values in the SS in the OB group after surgery (Fig 3B).

Abbreviation: ACR_L, left Anterior corona radiata; SS, sagittal stratum.
### Tables and Table Legends

**Table 1.** Demographic and clinical information of the obese and normal weight subjects.

<table>
<thead>
<tr>
<th></th>
<th>OB (N=15) PreBS (Mean ± SE)</th>
<th>OB (N=15) PostBS (Mean ± SE)</th>
<th>NW (N=18) (Mean ± SE)</th>
<th>F value</th>
<th>P Value</th>
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<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>25.80 ± 2.20</td>
<td>25.80 ± 2.20</td>
<td>27.00 ± 1.90</td>
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<td><strong>Gender</strong></td>
<td>5M/10F</td>
<td>5M/10F</td>
<td>6M/12F</td>
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<td>0.542</td>
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<tr>
<td><strong>Duration of Obesity (yrs)</strong></td>
<td>11.30 ± 2.00</td>
<td>11.30 ± 2.00</td>
<td>N/A</td>
<td>20.038</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Weight (Kg)</strong></td>
<td>107.90 ± 4.80</td>
<td>97.30 ± 5.00</td>
<td>59.50 ± 2.60</td>
<td>40.67</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>BMI (Kg/m^2)</strong></td>
<td>38.10 ± 1.50</td>
<td>34.40 ± 1.70</td>
<td>21.60 ± 0.70</td>
<td>47.736</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>WC (cm)</strong></td>
<td>118.20 ± 4.30</td>
<td>107.00 ± 5.30</td>
<td>82.00 ± 2.60</td>
<td>22.126</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>Food Intake (Kg/Meal)</strong></td>
<td>0.80 ± 0.15</td>
<td>0.18 ± 0.02</td>
<td>0.40 ± 0.03</td>
<td>12.161</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>YFAS</strong></td>
<td>4.80 ± 0.57</td>
<td>2.80 ± 0.52</td>
<td>1.80 ± 0.30</td>
<td>11.063</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>HAMD</strong></td>
<td>14.50 ± 3.10</td>
<td>12.39 ± 2.30</td>
<td>6.80 ± 1.00</td>
<td>3.702</td>
<td>0.016</td>
</tr>
<tr>
<td><strong>HAMA</strong></td>
<td>12.20 ± 2.60</td>
<td>8.90 ± 2.00</td>
<td>5.00 ± 0.70</td>
<td>4.067</td>
<td>0.007</td>
</tr>
</tbody>
</table>

OB, obese candidates for bariatric surgery; PreBS, obese subjects who received image-scanned before surgery; PostBS, obese subjects who received bariatric surgery and image-scanned again at one month postsurgically; NW, normal weight; SE, standard Error; BMI, body mass index; WC, waist circumference; YFAS, Yale Food Addiction Scale; HAMD, Hamilton Depression Rating Scale; 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 postsurgery (PreBS vs. PostBS) to investigate the effect of bariatric surgery.
Table 2. Statistical significance of clusters showing FA and MD differences between obese patients (OB) before surgery and controls (NW), and between OB patients before and after surgery (PreBS vs. PostBS).

<table>
<thead>
<tr>
<th>ROI</th>
<th>OB vs. NW</th>
<th>PreBS vs. PostBS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MNI</td>
<td>T Value</td>
</tr>
<tr>
<td></td>
<td>X Y Z</td>
<td></td>
</tr>
<tr>
<td>FA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR_L</td>
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</tr>
<tr>
<td>BCC</td>
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</tr>
<tr>
<td>GCC</td>
<td>-1 21 15</td>
<td>5.14</td>
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<tr>
<td>Fornix</td>
<td>-31 -21 -7</td>
<td>4.30</td>
</tr>
<tr>
<td>SS_L</td>
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<td>4.12</td>
</tr>
<tr>
<td>MD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR_L</td>
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<td>4.49</td>
</tr>
<tr>
<td>EC_L</td>
<td>-34 -17 -6</td>
<td>5.07</td>
</tr>
<tr>
<td>PCR_L</td>
<td>-28 -33 22</td>
<td>4.37</td>
</tr>
<tr>
<td>PLIC_L</td>
<td>-23 -7 14</td>
<td>4.60</td>
</tr>
<tr>
<td>SCR_L</td>
<td>-27 5 30</td>
<td>4.60</td>
</tr>
<tr>
<td>SLF_L</td>
<td>-39 -42 18</td>
<td>5.27</td>
</tr>
<tr>
<td>SS_L</td>
<td>-42 -24 -15</td>
<td>3.47</td>
</tr>
</tbody>
</table>

Abbreviation: ROI, region of interest; SD, standard deviation; ACR_L, left anterior corona radiata; BCC, body of corpus callosum; GCC, genu of corpus callosum; SS_L, left sagittal stratum; SCR_L, left superior corona radiata; PCR_L, left posterior corona radiata; EC_L, left external capsule; RLIC_L, left retrolenticular part of internal capsule; PLIC_L, left posterior limb of internal capsule; SLF_L, left superior longitudinal fasciculus.
Table 3. Statistical significance of clusters showing altered gray matter (GM) densities between obese patients (OB) before surgery and controls (NW), and between OB patients before and after surgery (PreBS vs. PostBS).

<table>
<thead>
<tr>
<th>ROI</th>
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<th>PreBS vs. PostBS MNI</th>
<th></th>
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<tr>
<td></td>
<td>X</td>
<td>Y</td>
<td>Z</td>
<td>T Value</td>
</tr>
<tr>
<td>Reward area</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caudate</td>
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<td>3</td>
<td>-5</td>
<td>-6.43</td>
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<tr>
<td>Putamen</td>
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<td>16</td>
<td>-6</td>
<td>-4.81</td>
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<tr>
<td>Limbic area</td>
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<td></td>
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<tr>
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<td>-4.90</td>
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<td>53</td>
<td>-4.24</td>
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<td>-6.24</td>
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<td>-3.54</td>
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<td>Temporal lobe</td>
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<td>-2</td>
<td>-4.81</td>
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<tr>
<td>STG</td>
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<tr>
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<td>Cuneus</td>
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<tr>
<td>Precuneus</td>
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<td>-5.56</td>
</tr>
</tbody>
</table>

Abbreviation: ROI, region of interest; MNI, Montreal Neurology Institute; HIPP_R, right hippocampus; IFG, inferior frontal gyrus; SFG, superior frontal gyrus; rACC, rostral anterior cingulate cortex; DMPFC, dorsal medial prefrontal cortex; OFC_R, right orbitofrontal cortex; ITG_L, left inferior temporal gyrus; MTG, middle temporal
gyrus; STG, superior temporal gyrus; Fusiform_L, left fusiform; IOG_L, left inferior occipital gyrus.
Table 4. Statistical significance of clusters showing altered white matter (WM) densities between obese patients (OB) before surgery and controls (NW), and between OB patients before and after surgery (PreBS vs. PostBS).

<table>
<thead>
<tr>
<th>ROI</th>
<th>OB vs. NW</th>
<th>PreBS vs. PostBS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MNI</td>
<td>T Value</td>
</tr>
<tr>
<td></td>
<td>X  Y  Z</td>
<td></td>
</tr>
<tr>
<td><strong>Reward area</strong></td>
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<tr>
<td>Caudate</td>
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<td><strong>Limbic area</strong></td>
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<tr>
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</tr>
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<td>PHIPP_L</td>
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<td>-5.45</td>
</tr>
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<td><strong>Frontal lobe</strong></td>
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<tr>
<td>IFG_R</td>
<td>33  6  27</td>
<td>-5.53</td>
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<td>OFC_R</td>
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<tr>
<td>Precuneus</td>
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<td>-5.56</td>
</tr>
</tbody>
</table>

Abbreviation: ROI, region of interest; MNI, Montreal Neurology Institute; HIPP, hippocampus; PHIPP_L, left parahippocampus; insula_R, right insula; IFG_R, right inferior frontal gyrus; rACC, rostral anterior cingulate cortex; OFC_R, right orbitofrontal cortex; MCC, middle cingulate cortex; IPL_R, right inferior parietal lobe; SPL, superior parietal lobe; Fusiform_R, right fusiform; SOG_L, left superior occipital gyrus.