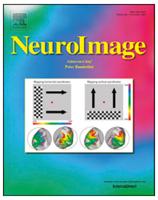
NeuroImage xxx (2017) 1–11

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage



Gastric-bypass surgery induced widespread neural plasticity of the obese human brain

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ARTICLE INFO

Keywords:
Magnetic resonance imaging
Gray matter density
White matter density
white matter diffusion
Amplitudes of low frequency fluctuations
ALFF
Regional homogeneity
ReHo
Brain plasticity
Body weight
Bariatric surgery
Gastric-bypass surgery

ABSTRACT

Bariatric surgery has become the gold standard for the treatment of morbid obesity (body mass index (BMI) ≥ 40 kg/m^2), but only few studies investigated its plastic influences on the obese brain. In this longitudinal study, we combined structural and functional magnetic resonance brain imaging (MRI) in 27 patients (BMI 47.8 ± 5.5 kg/m^2) undergoing gastric-bypass surgery and 14 non-obese matched controls (BMI 24.7 ± 3.4 kg/m^2). Over the first year after surgery, patients presented widespread changes in white matter density (WMD) as well as gray matter density (GMD) in the cerebral cortex of all lobes, subcortical structures, the brainstem as well as the cerebellum, but no changes in white matter water diffusivity throughout the brain. Voxel-by-voxel regression analyses revealed that all GMD and WMD changes were well associated with elevated regional homogeneity of spontaneous neural activity (ReHo) in blood-oxygenation level-dependent signals. Spatial-temporal integration of structural and functional MRI suggests that gastric-bypass surgery induces widespread plastic changes in brain structure that concurrently homogenizes the functional profile of the cortex, subcortical regions as well as white matter structures.

The current gold standard in the therapy of obesity is bariatric surgery, which encompasses a variety of surgical procedures with one common goal: bypassing or downsizing the stomach. This can be achieved by gastric band or through removal of a portion of the stomach (sleeve gastrectomy or biliopancreatic diversion with duodenal switch) or by resecting and re-routing the small intestine to a small stomach pouch (gastric bypass). In the largest prospective and controlled study so far which included 2010 patients (The Swedish Obese Subjects study), maximum weight loss over the 10-year observation period was found over the first year after surgery. Gastric bypass showed the strongest effect on patients' weight (mean body mass index (BMI, kg/m^2) reduction of 32%) (Sjostrom et al., 2007). Besides weight-loss, bariatric surgery also improves metabolic balance and hence diabetes, as well as other cardiovascular risk factors (Sjostrom, 2013). The U.S. National Institutes of Health therefore recommended bariatric surgery for patients with a BMI of at least 40 kg/m^2, or 35 kg/m^2, if serious medical conditions, such as refractory diabetes, exist (Robinson, 2009). Other therapy guidelines even propose that any patient with a BMI over 30 kg/m^2 and coexisting refractory comorbidities should be considered a potential candidate for bariatric surgery (Fajnwaks et al., 2008).

Although bariatric surgery has become the gold standard for the treatment of morbid obesity, only few studies to date investigated its plastic influences on the obese brain. Tuulari et al. used magnetic resonance imaging (MRI) together with voxel-based morphometry (VBM) to explore changes in gray and white matter prior to and six months after surgery. Prior to surgery, morbidly as compared to non-obese individuals presented lower gray matter density (GMD) in widespread cortical areas including frontal, parietal, and temporal regions as well as bilateral insula. Lower white matter density (WMD) was instead observed throughout the brain's white matter. Bariatric surgery and concomitant

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https://doi.org/10.1016/j.neuroimage.2017.10.062
Received 22 June 2017; Accepted 27 October 2017
Available online xxxx

Please cite this article in press as: Rullmann, M., et al., Gastric-bypass surgery induced widespread neural plasticity of the obese human brain, NeuroImage (2017), https://doi.org/10.1016/j.neuroimage.2017.10.062

weight loss caused global increase of WMD, suggesting global white matter recovery, whereas GMD increases were locally restricted to occipital and inferior temporal regions (Tuulari et al., 2016).

Besides those surgery-induced effects on brain morphology, a series of studies used functional MRI (fMRI) to predict weight loss after surgery by functional brain responses assessed prior to surgery. Enhanced activity in neural circuits involved in executive control, such as the dorsolateral prefrontal cortex (Goldman et al., 2013), and frontal regions, such as medial, middle, and superior frontal gyrus, together with posterior cingulate cortex (Ness et al., 2014) were found in patients with higher weight loss after surgery.

A more recent study used task-free, so-called resting-state or functional-connectivity fMRI pre-to post-meal to compare functional brain connectivity of behavioral dieters with patients undergoing bariatric surgery (Lepping et al., 2015). Three months after the intervention, behavioral dieters exhibited increased connectivity pre-to post-meal between left precuneus/superior parietal lobe, associated with processing of self-referent information, and bilateral insula, assumed to host interoceptive and gustatory processes. Patients after bariatric surgery instead exhibited decreased connectivity between these regions pre-to post-meal. This suggests potentially increased attention to hunger signals in the surgery group, whereas behavioral dieters may instead pay more attention to satiety signals (Lepping et al., 2015).

Despite these evidences on surgery-induced functional and structural brain plasticity, their interaction remains elusive.

In the present longitudinal study, we combined magnetic resonance imaging (MRI) of the brain's gray (i.e., GMD) and white matter (i.e., white matter density, or WMD and diffusion tensor imaging, or DTI to assess water molecule diffusivity in white matter) with task-free “resting-state” fMRI, before, half a year and one year after gastric-bypass surgery to investigate the link between bariatric surgery and corresponding structural and functional brain plasticity. With task-free “resting-state” fMRI, we investigated spontaneous fluctuations in blood oxygen-level-dependent (BOLD) signals. Specifically, we assessed the regional homogeneity of neural activity (ReHo) as well as amplitudes of low frequency fluctuations (ALFF). ReHo is a voxel-based measure of brain activity, which evaluates the similarity or synchronization between the time series of a given voxel and its nearest neighbors (Zang et al., 2004). This measure is based on the hypothesis that intrinsic brain activity is manifested by clusters of voxels rather than single voxels. Amplitudes of low frequency fluctuations (ALFF) (Zou et al., 2008) are a fundamental feature of the “resting” brain with high test-retest reliability (Raichle et al., 2001). They were shown to closely relate to spontaneous neuronal activity (Goldman et al., 2002; Logothetis et al., 2001; Lu et al., 2007; Mantini et al., 2007).

First, we asked whether GMD, WMD, white matter water molecule diffusivity, or markers of spontaneous neural activity (ReHo, ALFF) assessed prior to surgery correlate with the weight-loss after six and/or twelve months. Next, we applied the following statistical procedures step-by-step to analyze VBM, DTI and ReHo/ALFF data systematically: First, we computed DTI, GMD, WMD, ReHo and ALFF analyses to assess any significant surgery-induced changes throughout the brain. In case of significant GMD/WMD or white matter diffusivity changes over time, we also tested for significant changes of ReHo and ALFF within those significant GMD/WMD/white matter diffusivity effects. Next, we applied significant GMD/WMD or white matter diffusivity changes to voxel-by-voxel linear regression analyses together with significant changes in either ReHo or ALFF, as the functional predictor, to assess the voxel-by-voxel functional fraction of surgery-induced GMD/WMD or white matter diffusivity changes.

We hypothesized specific surgery-induced structural-functional plasticity of the brain's gray and white matter in and around brain regions controlling eating behavior, such as the ventral striatum including the Nc. accumbens, involved in goal-directed behavior, the dorsal striatum, assumed to underpin habitual eating (Stice et al., 2008), the insular cortex, assumed to host gustatory processes (Tuulari et al., 2016), as well as executive control regions in the dorsolateral prefrontal cortex (Hollmann et al., 2013). Based on previous observations (Tuulari et al., 2016), we expected an increase in GMD in those regions, as well as an increased WMD and water molecule diffusivity in adjacent white matter territories. We also expected to find either structural (i.e., GMD/WMD or white matter diffusivity parameters) or functional markers (i.e., ReHo or ALFF) in the same set of brain regions prior to surgery correlating with the weight loss after six and/or twelve months.

We assumed that six months after surgery, increases in GMD, WMD and white matter diffusivity were partly associated with changes in spontaneous neural fluctuations (i.e., ALFF, ReHo), suggesting that functional or functional-structural processes occurred over the first six month after surgery. In the following six months, we instead expected structural plasticity without strong functional associations.

Patients were, moreover, compared to a non-obese control group that was investigated once with the same MRI techniques as the patient group. We hypothesized that over the twelve months after surgery, patients' GMD/WMD, white matter diffusivity, ReHo, and ALFF progressively adapt to the levels obtained from those non-obese controls.

Materials and methods

Patients and non-obese controls

The study was carried out in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University of Leipzig. Patients as well as non-obese controls gave their written informed consent prior to their participation (see Table 1 for group characteristics). Exclusion criteria were any contraindications to magnetic resonance imaging (MRI) (see Suppl. Table 1 for the full list of contradictions). Before each MRI session, we assessed each participant's body weight and length to calculate the BMI (kg/m^2). Furthermore, we measured body fat mass (%) using the Nutriguard M system (Data Input GmbH, Pöcking, Germany) together with the BodyComposition software, version 9.0 (MEDI CAL HealthCare GmbH, Karlsruhe, Germany). From patients' venous blood samples, we assessed cholesterol levels (mmol/l), high-density lipoproteins (HDL, mmol/l), low-density lipoproteins (LDL, mmol/l), triglycerides (mmol/l), as well as glycated hemoglobin (HbA$_{1c}$, %). The latter is commonly used to evaluate the three-month average plasma glucose concentration. As an index of inflammation, we assessed the C-reactive protein (CrP, mg/l). Furthermore, we obtained levels of thyroid-stimulating hormone (TSH, mU/l) that stimulates the thyroid gland and hence the metabolism of almost every tissue in the body. As a marker of depression, we assessed PHQ-9 (Patient Health Questionnaire) in the patient group and BDI-II (Beck's Depression Inventory) in the control group. Both are self-report questionnaires that are validated for use in primary care. In Table 1, we summarize those parameters together with co-morbidities such as presence/absence of diabetes, hypertension, as well as the educational background of all participants. Twenty-seven morbidly obese patients (21 females, age 51.1 ± 9.6y, BMI 47.8 ± 5.5 kg/m^2) participated in the experiments prior to, and half a year after laparoscopic proximal Roux-en-Y gastric bypass, in which a very small gastric pouch is created and a Roux limb of jejunum is anastomosed. A subgroup consisting of 22 patients out of the 27 (18 females, age 52.6 ± 8.5y, BMI 47.6 ± 5.5 kg/m^2) took part in the experiments one year after surgery. Unfortunately, five patients cancelled the final session after twelve months without further justification. Another 14 non-obese individuals (9 females, age 52.0 ± 6.1y, BMI 24.7 ± 3.4 kg/m^2) served as controls. They were investigated once, with the same MRI techniques as the intervention group.

T1-weighted MRI for voxel-based gray and white matter morphometry (VBM)

MRI scanning was performed with a 3-T Siemens VERIO system (Siemens, Erlangen, Germany) equipped with a 12-channel head coil. All