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Published in:
Metabolism: Clinical and Experimental

Publication Status:
Published (in print/issue): 31/01/2023

DOI:
10.1016/j.metabol.2022.155341

Document Version
Publisher's PDF, also known as Version of record

Metabolism 138 (2023) 155341

Contents lists available at ScienceDirect

Metabolism

journal homepage: www.journals.elsevier.com/metabolism

Hypothalamic integrity is necessary for sustained weight loss after bariatric surgery: A prospective, cross-sectional study

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ARTICLE INFO

Keywords:
Obesity
RYGB
Craniopharyngioma
Bariatric surgery
Gut microbiota

ABSTRACT

Objective: The hypothalamus is the main integrator of peripheral and central signals in the control of energy homeostasis. Its functional relevance for the effectivity of bariatric surgery is not entirely elucidated. Studying the effects of bariatric surgery in patients with hypothalamic damage might provide insight.
Summary background data: Prospective study to analyze the effects of bariatric surgery in patients with hypothalamic obesity (HO) vs. matched patients with common obesity (CO) with and without bariatric surgery.
Methods: 65 participants were included (HO-surgery: n = 8, HO-control: n = 10, CO-surgery: n = 12, CO-control: n = 12, Lean-control: n = 23). Body weight, levels of anorexic hormones, gut microbiota, as well as subjective well-being/health status, eating behavior, and brain activity (via functional MRI) were evaluated.
Results: Patients with HO lost significantly less weight after bariatric surgery than CO-participants (total body weight loss %: 5.5 % vs. 26.2 %, p = 0.0004). After a mixed meal, satiety and abdominal fullness tended to be lowest in HO-surgery and did not correlate with levels of GLP-1 or PYY. Levels of PYY (11,151 ± 1667 pmol/l/h vs. 8099 ± 1235 pmol/l/h, p = 0.028) and GLP-1 (20,975 ± 2893 pmol/l/h vs. 13,060 ± 2357 pmol/l/h, p = 0.009) were significantly higher in the HO-surgery vs. CO-surgery group. Abundance of Enterobacteriaceae and Streptococcus was increased in feces of HO and CO after bariatric surgery. Comparing HO patients with lean-controls revealed an increased activation in insula and cerebellum to viewing high-caloric foods in left insula and cerebellum in fMRI.
Conclusions: Hypothalamic integrity is necessary for the effectiveness of bariatric surgery in humans. Peripheral changes after bariatric surgery are not sufficient to induce satiety and long-term weight loss in patients with hypothalamic damage.

1. Introduction

Hypothalamic obesity is mainly caused by hypothalamic damage, often due to a craniopharyngioma, which is a rare benign cerebral tumor with an incidence of approximately 0.12 per 100,000 per year [1]. Patients' quality of life is often impaired due to affection of adjacent cerebral tissue [2,3]. Beside hormonal pituitary insufficiency, visual impairment, or headaches [4], up to 50 % of individuals with craniopharyngioma develop obesity. However, also other tumors, like meningiomas or astrocytomas, can lead to damage of the hypothalamus and consecutively to obesity. Obviously, the functional damage depends on tumor location and size. It has been shown that the degree of

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https://doi.org/10.1016/j.metabol.2022.155341
Received 27 April 2022; Accepted 24 October 2022
Available online 27 October 2022

hypothalamic damage is a determinant for the development of hyperphagia and hypothalamic obesity (HO) [5,6]. This phenomenon can also occur in patients with any other damage or malformation of the hypothalamus [7]. These symptoms can not only arise due to the tumor expansion itself but are sometimes not preventable adverse effects of its surgical removal [8,9] as well as often necessary radiotherapy [10].

Bariatric surgery is a well-established and currently the most effective therapy in individuals with class II and III obesity (common obesity, CO). Beside a clinically relevant and sustained weight loss, bariatric surgery improves obesity related comorbidities and is associated with a longer life expectancy than usual obesity care [11–14]. Numerous studies have shown that the weight-reducing and metabolic effects of bariatric surgery are not primarily due to food restriction and malabsorption but due to reduction in hunger, increase in satiety and in some patients due to reduction of the rewarding aspect of food. These changes in eating behavior are mediated by changes in gut-derived signals, such as altered postprandial levels of anorexic gut hormones [15–17], bile acid signaling [18], changes in gut microbiota and associated neuromodulatory metabolites [19–23] and other not yet identified factors. However, the details of these complex mechanisms of action behind bariatric surgery are not entirely elucidated. Anorexic enteroendocrine gut hormones, with Glucagon-like peptide-1 (GLP-1) and Peptide YY (PYY) being the most studied, are increased postprandially after bariatric surgery [24,25], especially after the most common interventions sleeve gastrectomy and Roux-en-Y gastric bypass (RYGB) [26–28]. Thus, these gut hormones were considered a valuable conservative treatment option. Meanwhile the GLP-1 analogue semaglutide has shown to induce clinically relevant weight loss [29]. Translational data, however, at least questioned if gut hormone signaling is necessary for the beneficial effects of bariatric surgery [30–32]. Effects of GLP-1 and PYY are mainly mediated via the hypothalamus [33,34], which is the key integrator of peripheral and central signals controlling energy balance and food intake are necessary for the efficiency of bariatric surgery. There are retrospective studies demonstrating that bariatric surgery is less effective in patients with hypothalamic obesity (HO) compared to patients with common obesity [35,36].

In this prospective, cross-sectional study, we aimed to examine the clinical observation that bariatric surgery is less effective in people with HO. We, therefore, compared patients with common obesity versus hypothalamic obesity both with and without bariatric surgery in terms of eating behavior, psychological and health measures, brain responses to food cues, gut hormone responses and gut microbiota composition.

2. Methods

2.1. Study design and patients

In this prospective, cross-sectional study, we enrolled both individuals with common obesity (CO) and hypothalamic obesity (HO) with and without bariatric surgery prior to this study. Patients (HO-control with CO-control and HO-surgery with CO-surgery) were frequency-matched for age, sex and educational status as well as time since surgery (if applicable). HO was defined as development of obesity after diagnosis and/or surgical treatment of hypothalamic diseases. Patients with the following tumors were considered as eligible: Craniopharyngioma (n = 17) and astrocytoma (n = 1). In all patients, a board-certificated neurosurgeon experienced in hypothalamic/pituitary surgery, blinded for any other clinical information, reviewed the MRIs of HO patients and evaluated the structural hypothalamic damage (mild or severe). Lean/healthy (Lean-control) and obese patients without bariatric surgery served as controls (HO-control, CO-control). In total, 65 participants were recruited for the study. All patients with pituitary insufficiency (in the HO-control and HO-surgery group only) were adequately substituted as rated by two experienced endocrinologists. Concentrations of TSH, fT3, fT4, IGF-1, ACTH, cortisol, LH, FSH were measured as part of our clinical routine in the HO groups only. See Table 1 for all patients. The study was approved by the ethics committee of the University of Würzburg (AZ 43/17). Written informed consent was obtained from all participants.

Table 1
Characteristics of the study groups.

Group	HO-surgery	HO-control	CO-surgery	CO-control	Lean-control
N	8	10	12	12	12
Age	33.6 ± 11.9	37.3 ± 12.5	38.8 ± 9.6	33.9 ± 11.5	29.2 ± 12.4
Sex (f/m)	4/4	7/3	6/6	7/5	7/5
Education (basic/middle/high)	4/2/2	4/3/3	6/4/2	6/4/2	5/5/2
Type of bariatric surgery (SG/RYGB/BPD)	3/4/1	n/a	4/8/0	n/a	n/a
BMI in kg/m^2 before bar. surg.	53.3 ± 10.5	n/a	51.9 ± 5.1	n/a	n/a
BW kg before bar. surg.	151.7 ± 24.8	n/a	158.2 ± 26.9	n/a	n/a
BMI in kg/m^2 at time of the study	48.7 ± 9.3	44.7 ± 10.5	38.5 ± 8.7	47.2 ± 5	23 ± 2.6
BW in kg at time of the study	143.4 ± 22.6	127 ± 35.2	116.7 ± 27.5	144.3 ± 21.55	69.9 ± 12
Surgery of the hypothalamic/pituitary region, n (%)	8 (100 %)	10 (100 %)	n/a	n/a	n/a
Radiotherapy of the hypothalamic/pituitary region, n (%)	5 (62.5 %)	7 (70 %)	n/a	n/a	n/a
Severe hypothalamic damage according to MRI	4 (50 %)	5 (50 %)	n/a	n/a	n/a
Corticotropic insufficiency, n/% sufficiently replaced	6/100 %	7/100 %	n/a	n/a	n/a
Thyrotropic insufficiency, n/% sufficiently replaced	7/100 %	10/100 %	n/a	n/a	n/a
Gonadotropic insufficiency, n/% sufficiently replaced	7/100 %	7/100 %	n/a	n/a	n/a
Growth hormone deficiency, n/% sufficiently replaced	6/33 %	9/55 %	n/a	n/a	n/a
Diabetes insipidus centralis, n/% sufficiently replaced	5/100 %	7/100 %	n/a	n/a	n/a

BMI body mass index, BW body weight, SG sleeve gastrectomy, RYGB Roux-en-Y gastric bypass, BPD biliopancreatic diversion. Data presented as mean and standard deviation.

2.2. Eating behavior, psychological and health questionnaires

The following questionnaires on eating behavior, health and mood were completed by all study participants: Patient Health Questionnaire (PHQ-D), Beck's-Depression-Inventory (BDI), Food Cravings Questionnaire-Trait (FCQ-T), questionnaires regarding eating behavior (FEV and FEV-II) and Short Form 36 health questionnaire (SF-36) [37–43].

2.3. Sweet taste intensity and preference test

All participants took part in a sweet preference test adapted from Miras et al. [44]. This test took place on a different day than the mixed meal tolerance test, after 10 h of fasting. Participants tasted different solutions of saccharose prepared in water at different concentrations. Thirty cups filled with 30 ml of the respective saccharose solution were numbered from 1 to 30, placed in 3 rows of 10 cups, and filled with sugar-solutions or just water (see Supplement Table 1). Within 15 s,

participants had to rate the sweetness of each sample compared to the sweetness of their "ideal soft drink" using the "Just about right" visual analogue scale (JAR scale). After each tasting, participants rinsed their mouth with water for 15 s.

2.4. Mixed meal tolerance test

All participants consumed 200 ml of an energy drink (Ensure Plus (Abbott, Chicago, IL, USA) or Resource® Energy chocolate (Nestlé, Vevey, Switzerland), identical in terms of kcal) after a period of fasting of 10 h. Blood samples were taken immediately before (0 min) and 15, 30, 45, and 60 min. Every blood sample, processed immediately after taking and pretreated with a Dipeptidylpeptidase-4 inhibitor (DPP4, Merck, Darmstadt, Germany) and aprotinin (Merck) was analyzed for concentrations of plasma/serum glucose, insulin, total PYY 3–36, total GLP-1, GLP-2, oxyntomodulin and leptin (Phoenix Pharmaceuticals (Burlingame, CA, USA), EK-028-11, EK-059-02, EK-003-12, EK-028-14, EK-028-22). GLP-2, oxyntomodulin and leptin were measured at 0 min and 30 min in groups CO-surgery and HO-surgery only. The participants rated their appetite using visual analogue scales (VAS) at the same time points and thereby stated hunger, satiety, abdominal fullness, and how much to still be able to eat of his/her favorite food. Levels of GLP-1/PYY were correlated with VAS ratings.

2.5. Extraction of fecal genomic DNA extraction

Genomic DNA was extracted from 100 to 150 mg of feces using repeated bead beating [45]. Briefly, samples were placed in Lysing Matrix E tubes (MP Biomedicals, Eschwege, Germany) and extracted twice in lysis buffer (4 % w/v sodium dodecyl sulfate, 500 mmol/l NaCl, 50 mmol/l ethylenediaminetetraacetic acid, 50 mmol/l Tris·hydrochloride, pH 8) with bead beating at 5.0 m/s for 60 s in a FastPrep−24 instrument (MP Biomedicals). After each bead-beating cycle, samples were incubated at 95 °C for 15 min and then centrifuged at full speed for 5 min at 4 °C. Supernatants from the two extractions were pooled, and the DNA was recovered by isopropanol purification and then purified using the QIAamp DNA Mini kit (QIAGEN, Venlo, Netherlands).

2.6. 16S rRNA gene amplification, sequencing and data analysis

The V4 variable region of the 16S rRNA genes from each sample were amplified with 515F and 806R primers, designed for dual indexing in duplicate reactions [46]. PCR amplification was performed in 25 μl volume containing AccuPrime Pfx SuperMix (Thermo Fisher Scientific, Waltham, MA, USA), 200 nM of each primer and 20 ng of genomic DNA. PCR was carried out by initial denaturation for 3 min at 95 °C, followed by 25 cycles (denaturation for 45 s at 95 °C, annealing for 60 s at 52 °C and elongation for 90 s at 72 °C) and a final elongation step for 10 min at 72 °C. Duplicates were combined, purified with the NucleoSpin Gel and PCR Clean-up kit (MACHEREY-NAGEL, Düren, Germany) and quantified using the Qubit dsDNA HS Assay kit (Invitrogen). The amplified V4 region of the 16S rRNA gene was sequenced 250 bp paired-end on an Illumina MiniSeq instrument (RTA v. 2.11.4.0; MCS 2.0.0.16) with the MiniSeq Mid Output kit.

Sequencing data were analyzed using the Quantitative Insights into Microbial Ecology 2 (QIIME 2) [47]. Paired-end reads were merged, quality and chimera filtered using DADA2 [48]. We obtained an average of 60,054 ± 8793 sequences/sample (mean ± SD; range 46,607–77,242). In total, 2,402,143 reads were clustered into 1660 operational taxonomic units (OTUs). OTUs are then contrasted against the 16S rRNA gene reference Greengenes database (v.13.8) [49] using the Ribosomal Database Project Classifier [50] to distinguish the microorganisms present in the microbiota. Genus and species level analyses were made on abundance on OTUs collapsed to the same genus (L6-level) and species (L7-level). To correct for differences in sequencing depth, samples were subsampled to the same number of reads (46,000 reads). For the analysis of relative abundance on genera/L6-level and species (L7-level), counts were scaled to the total sum of counts (values given as relative abundance summing up to 1).

2.7. Functional magnetic resonance imaging (fMRI)

2.7.1. fMRI paradigm

We used a previously established one-back task to measure the neural correlates of high-caloric (HC), low-caloric (LC) and non-food picture (NF) processing [51]. In each category 60 different pictures were presented. To control for their attention, the participants were instructed to press a button with their index finger if an image was identical to the last one shown, or a second button with their middle finger if the image was not. A total of 36 blocks were presented, each block consisted of five stimuli from the same category. Two hours before the fMRI, all participants ate an apple and a pretzel to induce the same grade of satiety.

2.7.2. fMRI study

Forty-six participants underwent the fMRI paradigm. One healthy control had to be excluded due to movement artefacts. Only patients with a significant hypothalamic damage and a randomly chosen subgroup of CO-control and CO-surgery participants underwent fMRI. Therefore, the fMRI sample consisted of 45 individuals with obesity (CO-control: n = 6, mean body weight 136.2 ± 17.5 kg, CO-surgery: n = 8, 126 ± 30.3 kg, HO-control: n = 5, 142.9 ± 41.6 kg, HO-surgery: n = 4, 129.4 ± 5.2 kg) and 22 Lean-controls (69.7 ± 11.6 kg).

In the MRI imaging session, four different measurement sequences were performed, including localization, resting state measurement, fMRI with a one-back task, as well as a structural image. Siemens Magnetom Skyra syngo MR D13 whole-body scanner (Siemens Medical Systems, Erlangen, Germany) was used to collect the fMRI data. A T2-sensitive Echo Planar Imaging (EPI) with pulse sequences of TE = 30 ms and TR = 2000 ms was used to measure the BOLD signal. The field of view (FOV) was 230 × 230 mm with a matrix resolution of 64 × 64 pixels. The volume datasets consisted of 556 images with 37 contiguous axial slices aligned parallel to the AC-PC line and an in-plane resolution of 3.6 × 3.6 mm and a slice thickness of 3.0 mm. To eliminate T1 saturation effects, the first 9 scans ("dummy scans") of each session were discarded. A T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence was also recorded with TR = 1900 ms and TE = 2.26 ms, as well as a flip angle of * = 9° after the fMRI measurement. The image consisted of 176 individual slices with an image resolution of 1.0 × 1.0 mm and 1.0 mm slice thickness. The FOV was 250 × 250 mm, and the matrix resolution was 256 × 256 pixels.

2.8. Statistical analysis

Descriptively means and standard deviations were calculated for continuous data, frequencies and percentages for categorical data. Between group effects (for glucose, insulin, GLP-1 and PYY) were tested using mixed effect models based on R (version 4.2, R Core Team, 2022) and R-module lmerTest (Kuznetsova, Brockhoff and Christensen, 2017) with group as fixed effect factor, time as repeated measurement factor and the interaction of group by time. Descriptively, Fishers' exact test was used to determine differences between groups in categorical data (e.g. for demographic variables). Rank analyses of variance according to Kruskal & Wallis were calculated to show overall group differences in continuous data. Descriptively Mann-Whitney-tests were calculated to show differences in continuous data between pairwise groups. A p value less or equal 0.05 (2-sided) was considered statistically significant. ANOVA with Tukey's correction for multiple comparisons was used in Graph Pad Prism 9 (San Diego, CA, USA) to analyze the questionnaires. For the gut microbiome analysis, the differences in phylum, genus and species levels between the groups were tested using Wilcoxon rank-sum

test. Controlling for false discovery rate was done by estimating the q-values of significant p-values. Hormone and glucose levels were additionally presented as area under the curve (AUC). The EPI were preprocessed and analyzed using SPM 12 software (Statistical Parametric Mapping software, SPM; Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk). After standard preprocessing (spatial alignment to the first volume, slice-time correction) functional data were co-registered to the individual structural image. SPM segmentation was used to classify the proportions of the structural images into white matter, grey matter, cerebrospinal fluid and non-brain specific tissue. EPI images were normalized to standard MNI coordinates and smoothed with a Gaussian filter of 6 × 6 × 6 FWMH.

Following preprocessing of the fMRI data, the General Linear Model was used (Friston, 2005) for statistical analysis. In the analysis, ten regressors were included, four of which corresponded to the stimuli categories (high calorie, low calorie and non-food) and the fixation cross presentation. Additionally, 6 regressors corresponded to the movement parameters (X, Y, Z, pitch, roll, yawn) and were added as regressors of no interest. In the second level analyses, we first calculated the contrast of food > nonfood stimuli, showing the effect of the paradigm in the total sample. Significant clusters were overlaid on avg152T1 image.

3. Results

3.1. Patients' characteristics, hypothalamic damage, and change in body weight

Eight patients with HO treated with bariatric surgery (HO-surgery) were enrolled in this study and compared to four control groups: 10 patients with HO, but no bariatric surgery, patients with CO with (n = 12) and without (n = 12) bariatric surgery, and lean control cohort (n = 12). Participant characteristics are shown in Table 1.

In the HO-surgery group 4/8 patients had MRI-morphologically severe and 4/8 patients mild hypothalamic damage (see a representative MRI in Fig. 1). In the HO-control group 5/10 patients had a severe and 5/10 patients a mild hypothalamic damage. Both HO groups showed similar rates of dysfunction and replacement of the pituitary thyroid, gonadal and adrenal axis (Table 1). Baseline hormonal values were comparable between both groups.

There was no significant difference in body weight (p = 0.99) or BMI (p = 0.99) between CO-surgery and HO-surgery before bariatric surgery. Similarly, body weight and BMI of CO-control and HO-control were comparable at the time of the study visit (p = 0.68 and p = 0.95) (Table 1). The change of BMI in the first two years after bariatric surgery of HO-surgery and CO-surgery patients is shown in Fig. 2.

At the time of the study visit (mean time after surgery: 58 ± 23 months (HO-surgery) and 46 ± 21.9 months (CO-surgery)), HO-surgery patients lost significantly less bodyweight after bariatric surgery than the CO-surgery patients (8.3 ± 9.9 kg vs. 41.5 ± 20.0 kg respectively, p = 0.0004). This represents a percentage of total weight loss of 5.5 % vs. 26.2 % (p = 0.0003). Weight loss and change in BMI within the HO-surgery group were not significant (p = 0.50 and p = 0.38, respectively), whereas these parameters reached statistical significance within the CO-surgery group (p = 0.0014 and p = 0.0001, respectively; Fig. 2).

3.2. Eating behavior

Ratings of hunger, measured by the FEV, were highest in the HO-surgery group and lowest in the CO-surgery group, but this difference was not significant (Fig. 3). Similarly, no significant group differences were detected in terms of emotional eating, a subscale of the FEV-II questionnaire (p = 0.21). In contrast, the subscale "External eating" (food intake driven by external triggers) was significantly higher in the HO-surgery group compared to the CO-surgery group (21.9 vs. 31.6 points, p = 0.01). No significant differences could were in the FCQ-T questionnaire (p = 0.3).

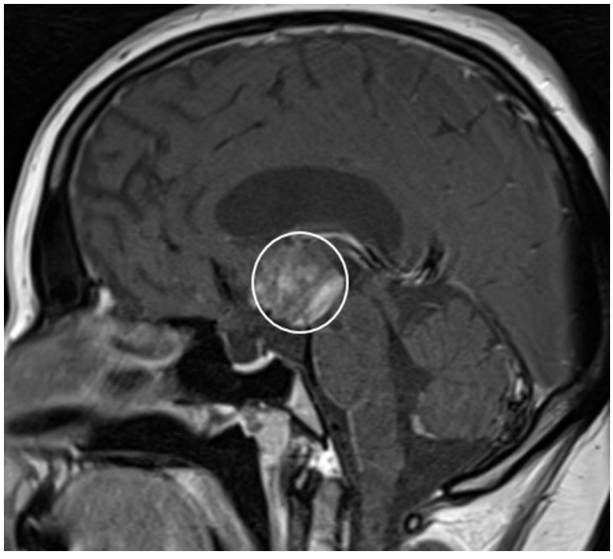

Fig. 1. MRI showing a typical hypothalamic tumor (encircled) in a patient with HO.

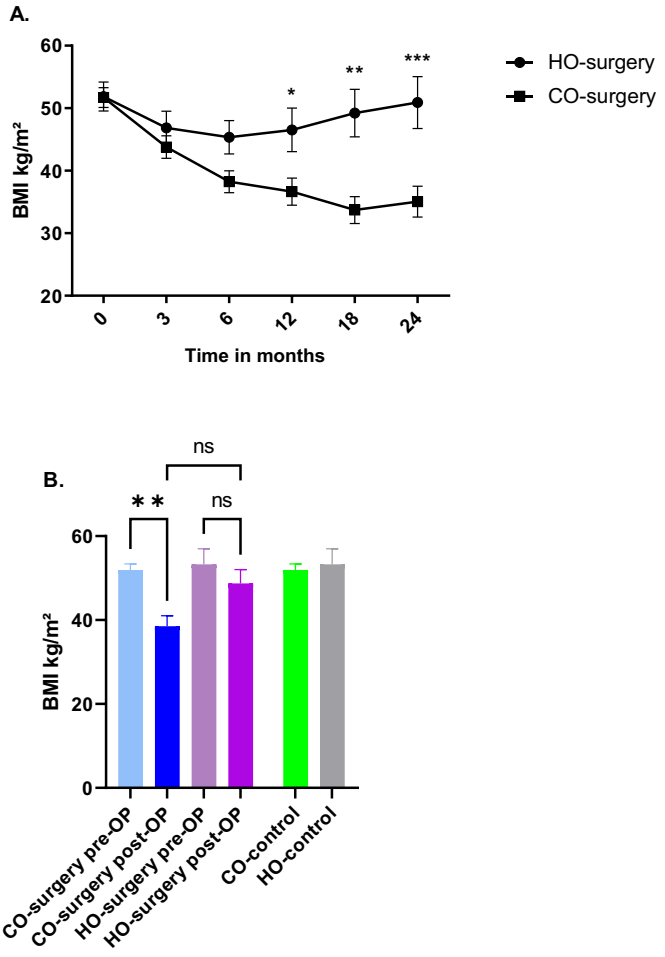

Fig. 2. A, Change of BMI of HO-surgery and CO-surgery patients in the first 24 month after bariatric surgery. * p ≤ 0.05, ** p ≤ 0.01, *** p ≤ 0.001 for differences in mean BMI. B, BMI (kg/m^2) of CO-control, HO-control, CO-surgery pre-OP, CO-surgery post-OP, HO-surgery pre-OP, HO-surgery post-OP. ** p ≤ 0.01 for differences in mean BMI. A, B, Data presented as mean and standard error of the mean.

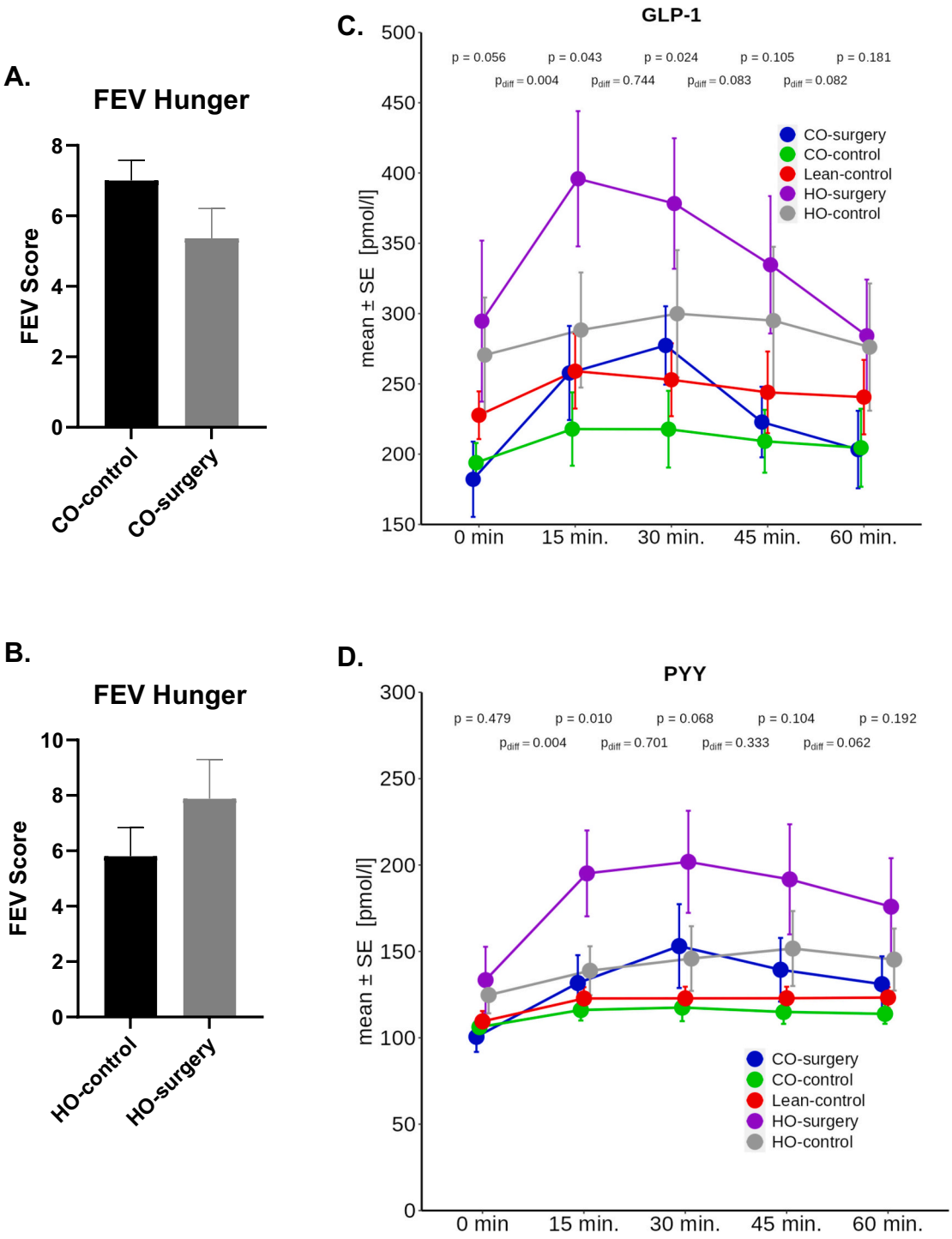

Fig. 3. Feeling of hunger as measured with the questionnaire FEV, A, in CO-control and CO-surgery individuals and B, in HO-control and HO-surgery individuals. Mean concentrations of C, plasma GLP-1 and D, plasma PYY after the test meal in HO-surgery and CO-surgery individuals. All data presented as mean and standard error of the mean. C and D, top p values for differences at the presented time points, bottom p values for significance of the difference between times.

The comparison of the VAS of the mixed meal test revealed no significant differences between groups regarding satiety ($p = 0.99$) or favorite food ($p = 0.98$) or hunger ($p = 0.96$). However, the HO-surgery group tended to be hungrier than the CO-surgery group (see Supplementary Fig. 1), whereas satiety tended to be lower in HO-surgery vs. CO-surgery patients. Additionally, there was a tendency for the amount of the favorite food which still could be imagined to be eaten during the course of the test meal to be higher in the HO-surgery vs. CO-surgery group.

There were no significant differences between groups with regards to taste function at the in the Sweet preference test ($p = 0.91$).

Table 4 includes all statistical analyses regarding questionnaires and visual analogue scales.

3.3. Plasma glucose and gut hormones

Basal values of GLP-1, GLP-2, PYY, leptin, oxyntomodulin, insulin and glucose are shown in Table 2. At baseline, levels of insulin were

Table 2
Basal levels of the measured hormones/peptides and glucose (mean ± sd).

Group	HO-surgery	HO-control	CO-surgery	CO-control	Lean-control	p-value
GLP-1 pmol/l	294.6 ± 162.1	270.5 ± 129.5	182.1 ± 84.6	194 ± 44.3	227.7 ± 58.8	0.06
PYY pmol/l	133.4 ± 54.6	124.7 ± 33.4	100.6 ± 27.6	106.2 ± 11.9	109.5 ± 20.7	0.48
Oxyntomodulin ng/ml	3.0 ± 1.6	n/a	2.4 ± 1.2	n/a	n/a	0.32
Leptin ng/ml	5.4 ± 7	n/a	1.6 ± 3	n/a	n/a	0.17
GLP-2 ng/ml	47.6 ± 62.8	n/a	32 ± 49.6	n/a	n/a	0.59
Insulin mU/l	20 ± 7	15 ± 9	10 ± 7	27 ± 18	5.8 ± 3.3	<0.001
Glucose mg/dl	103 ± 23	90 ± 17	89 ± 7	99 ± 30	89 ± 6	0.32
fT3 pmol/l[a]	5.1 ± 1.1	5.6 ± 1.0	n/a	n/a	n/a	0.29
fT4 pmol/l[a]	17.3 ± 4.7	17.7 ± 4.6	n/a	n/a	n/a	0.88
Cortisol µg/dl[a]	12.5 ± 9.5	13.7 ± 6.9	n/a	n/a	n/a	0.76
IGF-1 µg/l[a]	111.3 ± 90.7	95.4 ± 76.2	n/a	n/a	n/a	0.8
Estradiol ng/l[a]	40 ± 8.5	68.2 ± 34.8	n/a	n/a	n/a	0.36
Testosterone µg/l[a]	4.3 ± 1.6	3.9 ± 0.1	n/a	n/a	n/a	0.51

[a] Hormones should be interpreted with caution due to influence of replacement therapy. Testosterone/estradiol only for respective sex.

highest in the CO-control group, whereas levels of GLP-1, GLP-2, PYY, leptin, oxyntomodulin and glucose were not significantly different between groups. In addition, there were no significant differences in GLP-2, leptin and oxyntomodulin 30 min after mixed meal intake.

Regarding glucose, the mixed effect model showed no significant effect for the group factor ($p = 0.13$) or the time factor ($p = 0.96$) but for the group by time interaction ($p = 0.01$). Comparing glucose levels at the different time points revealed significantly higher concentrations in HO-surgery vs. HO-control at 15 and 30 min ($p = 0.01$ and $p = 0.02$). Levels in HO-surgery were significantly higher than in CO-surgery at 45 and 60 min ($p = 0.04$ and $p = 0.02$). Comparing CO-surgery and CO-control, significantly lower concentrations in the former were found at 60 min ($p = 0.014$). See Supplementary Table 2 for all results.

For insulin, the mixed effect model showed a significant effect for the time factor ($p = 0.009$) but not for the group factor ($p = 0.36$) or the group by time interaction ($p = 0.59$). Comparing insulin levels at the different time points revealed significantly higher concentrations in HO-surgery vs. HO-control at 15, 30, and 45 min ($p \leq 0.01$). Values in CO-surgery were significantly lower than in CO-control at 60 min ($p = 0.002$). Insulin levels in CO-surgery were also significantly lower than in HO-surgery at 60 min ($p = 0.013$). See Supplementary Table 3 for all results.

The highest levels of glucose and insulin after food exposure were measured in the HO-surgery patients. Whereas patients in the CO-surgery group experienced a steep increase in glucose and insulin level within the first 30 min, these levels dropped significantly afterwards. In contrast, this increase was even more pronounced in the HO-surgery group, but the levels were still clearly elevated at 45 min leading to a prominent, but not significant difference in the area under the curve (glucose AUC_{60min} in HO-surgery: 9696 ± 1090 mg/dl/h vs. 7525 ± 552 mg/dl/h in CO-surgery ($p = 0.076$); insulin AUC_{60min} in HO-surgery: 8537 ± 1821 mIU/l/h vs. 4893 ± 1057 mIU/l/h in CO-surgery ($p = 0.073$)).

Regarding GLP-1, the mixed effect model showed no significant effects for group ($p = 0.45$) or group by time interaction ($p = 0.7$), but for time ($p = 0.012$). The comparison of the GLP-1 levels at the different time points revealed significantly higher values in HO-surgery vs. CO-surgery at all time points ($p < 0.05$). Additionally, levels were significantly higher in CO-surgery vs. CO-control at 30 min ($p = 0.028$). See Fig. 3 and Supplementary Table 4 for all results.

For PYY, the mixed effect model showed no significant effects (group: $p = 0.96$, time: $p = 0.38$, group by time interaction: $p = 0.63$). Comparing PYY levels at the different time points revealed significantly higher concentrations in HO-surgery vs. HO-control at 15 min ($p = 0.02$) and HO-surgery vs. CO-surgery at 15 min ($p = 0.04$). See Fig. 3 and Supplementary Table 5 for all results.

For the two anorexigenic hormones PYY and GLP-1 (Fig. 3), we observed a similar pattern as with glucose/insulin in both surgery groups with a prominent increase of these hormones after food intake. However, the effect in the HO-surgery groups was significantly enhanced (PYY AUC_{60min} in HO-surgery: 11151 ± 1667 pmol/l/h vs. 8099 ± 1235 pmol/l/h in CO-surgery ($p = 0.028$); GLP-1 AUC_{60min} in HO-surgery: 20975 ± 2893 pmol/l/h vs. 13,060 ± 2357 pmol/l/h in CO-surgery ($p = 0.009$)).

Regarding the degree of correlation between levels of GLP-1/PYY and the VAS ratings, moderate positive correlations between PYY and ratings of satiety and moderate to strong negative correlations between PYY and how much of the patient's favorite food could still be consumed were detected in the CO-surgery group. A strong negative correlation between GLP-1 and satiety and a strong positive correlation between GLP-1 and how much of the patient's favorite food could still be consumed was detected.

Statistics for correlation analyses between the VAS results and GLP-1/PYY in the CO-surgery and HO-surgery group are shown in Table 3. Statistics for correlation analyses between the VAS results and GLP-1/PYY in CO-control/HO-control/Lean-control are shown in Supplementary Table 6.

3.4. Psychological and health questionnaires

Of all groups, HO-surgery patients had the highest scores in Beck's depression inventory, with an average of 18.9 ± 6.3 points, indicating mild depressive symptoms, while scores of the CO-surgery patients were within the reference range (8.6 ± 5.2 points; $p = 0.12$).

Similar results were found in the PHQ-9, higher scores indicating more symptoms of depression. HO-surgery patients reached 10.9 ± 4.8 points, which implies moderately severe depressive symptoms. HO-surgery patients presented with significantly higher scores than CO-surgery patients ($p = 0.027$. Fig. 4). Accordingly, HO-surgery patients had significantly lower quality of life scores than CO-surgery patients in the SF-36 health questionnaire ($p \leq 0.0001$, Fig. 4).

3.5. Gut microbiota

To identify the compositional differences between the groups, we analyzed the 16S rRNA sequencing data with focus on differences in the microbiota on phylum level. Two of the phyla differed strongly between the groups. Actinobacteria was exclusively abundant in the microbiota of CO-control patients, while Verrucomicrobia presented in highest abundance in the healthy lean controls and was exclusively omitted in the CO-control patients (Fig. 5A). Proteobacteria expanded in both obese groups with bariatric surgery but did not reach significance (Fig. 5 A, B).

Furthermore, we analyzed the microbiota on lower phylogenetic levels (genus and species) and questioned whether there were different microbes that change as result of the bariatric surgery in the CO and HO patients. We identified that that species related to *Streptococcus* increased in both groups with bariatric surgery (Fig. 5B). In contrast,

Table 3
Correlations between the levels of GLP-1/PYY and the results of the VAS ratings in the groups HO-surgery and CO-surgery. Significant values are printed in bold.

.Hormone/group	GLP-1 HO-surgery		PYY HO-surgery		GLP-1 CO-surgery		PYY CO-surgery	
	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value
Hunger 0 min	−0.476	p = 0.23	0.253	p = 0.55	−0.276	p = 0.44	−0.449	p = 0.19
Hunger 15 min	−0.371	p = 0.37	−0.108	p = 0.8	−0.444	p = 0.2	−0.614	p = 0.06
Hunger 30 min	0.310	p = 0.46	0.167	p = 0.69	−0.183	p = 0.61	−0.488	p = 0.15
Hunger 45 min	0.476	p = 0.23	0.286	p = 0.49	−0.614	p = 0.06	−0.485	p = 0.16
Hunger 60 min	0.563	p = 0.15	0.357	p = 0.39	−0.310	p = 0.38	−0.559	p = 0.09
Satiety 0 min	0.216	p = 0.61	−0.267	p = 0.52	−0.012	p = 0.97	0.579	p = 0.08
Satiety 15 min	0.072	p = 0.87	−0.383	p = 0.35	0.394	p = 0.26	**0.648**	**p = 0.04**
Satiety 30 min	−0.431	p = 0.29	0.048	p = 0.91	0.293	p = 0.41	0.415	p = 0.23
Satiety 45 min	−0.599	p = 0.12	−0.096	p = 0.82	0.600	p = 0.07	**0.650**	**p = 0.04**
Satiety 60 min	**−0.970**	**p = 0.0001**	0.143	p = 0.74	0.264	p = 0.46	0.571	p = 0.09
Fullness 0 min	−0.299	p = 0.47	−0.667	p = 0.07	0.430	p = 0.22	0.092	p = 0.8
Fullness 15 min	0.036	p = 0.93	−0.359	p = 0.38	−0.079	p = 0.83	0.115	p = 0.75
Fullness 30 min	−0.119	p = 0.78	−0.333	p = 0.42	−0.176	p = 0.63	−0.127	p = 0.73
Fullness 45 min	−0.467	p = 0.24	−0.359	p = 0.38	0.188	p = 0.60	−0.097	p = 0.79
Fullness 60 min	−0.084	p = 0.84	−0.595	p = 0.12	0.115	p = 0.75	−0.042	p = 0.91
Preferred meal 0 min	0.524	p = 0.18	−0.193	p = 0.65	−0.321	p = 0.37	−0.316	p = 0.37
Preferred meal 15 min	0.024	p = 0.96	0.192	p = 0.65	−0.604	p = 0.07	**−0.762**	**p = 0.01**
Preferred meal 30 min	0.452	p = 0.26	−0.143	p = 0.74	−0.448	p = 0.19	**−0.681**	**p = 0.03**
Preferred meal 45 min	0.611	p = 0.11	0.407	p = 0.32	−0.553	p = 0.1	−0.588	p = 0.07
Preferred meal 60 min	**0.790**	**p = 0.02**	0.048	p = 0.91	−0.201	p = 0.58	−0.559	p = 0.09

Table 4
Statistics of performed ANOVAs (interaction of group and time) for questionnaires and visual analogue scales.

Questionnaire	ANOVA	Post-hoc
Scale "Feeling of hunger", FEV	F (4, 47) = 4.22, p = 0.005	CO-control vs. Lean-control: p = 0.018 Lean-control vs. HO-surgery: p = 0.006
Scale "Emotional eating", FEV-II	F (4, 47) = 1.53, p = 0.21	n/a
Scale "External eating", FEV-II	F (4, 47) = 3.4, p = 0.016	HO-surgery vs. CO-surgery: p = 0.011
FCQ-T	F (20, 282) = 1.2, p = 0.3	n/a
Visual analogue scale (VAS), favorite food	F (20, 264) = 0.46, p = 0.98	n/a
Visual analogue scale (VAS), satiety	F (20, 264) = 0.39, p = 0.99	n/a
Visual analogue scale (VAS), hunger	F (20, 264) = 0.51, p = 0.96	n/a
Visual analogue scale (VAS), fullness	F (20, 264) = 0.75, p = 0.77	n/a
Sweet preference test	F (16, 210) = 0.57, p = 0.91	n/a
Beck's depression inventory	F (4, 47) = 3.3, p = 0.018	HO-surgery vs. Lean-control: p = 0.016
PHQ-9	F (4, 47) = 3.17, p = 0.022	HO-surgery vs. CO-surgery: p = 0.027
SF-36	$F_{(4, 28)}$ = 21.29, p ≤ 0.0001	HO-surgery vs. CO-surgery: p < 0.0001 HO-surgery vs. Lean-control: p < 0.0001 HO-surgery vs. CO-control: p = 0.036

species related to *Akkermansia muciniphila* and *Prevotella copri* expanded only in the CO-surgery group and were abundant in the healthy controls (Fig. 5C).

3.6. Brain responses to food stimuli

In a first step we compared the neural activation pattern during the fMRI task for the total sample and found higher activation for food stimuli compared to the non-food comparison stimuli in several areas (see Table 5, Fig. 6). To further analyze changes in neural processing of food cues in patients with HO and CO (pre and post bariatric surgery) we

Table 5
Functional brain activation during food stimuli processing (HC/LC > NF) for total sample at cluster level.

Region	Cluster size	T	pFWE	MNI coordinates		
				x	y	z
Lingual cortex	4389	9.40	0.001	0	−74	6
Ant. Cingulate Cortex	1543	7.32	0.001	−4	38	20
Post. Cingulate Cortex	318	5.79	0.001	−4	−38	24
Mid. Cingulate Cortex	133	5.45	0.007	−2	−4	34
Insula	183	5.06	0.01	−38	−2	−16
Cerebellum	134	5.57	0.001	−10	−40	−18

Note: FEW corrected, p < 0.001, extend threshold k = 90, coordinates are in MNI space. AAL3_V1 atlas was used to label regions.

calculated a full factorial model (factor with or without bariatric surgery and group HO vs CO) for the contrasts food vs non-food as well as HC vs LC stimuli. Here, we found no significant main or interaction effects. Especially, we found no significant differences between HO-surgery and CO-surgery. Comparing all HO patients (with and without surgery, n = 9) with healthy control (n = 22) revealed a significant interaction (HC > LC and HO > controls) in the left cerebellum (x = −10, y = −40, z = −18, t = 5.57, $P_{FWE\ corrected}$ = 0.001) and left insula (x = −38, y = −2, z = −16, t = 5.06, $P_{FWE\ corrected}$ = 0.01) at cluster level (see Fig. 7). Comparing all CO patients with healthy controls for the contrast HC > LC did not reveal any significant differences.

4. Discussion

In this first prospective cross-sectional study focusing on hypothalamic obesity, we compared the effects of bariatric surgery on body weight course, gut hormones, glucose control, gut microbiota, physical and mental health in individuals with HO and CO. Unoperated patients (with HO and CO) and healthy lean participants served as controls. While bariatric surgery was very effective in CO in terms of body weight loss and mental well-being, patients with HO experienced less and not sustained body weight loss, and no benefits in mental well-being or quality of life. In addition, patients of the HO-surgery group were hungrier throughout the test meal than patients of the CO-surgery group, whereas satiety tended to be lower in HO-surgery vs. CO-surgery. Postprandially, significantly higher levels of GLP-1 and PYY were detected in HO-surgery vs. HO-control and vs. CO-surgery participants (Fig. 3). High levels of GLP-1 and PYY in the HO-surgery group implicate

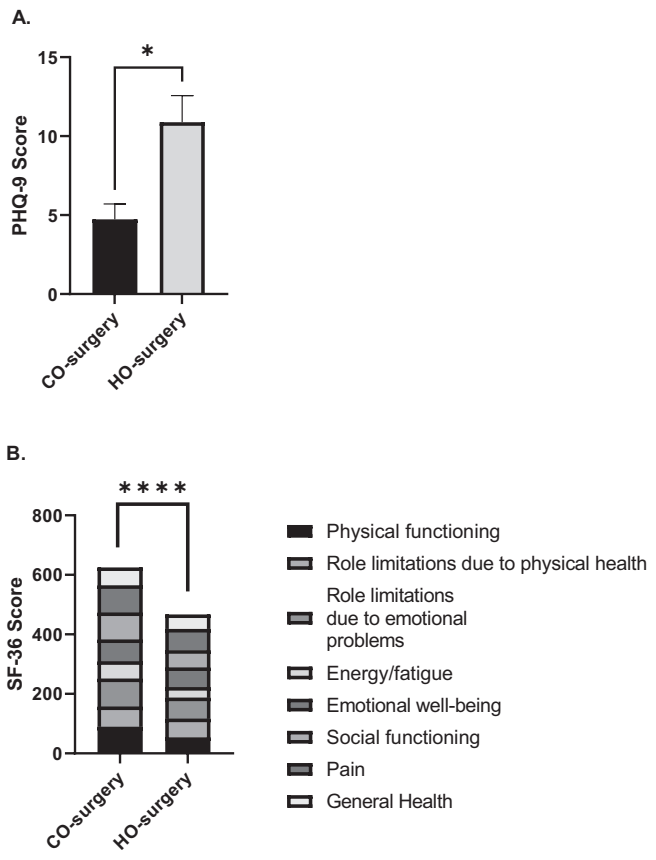

Fig. 4. Mean levels of scores for A, Patient Health Questionaire-9 (PHQ-9) and B, and Short Form 36 health questionnaire (SF-36). * $p \leq 0.05$, **** $p \leq 0.0001$. A, B, Data presented as mean and A, standard error of the mean.

that this known hormonal mechanism of bariatric surgery, especially RYGB and sleeve gastrectomy [26–28], is intact in these patients. However, most probably due to hypothalamic damage, these key neuroendocrine signals were not able to induce satiety. As expected, moderate positive correlations between plasma PYY and ratings of satiety and moderate to strong negative correlations between PYY and how much of the patient's favorite food could still be consumed were detected in the CO-surgery group. Contrary to this and demonstrating the disturbed gut-brain axis, a strong negative correlation between plasma GLP-1 and satiety and a strong positive correlation between GLP-1 and how much of the patient's favorite food could still be consumed was detected in the HO-surgery group.

To evaluate central signaling, most participants underwent fMRI to measure differences in motivational eating behavior. Functional MRI studies have shown that food-induced activation of the reward system, including regions like the orbitofrontal cortex and amygdala is reduced after RYGB compared to unoperated individuals with obesity [52,53]. Several studies have demonstrated that this effect is mediated via GLP-1 and PYY [54,55]. An enhanced functional connectivity between insula and cerebellum has been shown in healthy fasted participants [56]. A greater resting state low-frequency power in clusters located in the insula (amongst others) is detectable in the brains of females with severe obesity compared to normal-weight controls [57]. In our study, a higher activation of the insula and cerebellum, but not other parts of the reward system, was found in HO but not CO patients compared to the group of normal weight control individuals for the contrast of high versus low caloric pictures. This might be an explanation for the high appetitive behavior towards high-caloric food in HO patients. Due to small group sizes differentiation of operated vs. unoperated HO patients was not possible.

This finding builds on the well-known effects of the hypothalamus not only on hunger and fullness, but also on the rewarding value of food. This behavior is mediated through the neurocircuits connecting the hypothalamus to the mesolimbic reward system, comprising the ventral tegmental area and the nucleus accumbens [58]. The integration of

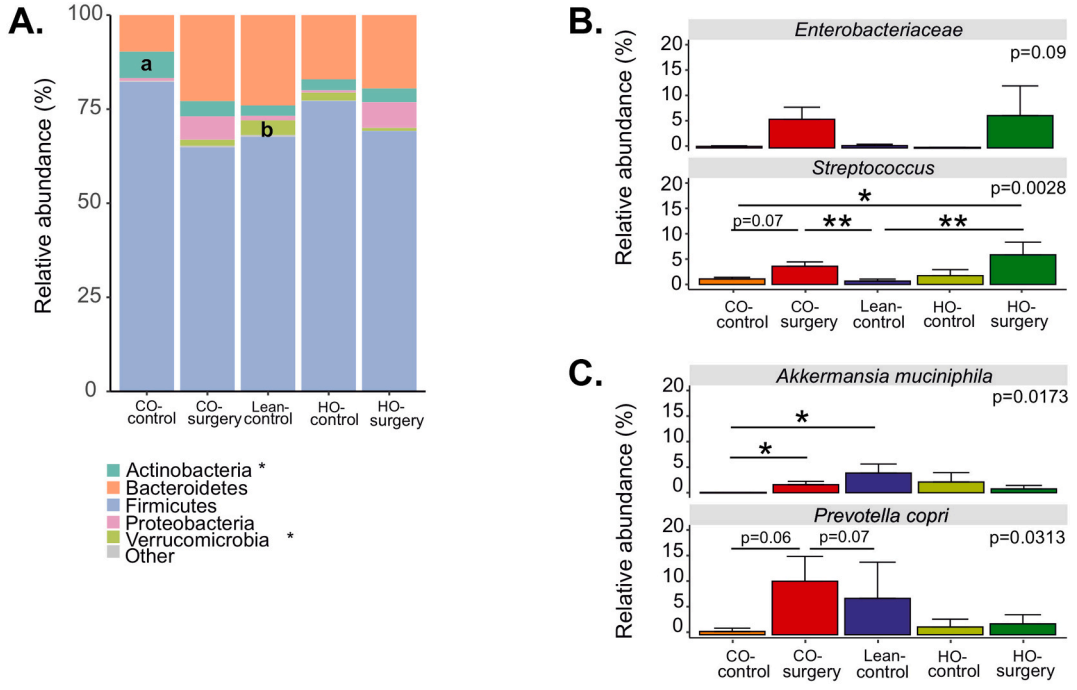

Fig. 5. Stool microbiota composition in CO-control, CO-surgery, HO-control, HO-surgery and Lean-control patients. A, Relative abundance of the major microbial phyla in the respective groups (a, $p_{adjust} < 0.01$; b, $p < 0.05$). B, C, Relative abundance of taxa significantly different between the respective groups B, Surgery associated microbiota. C, Weight loss associated microbiota. (Kruskal-Wallis Test, p-value in the right corner of each plot in B and C, indicates the overall p-value from the ANOVA analysis. Significant q-values from the subgroup comparisons are indicated above the respective groups; * $p_{adjust} < 0.05$; ** $p_{adjust} < 0.01$).

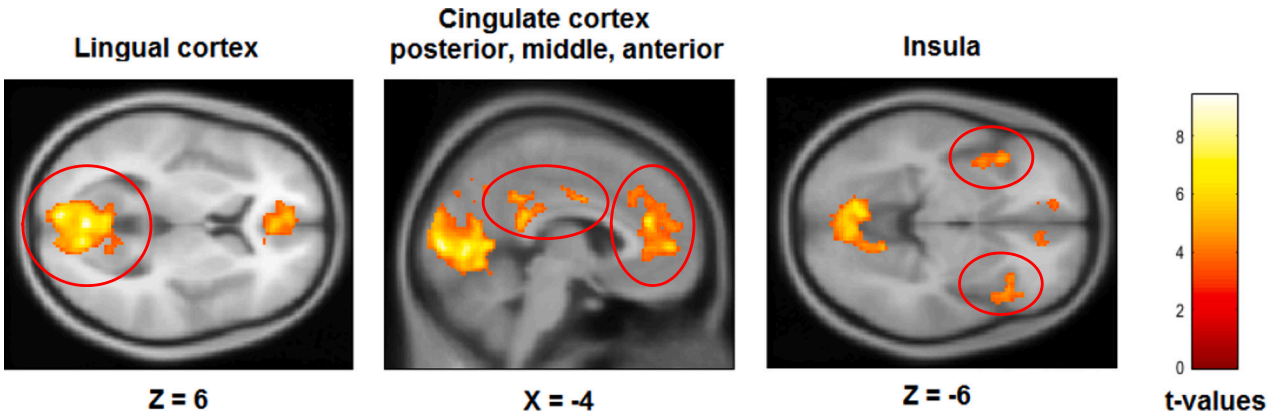

Fig. 6. Brain activation in lingual cortex, cingulate cortex and insula following high-caloric food stimuli and low-caloric food stimuli compared to non-food in the whole sample to evaluate the paradigm. The color scale represents the t-values for each voxel in the cluster.

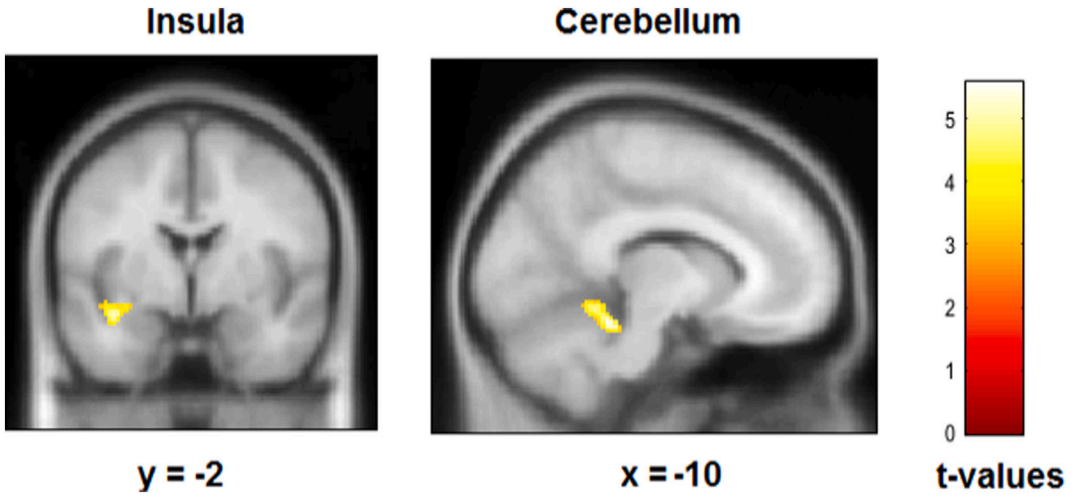

Fig. 7. Brain activation in insula and cerebellum to viewing high-caloric foods compared to low-caloric foods in all HO patients (n = 9) compared to the lean control individuals (n = 22). The color scale represents the t-values for each voxel in the cluster.

"homeostatic" with reward signals in the cortex determines both the number of calories ingested, but also the macronutrient composition of the meal. The hypothalamus also affects energy expenditure. Both the POMC and AgRP/NPY groups of neurons in the arcuate nucleus communicate through the periventricular nucleus with the brainstem and the sympathetic nervous system leading to brown adipose tissue activation [59,60]. In this study we did not measure energy expenditure, but we cannot exclude that lower diet-induced thermogenesis could explain the attenuated weight loss observed in patients with HO after bariatric surgery. The hypothalamus is also involved with glucose regulation. It receives metabolic signals from the periphery that include circulating glucose, insulin and leptin and responds through its projection to the brainstem and autonomic nervous system to modulate hepatic glucose production, skeletal muscle uptake of circulating glucose and pancreatic insulin secretion [61]. Measurement of metabolic responses in operated and unoperated patients with HO was beyond the scope of our study.

The major difference in the microbiota in CO and HO patients with and without bariatric surgery was an increased abundance of facultative anaerobic bacteria as *Enterobacteriaceae* and *Streptococcus*. Those are the most relevant microbial taxa reported to increase after RYGB [22], driven by the change in the gut environment, including oxygen, pH and redox potential [62,63]. However, the microbiota of the CO-surgery and HO-surgery patients differed in the abundance of *Prevotella copri* and *Akkermansia muciniphila,* which were augmented after surgery only in CO patients. These two bacteria species, previously reported to increase in patients with obesity after RYGB [64,65], have been shown to improve host metabolism, most probably via interaction with the consumed diet [66–68].

The microbiota of individuals with CO is characterized by a decreased phylogenetic diversity in comparison to healthy controls [69]. Interestingly, the HO microbiota was more similar to the microbiota of the healthy controls, which is opposite to the general consideration that obesity is associated with an altered microbiota composition [70]. Similar observations were recently reported in obese patients with Prader-Willi syndrome (PWS), whose microbiota were similar to that of their lean relatives, but different from that of individuals with obesity. Further, translational research in gnotobiotic mice revealed the metabolic benefit of the PWS gut microbiota for the host [71]. Since PWS is a model of genetically induced severe obesity with several similarities to the diseases in our HO cohort, these PWS data support the reliability of our results. However, further mechanistic studies (e.g. with gnotobiotic animal models with HO/CO-microbiota transfer) would be needed to validate the hypothesis that bariatric surgery is not able to modify the gut microbiota in HO in the same way as in CO and that this might be a relevant factor for the reduced effectiveness of bariatric surgery in HO.

By showing similar peripheral hormonal and partially microbiota changes in HO and CO after bariatric surgery, our work underlines the potential of bariatric surgery as a "neurosurgical" intervention, where changes on a hypothalamic level are key to the impressive weight loss

achieved. This observation provides further confirmation that the effects of bariatric surgery are not due to restriction or malabsorption.

Additionally, our work underlines the necessity to screen individuals suffering from HO carefully before performing bariatric surgery. Although bariatric surgery is generally safe, it comes along with the necessity of lifelong supplementation with vitamins and trace elements [72]. If multiple conservative treatment options have failed before, the relevance of hypothalamic damage for the obese state might be even more pronounced. We would be even more reluctant to offer bariatric surgery, if therapeutic attempts with GLP-1 receptor agonists were not successful in the past. It is well known that GLP-1 agonists mediate their effects via hypothalamic GLP-1 receptors [33,34,73]. Moreover, we showed that GLP-1 levels are markedly increased postprandially in HO-patients with bariatric surgery, although obviously ineffective due to hypothalamic damage. Therefore, a therapeutic attempt with GLP-1 agonists before bariatric surgery might be a potential tool to predict outcome of surgery in this subgroup of patients [74]. If this fails, bariatric surgery might be less effective or even completely ineffective. Alternatively, if good patient compliance is assured, a more malabsorptive bariatric procedure might be indicated.

This work has limitations. First of all, HO group sizes were small due to the rarity of the disease. In addition, there might be some selection bias, as HO-patients with weaker response to bariatric surgery or conservative interventions in the past are possibly more willing to take part in such a study. This might explain why we could show no beneficial effects of bariatric surgery in patients with HO contrary to some earlier studies [75–78]. As an additional limitation, we analyzed patients after RYGB and sleeve gastrectomy in one group. It has to be mentioned, however, that these two operations produce very similar results in terms of weight loss (~25 %) in the short and medium term, thus any small differences between the mechanisms through which these interventions work are unlikely to have a large confounding effect. Instead, we are suggesting that the different outcomes after bariatric surgery are more related to the distinct damage of specific hypothalamic regions than to the selection bias [8,9].

In conclusion, our results underline the complex mechanisms of action behind bariatric surgery. We showed that levels of GLP-1 and PYY are markedly elevated after food intake in patients with HO after bariatric surgery. Thus, our study provides additional evidence that bariatric surgery is some kind of hypothalamic intervention, as its efficiency is clearly reduced in case of hypothalamic damage.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2022.155341.

CRediT authorship contribution statement

Ulrich Dischinger: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft, Visualization, Supervision, Project administration. **Laura Kötzner:** Formal analysis, Investigation, Visualization, Writing – review & editing. **Petia Kovatcheva-Datchary:** Methodology, Validation, Formal analysis, Investigation, Writing – review & editing, Visualization. **Helena Kleinschmidt:** Formal analysis, Writing – original draft, Visualization. **Christina Haas:** Formal analysis, Investigation. **Jose Perez:** Validation, Formal analysis. **Cornelius Presek:** Methodology, Formal analysis. **Ann-Cathrin Koschker:** Conceptualization, Methodology, Writing – review & editing. **Alexander D. Miras:** Writing – review & editing. **Mohammed K. Hankir:** Writing – review & editing. **Jörg Vogel:** Writing – review & editing. **Christoph-Thomas Germer:** Writing – review & editing. **Martin Fassnacht:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Martin J. Herrmann:** Conceptualization, Methodology, Validation, Formal analysis, Visualization, Writing – review & editing. **Florian Seyfried:** Conceptualization, Methodology, Validation, Writing – original draft, Supervision.

Declaration of competing interest

The authors have no competing interests to declare.

Acknowledgements

We thank Dr. rer. nat. Ulrich Stefenelli for statistical support.

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