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Altered neural responsivity to food cues in relation to food preferences, but not appetite-related hormone concentrations after RYGB-surgery☆

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ABSTRACT

Background: After Roux-en-Y gastric bypass (RYGB) surgery, patients report a shift in food preferences away from high-energy foods.

Objective: We aimed to elucidate the potential mechanisms underlying this shift in food preferences by assessing changes in neural responses to food pictures and odors before and after RYGB. Additionally, we investigated whether altered neural responsivity was associated with changes in plasma endocannabinoid and ghrelin concentrations.

Design: 19 RYGB patients (4 men; age 41 ± 10 years; BMI 41 ± 1 kg/m^2 before; BMI 36 ± 1 kg/m^2 after) participated in this study. Before and two months after RYGB surgery, they rated their food preferences using the Macronutrient and Taste Preference Ranking Task and BOLD fMRI responses towards pictures and odors of high-, and low-energy foods and non-food items were measured. Blood samples were taken to determine plasma endocannabinoid and ghrelin concentrations pre- and post-surgery.

Results: Patients demonstrated a shift in food preferences away from high-fat/sweet and towards low-energy/savory food products, which correlated with decreased superior parietal lobule responsivity to high-energy food odor and a reduced difference in precuneus responsivity to high-energy versus low-energy food pictures. In the anteroventral prefrontal cortex (superior frontal gyrus) the difference in deactivation towards high-energy versus non-food odors reduced. The precuneus was less deactivated in response to all cues. Plasma concentrations of anandamide were higher after surgery, while plasma concentrations of other endocannabinoids and ghrelin did not change. Alterations in appetite-related hormone concentrations did not correlate with changes in neural responsivity.

Conclusions: RYGB leads to changed responsivity of the frontoparietal control network that orchestrates top-down control to high-energy food compared to low-energy food and non-food cues, rather than in reward related brain regions, in a satiated state. Together with correlations with the shift in food preference from high- to low-energy foods this indicates a possible role in new food preference formation.

Abbreviations: 2-AG, 2-arachidonoylglycerol; BMI, body mass index; BOLD, blood oxygenation level-dependent; DARTEL, diffeomorphic anatomical registration through exponentiated lie algebra; DHEA, docosahexaenoylethanolamide; DLE, dihomo-γ-linoleonylethanolamide; eCB, endocannabinoid; ELISA, enzyme-linked immuno sorbent assay; fMRI, functional magnetic resonance imaging; HFHS, high-fat/high-sugar; LC–MS/MS, liquid chromatography-tandem mass spectrometry; LFLS, low-fat/low-sugar; MNI, montreal neurological institute; MTPRT, macronutrient and taste preference ranking Task; OEA, oleoylethanolamide; PEA, palmitoylethanolamide; PFC, prefrontal cortex; PG, propylene glycol; PMSF, phenylmethylsulfonyl fluoride; RYGB, Roux-en-Y gastric bypass; SEA, stearoylethanolamide; TDI-score, threshold discrimination identification score; VAS, visual analogue scale; VTA, ventral tegmental area

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1. Introduction

Roux-en-Y gastric bypass (RYGB) surgery is currently the most effective long-term treatment for morbid obesity [1]. After RYGB, patients report decreased hunger and lower caloric intake. In addition, a shift in food preferences from high- to low-energy foods is typically observed [2]. This change in food preferences has been related to alterations in taste perception and food reward, with fMRI studies showing decreased activation in the mesocorticolimbic reward network in response to high-energy compared to low-energy food cues [3]. However, the exact mechanism behind this shift in food preferences and related neural responses is not completely understood. Potential mediators include changes in subjective hedonic evaluation of food (cues), changes in gut hormones signaling hunger and satiety, post-ingestive side effects of surgery, and changes in nutrient sensing in the gut [4]. A better understanding of the mechanisms behind changed food preferences may help to identify factors responsible for the success of this weight-loss intervention, and might guide novel non-surgical strategies that have less risk of complications.

As previously shown, the decreased desire to eat high-energy foods correlates with decreased activation in reward-related brain areas to pictures of high-energy compared to low-energy foods [2,3,5]. In a scanner setting it is difficult to realistically mimic an eating environment and thus far, neuroimaging studies used pictures as food cue. However, other sensory modalities might be equally or more important for food choice and the anticipation of food intake. Specifically, food odors play a crucial role in initiating food intake [6–8] by steering appetite [9] and cravings for specific foods [10,11]. Given their largely unconscious role in priming eating decisions, it is of interest to investigate (alterations in) neural reward responses to palatable food odors as well, in relation to changes in food preferences after RYGB.

There is mounting evidence that gut hormones play a role in altered food preferences after RYGB [12]. In general, gut hormones play an important role in food choice and food intake, by signaling nutritional status and food reward value to the brain [13]. Most gut hormones are anorexigenic, with higher circulating plasma concentrations resulting in a suppression of food intake. Ghrelin, however, is an orexigenic gut hormone that can stimulate food intake [14]. Moreover, ghrelin is not only involved in regulating homeostatic eating; eating to fill a need for energy or nutrients, but also in hedonic eating; eating for pleasure [15,16]. Thus far, only a few studies examined the role of ghrelin in relation to altered brain reward activation after RYGB and food preferences [22,23]. The orexigenic effect of ghrelin appears to be mediated through the endocannabinoid (eCB) system [17]. The eCB system is a neuromodulatory system that consists of endogenous ligands, so called endocannabinoids, their receptors and enzymes involved in their synthesis and breakdown (for a review regarding the role of the eCB system in appetite and food reward, see Jager and Witkamp [64] Nutr Res Rev). Ghrelin and eCB plasma concentrations increase in anticipation of hedonic eating [16,18], and neuroimaging studies suggest a role for ghrelin and the eCB system in reward processing [19–21]. While the eCB system appears to be a key player in modulating palatability-dependent appetite, and appears to be deregulated in eating disorders, this has not been explored in the context of altered food preferences after RYGB.

To improve our understanding of the changes in food preferences typically seen after RYGB, we assessed neural changes in response to high- and low-energy appetizing food cues in two different sensory modalities: odors and pictures. Additionally, to better explain these neural mechanisms, plasma eCB and ghrelin concentrations, as well as food preferences were measured and correlated to changes in brain activation pre- to post-surgery.

2. Participants and methods

2.1. Participants

Twenty-one morbidly obese individuals participated in this study. The required sample size was estimated based on previous fMRI literature and expert knowledge (*e.g.* [24,25]). All participants were enlisted to undergo RYGB surgery at Rijnstate hospital, Arnhem, the Netherlands. Requirements for the surgery were: Body Mass Index (BMI) of $> 40\,kg/m^2$ or $> 35\,kg/m^2$ with co-morbidity that was expected to improve after surgically-induced weight loss, long-lasting obesity ($>$ 5 years), proven failed attempts to lose weight in a conventional way, intention to adhere to a postoperative follow-up program. Reasons not to consider individuals for surgery were being pregnant or lactating, psychiatric disorders, alcohol or drug dependency, life threatening conditions or being dependent on the care of others. Between August 2014 and June 2015, individuals were screened for participation in the study at Rijnstate hospital. All participants were right-handed, non-smoking, did not have conditions that interfered with the MRI measurements (*e.g.* claustrophobic, metal implants, pacemaker, neurological disorders), had a normal sense of smell (scoring $\geq$10 on the identification part of the Sniffin' Sticks [26]), were not vegetarian and did not have allergies or intolerances to the foods used and cued (visual/olfactory stimuli) in the study. Participants received a monetary reward for their contribution. All participants provided written informed consent before entering the study. The protocol was approved by the Medical Ethical Committee of Wageningen University (NL45837.081.13) and was executed in accordance with the ethical principles of the Declaration of Helsinki of 1975, as revised in 2013.

2.2. Overall design and experimental procedure

This study had a within-subject design, investigating neural changes (pre- vs post-gastric bypass surgery), in response to high-fat/high-sugar (HFHS) food, low-fat/low-sugar (LFLS) food, and non-food (NF) cues, in two different sensory modalities: odors and pictures. This study is part of a larger study (n = 100) investigating behavioural and neural changes in food preferences in patients undergoing RYGB, over time, as registered at clinicaltrials.gov (NCT02068001).

The test sessions took place between September 2014 and October 2015. Participants visited the test facilities at three occasions. First, they were familiarized with the MRI test environment and the experimental task and stimuli used, in a dummy MRI scanner at Wageningen University (training session). Following the training session, there were two identical test sessions during which the actual measurements were taken. The first test session took place 3.4 (SD 1.8) weeks before and the second test session took place 9.2 (SD 1.3) weeks after RYGB. Each participant was scanned at approximately the same time of day for both sessions, between 14:00-17:00 at hospital Gelderse Vallei (Ede, The Netherlands). Participants were instructed to refrain from eating and drinking anything but water and weak tea in the three hours before a test session. Upon arrival at the hospital, blood samples were taken for analysis of plasma endocannabinoid and ghrelin concentrations. In order to measure responses underlying hedonic eating (eating for pleasure, in the absence of hunger), participants were offered orange juice, and after a short break they consumed a meal consisting of bread roll(s), cheese, ham and butter (see Supplementary Table S1 for more detailed information), standardized for men and women separately, to evoke a similar state of satiety in all participants (Table 1). Following this, they waited for 15 min to allow digestion. Before entering the MRI room, participants were presented with the odors and pictures used in the reward task to familiarize with the stimuli and reinforce the appropriate association with the stimuli. They also rated their hunger, fullness, prospective consumption, desire to eat, and thirst on 100-unit Visual Analogue Scales (VAS), ranging from 'not at all', to 'very much'. During the scan session, first, a reward task was performed while

Table 1
Demographic characteristics, and hunger ratings (100-unit VAS) pre- and post-RYGB.

Gender	4 men, 15 women		
Age	41 ± 10 years		
	Pre-surgery Mean ± *SD*	*Post-surgery* Mean ± *SD*	Significance
Weight (kg)	120 ± 14	104 ± 15	$p < .001$
BMI (kg/m^2)	41 ± 3	36 ± 4	$p < .001$
Hunger	13 ± 21	11 ± 24	$p = .738$
Fullness	70 ± 25	68 ± 34	$p = .867$
Prospective consumption	27 ± 25	8 ± 18	$p = .020$
Desire to eat	22 ± 20	12 ± 23	$p = .197$
Thirst	66 ± 26	51 ± 30	$p = .022$

RYGB: Roux-en-Y Gastric Bypass; VAS: visual analogue scale.

functional MR images were acquired. Second, structural MR images were collected. Thereafter, participants took part in two additional functional runs in which a food-related go/no-go task was performed (data reported elsewhere). At the end of the test session, olfactory performance was assessed using the Sniffin' Sticks (threshold, discrimination, identification [26]). The regular Identification 16 was used during screening, thus to prevent a potential learning effect, we used the Identification 16+ for the second test session [27]. Paired sample *t*-tests revealed that the overall olfactory performance (TDI score) was not different between test sessions (before: 33.7 ± 4.7; after: 35.0 ± 4.2; $p = .328$).

2.3. Food preferences

Food preferences were assessed at home two weeks (on average 9 days, max 16 days) before, and two months (on average 65 days, range 55–95 days) after RYGB using the online version of the macronutrient and taste preference ranking task (MTPRT [28]). In this task, participants were presented with four pictures of different food products at a time and asked to rank the products according to what they most desire to eat at that moment. Food products included in this task were either high in carbohydrate, high in fat, high in protein or low in energy, and had a sweet or savory taste. The MTPRT was presented in EyeQuestion software (Logic8 BV).

2.4. Food stimuli (odors and pictures)

Odors and pictures were selected to signal either high-fat, high-sugar food (HFHS), low-fat, low-sugar food (LFLS) or non-food (NF) items (as control) by means of pilot studies in separate samples of participants. Odors were selected to be similar in perceived intensity and liking, different in the associated energy-density, and correctly associated to the corresponding food product/object. The selected odors were Chocolate (HFHS; International Flavors and Fragrances (IFF) 10810180; 8.5% in Propylene Glycol (PG)), Caramel (HFHS; IFF 10895342; 20% in PG), Tomato (LFLS; IFF 15039016; 24% in PG), Cucumber (LFLS; IFF 73519595; 34% in PG), Fresh Green (NF; AllSens–Voit Aroma Factory No. 819; 2.2% in PG), Wood (NF; AllSens–Voit Aroma Factory No. 821; 2.2% in PG). Pictures were selected to be similar in liking, and consistently matched to a food product/object and to one of the selected odors. For each odor we selected three different pictures to reduce effects of boredom. We selected Chocolate muffin, Brownie, and Chocolate bonbons for Chocolate odor; Caramel ice-cream, Stroopwafel (Dutch caramel syrup waffle), and Boterkoek (Shortbread) for Caramel odor; Tomato slices with pepper, Tomato slices, and Tomato slices with basil for Tomato odor; Cucumber slices with peel, Cucumber salad, and Cucumber chunks for Cucumber odor; Green soap, Tulips, and White flowers for Fresh Green odor; and Chunk of wood, Pine branches, and Purple soap for Wood odor. Standardized food images used in the fMRI task were provided by the Image Sciences Institute, UMC Utrecht, and created as part of the Full4Health project (www.full4health.eu), funded by the European Union Seventh Framework Program (FP7/2007-2013) under grant agreement nr. 266408, and the I.Family project (http://www.ifamilystudy.eu), grant agreement nr. 266044 [29].

2.5. (f)MRI paradigm and measurements

The reward task lasted ± 40 min and consisted of olfactory and visual cues of HFHS food, LFLS food and NF were presented one by one,

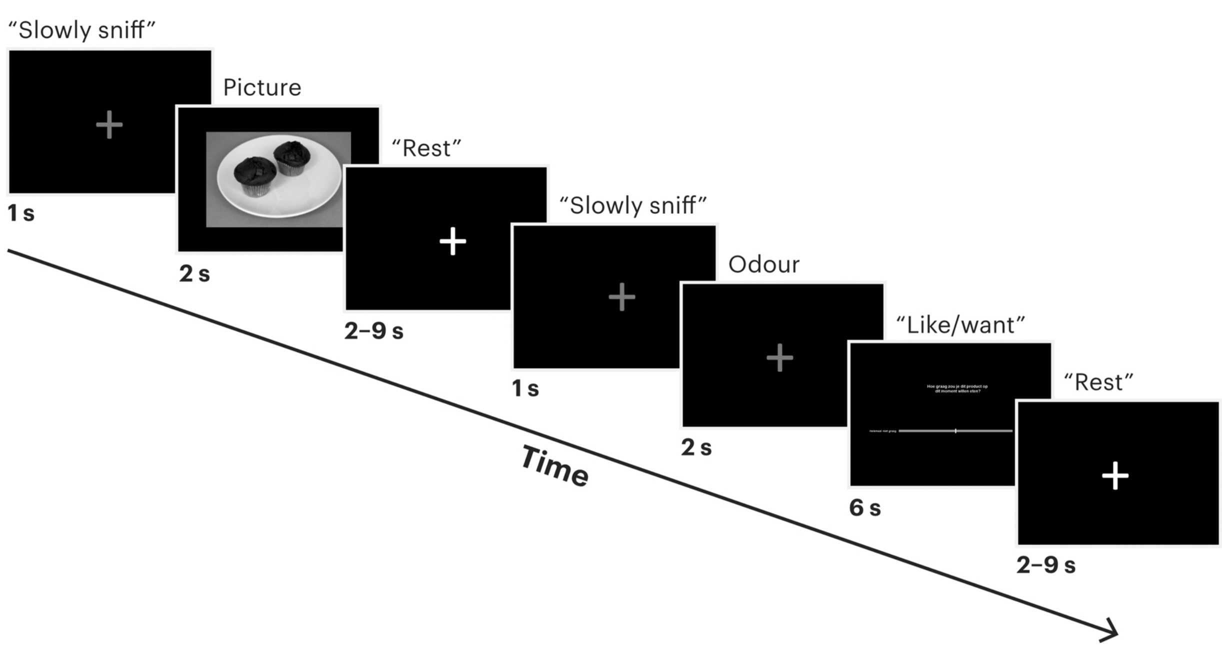

Fig. 1. Design of the fMRI reward paradigm. Trial presentation started with a red fixation cross for 1 s during which participants were instructed to slowly inhale via the nose ('slowly sniff'), an odor or picture was then presented for 2 s. Occasionally participants provided liking, wanting or intensity ratings on a 100-mm VAS within 7 s. Between trials a rest period (3–11 s) was included, during which a white fixation cross was visible.

in pseudo random order (see Fig. 1). Six olfactory stimuli and 18 visual stimuli (3 related to each odor) were presented. Each odor was presented 15 times and each picture was presented 5 times, resulting in a total of 90 odor and 90 visual presentations. Trials started with the presentation of a red fixation cross (1 s) during which participants were instructed to slowly inhale via the nose. Following this, either an odor or a picture (2 s) was presented. During presentation of an odor the red fixation cross remained on the screen. Over the entire run participants were asked to provide liking and wanting ratings twice for each stimulus, and intensity ratings for the odors (7 s). Between trials a rest period (3–11 s) was included, during which a white fixation cross was visible. The inter-stimulus interval between odor presentations was kept between 17–24 s to prevent adaptation and was jittered to prevent habituation. Olfactory stimuli were presented using an fMRI-compatible computer-controlled 8-channel olfactometer (Burghart, Wedel, Germany) that delivered the odors via a small nasal cannula in a constant air flow (8 L/min) that was heated to 37 °C and humidified to 80% relative humidity to prevent irritation of the nasal mucosa. Visual stimuli were projected using a back-projection screen, which could be viewed by the participants via a mirror positioned on the head coil. The reward task ran in E-Prime 2.0 Professional (Psychology Software Tools Inc.). An MR compatible button box was used to answer questions in the task. Head movements were restricted by placing foam cushions next to the participants' head. In addition, surgical tape was placed across the forehead to provide feedback on head movements. Earplugs were provided for noise reduction.

A 3-Tesla Siemens Magnetom Verio MRI scanner in combination with a 32-channel head coil was used, to acquire 993 T_2^*-weighted gradient echo images with BOLD contrast (repetition time = 2240 ms, echo time = 25 ms, flip angle = 90°, field of view = 192 × 192 mm, 45 axial slices, ascending order, voxel size 3 × 3 × 3 mm) in one functional run. The imaging volume was tilted at an oblique angle of 30° to the anterior-posterior commissure line to reduce signal dropout in the orbitofrontal and ventral temporal lobes [30]. A high-resolution T_1-weighted anatomical MRI scan was acquired (MPRAGE: repetition time = 1900 ms, echo time = 2.26 ms, flip angle = 9°, field of view = 256 × 256 mm, 192 sagittal slices, voxel size = 0.5 × 0.5 × 1 mm).

2.6. Data analyses

Results are expressed as means + SD unless otherwise specified. Behavioral data were analyzed in SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Results were considered statistically significant at $p < .05$. Paired-samples T-tests were used to test differences in weight, BMI and hunger ratings pre- and post-surgery. Mixed-models were used to analyze the differences in liking, wanting and intensity ratings that were provided in the test sessions before surgery and after surgery (see Supplementary Table S2).

2.6.1. Food preferences

Sixteen participants completed the online MTPRT pre- and post-surgery. Preference scores for high-fat sweet and low-energy savory products were calculated based on rankings in the MTPRT using the formula below. The higher the rank, the higher the score. The preference scores can range from 1 to 4 [28].

$$\textit{preference score} = \frac{4*(\#\,rank\ 1) + 3*(\#\,rank\ 2) + 2*(\#\,rank\ 3) + 1*(\#\,rank\ 4)}{8}$$

Paired samples *t*-test were used to compare preference scores for high-fat sweet and low-energy savory pre- and post-surgery.

2.6.2. Ghrelin and endocannabinoids

Blood was collected in tubes with EDTA as anticoagulant. To one tube, 4-(2-aminoethyl)benzenesulfonyl fluoride hydrochloride (Sigma-Aldrich) was added to reach a concentration of 1 mg/ml in the collected blood. The tubes were centrifuged at 1300 × *g* for 10 min at 4 °C. Plasma was then portioned into aliquots and stored at −80 °C. Prior to storage, hydrochloric acid was added to a final concentration of 0.05 N to the plasma that contained 4-(2-aminoethyl)benzenesulfonyl fluoride hydrochloride. This plasma was later used for ghrelin analyses. To another aliquot, phenylmethylsulfonyl fluoride (Sigma-Aldrich) and URB602 (Sigma-Aldrich) were added to a final concentration of 100 μM for both. This was used to measure plasma concentrations of the eCBs anandamide and 2-arachidonoylglycerol (2-AG), and the related *N*-acylethanolamines docosahexaenoyl ethanolamide (DHEA), dihomo-γ-linoleonylethanolamide (DLE), oleoylethanolamide (OEA), palmitoylethanolamide (PEA), stearoylethanolamide (SEA), using an LC–MS/MS technique described elsewhere [31]. ELISA was used to measure total ghrelin concentrations in plasma (Millipore).

For each biochemical parameter, normality was checked. Only DHEA was normally distributed and a paired-samples *T*-test was used to compare plasma concentrations before and two months after surgery. For all other parameters Related-Samples Wilcoxon Signed Rank Tests were used. Correlations between pre- to post- surgery changes in gut hormones (eCBs, ghrelin) and changes in BMI, changes in body weight, and changes in liking and wanting of the stimuli were tested in SPSS using Spearman's rho correlation coefficient.

2.6.3. fMRI

Two out of 21 datasets were excluded from further analyses, because realignment parameters indicated substantial movement artefacts (> 5 mm). Whole brain functional images of 19 individuals (4 men and 15 women; age 41 ± 10 years) were preprocessed and analyzed using the SPM12 software package (Wellcome Trust Centre for Neuroimaging, London, UK) run with MATLAB 7.12.0 (R2011a, The Mathworks Inc.). Functional images were slice timed, realigned and coregistered. A DARTEL framework was used to create a study-specific template and participant-specific deformation fields [32]. The images were then spatially normalized to the MNI standard brain using the study-specific DARTEL template and the participant-specific deformation fields. Smoothing was applied to the normalized images using an isotropic Gaussian kernel with a 6-mm full width at half maximum.

Subject level analyses: Each test session (pre-/post-surgery) was modelled separately. Motion related variance was corrected for by including motion-correction parameters in the model. Subject level analyses included calculation of six contrast images for odor, and six contrast images for picture presentations (HFHS vs rest; LFLS vs rest; NF vs rest; HFHS vs LFLS; HFHS vs NF; LFLS vs NF). Image calculation was used to subtract the contrast images post-surgery from the contrast images pre-surgery, creating a contrast image in which the within-subject changes from pre- to post-RYGB were captured.

Group level analyses: For our main contrast of interest, pre- to post-surgery changes in the difference between BOLD responses to HFHS and LFLS cues ($HFHS > LFLS_{pre}$-$HFHS > LFLS_{post}$) were analyzed for odors and pictures in two separate T-tests. Six T-tests were performed to analyze pre- to post-surgery differences in BOLD responses to the different stimulus categories ($HFHS_{pre}$-$HFHS_{post}$; $LFLS_{pre}$-$LFLS_{post}$; NF_{pre}-$NF_{post;}$), for visual and olfactory cues separately. Also, we performed four T-tests to analyze differences in BOLD responses between HFHS and NF stimuli and between LFLS and NF stimuli ($HFHS > NF_{pre}$-$HFHS > NF_{post}$; $LFLS > NF_{pre}$-$LFLS > NF_{post}$), separate for odors and pictures. We used a whole brain approach, with a significance level of $p = .001$ (unc.) and a cluster extent threshold of $k = 8$ contiguous voxels. For all contrasts, the mean beta values of significant clusters were extracted with use of the MarsBar toolbox (http://marsbar.sourceforge.net/). Mean beta values of each significant cluster were subsequently correlated with pre- to post- surgery changes in endocannabinoid and ghrelin concentrations, changes in BMI, changes in body weight, changes in liking and wanting of the stimuli, and changes in preference for high-fat sweet and low-energy savory products. Correlation analyses were performed in SPSS using Spearman's rho correlation coefficient.

3. Results

After RYGB surgery, the mean body weight of our study population decreased from 120 ± 3 to 104 ± 3 kg, a mean weight loss of 16 ± 4 kg. This weight change led to a decrease in BMI from 41 ± 1 to 36 ± 1 kg/m^2 (see Table 1).

3.1. Hunger, liking and wanting ratings

Our standardized meal was successful in achieving a state of satiety, as observed from the hunger, fullness and desire to eat ratings, and were similar before and after RYGB surgery. Ratings for prospective consumption and thirst were significantly higher pre- compared to post-surgery (see Table 1).

HFHS pictures were significantly less liked (pre: 47 ± 6, post: 29 ± 5) and wanted (pre: 42 ± 6, post: 26 ± 5) after surgery (both $p < .001$). Similarly, HFHS odors were less liked (pre: 50 ± 8, post: 30 ± 7; $p < .001$) and less wanted (pre: 40 ± 7, post: 24 ± 6; $p = .018$) after surgery. Liking and wanting ratings remained the same in both test sessions for LFLS pictures and odors, and for NF pictures. NF odors were significantly less liked (pre: 35 ± 7; post: 23 ± 7; $p = .008$) and wanting ratings were similar pre- and post-surgery. Intensity ratings for HFHS, LFLS and NF odors were similar between the two test sessions (for all, see Supplementary Table S2).

3.2. Food preferences

Preference for high-fat/sweet products decreased after surgery (pre: 2.6 ± 0.72, post: 2.0 ± 0.8; T [1,15] = 3.39, $p < .05$). Preference for low-energy/savory products increased after surgery (pre: 2.3 ± 0.6, post: 2.7 ± 0.6; $T(1,15) = -3.50$, $p < .05$).

3.3. Functional imaging data

3.3.1. Pictures: pre- to post-surgery differences

In the left precuneus, the difference in brain responses to HFHS and LFLS pictures was significantly smaller after compared to before surgery (see Table 2 and Fig. 2). Before surgery, viewing LFLS cues led to greater deactivation of the left precuneus than viewing HFHS cues. After RYGB, deactivation in response to food pictures was minimal in this region and did not differ between HFHS and LFLS. Participants showed significantly smaller responses to LFLS pictures in the left superior frontal gyrus (anteroventral PFC) after surgery (see Table 2). The pre-surgical deactivation of this region to LFLS pictures, was no longer present in the post-surgery session. Right superior parietal lobule responses to NF pictures were significantly different pre- and post-RYGB, showing deactivation pre- and activation post-surgery (see Table 2). Further, the difference in right precuneus response to HFHS compared to NF pictures was reversed from pre- to post-surgery (see Table 2 and Fig. 2). Deactivation in response to HFHS pictures was greater than deactivation to NF pictures before surgery, and smaller than deactivation to NF pictures after surgery.

3.3.2. Odors: pre- to post-surgery differences

During HFHS odor exposure significantly greater deactivation was found in the right precuneus and left superior parietal lobule pre- compared to post-surgery (see Table 2). We also observed significantly different precuneus responses to LFLS odors pre- versus post-surgery (see Table 2). The right precuneus was deactivated pre- and activated post-surgery. Before surgery there was an absence of response in the left precuneus, but after surgery this region was activated in response to LFLS odors. In response to NF odors deactivation of the left precuneus and left superior parietal lobule was observed pre- surgery, this was significantly different after surgery, when activation was seen in these regions (see Table 2). The difference in response of the left superior frontal gyrus (anteroventral PFC) to HFHS odors vs NF odors was significantly different pre- and post-surgery (see Table 2 and Fig. 2). This effect appears to be mainly driven by increased activation in response to NF odors after surgery.

3.3.3. Correlations between neural changes and behavioural measures

No significant correlations were found between changes in neural responses to odors or pictures, changes in BMI or body weight, and changes in liking, wanting and intensity ratings for odors (all $p > .05$). An increased reduction of deactivation of the left superior parietal lobule to HFHS odor after RYGB was correlated with a greater increase in preference for low-fat/savory food (r = −.550, $p = .027$), and albeit not significant, associated with a greater decrease in preference for high-fat/sweet food (r = .417, $p = .108$). An increased reduction in activation of the left precuneus to HFHS pictures relative to LFLS pictures was correlated with a greater decrease in preference for high-energy/sweet relative to low-energy/savory food (r = −.530, $p = .035$).

3.4. Endocannabinoids and ghrelin

Plasma concentrations of anandamide were significantly greater post- than pre-surgery (before: 0.38 ± 0.17 ng/ml, after:

Table 2
Significant differences in neural activation by food and non-food cue exposure (picture or odor), pre- to post-RYGB.

			cluster size	Z-score	Peak coordinates		
					x	y	z
PICTURE							
$HFHS\text{-}LFLS_{pre} > HFHS\text{-}LFLS_{post}$	L	Precuneus	9	3.43	−3	−54	69
$LFLS_{pre} < LFLS_{post}$	L	Superior Frontal gyrus/anteroventral PFC	13	3.73	−21	51	9
$NF_{pre} < NF_{post}$	R	Superior Parietal lobule	11	3.45	24	−66	63
$HFHS\text{-}NF_{pre} < HFHS\text{-}NF_{post}$	R	Precuneus	8	3.49	15	−54	21
ODOR							
$HFHS_{pre} < HFHS_{post}$	R	Precuneus	9	3.92	15	−42	51
	L	Superior Parietal lobule	8	3.66	−21	−54	51
$LFLS_{pre} < LFLS_{post}$	R	Precuneus	11	3.57	9	−48	72
	R	Superior Parietal lobule		3.52	15	−54	72
	L	Precuneus	10	3.51	−3	−66	45
$NF_{pre} < NF_{post}$	L	Superior Parietal lobule	20	3.89	−21	−54	69
	L	Precuneus	12	3.69	−12	−69	63
$HFHS\text{-}NF_{pre} > HFHS\text{-}NF_{post}$	L	Superior Frontal gyrus / anteroventral PFC	8	3.92	−21	63	3

HFHS: high-fat/high-sugar; LFLS: low-fat/low-sugar; L: left; NF: non-food; R: right; RYGB: Roux-en-Y Gastric Bypass; Whole brain results; p < .001 (unc).

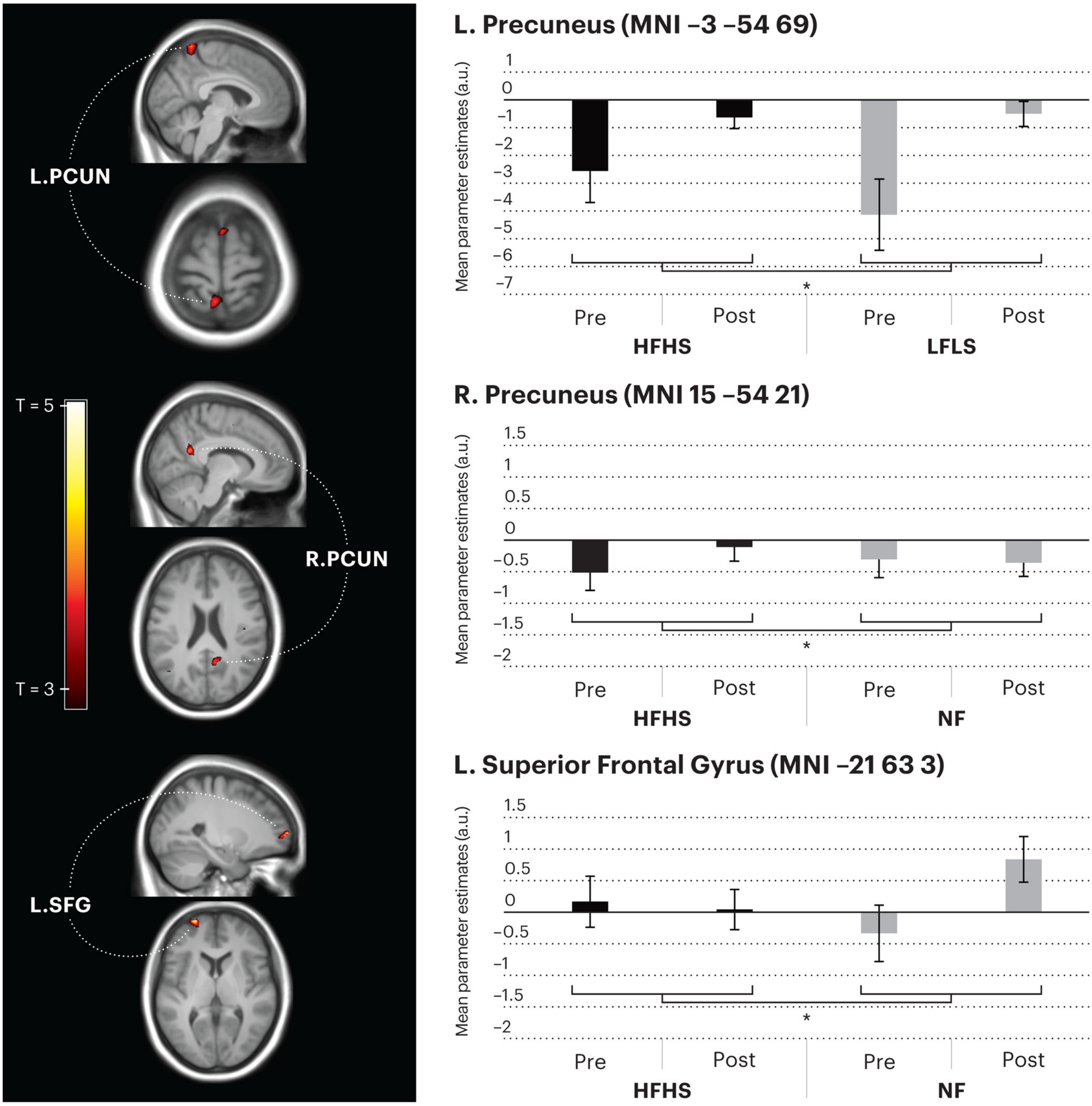

Fig. 2. Significant differences in neural activation by food and non-food cue exposure (picture or odor), pre- to post-RYGB. Results for the brain images were thresholded at p = .005 for visualization. **Upper:** Post-surgery, the left precuneus (L.PCUN, MNI: -3 -54 69) showed significantly less difference between activation to low-fat/low-sugar (LFLS) and high-fat/high-sugar (HFHS) food pictures (k = 9, z = 3.43). Pre-surgery, more deactivation was observed in response to LFLS compared to high-fat/high-sugar (HFHS) pictures while post-surgical responses to these two stimuli appeared similar. **Middle:** Post-surgery, the right precuneus (R.PCUN, MNI: 15 -54 21) showed significantly more difference between activation to high-fat/high-sugar (HFHS) food and non-food (NF) pictures (k = 8, z = 3.49). Pre-surgical deactivation in response to HFHS food pictures was higher, while post-surgical deactivation to HFHS food pictures was lower compared to non-food pictures. **Lower:** Post-surgery, the left superior frontal gyrus (L.SFG, MNI: -21 63 3) showed significantly less difference between activation to high-fat/high-sugar (HFHS) food and non-food (NF) odors (k = 8, z = 3.92). Post- compared to pre-surgery, activation to HFHS odor appeared similar, while increased activation was observed in response to NF odor.

0.48 ± 0.15 ng/ml. $Z = -2.77$, $p = .006$. For the other eCBs, 2-AG, DHEA, DLE, OEA, PEA, SEA, and ghrelin, concentrations did not change significantly (see Table 3 for values).

Changes in eCB and ghrelin concentrations did not correlate with changes in neural activation, nor with changes in liking and wanting of pictures and odors, nor with BMI or body weight changes (all $p > .05$).

4. Discussion

The aim of this study was to provide additional insights into the neural mechanisms underlying changes in food preferences after RYGB, using appetizing visual and olfactory cues representing high- and low-energy foods, and by including measures of appetite-related hormones (eCBs and ghrelin). After RYGB, patients demonstrated a shift in food preferences away from high-fat/sweet and towards low-energy/savory food products, which correlated with less deactivation of the superior parietal lobule to high-energy food odors and a smaller difference in activation of the precuneus to high-energy versus low-energy food pictures. Main findings further included less deactivation of the precuneus in response to all cues. After surgery, deactivation in the superior frontal gyrus was less towards low-energy food pictures and more similar to high-energy versus non-food odors. Further,

Table 3
Plasma concentrations of endocannabinoids and ghrelin pre- and post- RYGB surgery.[a]

Compound	*Pre-surgery* Mean ± *SD*	*Post-surgery* Mean ± *SD*	*Difference* Mean ± *SD*
Anandamide[b]	0.4 ± 0.2	0.5 ± 0.2	0.1 ± 0.2
2-arachidonoylglycerol	8 ± 3	14 ± 17	6 ± 17
Docosahexaenoylethanolamide	0.5 ± 0.1	0.4 ± 0.1	−0.1 ± 0.2
Dihomo-γ-linoleonylethanolamide	0.1 ± 0.05	0.09 ± 0.04	−0.01 ± 0.05
Oleoylethanolamide	2.6 ± 1	2.6 ± 1	0.0 ± 1
Palmitoylethanolamide	1.7 ± 0.7	1.6 ± 0.4	−0.17 ± 0.8
Stearoylethanolamide	2.5 ± 1	2.2 ± 1	−0.3 ± 1
Ghrelin	459 ± 190	442 ± 171	−17 ± 159

[a] Concentrations in ng/mL; n = 18, for endocannabinoids, n = 17 for ghrelin.
[b] Significant difference (p = .006) pre- and post- Roux-en-Y Gastric Bypass (RYGB).

anandamide concentrations were increased, while other eCB and ghrelin concentrations did not change. Neural changes did not correlate with changes in eCB and ghrelin concentrations.

In line with previous research [2], participants reported a shift in food preferences away from high-energy foods, and towards low-energy food products, on the MTPRT [28]. These alterations in food preferences may (in part) underlie the success of RYGB surgery as weight-loss intervention.

Post- compared to pre-surgery, the left superior frontal gyrus was less deactivated in response to low-, but not to high-energy pictures. Previous research into the effects of RYGB reported postsurgical reductions in prefrontal cortex activation that were more pronounced for high- relative to low-energy cues [33]. Moreover, decreased differences in desire to eat high- versus low-energy foods were predicted by a reduced difference in a more posterior part of the superior frontal gyrus response to high-energy versus low-energy food cues [5]. Unfortunately, these studies only compared surgery-related changes in responses to high- relative to low-energy food cues, rather than considering changes in responses to high and low-energy food cues separately. Perhaps, the decreased difference in activation between high- and low-energy food cues are in fact largely driven by a diminished response to low-energy food cues, similar to our observations. The anteroventral region of the superior frontal gyrus we found has been implicated in subjective reward value [34] and in processes of self-control [35]. Several studies have reported that activation patterns in this region can act as a predictor of food choices [34,36,37]. Although seemingly counterintuitive, changes in superior frontal activation could be related to the beneficial shift in food preferences, from high-energy towards more healthy low-energy foods, that is frequently reported after RYGB surgery [3,38–40] and is also confirmed by the current study.

Here we have extended previous research into RYGB by including olfactory food cues that predict the immediate presence of food and the rewarding effects of eating [8], and that can be processed even largely unconsciously [41]. After surgery, we observed less deactivation of the superior parietal cortex, in response to food odors but not pictures. Increased superior parietal activation was previously found during anticipation of reward [42]. This region was also proposed to be part of a top-down control system for attentional processes that is modulated by implicit contextual cues, with greater deactivation being associated with increased attentional demands [42,43]. Less deactivation of the superior parietal cortex after surgery found in this study could indicate a decrease in anticipated reward of high-energy food odors, and thereby a lowered attentional demand. In line with this, the diminished activation was positively, albeit not significantly, correlated with (lowered) preference for high-energy foods, and negatively correlated with (heightened) preference for low-energy foods.

After surgery, decreased activation of the bilateral precuneus was found in response to high-, but most pronounced to low-energy dense food cues (pictures and odors). In previous research, decreased precuneus responsivity to high- versus low-energy food cues was related to decreased food liking [5]. A role in food reward anticipation has been proposed by other studies [43–51]. Alternatively, the difference in precuneus activation before and after surgery could be related to changes in attentional control [43,52]. Greater deactivation in this region indicates increased attentional demand. In relation to our data this would mean that food cues in general, but low-energy food cues in particular, recruit less attention after surgery, though this interpretation is based on reverse inference. Further research should focus in more detail on how (changes in) attentional processes relate to changes in food preference and choice rather than food cue reactivity.

The neural regions (the superior frontal gyrus, superior parietal lobe and precuneus) in which we find altered responsivity to food cues are all part of a frontoparietal control network involved in adaptive top-down control [37,53]. In a study by Schonberg et al. [37] participants who were trained to choose less preferred food item showed decreased activation in this frontoparietal network during low-value food choices. The authors propose that over the course of extensive training the need for top-down frontoparietal control reduces as food preference responses move from goal-directed to more habitual behavior. Speculatively, a similar process is set in motion after RYGB. In RYGB patients, aversive consequences associated with consumption of sugary and fatty foods (e.g. nausea, light-headedness, flushing, and diarrhea; [52]) could lead to a relative preference for low-energy food products. Our current findings, around two months after surgery, suggest a neural food cue response that is in line with more habitual and automated, internalized behavior rather than a goal-directed pattern requiring (neural) effort.

Altered appetite-related hormone concentrations were proposed to mediate the changes in neural processing observed after RYGB [12,55,56] and could ultimately contribute to beneficial changes in food preference and intake [54]. In this study we did not find pre- to post-surgery differences in plasma ghrelin concentrations, which might be due the large variation in pre- to post surgery differences in plasma ghrelin concentrations, as also seen in previous studies [22,57]. Faulconbridge et al. [22] found a correlation between changes in ghrelin concentrations and changes in neural responses, which our data do not confirm. Discrepancies in neural activation and ghrelin concentrations could be related to a difference in the timing of the measurements (6 [22] vs 2 months post-surgery in the current study), as the effect of RYGB on ghrelin concentrations might change over time [58].

Endocannabinoids have been suggested to mediate the orexigenic effects of ghrelin [17] and are implicated in reward anticipation [16,18–21]. Increased eCB concentrations have been suggested to be a cause of obesity [59] and may be related to long-term weight loss and weight-regain after RYGB. Within the range of eCBs that we measured, we showed increased plasma anandamide concentrations after compared to before RYGB. Concentrations of the other eCBs we measured did not change. Previous studies assessing eCBs at alternate time points after RYGB included only few eCBs and suggest either decreased or unchanged anandamide concentrations, and unchanged concentrations of 2-AG, OEA and PEA [60–62]. Similar to ghrelin, eCB concentrations may change over time and future studies should monitor the progression of eCB concentrations at different time points after RYGB. Moreover, as food preferences may revert back, and longer-term weigh regain is also reported upon RYGB, a new generation of more longitudinal and interventional studies will be necessary to causally implicate the observed differences of neural activity in the changed eating behavior and weight loss, and to further understand how new food preferences are formed and what gut-brain signals are responsible after bariatric surgery.

It can be seen as limitation that blood samples for plasma eCB and ghrelin concentration determination were drawn after at least three hours of fasting, whereas the fMRI measurements were performed after a lunch meal. Concentrations directly after this meal may have been more closely associated with the neural responses we observed in a satiated state. A particular strength of this study was that participants were measured in a satiated state, to mimic potential overeating situations (eating beyond normal satiety) in obesity more realistically. However, this may have reduced reward related neural activation, and complicates direct comparisons to previous literature (*e.g.* [5,31]). Moreover, most other studies looked into pre- to post-surgery changes in the relative difference between high-energy and low-energy food cues [5,38,63], whereas we examined the changes in response to HFHS and LFLS cues relative to baseline, as well as compared to non-food cues, to be able to draw more specific conclusions. The seemingly small effects in this study, may also be the result of this (subtracted) comparison. Moreover, although the number of participants may seem limited, this is in fact, one of the larger within-subject fMRI studies on changes in neural responsivity upon RYGB.

The neural changes we find are in line with the observed increased preferences for low-energy, and decreased preferences for high-energy foods. The current results suggest that there is no relation between changes in ghrelin and endocannabinoid concentrations, and changes in neural responses to food cues in RYGB patients. Using olfactory food cues in addition to pictures did not reveal new information, but highlights the importance of odors for the anticipation of food. To conclude, RYGB leads to alterations in activation of the frontoparietal network, involved in cognitive control during (food) cue processing.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bbr.2018.07.016.

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