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Protocol article: 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 morbidly obese patients before and after RYGB relative to lean controls.

Methods and Analysis: This study is a pre-post case-control experiment. Using functional magnetic resonance imaging, the neural responses to food stimuli and a working memory task will be compared between 25 obese patients, pre and post RYGB, and a matched, lean control group. Functional connectivity will be measured with resting-state fMRI. 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 (PYY) and glucagon-like polypeptide-1 (GLP-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.

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Article Summary

Strengths and Limitations of this study

- ➔ Employing functional magnetic resonance imaging, the study will prospectively investigate neural plasticity of food processing and working memory following RYGB.
- ➔ Correlating neural data with hormonal and behavioural data will help to understand the mechanisms of neural plasticity after RYGB.
- ➔ 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 30kg/m^2 or higher[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, more than 1.9 billion adults were overweight with 65% obese adults among them[4].

The treatment of obesity can be roughly classified in three classes. B*ehavioural modification* methods comprise revision of food consumption behaviour (e.g., 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 (e.g., glucagon-like polypeptide-1receptor agonist that stimulates insulin secretion). While deep brain stimulation of the Ncl. accumbens has recently been described as being effective in morbid obesity in a case report, the only established invasive method to

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reduce weight is *bariatric surgery*[5]. Surgical techniques aiming at weight loss comprise of 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 behavior after RYBG is altered expression of hormones, including the anorexigenic intestinal hormones peptide tyrosine tyrosine (PYY) and glucagon-like polypeptide-1 (GLP-1). Both hormones show increased levels post-prandially 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 magnetic resonance imaging (fMRI) studies of the brain, changes in blood oxygen level-dependent (BOLD) signal for food stimuli have also been observed after RYGB. A post-surgical reduction in activation has been found within the mesolimbic pathway, i.e. in areas which have been associated with reward behaviour. These include the ventral tegmental area (VTA), amygdala, hippocampus, anterior insula, and ventral striatum. Interestingly, a selective reduction for high- vs. 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

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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 (OFC) 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. (2016) studied the patients' neural responses to actual sweet and salty tastes one year after surgery[8]. Despite well documented behavioural effects of RYGB after six years, a systematic long-term study investigating neural responses to food stimuli after one 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) i.e. 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 organization[22 24 25]. 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 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 blood oxygenation level dependent (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

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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 one year after RYGB surgery in obese patients. Here, a higher connectivity between regions involved in food-related saliency attribution and reward-driven eating behaviour was found prior to surgery compared to 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, did not provide a psychological profile of the participants and included only women. 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 hypothesize that prior to RYGB, obese individuals show increased neuronal activity to food cues in reward related brain areas compared to 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 to healthy individuals, prior to surgery with a respective change after 12 months. The hormonal status is expected to be correlated with the neuronal response to food images. We expect a lower performance in working memory in obese subjects compared to healthy controls. After RYGB, we assume a significant increase in working memory performance in the bariatric group, which is also reflected on the neuronal level by enhanced recruitment of brain areas associated with executive functioning. Compared to controls, functional connectivity is expected to differ in obese participants 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).

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H1: Obese patients show enhanced **activity** in reward related brain areas to food cues prior to RYGB compared to healthy controls.

H2: 12 months after RYGB, patients show a decrease in **neural responses** to food cues compared to pre-surgery.

H3: Working **memory performance** will be lower in obese patients prior to RYGB compared to healthy controls.

H4: Working **memory performance** will be improved 12 months after RYGB in obese patients, which is reflected in increased prefrontal activation.

H5: RYGB lead to decrease in functional connectivity regarding the salience network.

H6: Hormonal status is correlated with the neuronal response 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 behavioral data (derived from questionnaires)

Box 1 *Overview of the hypotheses and main outcome variables*

Methods

Participants

In total 50 participants (25 obese patients and 25 lean control subjects) aged from 18 to 60 years will be recruited at the centre for obesity in Friesoythe and at the Carl-von-Ossietzky University Oldenburg, Germany. The obese patients will be screened for suitability for bariatric surgery according to the German guideline for prevention and therapy of obesity[28]. Decision for treatment will be made independent of the current study. Anxiety will be no exclusion criterion since there is a high prevalence in obese people[29]. Obese participants need to have a BMI>35kg/m^2 to get enrolled in the study. Inclusion criteria for the lean, healthy control group are a BMI <25kg/m^2,

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no history of any psychiatric disorder, and no history of eating disorder. Exclusion criteria are substance abuse including nicotine, current major depression, psychopharmalogical treatment, pregnancy, claustrophobia, and MRI contraindications (e.g., metallic implants, cardiac pacemaker). The control group will be matched to the obese group for age, sex, and education.

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)[30]. 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, German version)[31].

In addition, the current state of hunger will be asked, since the subjects will be required not to eat 3h prior to the measurement. The energy intake earlier that day and the day before the measurement will also be recorded. The Fragebogen zum Essverhalten (Questionnaire of Eating Behaviour, FEV) will be administered[32]. 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[33]. 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[34]. Therefore, all participants will be asked to fill out the German version of the Behavioural Inhibition System (BIS), a questionnaire examining impulsivity[35]. Moreover, there is meta-analytic evidence for a significant association between obesity and attention deficit / hyperactivity disorder (ADHD)[36]. 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)[37 38]. 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 five-point Likert scale.

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Medical Assessment

Obesity-related co-morbidities will be recorded. These include diabetes mellitus, hypertension, sleep apnea, and dyslipidemia. Besides the BMI, the waist-to-hip-ratio will be measured and a body composition analyses will be done. These procedures together address fat distribution which is not provided from the BMI alone[39 40].

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 standardized 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 3 hours before the blood-sample collection.

fMRI task

Each participant undergoes a ~1h 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 (e.g., tools). Stimuli were taken from an existing and validated image database for experimental research on eating and appetite[41]. These images have been used in previous neuroimaging studies (e.g., Blechert et al., 2016)[42]. 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 pseudorandomized 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 1s with an interstimulus interval (ISI) of 200 ms. To ensure attention, participants will be asked whether a certain item was present after 15 images, followed by 10sec 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[43 44]. Here, high-and low-caloric food images will be presented. A sense of approaching or avoiding will be created by the

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participants' response to an image via a button press. By wanting a specific food item, the image will grow bigger and gets smaller when the item is unwanted by the participant. First, 10 practice trials will be performed with neutral objects, followed by the presentation of 30 high-caloric and 30 low-caloric food images in a pseudorandomized order. Participants will be asked to respond as quickly and accurate 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 working memory (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 2 trials before (2-back)[45]. 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 pseudorandomized with a white letter presentation on a black background. Each letter will be presented for 1sec and an ISI of 500msec. 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.

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 using an echo-planar T2*-weighted imaging sequence. A high-resolution T1-weighted anatomical image will be also being obtained.

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MRI data analysis

Analysis of the data will be carried out using FEAT (fMRI Expert Analysis Tool), part of FSL (FMRIB's software Library, www.fmrib.ox.ac.uk/fsl)[46]. Data will be motion corrected and temporally high-pass, and spatially smoothed using a Gaussian FWHM 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 hemodynamic response function to model the hemodynamic response. The temporal derivative of the hemodynamic response function will be included as regressor of no interest to model. Finally, individual data will be fitted to a general linear model (GLM) as it is implemented in FSL. Non-linear registration to the MNI152 standard space template will be realized using FLIRT and FNIRT (FMRIB's Linear and Non-linear Image Registration Tools). Group statistics will be carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 and stage 2 with automatic outlier de-weighting. For thresholding and correction for multiple comparisons, cluster-wise thresholding will be used. 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.

The resting-state functional connectivity will be identified an independent component analysis (ICA)-dual regression approach as it is implemented in the MELODIC tool of FSL. In the ICA, the data sets will be decomposed into sets of time courses and associated spatial maps which describe the temporal and spatial characteristics of underlying hidden signals[47]. This procedure does not only enable removal of artefacts (e.g., scanner drift) but also the isolation of neural networks, which results in template maps. One 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[48]. The subject-specific time courses and spatial maps will be between group-wise compared between the RYGB-group and the control group, as well as within group-wise between pre and post measurement.

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Behavioural Data Analysis

Statistical analysis will be performed using SPSS (IBM SPSS Statistics. V.24, 2013). Repeated measures analysis of variance (ANOVA) with the factors group X time 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 normalized to z-scores for statistical analysis with imaging data. Differences in hormonal status will be evaluated with Student's T-tests.

Sample size justification

The planned study will compare the neuronal response of obese participants to a healthy control group. Besides the group comparison, within group comparison will also be obtained. A study sample of 25 in an fMRI measurement lead to sufficient power as it is shown in Thirion et al. (2007)[49]. Using G*Power (http://www.gpower.hhu.de/) to estimate the effect size, based on a repeated measure ANOVA with within-between interaction (α=0.05) yield in a medium effect size (0.36) with a power of 0.95[50].

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 working memory 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

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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.

Funding Statement

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Conflict of interest

We declare no competing interests.

Authorship Contribution

MS, WV, PS, TM, and AP were involved in the design of the protocol for the study.MS wrote the first draft of this manuscript . WV, PS, TM, HM, and AP critically contributed to and redefined this manuscript. All authors approved the final manuscript.

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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) (Pat-Cont.)***	***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	NA / 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	NA / 3.4 ± 0.8 years
Goldman et al. (2013)[51]	5(26) - 0(0)	45.87 ± 11.08	Food craving/resisting task	NA / 3.07 ± 2.0 years
Ochner et al. (2011)[16]	0(10) - 0(0)	35 ± 9 NA	Visual /auditory food stimulation	1 month / 1 month
Ochner et al. (2012)[52]	0(5)- 0(0)	36 ± 13	Visual /auditory food stimulation	1 month / 1 month
Scholtz et al. (2013)[53]	4(26) - 3(17)	43.5 ± 2.0 39.1 ± 2.3	Food Picture Evaluation	NA / 8.1 months
Van de Sande-Lee et al. (2011)[54]	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

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Figure legends

Figure 1: schematic overview of A) study timeline; B) food stimulation paradigm; C) 2-back task, ISI= Interstimulus Interval

Box 1: Overview of the hypotheses and main outcome variables

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

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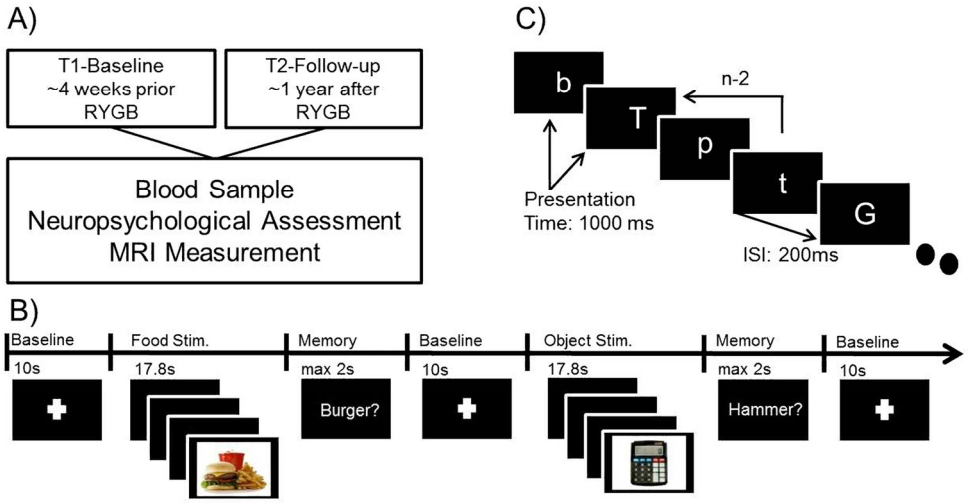

Figure 1 schematic overview of A) study timeline; B) food stimulation paradigm; C) 2-back task; ISI= Interstimulus Interval

schematic overview of A) study timeline; B) food stimulation paradigm; C) 2-back task, ISI= Interstimulus Interval

155x92mm (300 x 300 DPI)

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1
Roles and responsibilities: sponsor contact	#5b	Name and contact information for the trial sponsor	n/a

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information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	6-7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7-8
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7-8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions:	#11b	Criteria for discontinuing or modifying allocated	8

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modifications		interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8-9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence	7

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		until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a

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Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset,	n/a

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		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	n/a
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	13
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	9

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BMJ Open

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

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Secondary Subject Heading:	Diabetes and endocrinology, Neurology
Keywords:	Neurobiology < BASIC SCIENCES, Magnetic resonance imaging < RADIOLOGY & IMAGING, Neurophysiology < NEUROLOGY

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Protocol article: 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 morbidly obese patients before and after RYGB relative to lean controls.

Methods and Analysis: This study is a pre-post case-control experiment. Using functional magnetic resonance imaging, the neural responses to food stimuli and a working memory task will be compared between 25 obese patients, 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 (PYY) and glucagon-like polypeptide-1 (GLP-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.

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Article Summary

Strengths and Limitations of this study
➔ Employing functional magnetic resonance imaging, the study will prospectively investigate neural plasticity of food processing and working memory following RYGB. ➔ By including functional magnetic resonance imaging, 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 30kg/m^2 or higher[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, more than 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 (e.g., 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 (e.g., glucagon-like polypeptide-1receptor agonist that stimulates insulin secretion). While deep brain stimulation of the Ncl. accumbens has recently been described as being

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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 of 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 behavior after RYBG is altered expression of hormones, including the anorexigenic intestinal hormones peptide tyrosine tyrosine (PYY) and glucagon-like polypeptide-1 (GLP-1). Both hormones show increased levels post-prandially 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 magnetic resonance imaging (fMRI) studies of the brain, changes in blood oxygen level-dependent (BOLD) signal for food stimuli have also been observed after RYGB. A post-surgical reduction in activation has been found within the mesolimbic pathway, i.e. in areas which have been associated with reward behaviour. These include the ventral tegmental area (VTA), amygdala, hippocampus, anterior insula, and ventral striatum. Interestingly, a selective reduction for high- vs. low-energy food was observed, with greater reductions for high energy food stimuli[10]

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[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 (OFC) 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. (2016) studied the patients' neural responses to actual sweet and salty tastes one year after surgery[8]. Despite well documented behavioural effects of RYGB after six years, a systematic long-term study investigating neural responses to food stimuli after one 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) i.e. 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 organization[22 24 25]. 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 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 blood oxygenation level dependent (BOLD) signal without the involvement of a task can be measured with resting state functional MRI (rs-fMRI).

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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 one year after RYGB surgery in obese patients. Here, a higher connectivity between regions involved in food-related saliency attribution and reward-driven eating behaviour was found prior to surgery compared to 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 hypothesize that, prior to RYGB, obese individuals show increased neuronal activity to food cues in reward-related brain areas compared to 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 to 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 hypothesize 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 working memory in obese subjects compared to healthy controls. After RYGB, we assume a significant increase in working memory performance in the bariatric group, which is also reflected on the neuronal level by enhanced recruitment of brain areas associated with executive functioning. Compared to controls, functional connectivity is expected to differ in obese participants 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).

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H1: Obese patients show enhanced **activity** in reward-related brain areas to food cues prior to RYGB compared to healthy controls.

H2: 12 months after RYGB, patients show a decrease in **neural responses** to food cues compared to pre-surgery.

H3: Working **memory performance** will be lower in obese patients prior to RYGB compared to healthy controls, which is reflected in lower prefrontal activation.

H4: Working **memory performance** will be improved 12 months after RYGB in obese patients, 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)

Box 1 *Overview of the hypotheses and main outcome variables*

Methods

Participants

In total 50 female participants (25 obese patients 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 obese patients 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 obese people[29]. Obese participants need to have a BMI>35kg/m^2 to get enrolled in the study. Obesity-related comorbidities such as diabetes mellitus, hypertension, sleep apnea, and dyslipidemia will be no

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exclusion criteria. Inclusion criteria for the lean, healthy control group are a BMI <25kg/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 (e.g., metallic implants, 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 four hours before the measurement. All the measurements will take place at around the same time of the day, which will be between 3pm, and 5pm. The current state of hunger at time of the fMRI will be assessed on a ten-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

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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 five-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 apnea, and dyslipidemia. 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 standardized 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 ~1h 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 (e.g., tools). Stimuli were taken from an existing and validated image

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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 females 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 (e.g., Blechert et al., 2016)[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 pseudorandomized 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 1s with an interstimulus 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 maximize the neural responses to the visual stimuli. Our stimulus duration of 1 s is shorter than the stimulus duration used e.g. 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 10sec 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-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 trials will be performed with neutral objects, followed by the presentation of 30 high-caloric and 30 low-caloric food images in a pseudorandomized 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 working memory

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(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 2 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 pseudorandomized with a white letter presentation on a black background. Each letter will be presented for 1sec and an ISI of 500msec. 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 FEAT (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 hemodynamic response function to model the hemodynamic response. Some nuisance covariates such as head motion

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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 (GLM) as implemented in FSL. Non-linear registration to the MNI152 standard space template will be realized using FLIRT and FNIRT (FMRIB's Linear and Non-linear Image Registration Tools). Group statistics will be carried out using FLAME (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 (e.g., salience network). Associations between the timecourses 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 data sets 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 (e.g., 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 (IBM SPSS Statistics. V.24, 2013). If the data are normally distributed, we plan to perform repeated measures analyses

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of variance (ANOVA) with the factors group X time 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 normalized 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 obese participants to a healthy control group. Besides the group comparison, within group comparison will also be obtained. A study sample of 25 in an fMRI measurement lead to sufficient power as it is shown in Thirion et al. (2007)[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 working memory 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

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registration number: DRKS00012495. Presumably, the recruitment of the participants will be finished by July 2019.

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Conflict of interest

We declare no competing interests.

Authorship Contribution

MS, WV, PS, TM, and AP were involved in the design of the protocol for the study.MS wrote the first draft of this manuscript . WV, PS, TM, HM, and AP critically contributed to and redefined this manuscript. All authors approved the final manuscript.

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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) (Pat-Cont.)***	***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	NA / 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	NA / 3.4 ± 0.8 years
Goldman et al. (2013)[54]	5(26) - 0(0)	45.87 ± 11.08	Food craving/resisting task	NA / 3.07 ± 2.0 years
Ochner et al. (2011)[16]	0(10) - 0(0)	35 ± 9 NA	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	NA / 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

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Figure legends

Figure 1: schematic overview of A) study timeline; B) food stimulation paradigm; C) 2-back task, ISI= Interstimulus Interval

Box 1: Overview of the hypotheses and main outcome variables

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

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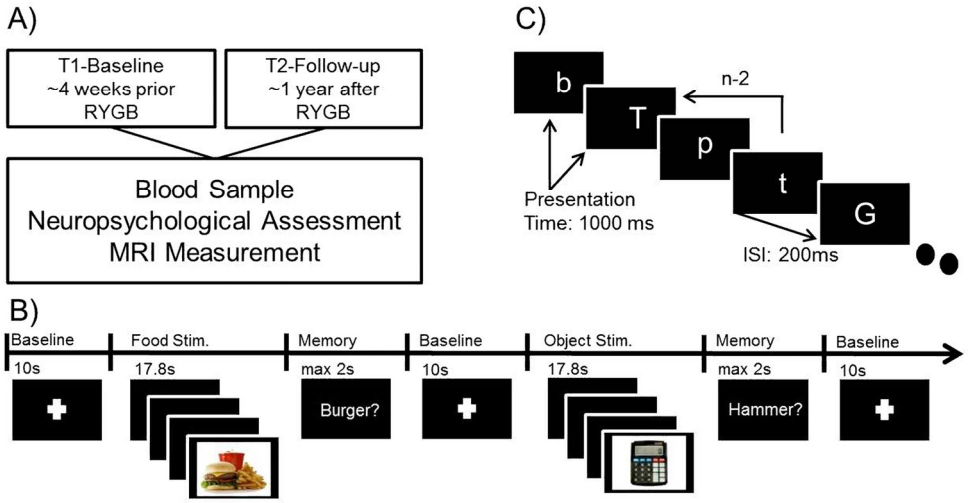

Figure 1 schematic overview of A) study timeline; B) food stimulation paradigm; C) 2-back task; ISI= Interstimulus Interval

schematic overview of A) study timeline; B) food stimulation paradigm; C) 2-back task, ISI= Interstimulus Interval

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1
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information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	6-7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7-8
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7-8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions:	#11b	Criteria for discontinuing or modifying allocated	8

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modifications		interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8-9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence	7

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		until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a

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Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset,	n/a

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		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	n/a
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	13
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	9

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