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Obese patients after gastric bypass surgery have lower brain-hedonic responses to food than after gastric banding

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ABSTRACT

Objectives Roux-en-Y gastric bypass (RYGB) has greater efficacy for weight loss in obese patients than gastric banding (BAND) surgery. We hypothesise that this may result from different effects on food hedonics via physiological changes secondary to distinct gut anatomy manipulations.

Design We used functional MRI, eating behaviour and hormonal phenotyping to compare body mass index (BMI)-matched unoperated controls and patients after RYGB and BAND surgery for obesity.

Results Obese patients after RYGB had lower brain-hedonic responses to food than patients after BAND surgery. RYGB patients had lower activation than BAND patients in brain reward systems, particularly to high-calorie foods, including the orbitofrontal cortex, amygdala, caudate nucleus, nucleus accumbens and hippocampus. This was associated with lower palatability and appeal of high-calorie foods and healthier eating behaviour, including less fat intake, in RYGB compared with BAND patients and/or BMI-matched unoperated controls. These differences were not explicable by differences in hunger or psychological traits between the surgical groups, but anorexigenic plasma gut hormones (GLP-1 and PYY), plasma bile acids and symptoms of dumping syndrome were increased in RYGB patients.

Conclusions The identification of these differences in food hedonic responses as a result of altered gut anatomy/physiology provides a novel explanation for the more favourable long-term weight loss seen after RYGB than after BAND surgery, highlighting the importance of the gut–brain axis in the control of reward-based eating behaviour.

INTRODUCTION

Bariatric surgery is currently the most effective long-term treatment for obesity and its associated comorbidities.¹ Over 20 years, Roux-en-Y gastric bypass (RYGB) surgery achieves on average 25% weight loss compared with 14% with gastric banding (BAND) surgery.¹ This suggests that the specific anatomical manipulations of the gut in each procedure may have very different physiological effects.²

In RYGB, the formation of a small gastric pouch enables food to have earlier contact with the mid and distal small bowel. Food bypasses the stomach

Significance of this study

What is already known about this subject?

- Bariatric surgery is the most effective long-term treatment for obesity.
- Gastric bypass surgery results in more weight loss than gastric banding surgery.
- Gastric bypass, but not gastric banding surgery, leads to increased postprandial anorexigenic gut hormones.
- Gastric bypass surgery patients report a shift in food preference that is away from high-calorie foods.

What are the new findings?

- Using functional MRI, activation in brain reward systems, including orbitofrontal cortex, amygdala, putamen, caudate and nucleus accumbens, during evaluation of the appeal of high-calorie food pictures was less after gastric bypass than after gastric banding surgery.
- High-calorie foods were less appealing and consumed less after gastric bypass than gastric banding surgery.
- These differences were not explicable by differences in hunger levels or psychological traits.
- Plasma GLP-1, PYY, bile acids and postingestive dumping symptoms were higher after gastric bypass than gastric banding surgery.

How might it impact on clinical practice in the foreseeable future?

- A more personalised approach to the choice of bariatric procedure including assessment of food hedonics may be warranted.
- Targeting the gut–brain food hedonic axis is important in the development of future non-surgical treatments of obesity.

and proximal small bowel, but undiluted bile has contact with the proximal small bowel. Vagal fibres across the stomach may be disrupted.^{3–4} Reduced hunger and increased satiety after RYGB are in part due to early and exaggerated responses of

anorexigenic intestinal hormones, such as peptide YY (PYY) and glucagon-like polypeptide-1 (GLP-1), part of the gut-brain axis regulating ingestive behaviour.⁵ These gut hormone changes are absent after BAND surgery, where the adjustable band around the proximal stomach reduces hunger through increased intraluminal pressure on vagal afferent mechanoreceptors.⁶

Human eating behaviour is affected by hunger, and also by the reward value of food.⁷ An advantageous shift away from consumption of high-fat and sweet food after RYGB surgery has been reported in animal and human studies.^{7–9} However, differences in food hedonics between RYGB and BAND surgery, the two most commonly performed procedures around the world, and their underlying neural basis, have not been explored.

Functional MRI (fMRI) allows study of brain reward-cognitive systems related to eating behaviour by measuring regional changes in the blood oxygen level-dependent (BOLD) signal to food stimuli, a marker of neuronal activation.¹⁰ These include corticolimbic networks: striatal nucleus accumbens and caudate nucleus (reward conditioning, expectancy, motivation and habitual behaviour), amygdala (emotional responses to rewarding stimuli), anterior insula (integrating gustatory and other sensory information) and orbitofrontal cortex (OFC) (encoding of reward value and salience, decision making).^{11–12}

We hypothesised that RYGB and BAND procedures have different effects on brain reward systems, and hence, on eating behaviour, which may explain the greater weight loss seen after RYGB. We compared body mass index (BMI)-matched patients after RYGB and BAND surgery, with BMI-matched unoperated controls that had not lost weight. The primary outcome measure was reward system activation to food pictures using fMRI, and secondary outcomes were behavioural and metabolic phenotyping measures.

METHODS

Further details are given in online supplementary methods.

Participants

Eighty-three participants (30 RYGB, 28 BAND, 25 BMI-matched (BMI-M) unoperated controls) were recruited from obesity clinics and public advertisement. Surgical patients were recruited more than 2 months after surgery, after losing at least 8% body weight (see online supplementary table S1). Unoperated BMI-matched controls were weight stable. Of these, 61 participants (21 RYGB, 20 BAND, 20 BMI-M) were eligible for a scanning visit (table 1). fMRI scans of two subjects (1 RYGB, 1 BMI-M) were excluded from analysis due to excess motion and/or poor image quality. For inclusion and exclusion criteria see online supplementary methods.

Psychological and eating behaviour phenotyping

All subjects completed questionnaires to assess eating behaviour, mood, impulsivity, personality and reward sensitivity.

fMRI protocol

Eligible subjects had structural MRI and BOLD fMRI for 1 h after an overnight fast (figure 1). During a food picture evaluation task, subjects viewed photographs of high-calorie foods, low-calorie foods, non-food-related household objects and blurred images.¹³ Subjects simultaneously rated the appeal of each picture. An auditory-motor-visual control fMRI task was performed to exclude non-specific changes in BOLD signal between groups.

fMRI analysis

fMRI data processing used the fMRI Expert Analysis Tool V5.98 (<http://www.fmrib.ox.ac.uk/fsl>). General linear model analysis was used to measure BOLD activation to (i) any food (high-calorie or low-calorie); (ii) only high-calorie foods or (iii) only low-calorie foods (compared with objects) in the food evaluation task; and for (iv) auditory, motor or visual tasks in the control paradigm.

Table 1 Characteristics of obese patients after gastric bypass and gastric banding and unoperated controls at time of fMRI scanning

	BMI-M	BAND	RYGB	p Values*
n	20	20	21	
Age (years)	39.1±2.3 (20.0–55.0)	40.9±2.5 (22.0–59.0)	43.5±2.0 (23.0–59.0)	0.38
Gender (Male:Female)	3:17	1:19	4:26	0.57
Postmenopausal women, n (%)	5 (25%)	5 (25%)	6 (29%)	0.96
Ethnicity: European Caucasians, n (%)	10 (50%)	15 (75%)	16 (76%)	0.14
Preoperative BMI (kg/m ²)	n/a	44.8 [41.9–49.2] (36.5–57.0)	48.4 [40.7–58.0] (34.7–74.6)	0.23
Current BMI (kg/m ²)	35.4±1.9 (24.7–55.6)	35.1±1.4 (25.3–49.2)	35.3±1.7 (22.6–52.4)	0.99
Current height (m)	1.64±0.02 (1.49–1.78)	1.66±0.02 (1.53–1.79)	1.66±0.02 (1.52–1.85)	0.64
Current weight (kg)	97.0±3.1 (73.9–119.8)	97.0±3.1 (73.9–119.8)	98.1±4.9 (63.7–137.9)	0.97
Current body fat (%)	42.1±2.2 (26.0–58.2)	41.9±1.8 (23.3–54.7)	41.3±1.9 (28.4–56.0)	0.96
Weight loss (% of preoperative weight)	n/a	23.1 [14.5–29.3] (9.7–52.4)	29.9 [23.4–36.5] (16.3–40.4)	0.018 RYGB > BAND
Time since surgery (months)	n/a	9.1 [5.2–19.2] (3.6–64.6)	8.1 [5.9–11.5] (2.6–26.2)	0.25
Preoperative DM, n (%)	n/a	2 (10%)	10 (48%)	0.02 RYGB > BAND
Current DM, n (%)	2 (10%)	0 (0%)	3 (14%)	0.23
Preoperative obesity comorbidity score	n/a	6.0 [4.5–6.0] (1.0–10.0)	10.0 [6.6–11.5] (3.0–19.0)	<0.001 RYGB > BAND
Current obesity comorbidity score	0.0 [0.0–5.0] (0.0–18.0)	0.0 [0.5–2.0] (0.0–9.0)	1.0 [0.8–3.0] (0.0–10.0)	0.85
Preoperative BED, n (%)	n/a	4 (25%)	4 (19%)	1.00
Current BED, n (%)	2 (10%)	2 (10%)	1 (5%)	0.78

Data included only for those subjects who had fMRI scanning. Data presented as mean±SEM or median [IQR] for data that are not normally distributed and (range).

*p Value for overall comparison between groups.

BAND, gastric banding; BED, binge eating disorder; BMI, body mass index; BMI-M, BMI-matched; DM, type 2 diabetes mellitus; n/a, not applicable; RYGB, gastric bypass.

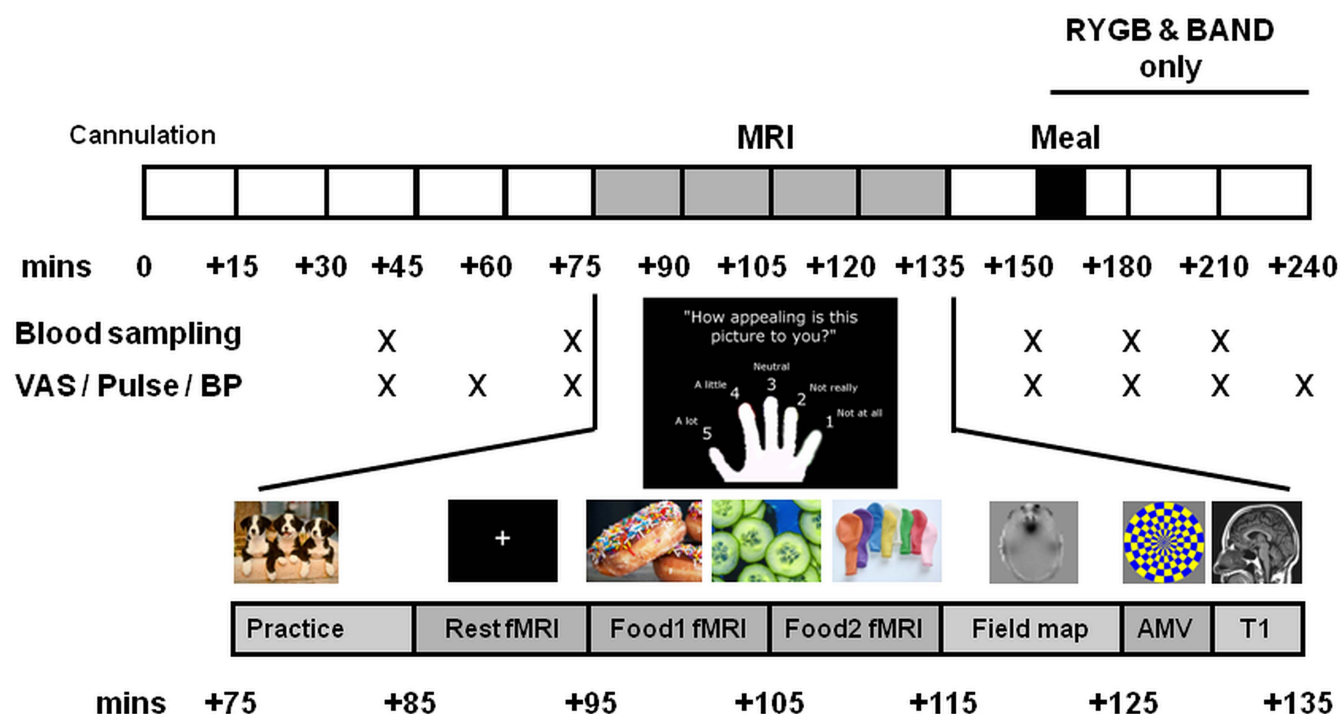


Figure 1 Study protocol. AMV, audio-motor-visual task; BAND, gastric banding; BP, blood pressure; fMRI, functional MRI; RYGB, gastric bypass; VAS, visual analogue scales.

Whole brain mixed effects analysis compared BOLD signal between surgical groups using unpaired *t* test, with both voxel-wise false discovery rate (FDR) corrected $p < 0.05$ and cluster-wise threshold $Z > 2.1$, familywise error corrected $p < 0.05$, including age, gender and BMI as covariates. Activation in a priori functional regions of interest (fROIs) was compared between all groups for the food evaluation task using the following ROIs (see online supplementary figure S1 and table S4): bilateral OFC, amygdala, nucleus accumbens, anterior insula and caudate nucleus. These fROIs were determined from a separate cohort of 24 overweight/obese subjects who had the same fMRI protocol (see online supplementary tables S2 and S3). The anatomically constrained functional ROIs were defined by masking average activation for the food > object contrast (voxel-wise FDR, $p < 0.05$) with the Harvard anatomical atlas (see online supplementary methods). fROIs for the control paradigm were bilateral superior posterior temporal gyrus (auditory), left precentral gyrus (motor) and bilateral lingual gyrus (visual) (see online supplementary figure S2A and table S4).

Appetite and food palatability

Visual analogue scales (VAS) were used to measure appetite ratings, lunch palatability and other confounding symptoms (figure 1). Scanning was followed by an ad libitum ice cream test meal for the two surgical groups.

Dietary habits

Diet macronutrient composition was assessed using 3-day self-reported home dietary records in the two surgical groups, analysed using Dietplan6 (Foresfield Software Ltd, West Sussex, UK).

Hormonal and metabolic phenotyping

Serial blood samples before and after scanning were collected for measurement of plasma glucose, insulin, gut hormones (PYY, GLP-1 and acyl ghrelin) and bile acids (see online supplementary figure S1).

Dumping syndrome

Symptoms and signs of dumping syndrome in the surgical groups were assessed from postprandial changes in nausea, sleepiness, blood pressure and heart rate and retrospective completion of validated questionnaires (Sigstad's and Arts') for the 3 months following surgery.

Statistical analysis

Results are presented as mean \pm SEM or median [IQR] for data that were not normally distributed. Comparisons of averages between groups used unpaired *t* tests or one-way analysis of variance (ANOVA) with post hoc Fisher's least significant difference test or, if not normally distributed, Mann-Whitney U test or Kruskal-Wallis ANOVA on Ranks with post hoc Dunn's test. Comparison of prevalence between groups used χ^2 test. Comparisons between groups for fMRI activation and eating behaviour and psychological questionnaires were adjusted for age, gender and BMI. To further investigate the link between brain responses to food cues, food hedonics and potential mediators, correlations between BOLD activation (adjusted for age, gender and BMI) and ice cream palatability or gut hormones/bile acids/dumping syndrome scores were performed to determine Pearson, or if not normally distributed Spearman, correlation coefficients. Significance was taken as $p < 0.05$. Analyses used SPSS V19.0 and Prism V5.01.

RESULTS

Participant characteristics

There were no significant differences between the groups in age, gender ratio, prevalence of postmenopausal women, ethnicity, current BMI, percentage body fat, prevalence of type 2 diabetes mellitus (T2DM) or binge eating disorder (BED), for both the whole cohort (see online supplementary table S1) and the scanned subjects only (table 1). The two surgical groups had similar preoperative BMI and prevalence of BED. The RYGB group had more obesity-associated comorbidities preoperatively,

but not postoperatively, compared with the BAND group. There were no significant differences between the groups in any psychological questionnaire measures of depression, mood, reward sensitivity, impulsivity or personality traits (see online supplementary table S5).

Brain activation to food pictures

In whole brain analysis, there was lower BOLD activation in the RYGB group compared with the BAND group when viewing *high-calorie* foods in clusters within the OFC, subcallosal cortex, putamen, caudate, nucleus accumbens, hippocampus, cingulate and paracingulate gyri (figure 2, see online supplementary table S6). BOLD activation when viewing *low-calorie* foods was also lower in the OFC and subcallosal cortex in the RYGB group than in the BAND group. By contrast, there were no clusters with *greater* BOLD activation in the RYGB group compared with the BAND group when viewing high-calorie or low-calorie foods (see online supplementary table S6).

In the functional region of interest (fROI) analysis, BOLD activation within the whole reward system (average activation in the OFC, amygdala, anterior insula, nucleus accumbens and caudate) was *lower* in the RYGB group compared with the BAND group when viewing high-calorie, but not low-calorie, foods (figure 3A and see online supplementary figure S1, tables S4 and S7).

When examining individual fROIs, BOLD activation in the OFC and amygdala was lower in the RYGB group compared with the BAND group, and for amygdala also the control

BMI-M group, when viewing any food (figure 3B,C and see online supplementary table S7). Similar patterns were seen for high-calorie and low-calorie foods.

There were no differences in BOLD activation of the other fROIs in the food evaluation task (figure 3D–F, see online supplementary table S7). There were also no differences in BOLD activation in the auditory, motor or visual cortices for the auditory–visual–motor control fMRI task between the three groups in either the whole brain or fROI analysis (see online supplementary figure S2A,B, tables S4 and S7).

Food appeal scores

During scanning, high-calorie foods, but not low-calorie foods or objects, were rated as less appealing by patients after RYGB than those after BAND surgery and control BMI-M subjects (figure 4A,B).

Appetite VAS

Over the scanning period both the RYGB and BAND groups rated their ‘hunger’, ‘pleasantness to eat’ and ‘volume of food they could eat’ as lower than the control group, but there was no difference between the two surgical groups (figure 5A,E,G). RYGB patients were also less nauseated than BAND patients before the test meal, but absolute nausea ratings were still low (figure 5C).

After scanning, during a test meal, patients after RYGB and BAND surgery consumed similar amounts of ice cream ($p=0.54$), but patients after RYGB rated it as less ‘pleasant to eat’ than

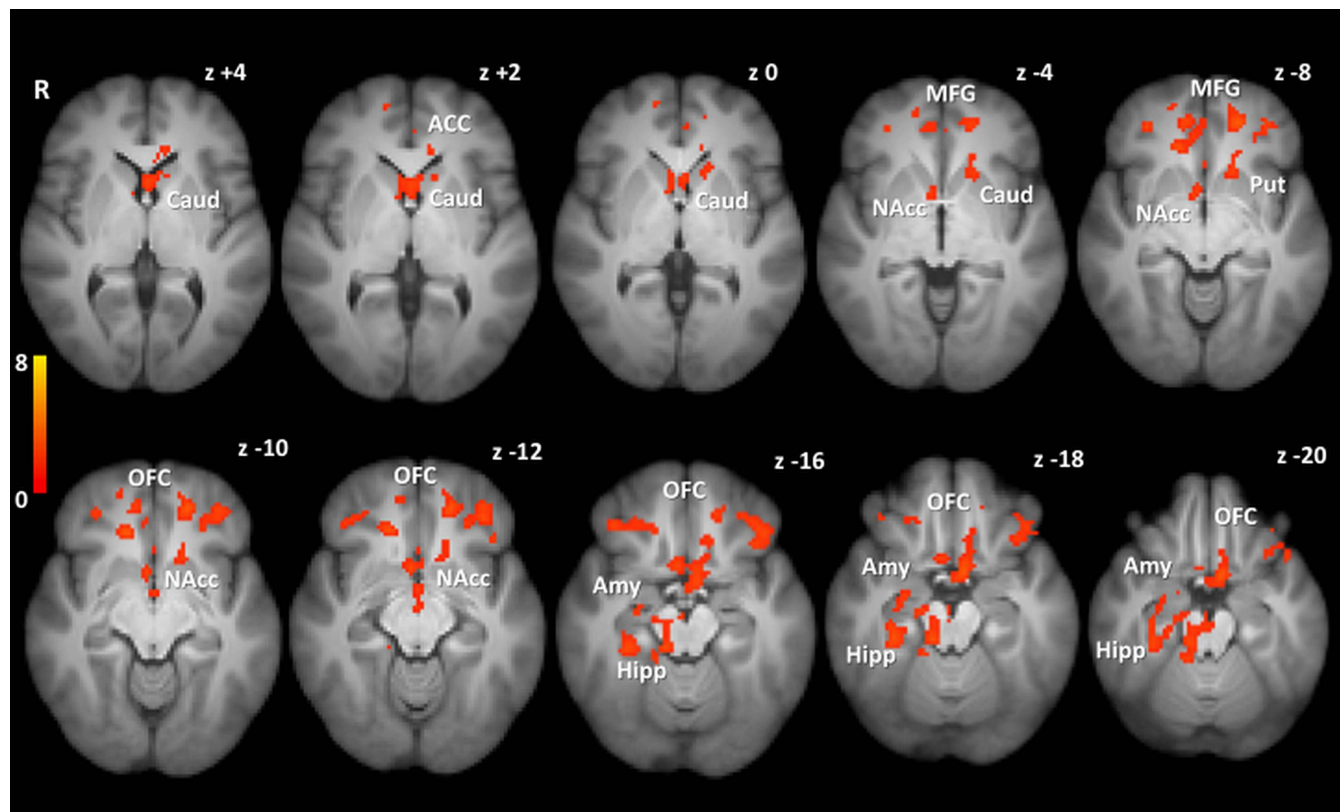


Figure 2 Whole brain comparison of activation to high-calorie foods between obese patients after gastric bypass and gastric banding. Whole brain group level comparison for high-calorie versus object picture contrast to demonstrate clusters in which blood oxygen level-dependent (BOLD) signal was lower in patients after gastric bypass (RYGB) compared with gastric banding (BAND) surgery, adjusting for age, gender and body mass index. No clusters showed greater activation in RYGB than BAND groups. Colour bar indicates Z values. Cluster activation thresholded at $Z > 2.1$, familywise error $p < 0.05$, overlaid onto the average T1 scan for all subjects ($n=20$ per group). Co-ordinates given in standard Montreal Neurological Institute (MNI) space. ACC: anterior cingulate cortex, Amy: amygdala, Caud: caudate, NAcc: nucleus accumbens, Hipp: hippocampus, MFG: middle frontal gyrus, OFC: orbitofrontal cortex, Put: putamen. Voxel-wise differences in BOLD activation between groups did not survive false discovery rate $p < 0.05$ correction.

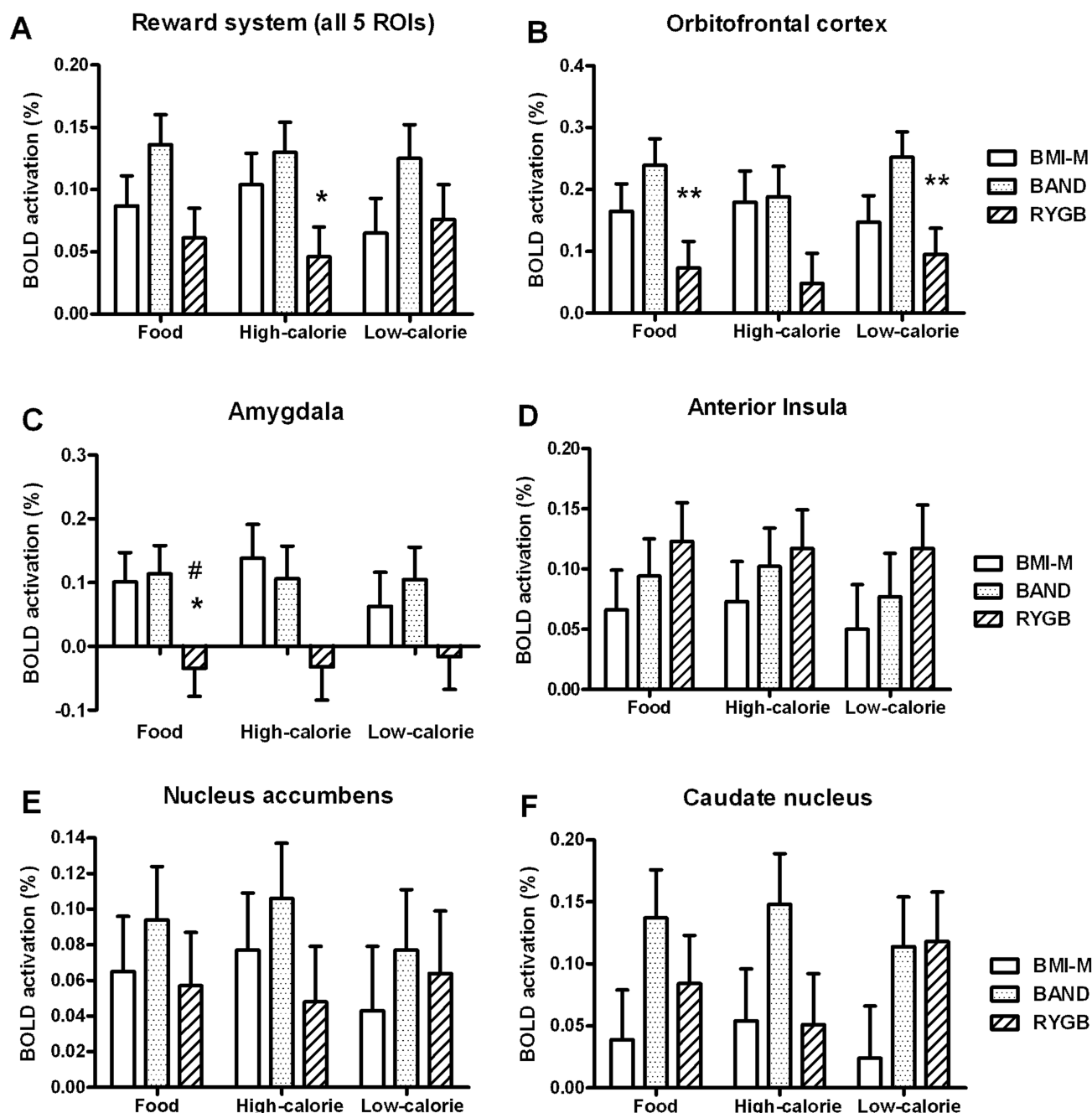


Figure 3 Region of interest activation to food in obese patients after gastric bypass and gastric banding and unoperated controls. Comparison of blood oxygen level-dependent (BOLD) signal to any food, only high-calorie or only low-calorie food (vs objects) in a priori functional regions of interest (fROI) between body mass index-matched unoperated controls (BMI-M, white), and obese patients after gastric banding (BAND, dotted) and gastric bypass (RYGB, striped) surgery, adjusting for age, gender and BMI. (A) Average in all five fROIs, (B) orbitofrontal cortex, (C) amygdala, (D) anterior insula, (E) nucleus accumbens, (F) caudate. Data are presented as mean±SEM. # $p<0.05$, ## $p<0.01$, ### $p<0.005$ versus BMI-M; * $p<0.05$, ** $p<0.01$, *** $p<0.005$ versus BAND; $n=19-20$ per group.

those after BAND ($p=0.047$), but similarly sweet ($p=0.96$) (figure 4C,D). The two surgical groups had similar decreases in hunger and increases in fullness after the meal (figure 5B,J).

Dietary records

Analysis of home food diaries showed that the percentage of energy intake derived from fat was lower in patients after RYGB than after BAND surgery (figure 4E).

Eating behaviour assessment

In the whole cohort, eating behaviour questionnaires indicated that patients after RYGB had healthier eating behaviour and less eating disorder psychopathology compared with the BAND and/or control groups, with significantly lower scores for dietary restraint, external eating and weight and shape concerns (figure 6).

Metabolic and hormonal phenotyping

Plasma GLP-1 levels were similar between the three groups during scanning, but increased significantly more in the RYGB group than

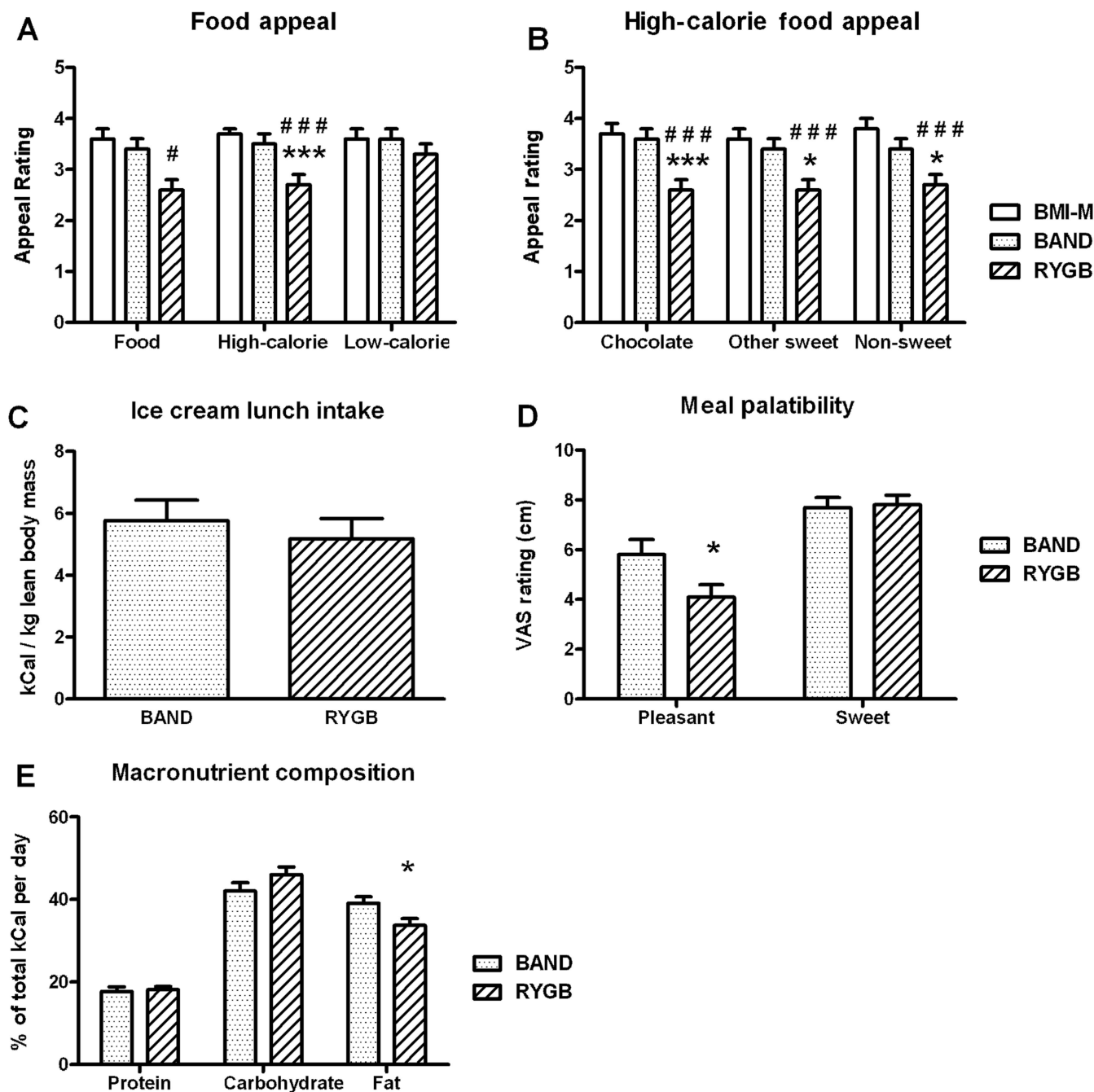


Figure 4 Food hedonics and dietary composition in obese patients after gastric bypass and gastric banding. Comparison of (A) appeal of any food, only high-calorie or only low-calorie food pictures; (B) appeal of subcategories of high-calorie food pictures; (C) ice cream consumption and (D) ice cream palatability rating at meal after fMRI scan; and (E) average percentage of total calories from fat from 3 day food diary, between body mass index-matched unoperated controls (BMI-M, white) and obese patients after gastric banding (BAND, dotted) and gastric bypass (RYGB, striped) surgery. Data are presented as mean±SEM. [#]*p*<0.05, ^{###}*p*<0.005 versus BMI-M; ^{*}*p*<0.05, ^{***}*p*<0.005 versus BAND; *n*=20–21 per group.

in the BAND group after the meal (figure 7A,B). Plasma PYY levels during scanning were higher in the RYGB group than in the BMI-M group, and increased more in the RYGB group than in the BAND group after the meal (figure 7C,D). There were no differences in plasma acyl ghrelin levels between the groups (figure 7E,F).

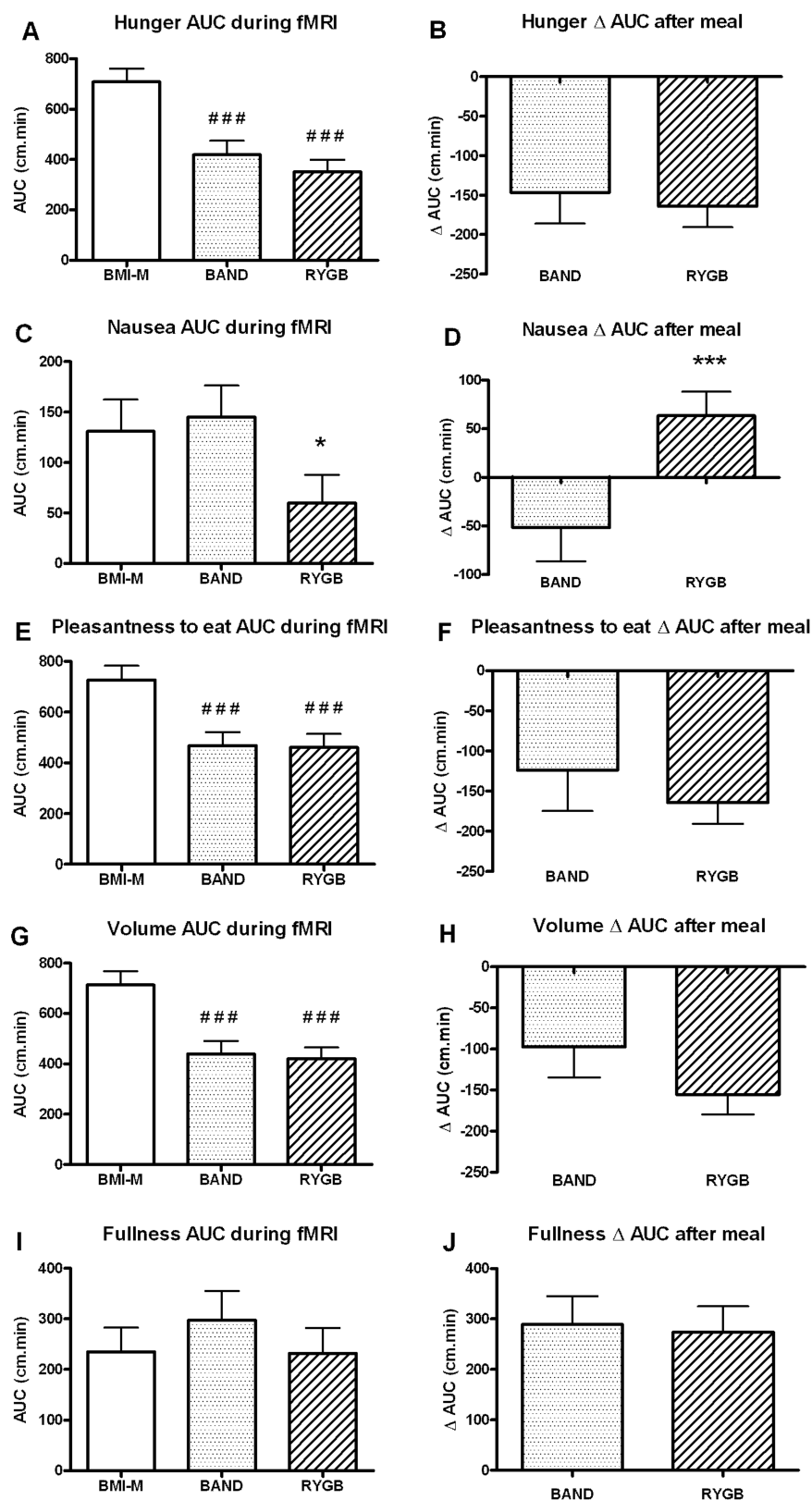
Plasma levels of total and glycine conjugated bile acids were higher in RYGB than BAND groups both during scanning and after the meal (figure 7G,H, see online supplementary figure S3A,B). The subfractions of primary and deoxycholic bile acids were higher in the RYGB patients than the BAND patients only after the meal (see online supplementary figure S3C–F).

Plasma glucose and insulin levels during the scanning period did not differ between the two surgical groups (see online supplementary figure S3G,I). Glucose levels increased more after the meal in the RYGB group compared with the BAND group (see online supplementary figure S3H), but there were similar increases in insulin levels (see online supplementary figure S3J).

Dumping symptoms and signs

Both retrospective dumping symptom questionnaire scores were higher for the patients after RYGB than after BAND surgery (figure 8). The RYGB group had a greater increase in symptoms of 'feeling sick' than the BAND group after the meal (figure 5D, see

Figure 5 Appetite visual analogue scales during fMRI and after meal. Comparison of visual analogue scale ratings of (A and B) hunger, (C and D) nausea, (E and F) pleasantness to eat, (G and H) volume of food that could be eaten and (I and J) fullness. (A,C,E, G and I) Levels during fMRI scanning (area under curve (AUC) +40 to +150 min) between body mass index-matched unoperated controls (BMI-M, white) and obese patients after gastric banding (BAND, dotted) and gastric bypass (RYGB, striped) surgery. (B,D,F,H and J) change in levels after ice cream meal (Δ AUC +150 to +210 min) in surgical groups. Data are presented as mean \pm SEM. ### p <0.005 versus BMI-M; * p <0.05, *** p <0.005 versus BAND; n =20–21 per group.



online supplementary table S8), but there were no differences in the change in blood pressure or heart rate after the meal between the surgical groups (see online supplementary table S8).

Confounding variables

There were no significant differences between the groups in potential confounding factors known to affect BOLD activation

to food cues or non-specifically, including sleepiness, mood, sleep duration, time since last meal or head motion during scanning (see online supplementary table S10).

Correlation between outcome measures

BOLD activation to high-calorie food pictures in the whole reward system was positively correlated with VAS pleasantness

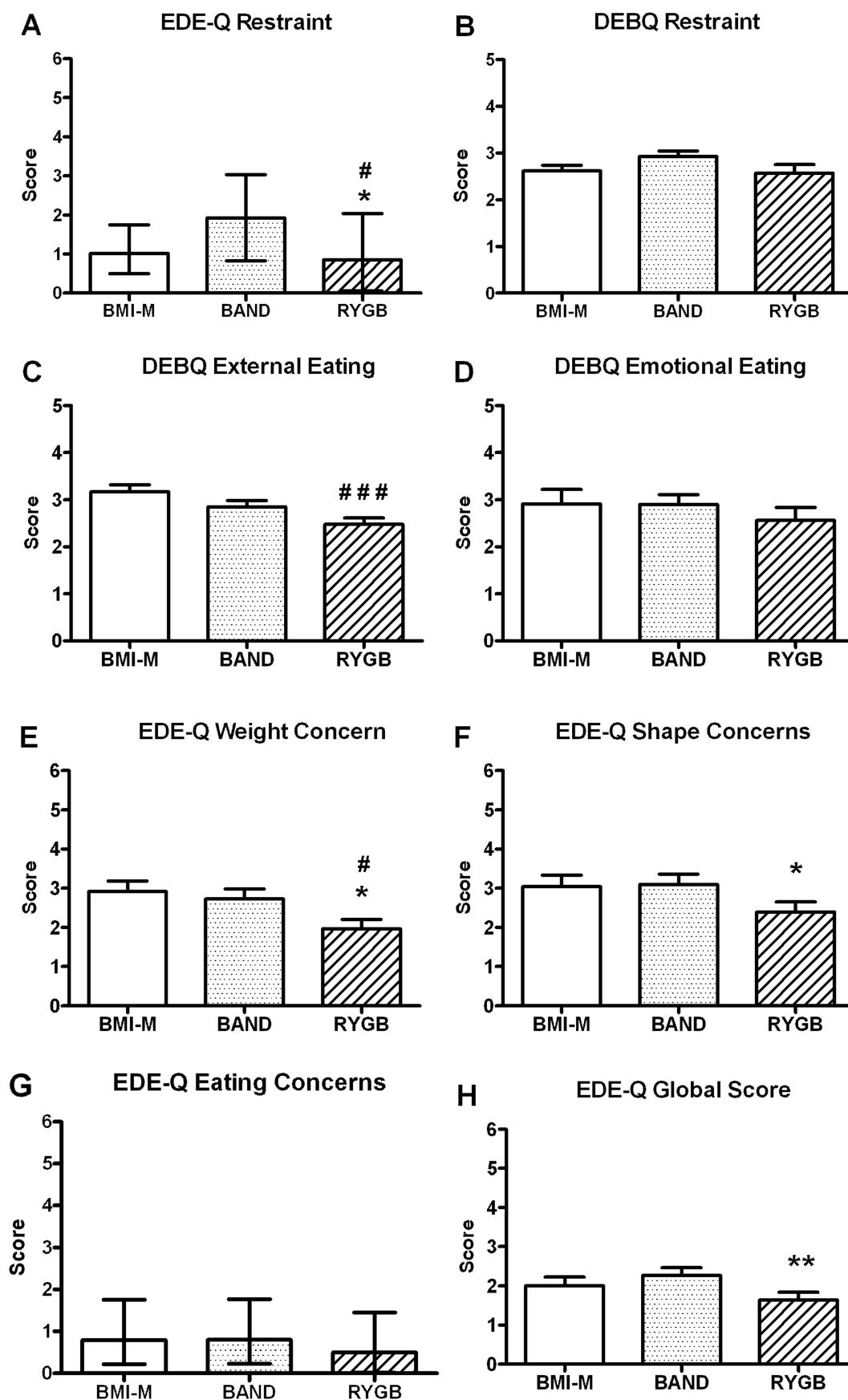


Figure 6 Eating behaviour. (A) EDE-Q dietary restraint, (B) DEBQ dietary restraint, (C) DEBQ external eating, (D) DEBQ emotional eating and EDE-Q (E) weight concerns, (F) shape concerns, (G) eating concerns and (H) global score of body mass index-matched unoperated controls (BMI-M, white) and obese patients after gastric banding (BAND, dotted) and gastric bypass (RYGB, striped) surgery. Data are presented as (A and G) median and IQR, or (B,C-F and H) mean \pm SEM. # p <0.05, ### p <0.005 versus BMI-M; * p <0.05, ** p <0.01 versus BAND; n =20–21 per group. DEBQ: Dutch Eating Behaviour Questionnaire, EDE-Q: Eating Disorders Examination Questionnaire.

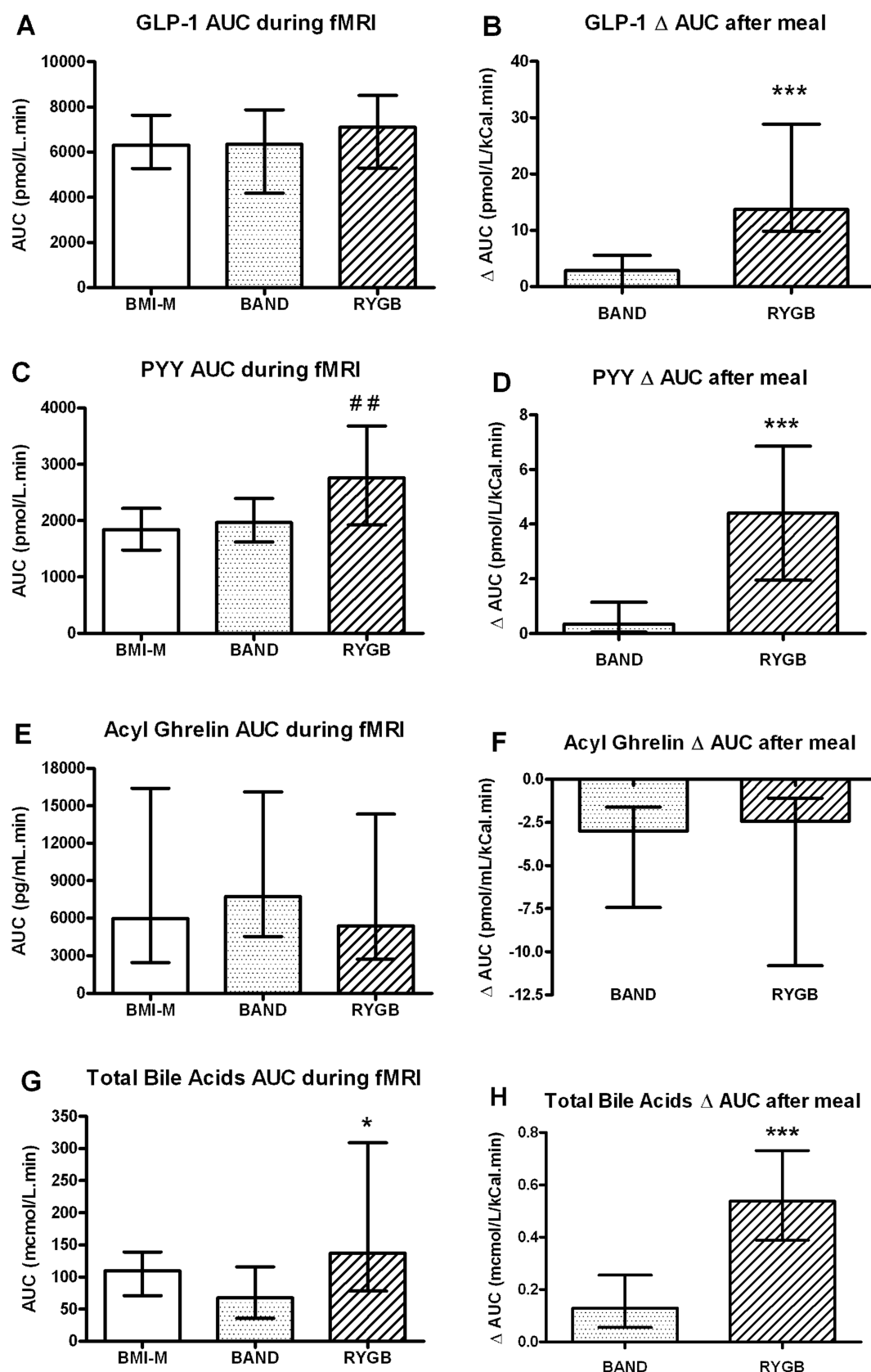


Figure 7 Plasma levels of gut hormones and bile acids in obese patients after gastric bypass and gastric banding and controls. Comparison of (A, C and E) plasma hormone levels (GLP-1, peptide YY, acyl ghrelin, area under curve (AUC) +40 to +150 min) and (G) total bile acid levels during fMRI scan (AUC +70 to +150 min) between body mass index-matched unoperated controls (BMI-M, white) and obese patients after gastric banding (BAND, dotted) and gastric bypass (RYGB, striped) surgery. Comparison of (B,D and F) change in plasma hormone levels and (H) change in total bile acid levels after ice cream meal (both Δ AUC +150 to +210 min) between two surgical groups. Data are presented as median and IQR. ## $p < 0.01$ versus BMI-M; * $p < 0.05$, *** $p < 0.005$ versus BAND; $n = 20-21$ per group.

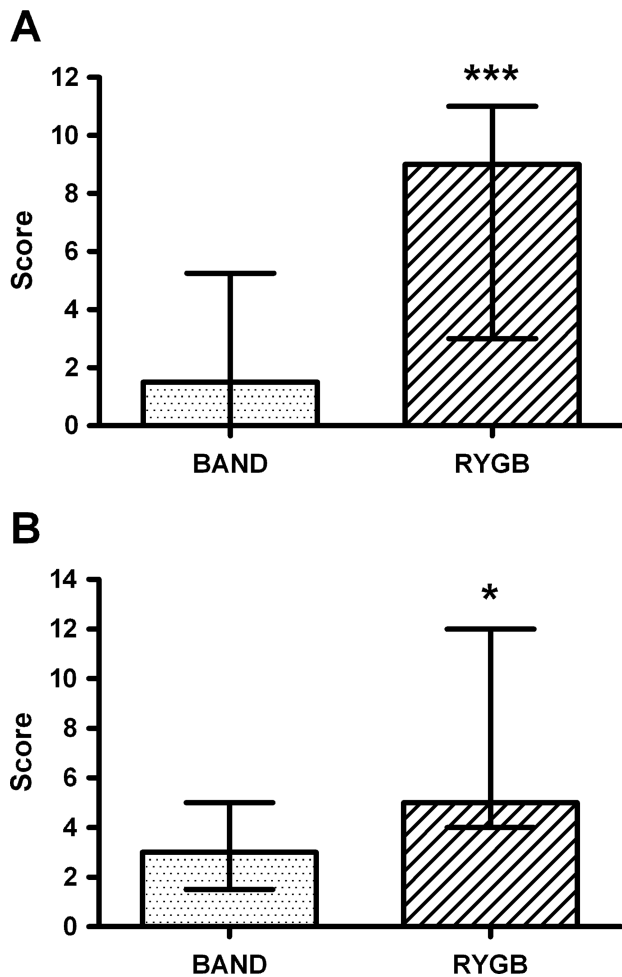


Figure 8 Assessment of dumping syndrome in surgical groups. Comparison of retrospective (A) Sigstad's and (B) Arts' dumping syndrome scores during first 3 months after surgery ($n=18-19$ per group), between obese patients after gastric banding (BAND, dotted) and gastric bypass (RYGB, striped) surgery. Data are presented as median and IQR. * $p<0.05$, *** $p<0.005$ versus BAND.

ratings of the high-calorie ice cream lunch in the RYGB group (Pearson $r=+0.49$, $p=0.029$), and a similar trend was seen in the BAND group ($r=+0.45$, $p=0.055$).

However, within the RYGB group, there was no significant correlation between BOLD activation to any food, or high-calorie or low-calorie food pictures in the whole reward system, OFC or amygdala with any of the following secondary outcome measures: GLP-1, PYY or total bile acids area under curve (AUC) during fMRI scan (correlation coefficient -0.35 to $+0.31$, $p=0.13-0.92$); absolute GLP-1, PYY or total bile acids AUC after ice cream meal (-0.24 to $+0.29$, $p=0.22-1.0$); or either of the dumping questionnaire scores (-0.39 to $+0.27$, $p=0.11-1.0$).

DISCUSSION

This study has demonstrated that obese patients after RYGB have a markedly different brain-hedonic response to food compared with BAND surgery. The primary finding was that patients after RYGB had lower activation in several brain regions to food, especially high-calorie, including the OFC, amygdala, caudate nucleus, nucleus accumbens and hippocampus. These differences in brain reward systems were accompanied by beneficial differences in dietary behaviour and food hedonics, as seen

from the secondary outcomes. After RYGB, patients consumed proportionately less dietary fat, found sweet, high-fat food less palatable, rated high-calorie foods as less appealing and had healthier eating behaviour than after BAND surgery. These differences were unrelated to differences in hunger or psychological traits between the surgical groups. The identification of these phenotypic differences provides a novel explanation for the more favourable long-term weight loss seen after RYGB than BAND surgery, with important clinical and pathophysiological implications.

Our finding of lower reward system activation to food pictures in the RYGB group is consistent with reduced food hedonics and consummatory behaviour. Lower neural responses to food cues in these brain regions are seen in the fed state¹⁴⁻¹⁶ and are associated with decreased appeal of high-calorie food pictures,¹⁶ finding high-calorie foods such as ice cream less palatable (as seen in our study), sensory-specific satiety,^{17, 18} deliberate inhibition of the desire for pleasant foods,¹⁹ lower prospective food consumption,²⁰ less longitudinal weight gain^{21, 22} and greater success in a lifestyle weight loss programme.²³

Although some fMRI studies have shown greater activation in these regions to viewing high-calorie foods, or anticipation of food delivery, in people with obesity, higher BMI, or BED, results have been inconsistent and even contradictory.^{24, 25} Nevertheless, the inclusion of a lean, rather than BMI-matched control group in our study may have been helpful, to assess whether the magnitude of the reward system responses in the RYGB group are similar to those of never-obese healthy subjects.

The neuroimaging findings in this cross-sectional study in RYGB patients are consistent with prospective human studies of RYGB.² A prospective fMRI study found correlations between reduced food wanting and reduced brain activation, including caudate, frontal gyri and anterior cingulate cortex, to high-calorie food in the first month after RYGB.²⁶ This smaller study did not, however, control for order effects, changes in BMI or for the early postoperative dietary restrictions. By contrast, in our study, the comparison with BAND patients avoided order effects and controlled for BMI differences, and all scanning took place at least 3 months after surgery, after liquid diet restrictions had ended.

The secondary behavioural outcomes were also in agreement with prospective animal and human studies of RYGB. Animal models of RYGB show a reduced preference for sweet and/or fatty stimuli compared with sham-operated animals.^{9, 27} Obese patients work less hard in a progressive ratio task for sweet/fatty taste stimuli after RYGB than preoperatively.⁸ Longitudinal shifts away from a calorie-dense diet have also been described after RYGB.²⁸

Metabolic phenotyping results point to potential mediators behind these differences in food hedonic responses, although direct causal inference has not been established. As expected, postprandial plasma GLP-1 and PYY gut hormone levels, and pre-lunch PYY levels, were higher in this cohort after RYGB than BAND and/or unoperated groups.⁵ In addition to increasing satiety through homeostatic appetite centres (vagal-brainstem-hypothalamic), these hormones also modify activity in brain reward systems and dopaminergic signalling.^{29, 30} GLP-1 and/or PYY acutely reduce BOLD signal to visual food cues in non-obese subjects in similar brain regions to our study,³¹ mediate changes in taste away from high-fat, sweet foods³² and plasma levels correlate with longitudinal reductions in uncontrolled eating after RYGB.³³ Brain hedonic-reward systems may therefore respond not only acutely but also to chronic exposure to the repeated exaggerated postprandial increases in GLP-1 and PYY.³⁴

Plasma bile acids were also higher in the RYGB than BAND group, not only postprandially but also before lunch.³⁵ This could be an alternative modulator of central hedonic processing of food after RYGB. Indeed, bile acids cross the blood–brain barrier,³⁶ and the bile acid receptor TGR5 is present in the brain.³⁷ Bile acids also stimulate small bowel production of fibroblast growth factor 19 (FGF19), which reduces food intake centrally,³⁸ and increases after RYGB.³⁵ A direct role for bile acids or FGF19 after RYGB may therefore be worthy of further exploration.

RYGB patients also reported greater prevalence of symptoms consistent with dumping syndrome in the early postoperative period, and were more nauseated after ingestion of the high-calorie test meal, than after BAND surgery. Learned conditioned aversion due to postingestive effects of high-calorie foods may also therefore play a role in the reduced food hedonic responses after RYGB, potentially mediated by changes in GLP-1 and PYY.⁹

Although the orexigenic hormone ghrelin has stimulatory effects on food hedonics and reward system activation to food cues,²⁹ we did not find any significant difference in plasma acyl ghrelin between surgical groups. Some studies have found reduced fasting and/or postprandial ghrelin levels after RYGB compared with before surgery or unoperated controls. This finding is, however, not universal, related to differences in surgical techniques, assay of total versus active acyl ghrelin, problems with handling and storage of plasma samples.²

It was not possible to further clarify which of these potential mediators might contribute to the reduced brain-hedonic response to food after RYGB, as within the RYGB group, none were correlated with BOLD activation to food cues (in those ROIs that displayed differences between surgical groups). The ability to detect such an association may have been hindered by the sample size, cross-sectional nature of the study and other physiological factors contributing to the variability in BOLD responses between individuals within the group.³⁹

Although our study was cross-sectional, preoperative and postoperative confounding variables were generally similar between surgical groups, including the prevalence of BED and current T2DM. Although weight loss was greater in the RYGB patients than in the BMI-matched BAND patients, this is unlikely to explain our findings, since this would be anticipated to increase reward responses to food cues.⁴⁰ Patient allocation to surgery was not randomised. Nevertheless, the choice of surgical procedure is not influenced by preoperative food hedonics. If anything, patients who chose RYGB tended to be heavier preoperatively and therefore less likely to have healthier food hedonics than BAND patients.

Our sample size of scanned subjects is comparable with other fMRI studies investigating food reward^{10–31} and phenotyping studies after bariatric surgery,⁵ but there were a large number of outcome measures that were not corrected for multiple comparisons. We cannot, however, exclude the possibility that type 1 or 2 errors may have occurred for some results. Nevertheless, several complimentary behavioural measures showed results in the same direction as the primary fMRI endpoint.

We were surprised not to observe lower consumption of ice cream in the RYGB compared with BAND group. A possible explanation is that the test meal was not specifically designed to examine food preference, as subjects were not given a choice of foods of different caloric density. Analysis of macronutrient intake outside of the laboratory did reveal lower fat intake after RYGB compared with BAND surgery.

Our results have revealed novel differences in food reward and hedonics between these surgical treatments of obesity. This

may prompt the development of more personalised approaches to surgical choices that incorporate preoperative assessment of food preference and craving. Other factors influencing the choice of bariatric procedure include local expertise and patient preference. There are potentially greater improvements in glycaemic control after RYGB,^{3–35} contrasting with shorter operation time and hospital stay, lower cost and lower mortality rates with BAND surgery.⁴¹ However, in appropriately experienced centres, absolute mortality rates are less than 0.3% for either procedure.⁴¹

In conclusion, RYGB and BAND surgical treatments for obesity are distinct in their mechanisms of weight loss. Postoperatively patients have reduced hunger after both procedures, but there are lower brain hedonic and exaggerated gut hormone and bile acid responses to food after RYGB that would explain its greater efficacy for weight loss. This implicates the gut–brain axis in regulating reward-driven eating behaviour as well as homeostatic appetite, and hence, body weight. Further in-depth interrogation of these gut–brain mechanisms will accelerate development of efficacious, cheaper and safer non-surgical treatments for hedonic overeating and obesity.

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Contributors Patient recruitment (SS, ADM, CGP, MLS, NMD, NAI and APG), study design (SS, JDB, CWIR and APG), data collection (SS, ADM, NC, CGP, MLS, NMD, NAI, GD, ARA, TO and APG), data analysis (SS, ADM, NC, CGP, MLS, NMD, NAI, GD, RPV, JA-Z, MAG, ADW, GSF, JDB, CWIR and APG), data interpretation (SS, ADM, MLS, NMD, NAI, TO, RPV, JA-Z, MAG, ADW, GSF, JDB, CWIR and APG), writing of manuscript (SS, ADM and APG), review and approval of manuscript (all authors).

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SUPPLEMENTAL INFORMATION

Obese patients after gastric bypass surgery have lower brain hedonic responses to food than after gastric banding.

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Supplemental Figures

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fMRI analysis

Food palatability

Dietary habits

Metabolic, hormone and bile acid assays

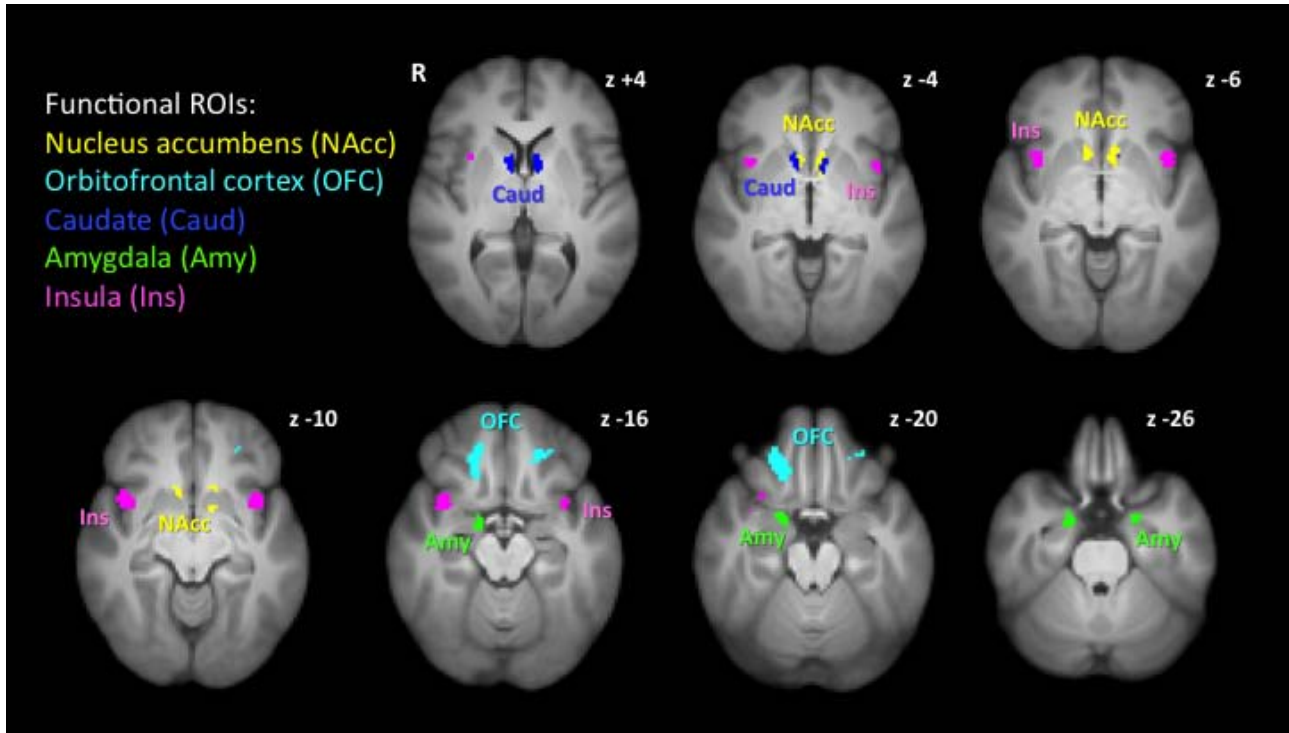
Dumping symptoms

Role of funders

Supplemental References

SUPPLEMENTAL FIGURES

Figure S1. *A priori* functional regions of interest for reward system activation during food evaluation task

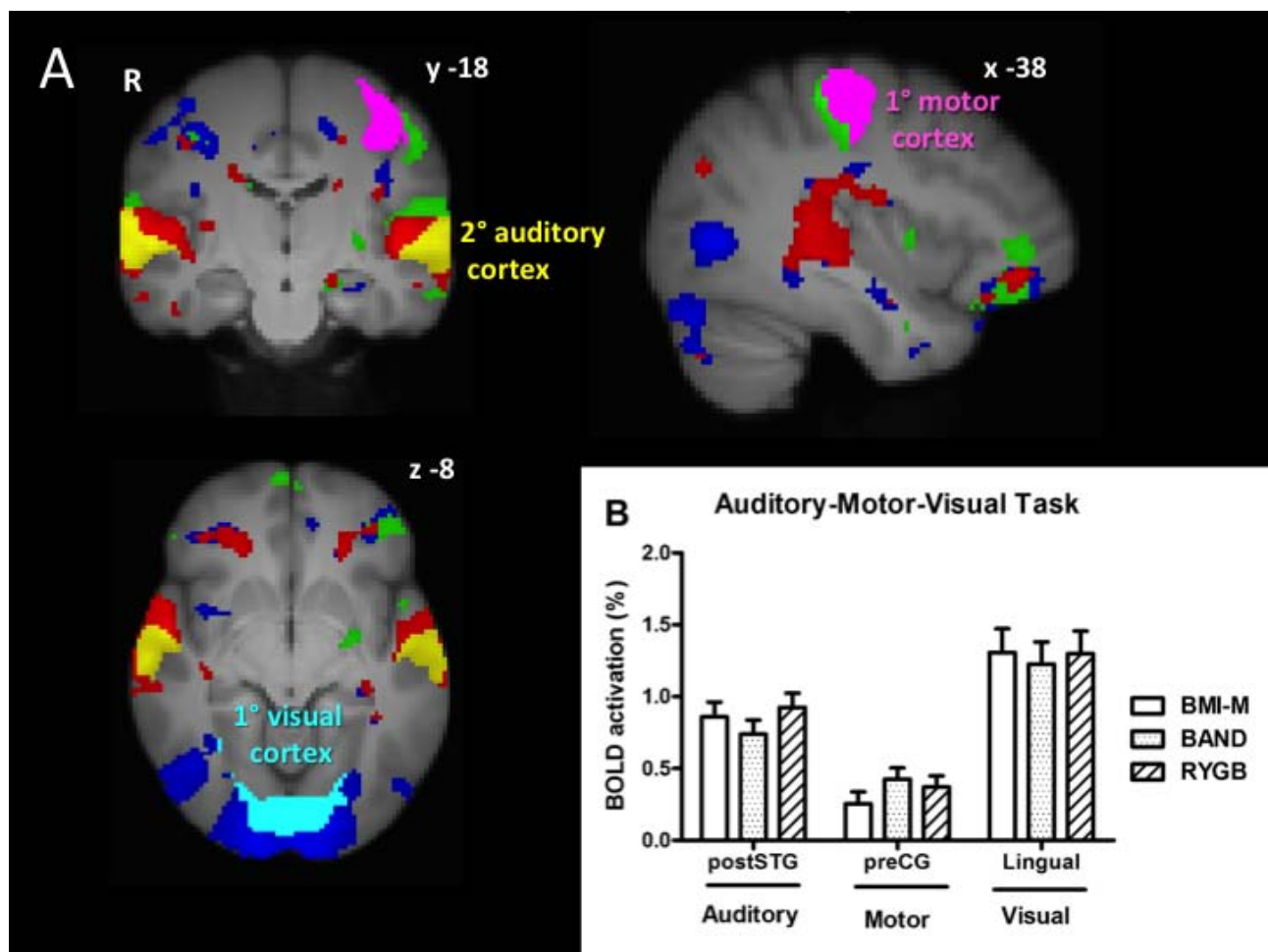


Group activation in separate cohort of obese/overweight patients for any food (high-calorie or low-calorie) vs. object picture contrast.

Activation is thresholded at voxel-wise FDR $P < 0.05$, overlaid onto the average T1 scan for all subjects ($n=24$).

A priori functional regions of interest (ROIs) are indicated: nucleus accumbens (NAcc, yellow), orbitofrontal cortex (OFC, light blue), caudate (Caud, dark blue), amygdala (Amy, green), anterior insula (Ins, magenta). Co-ordinates are given in standard MNI space.

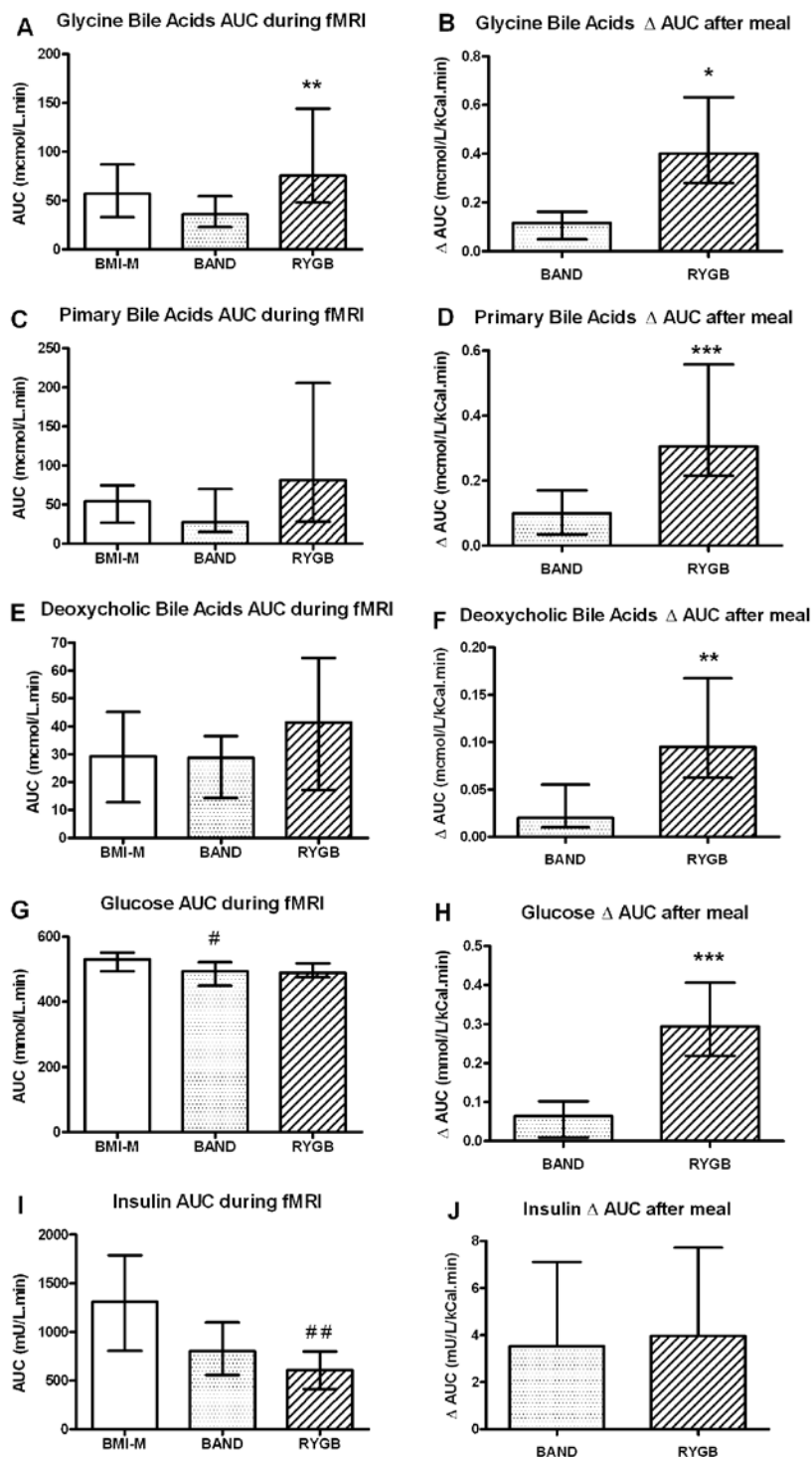
Figure S2. *A priori* functional regions of interest for auditory, motor and visual cortex activation during control task



(A) Group activation maps of separate cohort of overweight/obese subjects overlaid with *a priori* anatomical regions of interest for control auditory-motor-visual task: auditory (red: listening to story) with bilateral posterior division of superior temporal gyrus (overlaid in yellow), motor task (green: button press) with left pre-central gyrus (overlaid in magenta), and visual (dark blue: flashing checkerboard) with lingual gyrus (overlaid in light blue). Activation is thresholded at voxel-wise FDR $P < 0.05$, overlaid onto the average T1 scan for all subjects ($n = 24$). Co-ordinates are given in standard MNI space.

(B) Comparison of BOLD signal for auditory, motor and visual control task in *a priori* functional regions of interest between body mass index-matched unoperated controls (BMI-M, white), and obese patients after gastric banding (BAND, dotted) and gastric bypass (RYGB, striped) surgery, adjusting for age, gender and BMI. Data are presented as mean \pm SEM. $n = 19-20$ per group.

Figure S3. Plasma levels of bile acid sub-fractions, glucose and insulin



Comparison of plasma (A-F) bile acid sub-fractions (glycine, primary bile acid, deoxycholic bile acid), (G,H) glucose and (I,J) insulin levels. (A,C,E) levels during fMRI scan (area under curve (AUC) +70 to +150 mins), and (G,I) during fMRI scan (AUC +40 to +150 mins) between body mass index-matched unoperated controls (BMI-M, white), and obese patients after gastric banding (BAND, dotted) and gastric bypass (RYGB, striped) surgery. (B,D,F,H,J) change in levels after ice-cream meal (Δ AUC +150 to +210 mins) in surgical groups.

Data are presented as median and interquartile range. #P<0.05, ##P<0.01 vs. BMI-M; *P<0.05, **P<0.05, ***P<0.005 vs. BAND; n=20-21 per group.

SUPPLEMENTAL TABLES

Table S1. Subject characteristics of whole cohort

	BMI-M	BAND	RYGB	P value ^a
n	25	28	30	
Age (years)	41.0 [30.5 - 47.5] (20.0 - 56.0)	42.5 [32.5 - 48.0] (22.0 - 59.0)	44.5 [40.0 - 49.0] (23.0 - 59.0)	0.35
Gender (Male : Female)	4:21	2:26	4:26	0.59
Post-menopausal females, n (%)	6 (24%)	6 (21%)	6 (20%)	0.95
Ethnicity: European Caucasians, n (%)	15 (60%)	22 (79%)	22 (73%)	0.31
Pre-operative BMI (kg/m ²)	n/a	46.0 [42.2 - 51.5] (36.5 - 60.6)	47.6 [42.8 - 53.8] (34.7 - 74.6)	0.53
Current Weight (kg)	99.9 [81.9 - 120.9] (65.5 - 168.0)	96.8 [88.3 - 106.9] (68.3 - 126.3)	93.8 [84.3 - 106.2] (63.6 - 144.0)	0.73
Current BMI (kg/m ²)	39.5 [29.3 - 44.1] (24.7 - 59.5)	35.6 [32.4 - 38.2] (24.8 - 50.0)	34.4 [30.2 - 38.4] (23.4 - 54.2)	0.47
Current Body fat (%)	44.2 ± 1.9 (26.0 - 63.2)	43.3 ± 1.4 (21.7 - 54.1)	41.4 ± 2.0 (16.8 - 68.2)	0.54
Weight loss (% of pre-operative weight)	n/a	22.0 [15.2 - 29.4] (8.9 - 52.4)	28.0 [23.4 - 33.0] (16.3 - 40.4)	0.01 RYGB > BAND
Time since surgery (months)	n/a	15.5 [6.25 - 28.5] (2 - 45)	9.75 [8 - 13] (4 - 18)	0.03 BAND > RYGB
Pre-operative DM, n (%)	n/a	3 (11%)	13 (43%)	0.01 RYGB > BAND
Current DM, n (%)	3 (12%)	1 (4%)	3 (10%)	0.51
Pre-operative obesity co-morbidity score	n/a	6.0 [4.5 - 8.0] (1.0 - 13.0)	9.0 [7.0 - 11.0] (2.0 - 19.0)	0.001 RYGB > BAND
Current obesity co-morbidity score	2.0 (0.0 - 7.3) (0.0 - 18.0)	1.5 [1.0 - 2.5] (0.0 - 9.0)	1.0 [0.0 - 2.0] (0.0 - 10.0)	0.60
Pre-operative BED, n (%)	n/a	7 (25%)	9 (30%)	0.90
Current BED, n (%)	4 (16%)	2 (7%)	1 (3%)	0.23

Data included for the whole cohort. Data presented as mean \pm SEM or median [interquartile range] for data that is not normally distributed, and (range).

^a P value for overall comparison of averages or prevalence between groups.

Abbreviations: BAND: gastric banding, BED: binge eating disorder, BMI: body mass index, BMI-M: BMI-matched, DM: type 2 diabetes mellitus, n/a: not applicable, RYGB: gastric bypass.

Table S2. Characteristics of separate cohort of overweight/obese subjects used to create functional regions of interest in brain activation analysis.

n	24
Age (years)	29.0 [26.0 - 38.5] (20.0 - 48.0)
Gender (Male : Female)	6:18
Ethnicity: European Caucasians, n (%)	14 (58%)
Current BMI (kg/m²)	30.7 [26.3 - 32.8] (25.4 - 42.7)
Current body fat (%)	36.3 ± 2.0 (17.1 - 54.5)
Current DM, n (%)	0 (0%)
Current obesity co-morbidity score	0.0 [0.0 - 0.0] (0.0 - 8.0)
Duration fasting (hours)	15.9 [15.16.8] (13.7 - 19.7)

Data presented as mean ± SEM or median [interquartile range] for data that is not normally distributed, and (range).

Abbreviations: BMI: body mass index, DM: type 2 diabetes mellitus.

Table S3. Spatial co-ordinates of whole brain activation for food > objects contrast in separate cohort of overweight/obese subjects.

Contrast	Number of voxels	Z statistic	x	y	z	Brain region
Any food (high-calorie or low-calorie)	11961	6.85	8	-84	-6	R lingual gyrus
> object	2416	5.08	40	8	-14	L insula cortex / temporal pole
	504	4.29	4	26	26	R cingulate gyrus
	358	4.32	-22	-56	40	L superior parietal lobe/ lateral occipital cortex
	322	4.8	-36	-8	8	L insula cortex
	199	3.88	40	38	8	R frontal pole/ inferior frontal gyrus
	187	4.01	-20	-26	-12	L hippocampus/ parahippocampal gyrus
	184	3.84	48	10	20	R inferior frontal gyrus/ precentral gyrus
	149	3.66	4	-30	26	R cingulate gyrus
	131	3.83	-6	2	28	L cingulate gyrus
	105	3.34	52	-24	44	R postcentral gyrus
	102	3.42	28	-4	46	R precentral gyrus / middle frontal gyrus
	101	3.51	-14	-68	-48	L cerebellum
	93	4.05	-48	-18	42	L postcentral gyrus / precentral gyrus
	84	4.28	-52	-44	-22	L inferior temporal gyrus
	63	3.6	-20	38	-14	L frontal pole / orbitofrontal cortex
	51	3.56	-18	-44	-44	L cerebellum
	44	3.41	24	-34	-50	L cerebellum
	43	3.48	22	-68	-54	L cerebellum
	36	3.41	-18	-14	4	L thalamus
	35	3.34	-26	-46	-56	L cerebellum
	29	3.07	-40	-40	40	L supramarginal gyrus / superior parietal lobe
	28	3.43	14	38	36	R frontal pole
	26	3.31	-66	-14	2	L superior temporal gyrus
	24	3.1	12	4	32	R cingulate gyrus

	24	3.21	-60	-24	24	L supramarginal gyrus / postcentral gyrus
	23	3.18	8	-58	66	R precuneus / superior parietal lobe / lateral occipital
	22	3.11	8	64	2	R frontal pole
	19	3.23	-2	-24	-38	L brainstem
	19	3.03	-42	-58	-46	L cerebellum
	17	3.15	52	-20	24	R parietal operculum / supramarginal gyrus /
	15	3.33	60	-50	-22	R inferior temporal gyrus

Stereotactic coordinates (x, y, z given in standard MNI space) for peak voxel within each cluster at group level activation, adjusting for age, gender and BMI, thresholded at voxel-wise FDR $P < 0.05$ ($n=24$), and cluster size > 10 voxels.

Table S4. Spatial coordinates of functional regions of interest in brain activation analysis.

Functional region of interest	Hemisphere	Number of voxels	Z statistic	x	y	z
Food vs. Object contrast						
Orbitofrontal cortex	Right	170	3.81	18	36	-18
	Left	63	3.60	-20	38	-14
Amygdala	Right	110	3.85	18	0	-26
	Left	16	3.99	-18	0	-26
Nucleus Accumbens	Right	62	3.45	8	14	-4
	Left	91	4.11	-6	10	-2
Anterior Insula	Right	188	5.08	40	8	-14
	Left	116	4.43	-38	8	-12
Caudate	Right	129	3.88	8	6	2
	Left	74	4.18	-6	-6	0
Auditory task						
Posterior division of superior temporal gyrus	Right	1109	5.56	64	-14	4
	Left	1108	5.39	-62	-22	2
Motor task						
Precentral gyrus	Left	873	5.78	-36	-24	56
Visual task						
Lingual gyrus	Bilateral	1412	5.59	6	-90	-10

Stereotactic coordinates (x, y, z given in standard MNI space) for peak voxel of group activation, adjusting for age, gender and BMI, thresholded at voxel-wise FDR $P < 0.05$ ($n=24$).

Table S5. Psychological questionnaires from subjects in whole cohort

	BMI-M	BAND	RYGB	P value ^a
n	25	28	30	
Beck Depression Inventory II (score/63)	8.0 [2.0 - 14.0] (1.0 - 44.0)	6.0 [3.0 -14.5] (1.0 - 38.0)	4.5 [2.0 - 11.0] (0.0 - 32.0)	0.99
Moderate-severe depression (>15), n (%)	5 (20%)	7 (25%)	7 (23%)	0.22
On antidepressants treatment, n (%)	3 (12%)	5 (18%)	8 (27%)	0.38
PANAS				
Negative affect (score /50)	18.0 [12.5 - 24.3] (10.0 - 43.0)	15.0 [13.0 - 20.5] (9.0 - 33.0)	15.0 [12.0 - 18.0] (10.0 - 35.0)	0.67
Positive affect (score /50)	32.3 ± 1.7 (18.0 - 49.0)	30.6 ± 2.0 (15.0 - 49.0)	32.8 ± 1.7 (12.0 - 47.0)	0.63
Behavioural activation and inhibition scale				
BAS drive (score /16)	11.0 [9.0 - 13.0] (7.0 -15.0)	10.0 [8.5 - 11.5] (5.0 - 15.0)	10.0 [7.0 - 12.0] (4.0 - 16.0)	0.35
BAS reward responsiveness (score /20)	18.0 [15.8 - 19.0] (9.0 -20.0)	17.0 [15.0 - 19.5] (8.0 - 20.0)	17.0 [14.0 - 19.0] (11.0 - 20.0)	1.00
BAS fun-seeking (score /16)	12.1 ± 0.4 (8.0 - 16.0)	11.6 ± 0.4 (7.0 - 16.0)	11.0 ± 0.5 (5.0 - 16.0)	0.32
BIS (score /28)	21 [17.8 -24.0] (11.0 - 28.0)	21.5 [19.0 - 22.5] (11.0 - 28.0)	20.0 [18.0 - 21.0] (12.0 -28.0)	0.87
Impulsivity				
Barratt impulsivity scale (score /120)	60.5 ± 2.4 (30.0 -77.0)	66.6 ± 2.6 (45.0 - 99.0)	63.2 ± 2.4 (25.0 - 93.0)	0.20
EPQ-R				
Extraversion (score /23)	14.9 ± 0.9 (2.0 - 22.0)	14.2 ± 1.0 (5.0 - 23.0)	13.7 ± 1.0 (4.0 - 23.0)	0.49
Psychoticism (score /32)	6.4 ± 0.6 (0.0 - 13.0)	6.6 ± 0.5 (2.0 - 13.0)	5.4 ± 0.6 (1.0 - 13.0)	0.35
Neuroticism (score /24)	12.9 ± 0.9 (6.0 - 23.0)	11.9 ± 1.3 (1.0 - 24.0)	12.6 ± 1.0 (2.0 - 24.0)	0.73
Lying (score /21)	8.7 ± 1.0(1.0 - 17.0)	9.6 ± 0.7 (3.0 - 17.0)	9.8 ± 0.8 (0.0 - 18.0)	0.83

Data included for the whole cohort. Data presented as mean \pm SEM or median [interquartile range] for data that is not normally distributed, and (range), adjusted for age gender and BMI.

^a P value for overall comparison of averages or prevalence between groups.

Note that similar results were obtained when limiting the analysis to the scanned subjects only (data not shown).

Abbreviations: BAND: gastric banding, BAS/BIS: Behavioural Activation and Inhibition Scale, BMI-M: body mass index matched, EPQ-R: Eysenck Personality Questionnaire, PANAS: Positive and Negative Affect Schedule, RYGB: gastric bypass.

Table S6. Spatial coordinates of whole brain comparison of activation to food between surgical groups.

Contrast	Number of voxels	Z statistic	x	y	z	Brain region
GASTRIC BANDING > GASTRIC BYPASS						
Any food (high-calorie or low-calorie)	Cluster 1 - 1470	4.12	16	30	-12	Right orbitofrontal cortex
> object		3.69	-18	44	-8	Left orbitofrontal cortex
		3.61	-6	8	-20	Left orbitofrontal cortex
		3.45	-16	40	-14	Left orbitofrontal cortex
		3.42	16	16	-18	Right orbitofrontal cortex
		3.20	0	22	-8	Right orbitofrontal cortex
		3.18	4	10	-14	Right subcallosal cortex
		2.93	38	34	-16	Right orbitofrontal cortex / subcallosal cortex
		2.89	-8	18	-20	Left orbitofrontal cortex / subcallosal cortex
		2.83	-16	18	-8	Left putamen / caudate / nucleus accumbens
High-calorie food > object	Cluster 1 - 980	4.05	-38	18	-30	Left temporal cortex
		3.55	-18	44	-10	Left orbitofrontal cortex
		3.51	16	30	-10	Right orbitofrontal cortex
		3.21	-42	26	-14	Left orbitofrontal cortex
		3.17	40	34	-14	Right orbitofrontal cortex
		3.12	-36	38	-12	Right orbitofrontal cortex
		3.04	32	42	-8	Right orbitofrontal cortex / frontal pole
		3.03	-42	30	-16	Left orbitofrontal cortex / frontal pole
		3.00	10	46	-8	Right cingulate/paracingulate gyrus
		2.92	-34	44	-8	Left frontal pole
	Cluster 2 - 1232	3.54	-6	6	-18	Left subcallosal cortex
		3.28	10	-32	-18	Right brainstem
		3.22	4	10	-14	Right subcallosal cortex
		3.21	32	-32	-18	Right hippocampus
		3.05	10	-22	-24	Right brainstem
		3.04	2	-22	-22	Right brainstem
		2.89	-16	18	-8	Left putamen / caudate / nucleus accumbens
		2.88	12	-40	-22	Left brainstem

Contrast	Number of voxels	Z statistic	x	y	z	Brain region
Low-calorie food > object	Cluster 1 - 1041	3.95	14	30	-12	Right orbitofrontal cortex
		3.46	-16	40	-14	Left orbitofrontal cortex
		3.43	4	22	-8	Right subcallosal cortex
		3.32	-4	8	-18	Left subcallosal cortex
		3.25	16	16	-18	Left orbitofrontal cortex
		3.20	-16	46	-6	Left orbitofrontal cortex
		3.17	12	8	-18	Right orbitofrontal cortex / subcallosal cortex
		3.02	-6	18	-18	Left subcallosal cortex
		3.01	-18	42	-20	Left orbitofrontal cortex / frontal pole
		2.94	-8	12	-22	Left orbitofrontal cortex / subcallosal cortex
GASTRIC BYPASS > GASTRIC BANDING						
Any food (high-calorie or low-calorie) > object						Nil significant
High-calorie food > object						Nil significant
Low-calorie food > object						Nil significant

Stereotactic coordinates (x, y, z) for peak voxel of group activation for food category vs. objects, adjusted for age, gender and BMI, cluster thresholded at $Z > 2.1$, FWE $P < 0.05$ ($n = 20$ per group), given in standard MNI space. Voxel-wise differences in BOLD activation between groups did not survive FDR $P < 0.05$ correction.

Table S7. Region of interest activation during food evaluation and auditory-motor-visual control task.

Region of interest	Contrast ^b	BMI-M	BAND	RYGB	P value ^a
n		19	20	20	
FOOD EVALUATION TASK					
Reward system (all 5 ROIs)	Food	0.082 ± 0.029 (-0.127 to 0.335)	0.138 ± 0.020 (0.005 to 0.340)	0.064 ± 0.021 (-0.101 to 0.225)	0.08 BAND > RYGB 0.03
	High-calorie	0.100 ± 0.027 (-0.152 to 0.294)	0.131 ± 0.022 (-0.012 to 0.372)	0.049 ± 0.023 (-0.176 to 0.235)	0.05 BAND > RYGB 0.02
	Low-calorie	0.060 ± 0.033 (-0.150 to 0.348)	0.128 ± 0.026 (-0.042 to 0.472)	0.078 ± 0.022 (-0.060 to 0.253)	0.28
Orbitofrontal cortex	Food	0.177 ± 0.050 (-0.064 to 0.878)	0.235 ± 0.040 (-0.121 to 0.543)	0.066 ± 0.040 (-0.459 to 0.306)	0.029 BAND > RYGB 0.008
	High-calorie	0.191 ± 0.060 (-0.099 to 0.853)	0.182 ± 0.044 (-0.285 to 0.474)	0.043 ± 0.045 (-0.357 to 0.478)	0.09
	Low-calorie	0.160 ± 0.046 (-0.076 to 0.793)	0.250 ± 0.038 (-0.04 to 0.646)	0.085 ± 0.042 (-0.498 to 0.372)	0.03 BAND > RYGB 0.01
Amygdala	Food	0.086 ± 0.051 (-0.172 to 0.592)	0.121 ± 0.035 (-0.187 to 0.543)	-0.027 ± 0.047 (-0.694 to 0.243)	0.04 BAND > RYGB 0.02
	High-calorie	0.124 ± 0.056 (-0.187 to 0.787)	0.110 ± 0.046 (-0.345 to 0.527)	-0.023 ± 0.055 (-0.690 to 0.298)	0.059
	Low-calorie	0.049 ± 0.056 (-0.263 to 0.624)	0.114 ± 0.039 (-0.087 to 0.589)	-0.011 ± 0.056 (-0.633 to 0.425)	0.24
Nucleus accumbens	Food	0.061 ± 0.035 (-0.21 to 0.356)	0.097 ± 0.024 (-0.058 to 0.259)	0.060 ± 0.030 (-0.182 to 0.333)	0.67
	High-calorie	0.075 ± 0.034 (-0.295 to 0.376)	0.107 ± 0.026 (-0.063 to 0.367)	0.048 ± 0.032 (-0.281 to 0.297)	0.43
	Low-calorie	(0.038 ± 0.038) (-0.28 to 0.298)	0.080 ± 0.033 (-0.209 to 0.428)	0.065 ± 0.031 (-0.217 to 0.454)	0.79

Region of interest	Contrast ^b	BMI-M	BAND	RYGB	P value ^a
Anterior Insula	Food	0.0534 ± 0.025 (-0.212 to 0.256)	0.095 ± 0.034 (-0.094 to 0.496)	0.134 ± 0.037 (-0.218 to 0.532)	0.47
	High-calorie	0.062 ± 0.032 (-0.237 to 0.254)	0.102 ± 0.028 (-0.132 to 0.336)	0.127 ± 0.037 (-0.240 to 0.468)	0.64
	Low-calorie	0.038 [-0.058 to 0.107] (-0.148 to 0.310)	0.051 [-0.034 to 0.106] (-0.181 to 0.678)	0.129 [0.040 to 0.182] (-0.192 to 0.545)	0.43
Caudate	Food	0.031 ± 0.051 (-0.371 to 0.638)	0.141 ± 0.033 (-0.059 to 0.605)	0.087 ± 0.032 (-0.100 to 0.411)	0.23
	High-calorie	0.040 [-0.045 to 0.177] (-0.403 to 0.595)	0.013 [0.081 to 0.197] (-0.094 to 0.733)	0.038 [-0.057 to 0.150] (-0.189 to 0.415)	0.15
	Low-calorie	0.025 [-0.120 to 0.117] (-0.375 to 0.639)	0.075 [0.019 to 0.166] (-0.117 to 0.488)	0.010 [0.017 to 0.170] (-0.075 to 0.432)	0.15
CONTROL AMV TASK					
Combined (all 3 ROIs)		0.816 ± 0.089 (0.221 - 1.815)	0.856 ± 0.077 (0.323 - 1.605)	0.798 ± 0.068 (0.415 - 1.331)	0.85
Posterior division superior temporal gyrus	Auditory	0.853 ± 0.134 (0.168 to 2.172)	0.942 ± 0.117 (0.065 to 2.098)	0.728 ± 0.074 (0.288 to 1.443)	0.41
Left precentral gyrus	Motor	0.276 ± 0.104 (-0.807 to 0.846)	0.415 ± 0.077 (-0.076 to 0.973)	0.360 ± 0.057 (-0.049 to 0.727)	0.33
Lingual gyrus	Visual	1.320 ± 0.169 (0.156 to 2.906)	1.212 ± 0.152 (0.152 to 2.739)	1.304 ± 0.146 (0.357 to 2.581)	0.92

Average group activation in separate and combined *a priori* regions of interest (ROI) for food category vs. objects during food evaluation task, or auditory, motor or visual cortex during control task, adjusted for age, gender and BMI. Data presented as mean ± SEM and (range).

^a P value for overall comparison of averages between groups using ANOVA, with post-hoc comparison given beneath.

^b Contrasts with food pictures are compared to object pictures.

Abbreviations: AMV: auditory-motor-visual, BAND: gastric banding, BMI-M: body mass index matched, RYGB: gastric bypass.

Table S8. Assessment of dumping syndrome in surgical groups.

	BAND	RYGB	P value
n	20	21	
Sigstad's score ^a	1.5 [0.0 - 5.0] (-4.0 to 11.0)	9.0 [3.0 - 11.0] (0.0 - 29.0)	0.002 RYGB > BAND
Arts' score ^a	3.0 [2.0 - 5.0] (0.0 - 8.0)	5.0 [4.0 - 12.0] (0.0 - 24.0)	0.02 RYGB > BAND
Δ Heart rate (beats per minute)	7.9 ± 1.4 (-6.0 to 20.0)	5.3 ± 1.7 (-7.0 to 21.0)	0.24
Δ Systolic BP (mm Hg)	-2.4 ± 3.8 (-23.0 to 38.0)	-10.7 ± 3.4 (-40.0 to 19.0)	0.11
Δ Diastolic BP (mm Hg)	-2.5 ± 2.9 (-28.0 to 17.0)	-3.7 ± 1.8 (-16.0 to 10.0)	0.72
VAS Sleepiness			
After meal Δ AUC (cm.min)	0.0 [-78.0 to 28.5] (-396.0 to 442.5)	-30.0 [-113.6 to 3.0] (-217.5 to 63.0)	0.34
VAS Nausea			
After meal Δ AUC (cm.min)	-19.5 [-69.8 to 0.0] (-549.0 to 186.0)	9.0 [0.0 to 79.1] (-10.5 to 408.0)	<0.001 RYGB > BAND

Data presented as mean ± SEM or median [interquartile range] for data that is not normally distributed, and (range).

^a n=18-19 per group

Δ heart rate and blood pressure: change between time points +150 and +210 min. Δ AUC for VAS: change in AUC between time points +150 to +210 min.

Abbreviations: AUC: area under the curve BAND: gastric banding group, BMI-M: body mass index matched group, BP: blood pressure, mm: millimeters, RYGB: gastric bypass, VAS: visual analogue scale.

Table S9. Potential confounding variables at scanning visit.

	BMI-M	BAND	RYGB	P value ^a
n	20	20	21	
PANAS positive (score /50)	32.0 ± 1.9 (16.0 - 51.0)	28.9 ± 2.0 (14.0 - 44.0)	31.0 ± 1.9 (11.0 - 44.0)	0.52
PANAS negative (score /50)	15.0 [12.0 - 20.0] (10.0 - 33.0)	13.5 [11.0 - 16.5] (9.0 - 26.0)	13.0 [11.0 - 16.5] (10.0 - 24.0)	0.33
Sleep duration previous night (hours)	6.8 [6.0 - 7.8] (4.2 - 12.0)	7.5 [7.0 - 7.5] (6.0 - 10.0)	6.5 [5.2 - 7.6] (4.3 - 9.3)	0.16
Time since supper to fMRI scan (hours)	16.4 [15.7 - 17.0] (14.8 - 19.1)	16.1 [15.6 - 16.7] (14.9 - 20.3)	16.5 [16.0 - 17.3] (15.0 - 18.6)	0.41
Absolute motion during food task (mm)	0.24 [0.19 - 0.38] (0.13 - 1.09)	0.37 [0.25 - 0.50] (0.1 - 0.9)	0.36 [0.26 - 0.52] (0.17 - 1.03)	0.13
Relative motion during food task (mm/TR)	0.10 [0.08 - 0.13] (0.05 - 0.22)	0.07 [0.15 - 0.09] (0.05 - 0.23)	0.11 [0.08 - 0.13] (0.06 - 0.36)	0.66
Absolute motion during Audio-Motor-Visual task (mm)	0.23 [0.17 - 0.43] (0.09 - 1.25)	0.28 [0.14 - 0.44] (0.09 - 0.91)	0.20 [0.19 - 0.37] (0.09 - 1.20)	0.99
Relative motion during Audio-Motor-Visual task (mm/TR)	0.09 [0.07 - 0.12] (0.05 - 0.22)	0.10 [0.07 - 0.12] (0.05 - 0.39)	0.09 [0.08 - 0.12] (0.06 - 0.35)	0.79

Data are presented as mean ± SEM or median [interquartile range] for data that is not normally distributed, and (range).

^a P value for overall comparison of averages between groups using ANOVA.

Abbreviations: BAND: gastric banding group, BMI-M: body mass index matched group, mm: millimeters, PANAS: positive and negative affect schedule, RYGB: gastric bypass, TR: repetition time. VAS: visual analogue scale.

SUPPLEMENTAL METHODS

Participants

Obese patients who had previously undergone gastric bypass (RYGB) or gastric banding (BAND) surgery were recruited between June 2009 and June 2011 from the Imperial Weight Centre, Charing Cross Hospital, London, UK at follow-up clinics or through invitation letters. A BMI-matched unoperated control group was recruited from the clinic or by public advertisement. The study was approved by the Local Research Ethics Committee, performed in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent.

Exclusion and inclusion criteria

Inclusion criteria for the study were: for surgical groups (i) loss of more than 8% of their total body weight since surgery, and (ii) surgery more than 2 months ago. All surgical procedures were performed by one of two surgeons (A.A. and T.O.), with RYGB as previously described (Olbers et al. 2003).

Exclusion criteria for the study were: (i) smoking, (ii) pregnancy or breast feeding, (iii) significant neurological, psychiatric or cardiovascular disease including addiction, stroke and epilepsy, other than previous depression, (iv) commencement of anti-depressants less than 6 months ago, (v) type 2 diabetes mellitus (T2DM) treated with agents other than metformin alone, (vi) type 1 diabetes mellitus.

Exclusion criteria for the scanning visit were: (i) inability to use right-handed button keypad, (ii) claustrophobia, (iii) shoulder width >58cm (inability to fit in scanner bore), (iv) metal implants which would preclude safe MRI scanning, (v) vegetarianism or veganism, (vi) reported gluten or lactose intolerance, and (vii) non-Western diet assessed by dietary record.

Patient characteristics

Eligible subjects attended an initial assessment visit during which they completed a medical history, physical examination and questionnaires to assess mood, psychological traits and eating behaviour. Medical notes were examined to ascertain pre-operative clinical information including body weight, presence of T2DM, and binge eating disorder (BED) from review by the clinic psychiatrist (S.S.) or psychologist, and calculation of obesity co-morbidity score using the Kings criteria (Aylwin & Al-Zaman 2008).

In line with standard policy of the obesity clinic, patients in this study had chosen themselves which surgical procedure to undergo. There was therefore no specific selection bias introduced by medical professionals as to which patients had which surgery, as there were no evidence based guidelines to inform bariatric procedure selection. However, in practice patients with T2DM tended to choose RYGB more often due to its more beneficial effects on glycemic control and T2DM resolution (Kashyap et al. 2010, Pournaras et al. 2012). There was therefore a significantly greater prevalence of T2DM and thus obesity co-morbidity score in the RYGB group, but no significant difference in current post-operative T2DM prevalence or other characteristics between surgical groups (see Table 1 and Table S1).

Psychological and eating behaviour questionnaires

The following questionnaires were completed at the initial assessment visit:

1. Dutch Eating Behaviour Questionnaire (DEBQ): to measure dietary restraint, emotional (e.g. stress-induced eating) and external (e.g. food palatability) influences on eating behavior (van Strien 1986).

2. Eating Disorder Examination Questionnaire (EDE-Q): to measure dietary restraint, preoccupation with weight and shape, and binge eating (Fairburn & Beglin 1994).
3. Positive and Negative Affect Schedule (PANAS): to measure symptoms of positive and negative affect over the previous week, which have previously been correlated with fMRI responses to food pictures (Watson et al. 1988, Killgore & Yurgelun-Todd 2006).
4. Beck Depression Inventory (BDI-II): to identify symptoms of depression (Beck et al. 1996)
5. Barratt Impulsivity Scale: to measure impulsivity which has been linked to overeating (Patton et al. 1995, Schag et al. 2013).
6. Eysenck Personality Questionnaire (EPQ-R): to measure extraversion, psychoticism, neuroticism and tendency to lying (Eysenck 1985).
7. Behavioural Activation / Behavioural Inhibition Scales (BAS/BIS): to measure punishment and reward sensitivity. BIS/BAS (reward responsiveness) scores have previously been correlated with fMRI responses to food pictures (Carver & White 1994, Beaver et al. 2006).

Scanning visit protocol

On the day before scanning, subjects were instructed to avoid exercise and alcohol intake, to eat their usual supper at 8.00pm, and then attend the Sir John McMichael Centre Clinical Investigation Unit in the morning having eaten nothing since supper the evening before. Subjects had measurements of height, weight, % body fat by bio-electrical impedance analysis (Bodystat 1500, Isle of Man, UK), and completed the Positive and Negative Affect Schedule (PANAS) to measure mood over the preceding week. Visual analogue scale (VAS) ratings (0-10 cm) of appetite and other symptoms were recorded at serial time points to measure hunger, pleasantness to eat, volume of food wanting to eat, fullness, sickness, sleepiness and stress (Flint et al. 2000, Blundell et al. 2010).

The visit protocol is illustrated in Figure S1. Area under the curve (AUC) for VAS ratings were calculated from +40 to +150 mins to cover the period over the MRI scan in all three groups; and post-prandial changes in VAS ratings were calculated as delta AUC from baseline at +150 to +240 mins in the two surgical groups.

fMRI protocol

Patients were asked to refrain from strenuous exercise and alcohol the day before and day of the study. Patients were scanned for 1 hour starting between 11am and noon (Goldstone et al. 2009). Female participants were scanned in first half phase of menstrual cycle (apart from one BMI-matched control subject who was scanned on day 16 of her cycle) to avoid variations in reward responses including food over the menstrual cycle (Frank et al. 2010). Pregnancy was excluded at each visit.

fMRI confounding variables

There were no significant differences between the three groups in BMI, % body fat, time since last meal, sleep duration the night before the visit (Benedict et al. 2012, St-Onge et al. 2012), or positive or negative affect (PANAS) at the scanning visit (Table S10) (Killgore & Yurgelun-Todd 2006). During scanning there were no significant differences between the groups in absolute or relative head motion during the food evaluation or auditory-motor-visual fMRI tasks (Table S10).

fMRI acquisition

Whole-brain fMRI data were acquired on a 3T Philips Achieva MRI scanner (Robert Steiner MRI Unit, Hammersmith Hospital, London, UK) with T2* weighted gradient-echo echoplanar imaging with an automated higher-order shim procedure: 44 ascending contiguous 3.25 mm thick slices, 2 x 2 mm voxels; SENSE factor 2 repetition time (TR) 3000 ms; echo time (TE) 30 ms; 90° flip angle;

FOV 190x219, matrix 112x112, slice acquisition angle -30° from AC-PC line to reduce frontal lobe signal drop out (Deichmann et al. 2003).

High-resolution T1-weighted turbo field echo structural scans were also collected: (TE 4.6 ms; TR 9.7 ms; flip angle 8° ; FOV 240 mm; voxel dimensions, 0.94 x 0.94 x 1.2 mm). B_0 field maps were used to correct for geometric distortions caused by inhomogeneities in the magnetic field as follows: TR 29 ms; TE 3.6ms, 30° flip angle; FOV 190 x 219, 44 ascending contiguous 3.25mm thick slices, 2 x 2 mm voxels, δTE 0 and 2.5.

Food picture evaluation fMRI paradigm

During the fMRI food picture paradigm, four types of colour photographs were presented in a block design split across two 9 minute, 192 volume runs: (1) 60 high-calorie foods (e.g. pizza, cakes and chocolate), (2) 60 low-calorie foods (e.g. salads, vegetables, fish), (3) 60 non-food related household objects (e.g. furniture, clothing) and (4) 180 Gaussian blurred images of the other pictures (as a low-level baseline), similar to those used previously (Goldstone et al. 2009). Food images were selected to represent familiar foods that are typical to the modern Western diet. Pictures were obtained from freely available websites and the International Affective Picture System (IAPS, NIMH Center for the Study of Emotion and Attention, University of Florida, Gainesville, FL, USA). Food and object pictures were of similar luminosity and resolution.

Each run contained different pictures in 5 blocks each of high-calorie and low-calorie foods and objects interleaved with 31 blocks of blurred pictures (6 pictures per 18 secs) using one of four pseudorandom block orders with a randomized picture order within each block. Every image was displayed for 2500 ms, followed by a 500 ms inter-stimulus interval of a fixation cross. Each high-

calorie food block consisted of equal numbers of foods containing chocolate, non-chocolate sweet and savory non-sweet foods (2 of each).

Images were viewed via a mirror mounted above an 8 channel RF head coil which displayed images from a projector using the IFIS image presentation system (In Vivo, Wurzburg, Germany) and ePrime 2 software (Psychology Software Tools Inc., Pittsburgh, PA, USA). Whilst each image was on display to subjects in the scanner, they were asked to immediately and simultaneously rate how 'appealing' each picture was to them using a 5 button hand-held keypad (1=not at all, 2=not really, 3=neutral, 4=a little, 5=a lot) (Goldstone et al. 2009). The appeal rating was thus made and recorded simultaneously with the stimulus presentation used for fMRI activation.

In our fMRI paradigm we studied the differences in BOLD activation to food pictures between surgical groups, rather than food receipt itself. fMRI paradigms with food pictures have been widely used to study human eating behavior (Carnell et al. 2012), and allow exposure to more complex, real-life food stimuli than can be achieved with the restricted nature of tastants such as milkshakes. Furthermore qualitatively similar correlations of fMRI responses to food pictures, anticipation of food receipt and actual food receipt have been reported (Stice et al. 2013). Furthermore our study has demonstrated that greater activation of brain reward systems during evaluation of high-calorie food pictures is associated with greater palatability of high-calorie foods when actually consumed (see Results - Correlation between outcome measures).

Food pictures

The total caloric load, caloric density and macronutrient composition of the food pictures used in the fMRI task were assessed using Dietplan6 (Foresfield Software Ltd, West Sussex, UK) - high-calorie foods: 834 ± 100 kCal, 321 ± 13 kCal/100g, 42 ± 2 % fat, 48 ± 1 % carbohydrate, 10 ± 1 %

protein; low-calorie foods: 157 ± 18 kCal, 64 ± 5 kCal/100g, 35 ± 3 % fat, 35 ± 3 % carbohydrate, 29 ± 3 % protein; high-calorie vs. low-calorie foods: $P < 0.001$ for energy content, density, % protein and % carbohydrate; and $P = 0.03$ for % fat (unpaired t-test).

Auditory-motor-visual control fMRI paradigm

A 6 min, 114-volume auditory-motor-visual (AMV) control task was performed. Over nine 30 second blocks, subjects performed two of each of the following tasks simultaneously: (i) listening to a story, (ii) tapping their right index finger once every second, or (iii) watching a 4Hz colour (yellow/blue) flashing checkerboard, with each task performed in 6 blocks, and instructions about whether to start or stop the motor task displayed for 3 seconds prior to each block.

fMRI analysis

The first 6 scans were discarded to allow for the BOLD signal to stabilize. The following preprocessing was applied: motion correction using MCFLIRT (Beckmann et al. 2003), fieldmap-based EPI unwarping using PRELUDE+FUGUE (Woolrich et al. 2004, Chang et al. 2012), non-brain removal using BET (Smith 2002), spatial smoothing using a Gaussian kernel of FWHM 6.0mm, grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, and high pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with $\sigma = 100.0$ s).

Time-series statistical analysis was carried out using FILM with local autocorrelation correction including picture onsets, temporal derivative and motion parameters as co-variates. Two subjects (1 gastric bypass, 1 BMI-matched control) were excluded from fMRI analysis as their average relative motion over the food evaluation or control AMV fMRI tasks was greater than 0.5 mm/TR.

Registration to high resolution T1 structural and/or standard space images was carried out using FLIRT. Registration from high resolution structural to standard space was then further refined using FNIRT non-linear registration (Anderson et al. 2007b, Anderson et al. 2007a).

For the food pictures, higher level analysis was carried out using a fixed effect model to combine the two runs, by forcing the random effects variance to zero in FLAME (FMRIB's Local Analysis of Mixed Effects) to determine activation for the following contrasts: food > objects (high-calorie or low-calorie food), high-calorie food only > objects and low-calorie food only > objects (Beckmann et al. 2003, Woolrich et al. 2004).

Similar time-series statistical analysis was performed for the single run AMV paradigm including the onsets of each task (auditory, motor and visual), with temporal derivative and motion parameters as co-variables, to contrast activation during performance of each task with that when the other tasks were being performed.

All higher-level analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 (Beckmann et al. 2003, Woolrich et al. 2004).

fMRI regions of interest

Functional regions of interest (fROIs) for the following areas: bilateral OFC, amygdala, nucleus accumbens, anterior insula and caudate nucleus (Figure S2) were determined from a separate cohort of 24 overweight/obese subjects (Table S2) who underwent an identical protocol after fasting overnight. Higher level whole brain analysis was carried out with mixed effects analysis to identify those voxels which were significantly more activated at the group level, with correction for multiple comparisons made using false discovery rate (FDR) at $P < 0.05$ for the food>objects

contrast (high-calorie or low-calorie food minus objects) (Table S3). Similar functional localizers were made from this separate cohort for the control auditory, motor and visual tasks for bilateral superior posterior temporal gyrus (auditory), left pre-central gyrus (motor), bilateral lingual gyrus (visual) (Figure S3, Table S3).

The functional anatomically constrained ROIs were obtained by masking these group activation maps with the *a priori* anatomical ROI. These were defined by the relevant bilateral ROIs from the cortical and subcortical structural Harvard FSL atlases thresholded at 10% probability. The OFC fROI included regions in the OFC and frontal pole with $y > 22$ and $z < -6$, since analysis of functional activation in this region demonstrated distinct bilateral clusters overlapping the anatomical Harvard atlas regions (Figure S2). The insula mask was subdivided into the anterior insula ($y > 4$) (Chang et al. 2012).

The average (median) magnitude of bilateral BOLD activation within each *a priori* fROI was then extracted for each individual subject separately for any food, high-calorie food and low-calorie food (> object) contrasts using featquery in FSL, to measure the differences in activation between groups for the different picture categories, or different control auditory-motor-visual tasks. Average BOLD activation for each of these contrasts within each ROI was then compared between groups outside FSL, adjusting for age, gender and BMI.

Food palatability

Ad libitum Hagen Daz™ vanilla or pralines and cream flavoured ice cream, was given to subjects in the operated groups in 50ml (43g) portions every 5 minutes and subjects were asked to eat until comfortably full (le Roux et al. 2007). Upon completion, they were asked to rate by VAS how 'pleasant' and 'sweet' the ice cream test meal was to eat. BMI-M control subjects did not have an

ice cream test meal.

Dietary habits

Diet macronutrient composition was assessed using 3-day self-reported dietary records at home in the two surgical groups and analyzed using Dietplan6 (Foresfield Software Ltd., West Sussex, UK).

Metabolic, hormone and bile acid assays

Blood samples for gut hormone analysis were collected into chilled lithium heparin polypropylene tubes, containing 4-(2-Aminoethyl) benzenesulfonyl fluoride hydrochloride (AEBSF) (A8456 Sigma-Aldrich) and aprotinin (Nordic Pharma UK) protease inhibitor to give final concentration of 1 mg/mL and 200 kIU/mL whole blood respectively. Blood samples were centrifuged at 4°C, 4000 rpm for 10 min. Aliquots of separated plasma were immediately mixed with HCl (final concentration of 0.05M) for subsequent assay of acyl ghrelin, and separate unacidified aliquots for assay of other gut hormones (GLP-1 and PYY). All plasma samples were stored at -80°C until assay. Other metabolic and hormonal assays were done on plain serum or fluoride oxalate plasma samples sent immediately to the routine clinical laboratory.

Plasma glucose and serum insulin were measured in the Department of Clinical Biochemistry, Imperial College Healthcare NHS Trust using either an Abbott Architect ci8200 analyzer (Abbott Diagnostics, Maidenhead, UK) or an AxSYM analyzer (Abbott Diagnostics, Maidenhead, UK). Intra-assay coefficients of variation of all measurements were 1.0–5.0%. Plasma GLP-1 (GLP-1₁₋₃₆ amide, GLP-1₇₋₃₆ amide and GLP-1₉₋₃₆ amide) and PYY (total PYY₁₋₃₆ and PYY₃₋₃₆) were assayed using established in-house radio-immunoassays (Allen et al. 1984, Kreymann et al. 1987). Plasma acyl ghrelin was measured by a two-site sandwich ELISA in a single run (Liu et al. 2008). Intra-assay coefficients of variation (CV) for gut hormones were <10%.

Extraction of bile acids (BA) from plasma was performed as described previously.(Tagliacozzi et al. 2003) BA fractions were analysed using high-performance liquid chromatography (Jasco, Essex, UK) tandem mass spectrometry (Applied Biosystems, Cheshire, UK). The method was linear between 0.1 and 10 $\mu\text{mol/L}$ for all BAs and their conjugates with CV of 1.5-6.8% at the lower limit of quantitation (0.1 $\mu\text{mol/L}$). The inter-assay CV was 3.6-8.0%.

Area under the curve (AUC) for metabolites and hormones were calculated from +40 to +150 mins, and for bile acids from +70 to +150 mins, to cover the period before and over the MRI scan in all three groups; and in the two surgical groups post-prandial changes in metabolites, hormones and bile acids were calculated as delta AUC from baseline at +150 to +210 mins per kCal ice cream eaten at lunch.

Dumping symptoms

The presence of symptoms of possible 'dumping syndrome' was assessed using change in nausea and sleepiness from before lunch to 1.5 hours after lunch (ΔAUC +150 to +240 mins), and change in physiological markers indicative of dumping syndrome, pulse and blood pressure, from before lunch to one hour after lunch (difference +150 to +210 min) (Ukleja 2005). In addition patients retrospectively completed two validated questionnaires to assess post-prandial symptoms of dumping (e.g. fainting, breathlessness, sleepiness, palpitations, headaches and nausea) in the 3 months following surgery (Sigstad 1970, Arts et al. 2009).

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