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Impact of bariatric surgery on neural food processing and cognition: an fMRI study

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ABSTRACT

Introduction The Roux-en-Y gastric bypass (RYGB) is one of the most widely used techniques for bariatric surgery. After RYGB, weight loss up to 50%–70% of excess body weight, improvement of insulin-resistance, changes in food preferences and improvements in cognitive performance have been reported. This protocol describes a longitudinal study of the neural correlates associated with food-processing and cognitive performance in patients with morbid obesity before and after RYGB relative to lean controls.

Methods and analysis This study is a pre–post case–control experiment. Using functional MRI, the neural responses to food stimuli and a working memory task will be compared between 25 patients with obesity, pre and post RYGB, and a matched, lean control group. Resting state fMRI will be measured to investigate functional brain connectivity. Baseline measurements for both groups will take place 4 weeks prior to RYGB and 12 months after RYGB. The effects of RYGB on peptide tyrosine tyrosine and glucagon-like polypeptide-1 will also be determined.

Ethics and dissemination The project has received ethical approval by the local medical ethics committee of the Carl-von-Ossietzky University of Oldenburg, Germany (registration: 2017-073). Results will be published in a peer-reviewed journal as original research and on international conferences.

Trial registration number DRKS00012495; Pre-results.

Strengths and limitations of this study

- ► Employing functional MRI, the study will prospectively investigate neural plasticity of food processing and working memory following Roux-en-Y gastric bypass (RYGB).
- ► By including functional MRI, genetic analysis and behavioural measurements, RYGB-associated neural changes can be tracked longitudinally.
- ► Due to the longitudinal nature of the study, withdrawals of participants are expected, leading to participants with incomplete data.

BACKGROUND

Obesity is defined as having a body mass index (BMI) of ≥30 kg/m^2.[1] The prevalence of obesity has constantly been rising leading to significant health concerns since obesity is accompanied by health issues including diabetes mellitus, gallbladder disease, osteoarthritis, hypertension and cardiovascular diseases.[2 3] In 2016 worldwide, >1.9 billion adults were overweight of which 65% were obese.[4]

The treatment of obesity can be roughly classified in three classes. B*ehavioural modification* methods comprise revision of food consumption behaviour (eg, decreasing portion sizes and regular eating time), increasing the amount of physical activity, analysing the lifestyle (and identification of trigger habits), as well as the identification of the emotional contents that might lead to imbalanced consumption behaviour. These measures can be supplemented by the use of *medications* such as lipase inhibitors, insulin sensitivity enhancer or modulators of hormone action (eg, glucagon-like polypeptide-1 (GLP-1) receptor agonist that stimulates insulin secretion). While deep brain stimulation of the nucleus accumbens has recently been described as being effective in morbid obesity in a case report,[5] the only established invasive method to reduce weight is *bariatric surgery*. Surgical techniques aiming at weight loss comprise sleeve gastrectomy, gastric banding and gastric bypass surgery.[6] Gastric bypass surgery is one of the most commonly employed weight loss techniques with average weight loss of around 50%–70% of excess body weight.[7 8] The Roux-en-Y gastric bypass (RYGB) surgery is an irreversible procedure and is the most frequently applied bariatric technique. Here, the stomach is divided to create a small pouch which enables the food to bypass parts of the digestive tract. The pouch and the duodenum are reattached further down to the small intestine.[9] After surgery, many patients show a marked decrease of weight, feel less hungry, eat less, show lower drive for food and are

less preoccupied with food.[10] Also, the food preferences change after surgery, which is reflected in lower ratings for high-fat and high-calorie food.[11]

One mechanism underlying the changes in food consumption behaviour after RYBG is altered expression of hormones, including the anorexigenic intestinal hormones peptide tyrosine tyrosine (PYY) and GLP-1. Both hormones show increased levels postprandially after surgery.[10 11] Therefore, the regulation of appetite is modulated through a delay in gastric emptying (through increased levels of PYY) and an increased glucose-dependent insulin release (through increased levels of GLP-1).[12] In contrast, decreased levels of ghrelin, an orexigenic hormone showing stimulatory effects on food hedonics, were found after RYGB.[11 13] It has to be pointed out, however, that in about one-fifth of patients treated with bariatric surgery, the commonly accepted threshold of 50% excess weight loss (EWL) is not reached.[14] This has particularly been attributed to intrapersonal factors such as external, reward-based eating behaviour and personality traits.[14 15] This calls for an investigation of the neural and behavioural changes of RYGB.

In functional MRI (fMRI) studies of the brain, changes in blood oxygen level-dependent (BOLD) signal for food stimuli have also been observed after RYGB. A postsurgical reduction in activation has been found within the mesolimbic pathway, that is, in areas which have been associated with reward behaviour. These include the ventral tegmental area, amygdala, hippocampus, anterior insula and ventral striatum. Interestingly, a selective reduction for high-energy versus low-energy food was observed, with greater reductions for high-energy food stimuli.[10 11] Further, an increased sensitivity to salty taste and a decreased activation in the reward system for sweet taste has been reported.[8] The mesolimbic pathway underlies the executive control of the prefrontal cortex, a structure responsible to initiate appropriate behavioural response to a given stimulus.[16] Here, lower activations in the orbitofrontal cortex and medial prefrontal cortex have been reported after RYGB.[13 17] Of note, most previous studies showing changes in reward-related circuitry in patients undergoing RYBG have been performed within a relatively short interval between surgery and fMRI measurement of 4–12 weeks[16 18 19]. As an exception, Wang *et al* studied the patients' neural responses to actual sweet and salty tastes 1 year after surgery.[8] Despite well-documented behavioural effects of RYGB after 6 years, a systematic long-term study investigating neural responses to food stimuli after 1 year of RYBG is lacking[20] (see table 1 for an overview).

In addition to changes in hormone levels and brain circuitry underlying food intake control and processing, changes in cognitive functions after RYGB have also been reported. A key component contributing to cognitive performance are the executive functions (EF), that is, metacognitive processes allowing regulation of behaviour towards a goal, self-regulation and decision-making.[21 22] On a neural level in healthy participants, EF have been associated (among other areas) with activation in the dorsolateral prefrontal cortex (Brodmann Area (BA) 9, 46), anterior cingulate cortex (BA 32), superior and inferior parietal lobe (BA 7, 40), prefrontal cortex (BA 6, 10) and temporal cortex (BA 13).[23] Obesity is associated with decreased EF performance, including attention and set shifting, inhibitory control, abstract reasoning, memory and visuospatial organisation.[22 24 25]

Table 1 Overview of studies investigating the impact of RYGB on neuronal processing of food relevant items and cognition

Author	No. of patients–controls (M–F)	Age (SD) (patients–controls)	fMRI task	Pre/post interval
Faulconbridge *et al* (2016)[13]	0 (22)–0 (19)	37.2±9.3 36.4±8.2	Food images	4 weeks / 6 months±2 weeks
Frank *et al* (2016)[7]	2 (10)–6 (6)	50±2.67 50.7±3.29	Food reward task	- / 17.73±2.68 months
Frank *et al* (2014)[19]	0 (9)–0 (11)	42.0±2.8 36.6±3.8	One-back food task	- / 3.4±0.8 years
Goldman *et al* (2013)[54]	5 (26)–0 (0)	45.87±11.08	Food craving/resisting task	- / 3.07±2.0 years
Ochner *et al* (2011)[16]	0 (10)–0 (0)	35±9 -	Visual/auditory food stimulation	1 month / 1 month
Ochner *et al* (2012)[55]	0 (5)–0 (0)	36±13	Visual/auditory food stimulation	1 month / 1 month
Scholtz *et al* (2013)[56]	4 (26)–3 (17)	43.5±2.0 39.1±2.3	Food picture evaluation	- / 8.1 months
Van de Sande-Lee *et al* (2011)[57]	2 (11)–2 (6)	34.0±10 29.5±4	D-glucose ingestion	0 / ~8.3 months
Wang *et al* (2016)[8]	3 (2)–5 (2)	46.2±7.7 51.7±7.8	Taste testing (salt/sweet)	1 month / 12 months

Additionally, cognitive processing speed is slowed, which has been observed in tasks such as the Stroop task, the controlled oral word association task and the digit symbol substitution task.[22] In contrast, weight loss is associated with improvement in EF across different cognitive domains.[26] One behavioural study reported improved working memory (WM) 12 weeks after bariatric surgery, which was reflected in an improved performance in the Digit Span test.[24] Currently available studies showing the neural correlates of increased cognitive functioning after bariatric surgery are limited, though.

Changes in BOLD signal without the involvement of a task can be measured with resting state functional MRI (rs-fMRI). Correlated spontaneous fluctuations of the BOLD signal in different regions have been taken to indicate functional coupling of these regions to large-scale networks and are generally denoted as 'functional connectivity'.[27] Only one study reported changes in functional connectivity 1 year after RYGB surgery in patients with obesity. Here, a higher connectivity between regions involved in food-related saliency attribution and reward-driven eating behaviour was found prior to surgery compared with lean controls.[9] One year after bariatric surgery, changes in networks related to cognitive control over eating and bodily perception were reported. Despite a well-chosen experimental design this study suffered from a small sample size and did not provide a psychological profile of the participants. To further elucidate the change in functional connectivity associated with RYGB, the current study will include rs-fMRI.

STUDY AIMS

The planned study will examine neural changes associated with RYGB. We hypothesise that, prior to RYGB, obese individuals show increased neuronal activity to food cues in reward-related brain areas compared with a healthy, lean control group. The enhanced food processing is expected to be reduced 12 months post-surgery. Hormonal status will also be affected by RYGB; we expect lower PYY and GLP-1 levels, compared with healthy individuals, prior to surgery with a respective change after 12 months. The hormonal status of PYY and GLP-1 are expected to be negatively correlated with the neuronal response in reward-related brain areas to food images. We hypothesise that lower hormonal levels are negatively correlated to a heightened brain response in reward-related areas to food stimuli prior to RYGB. Respectively, we expect higher hormonal levels are negatively correlated with a lowered brain response in reward areas to food stimuli 12 month after RYGB. We expect a lower performance in WM in obese subjects compared with healthy controls. After RYGB, we assume a significant increase in WM performance in the bariatric group, which is also reflected on the neuronal level by enhanced recruitment of brain areas associated with executive functioning. Compared with controls, functional connectivity is expected to differ in participants with obesity prior to RYGB in terms of a stronger connectivity in the salience network with diminishing effects at the 12-month follow-up measurement (see box 1).

Box 1 Overview of the hypotheses and main outcome variables

- H1: patients with obesity show enhanced activity in reward-related brain areas to food cues prior to RYGB compared with healthy controls.
- H2: 12 months after RYGB, patients show a decrease in *neural responses* to food cues compared with pre-surgery.
- H3: working *memory performance* will be lower in patients with obesity prior to RYGB compared with healthy controls, which is reflected in lower prefrontal activation.
- H4: working *memory performance* will be improved 12 months after RYGB in patients with obesity, which is reflected in increased prefrontal activation.
- H5: RYGB leads to a decrease in functional connectivity, in particular, in the salience network.
- H6: hormonal status is negatively correlated with the neural response in reward-related brain areas to food images.
- Primary outcome variables: neural processing of food stimuli, cognitive performance during the 2-back task and functional connectivity.
- Secondary outcome variables: hormonal status and behavioural data (derived from questionnaires).

RYGB, Roux-en-Y gastric bypass.

METHODS

Participants

In total, 50 female participants (25 patients with obesity and 25 lean control subjects) aged from 18 to 60 years will be recruited at the Centre for Obesity in Friesoythe, Germany and at the Carl-von-Ossietzky University Oldenburg, Germany. The patients with obesity will be screened for suitability for bariatric surgery according to the German guideline for prevention and therapy of obesity[28] by an experienced surgeon (WV). Decision for treatment will be made independent of the current study. Anxiety will be no exclusion criterion since there is a high prevalence in people with obesity.[29] Participants with obesity need to have a BMI >35 kg/m^2 to get enrolled in the study. Obesity-related comorbidities such as diabetes mellitus, hypertension, sleep apnoea and dyslipidaemia will be no exclusion criteria. Inclusion criteria for the lean, healthy control group are a BMI <25 kg/m^2, no history of any psychiatric disorder and no history of eating disorder. Exclusion criteria are substance abuse including nicotine, current major depression, psychopharmalogical treatment, neurological disorders, pregnancy, claustrophobia and MRI contraindications (eg, metallic implants and cardiac pacemaker). The control group will be matched to the obese group for age, sex and education. Since the study will only enrol female participants, the menstrual cycle will be controlled for by assessing only in the midfollicular phase (days 4–8 after onset of menses) due to

differences in brain responses to reward between the follicular and the luteal phase.[30]

Patient and public involvement

Patients were not involved in the development of the research question, outcome measures or study design.

Behavioural assessment

At the baseline measurement (up to 4 weeks prior to RYGB) and at the follow-up measurement (between 12 and 13 months after RYGB), the participants will be asked to fill out a demographic questionnaire and the Freiburger Persönlichkeitsinventar (Freiburg Personality Inventory, FPI-R).[31] The FPI-R is a personality test, which assesses personality traits on 12 scales. To assess psychiatric comorbidity, the structured clinical interview for DSM-V will be administered (SKID-I/II, German version).[32]

The participants will be in a fasting period for 4 hours before the measurement. All the measurements will take place at around the same time of the day, which will be between 3 pm and 5 pm. The current state of hunger at time of the fMRI will be assessed on a 10-point Likert scale. Additionally, the time of the previous meal and the portion size of the previous meal will be recorded. To have a measurement on food consumption before the fMRI recording, the participants will be asked to complete a food diary 1 week prior to the pre/post recording in order to document what has been eaten, at which time of the day and also how much was eaten. The Fragebogen zum Essverhalten (Questionnaire of Eating Behaviour, FEV) will be administered.[33] The FEV measures the cognitive control of the eating behaviour, how impulsive the eating behaviour is and how the feeling of hunger is perceived. For assessing depressive symptoms, the German version of the Beck Depression Inventory (BDI) will be administered.[34] Abnormal eating behaviour and the inability to control the overconsumption of food has been linked to impulsivity. Moreover, it was found that impulsivity measures can predict weight reduction in patients undergoing bariatric surgery.[35] Therefore, all participants will be asked to fill out the German version of the Behavioural Inhibition System (BIS), a questionnaire examining impulsivity.[36] Moreover, there is meta-analytic evidence for a significant association between obesity and attention-deficit/hyperactivity disorder (ADHD).[37] To assess ADHD symptoms, the German versions of the Wender-Utah Rating scale and the Conners' adult ADHD self-rating scales will be applied (CAARS).[38 39] To control for a possible change in food preferences due to RYGB, the participants will rate the liking and wanting of each food image after the fMRI task on a 5-point Likert scale. Also, to have a measurement on weight after RYGB, the participants need to record the body weight on a weekly basis during the pre–post interval.

Medical assessment

Obesity-related comorbidities will be recorded. These include diabetes mellitus, hypertension, sleep apnoea and dyslipidaemia. Besides the BMI, the waist-to-hip-ratio will be measured and a body composition analysis will be done. These procedures together address fat distribution which is not provided by the BMI alone.[40 41]

Blood sample

A venous blood sample will be collected. The sample will then be centrifuged and the plasma will be aliquoted and stored at −80°C. The plasma concentrations of PYY and GLP-1 will be determined using standardised methods. Important, the blood sample will be collect at the same time point to prevent circadian influences. The participants will be asked not to eat 4 hours before the blood sample collection.

fMRI task

Each participant undergoes a ~1 hour MRI session at baseline (up to 4 weeks prior to RYGB) and at the follow-up time point (between 12 and 13 months after RYGB).

Food stimuli processing

During fMRI, participants will be required to watch images that show food or non-edible objects (eg, tools). Stimuli were taken from an existing and validated image database for experimental research on eating and appetite.[42] To account for possible differences on arousal and valence between pictures, we did an in-house rating: each picture was rated by 20 women with the self-assessment manikin on the scales arousal and valence.[43] Further, the food pictures were rated either as high- or low-caloric. These images have been used in previous neuroimaging studies (eg, Blechert *et al*).[44] In total, 190 food images and 190 neutral images will be shown, split in two runs containing 95 food and 95 object images, each. These images will be shown in a pseudorandomised order of 13 blocks containing 15 images of food items and in 13 blocks of 15 images of non-edible objects. Within each block, each image will be presented for 1 s with an inter-stimulus interval (ISI) of 200 ms. We decided to use a block design fMRI experiment with 1 s of image presentation and a brief ISI to maximise the neural responses to the visual stimuli. Our stimulus duration of 1 s is shorter than the stimulus duration used for example, by Blechert *et al*[44] who presented their images for 2.5 s in an event-related paradigm. The shorter stimulus duration of 1 s helps to avoid excessive eye movement. To ensure attention, participants will be asked whether a certain item was present after 15 images, followed by 10 s of baseline (black screen with fixation cross, see figure 1).

Desire for food

To assess food preferences at an explicit level, participants will perform a modified version of the approach-avoidance task.[45 46] Here, high-caloric and low-caloric food images will be presented. A sense of approaching or avoiding will be created by the participants' response to an image via a button press. By wanting a specific food item, the image will grow bigger and get smaller when the item is unwanted by the participant. First, 10 practice

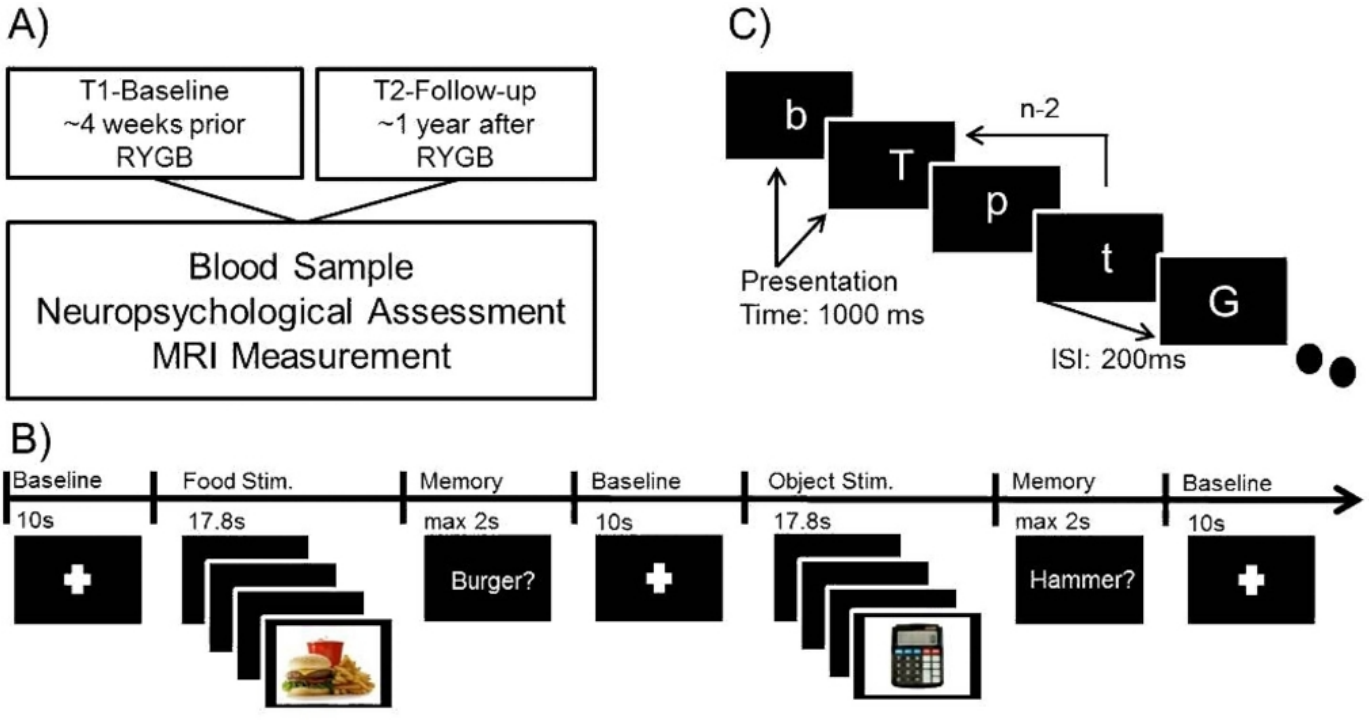

Figure 1 Schematic overview of (A) study timeline; (B) food stimulation paradigm; (C) 2-back task. ISI, interstimulus interval.

trials will be performed with neutral objects, followed by the presentation of 30 high-caloric and 30 low-caloric food images in a pseudorandomised order. Participants will be asked to respond as quickly and accurately as possible. The image will disappear once the item will be at largest or smallest size determined by the participants' response.

Working memory

Participants will be performing a letter version of the n-back task. The task demands the maintenance and permanent updating of new information in WM. It is required to observe a series of stimuli and to respond as soon as possible whenever a stimulus is presented that is the same as the one presented two trials before (2-back).[47] To reduce phonological and visual strategies, phonologically similar letters will be presented in lower and upper case: b, B, d, D, g, G, p, P, t, T, v, V. The case of the letters has to be ignored. The participants have to respond with a button press for a hit. Two blocks with a total duration of 14 min will be pseudorandomised with a white letter presentation on a black background. Each letter will be presented for 1 s and an ISI of 500 ms. In order to ensure a proper understanding of the task, participants will practice the 2-back task outside the scanner (figure 1).

Resting state

Resting state fMRI will be measured for 9 min. The participants will be instructed to not focus on specific thoughts and remain still with eyes open. The participants will be instructed to fixate a cross during the recording.

MRI data acquisition

Whole-brain fMRI blood oxygen-level dependent data will be acquired on a 3 T Siemens Magnetom Prisma with a 64-channel head coil at the Neuroimaging Unit, University of Oldenburg (https://www.uni-oldenburg.de/neuroimaging/) using an echo-planar T2*-weighted imaging sequence. A high-resolution T1-weighted anatomical image will be also be obtained. To ensure the absence of structural abnormalities in the brain, an experienced MRI technologist will examine all structural images. In case of an abnormality, we will contact a radiologist for further diagnostic scanning.

MRI data analysis

Analysis of the data will be carried out using fMRI Expert Analysis Tool), part of FSL (FMRIB's software Library, www.fmrib.ox.ac.uk/fsl).[48] For preprocessing, functional data will be motion corrected, temporally filtered with a high-pass filter and spatially smoothed using a Gaussian kernel. For each condition (visual stimulation: food images; object images; n-back task: hits, misses and false alarms), the BOLD response will be modelled using separate explanatory variables (EV). Each EV will be convolved with a canonical haemodynamic response function to model the haemodynamic response. Some nuisance covariates such as head motion parameters, global mean signal, white matte signal and cerebrospinal fluid signal will be regressed out to reduce the signal of no interest. Finally, individual data will be fitted to a general linear model as implemented in FSL. Non-linear registration to the MNI152 standard space template will be realised using FMRIB's Linear Image Registration Tool

and Non-linear Image Registration Tool. Group statistics will be carried out using FMRIB's Local Analysis of Mixed Effects stage 1 and stage 2 with automatic outlier de-weighting. For correction of multiple comparisons, clusters will be thresholded at Z=3.1 (p<0.05). Repeated measured analysis of variance (ANOVA) with the factors group, time and condition will be used to determine group differences in food stimuli processing, approach avoidance task and 2-back task performance.

Resting state fMRI will be analysed with the seed-to-voxel method using the toolbox CONN (http://www.conn-toolbox.org) and with independent component analysis using dual regression as implemented in FSL.[49] For the seed-to-voxel analysis, regions of interest will be chosen a priori based on the findings of relevant earlier studies (eg, salience network). Associations between the time courses of the fMRI signal in these seed regions and in all other voxels of the brain will be computed. For dual regression, a model-free approach based on FSL's MELODIC will be used.[50]

All resting state datasets will be decomposed into sets of time courses and associated spatial maps which describe the temporal and spatial characteristics of underlying hidden signals.[51] This procedure does not only enable removal of artefacts (eg, scanner drift) but also the isolation of neural networks, which results in template maps. Once the group ICA templates are created, they are regressed against the individual spatial maps (spatial regression) in order to identify the subject-specific time courses. To identify the subject-specific spatial maps, the network-specific time courses from the first regression step are used as predictors in a second regression stage.[49] The subject-specific time courses and spatial maps will be compared between the RYGB group and the control group, as well as between the pre and post intervention measurements.

Behavioural data analysis

Statistical analysis will be performed using SPSS (V.24, 2013). If the data are normally distributed, we plan to perform repeated measures ANOVA with the factors group X time which will be used to determine group and time differences for the demographic, psychometric and neuropsychological data. A linear regression will be performed with the test scores to clarify whether there has been an influence of the finding in the behavioural assessment on performance during food processing, approach avoidance task, and 2-back task. The test scores will be normalised to z-scores for statistical analysis with imaging data. Differences in hormonal status will be presumably evaluated with Student's t-tests, given that the data are normal distributed.

Sample size justification

The planned study will compare the neuronal response of participants with obesity with a healthy control group. Besides the group comparison, within group comparison will also be obtained. A study sample of 25 in an fMRI measurement leads to sufficient power as it is shown in Thirion *et al*.[52] Using G*Power (http://www.gpower.hhu.de/) to estimate the effect size, based on a repeated measures ANOVA with within-between interaction (α=0.05) yield in a medium effect size (0.36) with a power of 0.95.[53]

Value of the study

The current study, with its longitudinal design, will add information about the neuronal correlates of food processing before and after a RYGB to the existing literature. In particular, it is unknown so far whether RYGB leads to long-term adjustments in the neural responses to food and to lasting improvements of cognitive functions. This gap will be closed by food processing and WM tasks of the current study.

ETHICS AND DISSEMINATION

The study will be conducted in accordance with the Declaration of Helsinki in order to ensure the well-being and rights of the participants. The project has received ethical approval by the local medical ethics committee of the Carl-von-Ossietzky University of Oldenburg (registration: 2017-073). Written informed consent will be obtained from all participants. Participants will be able to withdraw from the study at any time without giving any reasons. During all measurement, medical professionals will be present. The study is registered at the German Clinical Trial Register with the trial registration number: DRKS00012495. Presumably, the recruitment of the participants will be finished by July 2019.

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